PROTOCOL TITLE:	An Open-label, Single Arm, Multicenter Study to Broaden Access to
	Emapalumab, an Anti Interferon Gamma (Anti-IFNγ) Monoclonal
	Antibody, and to Assess its Efficacy, Safety, Impact on Quality of Life,
	and Long-term Outcome in Pediatric Patients with Primary
	Hemophagocytic Lymphohistiocytosis

NCT Number: NCT03312751





Sponsor	Sobi AG
Protocol Title:	An Open-label, Single Arm, Multicenter Study to Broaden Access to Emapalumab, an Anti-Interferon Gamma (Anti-IFNy) Monoclonal Antibody, and to Assess its Efficacy, Safety, Impact on Quality of Life, and Long-term Outcome in Pediatric Patients with Primary Hemophagocytic Lymphohistiocytosis
Protocol Number:	NI-0501-09
Premier Research PCN:	176784
Document Version:	Final Version 2.0
Document Date:	24Oct2022

Approvals

Role	Signatures
	Print Name:
	Sign Name:
Biostatistician	
	Print Name:
	Sign Name:
Sobi	
Representative	





Document History

Version	Date	Reason for Amendment
1.0	09-Apr-2021	Not applicable.
2.0	24-Oct-2022	<u>Section 5</u> Added the analysis set Evaluable Analysis Set Without Major Protocol Deviations so it is clear which analysis set is used in sensitivity analysis 5. <u>Section 6.1.5</u> Revision of analysis visit windows in order to clarify which visit should be used as the EOT/Week 8 visit.
		Section 6.1.9.4/Section 9 Supplementary analysis included using an updated definition of overall response. The number of abnormalities at baseline is considered along with the number of abnormalities which worsen from baseline. Section 6.1.9.4 Clarification of the response definition.

AD-ST-33.06 Effective date: 12-Nov-2020

Version 2.0 | Date 24-Oct-2022 | AD-PR-109.02 Effective date: 17-Aug-2020

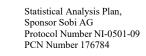
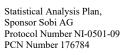




Table of Contents

	•		
Do	cument	History	2
Ta	ble of C	ontents	3
Lis	t of Tal	bles	5
Lis	t of Fig	ures	6
Lis	t of Ab	breviations	7
1.		erview	
2.		Idy Objectives and Endpoints	
	2.1.	Study Objectives	. 9
	2.2.	Study Endpoints	10
	2.2.1.	Efficacy Endpoints	10
	2.2.1.1	5 5 1	
	2.2.1.2	. Secondary Efficacy Endpoint(s)	10
	2.2.2.		
		Pharmacokinetic/Pharmacodynamic Variable(s)	
3.	Ov	erall Study Design and Plan	
	3.1.	Overall Design	
	3.2.	Sample Size and Power	12
	3.3.	Study Population	12
	3.4.	Treatments Administered.	
	3.5.	Method of Assigning Subjects to Treatment Groups	
	3.6.	Blinding and Unblinding	
	3.7.	Schedule of Events	
4.	Sta	tistical Analysis and Reporting	
	4.1.	Introduction	
	4.2.	Interim Analysis and Data Monitoring	
5.	An	alysis Sets	14
6.	Ge	neral Issues for Statistical Analysis	
	6.1.	Statistical Definitions and Algorithms	
	6.1.1.	Baseline	
	6.1.2.	Adjustments for Covariates	15
	6.1.3.	Multiple Comparisons	15
	6.1.4.	Handling of Dropouts or Missing Data	15

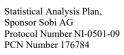




	6.1.5.	Analysis Visit Windows	16
	6.1.6.	Treatment naïve / experienced patients	19
	6.1.7.	Subgroup Analyses	
	6.1.8.	Pooling of Sites	
	6.1.9.	Derived Variables	
	6.1.9.1	. General	
	6.1.9.2	. Demography and Baseline Parameters	
	6.1.9.3	Safety Parameters	
	6.1.9.4	Efficacy Parameters	
	6.1.10.	Data Adjustments/Handling/Conventions	42
	6.1.11.	. COVID-19	44
7.	Stu	dy Patients/Subjects and Demographics	
	7.1.	Disposition of Patients/Subjects and Withdrawals	
	7.2.	Protocol Violations and Deviations	
	7.3.	Demographics and Other Baseline Characteristics	
	7.4.	Exposure and Compliance	
8.	Eff	ficacy Analysis	
	8.1.	Primary Efficacy Analysis	
	8.2.	Secondary Efficacy Analysis	49
	8.2.1.	Overall Survival	49
	8.2.2.	Event-free Survival	49
	8.2.3.		
	8.2.4.	Duration of Response	50
	8.2.5.	Time to Response	50
	8.2.6.	Clinical Response	50
		Glucocorticoids Reduction.	
	8.2.8.	Number of Patients Proceeding to HSCT	50
	8.2.9.	Quality of Life Assessed Through PedsQL TM , Pediatric Quality of Life Inventory	50
	8 2 10	· · ·	
9.		pplementary Analysis	
9. 10.		fety and Tolerability Analysis	
10.	10.1.	Adverse Events	
		Adverse Events Leading to Study Drug Withdrawal	
		Deaths and Serious Adverse Events	
	10.1.2.		



Page 5 of 73



	10.1.3.	Treatment-Emergent Adverse Events with Infections	53
	10.1.4.	Infusion-related reactions	53
	10.2.	Clinical Laboratory Evaluations	53
	10.2.1.	Hematology, Coagulation and Clinical Chemistry	53
	10.2.2.	Urinalysis	54
	10.2.3.	Cerebrospinal Fluid Data	54
	10.3.	Vital Signs	54
	10.4.	Physical examination	54
	10.5.	Electrocardiograms	54
	10.6.	Imaging Test Results	54
	10.7.	Systematic Search for Infections	
	10.8.	Hematopoietic Stem Cell Transplantation (HSCT)	55
	10.9.	Concomitant Medications and Procedures	55
11.	Ch	anges from Planned Analysis	55
12.	Oth	her Planned Analysis	56
	12.1.	Pharmacokinetic/Pharmacodynamic/Immunogenicity Analysis	56
13.	Re	ferences	56
14.	Tal	bles, Listings, and Figures	57
	14.1.	Planned Table Descriptions	57
	14.2.	Planned Listing Descriptions	63
	14.3.	Planned Figure Descriptions	66
15.	Tal	bles, Listings, and Listing Shells	68
	15.1.	Standard Layout for all Tables, Listings, and Figures	68
	15.2.	Planned TFL Shells	69
16.	AP	PENDICES	70
	16.1.	Calculation of Dexamethasone daily dose	70
	16.2.	Concomitant Medications for HSCT Conditioning	71
	16.3.	Disease Indicating Central Nervous System (CNS) Involvement / CSF abnormalities by Medical History/AE Preferred Term and Code	72
	16.4.	Adverse Events Indicating Organ Failure by MedDRA Preferred Term and Code	73

List of Tables

Table 1: Treatment Visit Windows, treatment	t duration < 8 weeks 17
---	-------------------------





Table 2: Treatment Visit Windows, treatment duration >= 8 weeks	18
Table 3: Patient Populations for Each Analysis/Summary	22
Table 4: Definition of Drug Administration Variables	25
Table 5: Definition of Adverse Events	25
Table 6: Definition of Response for the Primary Endpoint	28
Table 7: Definition of Response for Supplementary Analysis	31
Table 8: Overall Survival	34
Table 9: Survival to HSCT	34
Table 10: Survival post HSCT	35
Table 11: Event-Free Survival	36
Table 12: Duration of Response	36
Table 13: Time to Response	37
Table 14: Derivations for Medications	38
Table 15: Planned Tables	58
Table 16: Planned Listings	64
Table 17: Planned Figures	67
Table 18: Dexamethasone Daily Dose	70
Table 19: Concomitant HSCT Conditioning Medication Preferred Terms	71
Table 20: Medical History/AE Preferred Terms for CNS Involvement / CSF Abnormalities	72
Table 21: AE Preferred Terms for Organ Failure	73

List of Figures

Figure 1: Standardized Layo	ut
-----------------------------	----





List of Abbreviations

Abbreviation	Definition
ADA	anti-drug antibody
AE	adverse event
ATC	anatomical therapeutic chemical
BAL	bronchoalveolar lavage
BASES	behavioral, affective and somatic experiences questionnaire
CBC	complete blood cell
CMV	cytomegalovirus
CNS	central nervous system
COVID-19	coronavirus disease 2019
CSF	cerebrospinal fluid
CSR	clinical study report
iDMC	independent data monitoring committee
ECG	electrocardiogram
eCRF	electronic case report form
EBV	Epstein-Barr virus
EMA	European Medicines Agency
ЕОТ	end of treatment
FDA	food and drug administration
HLGT	high level group term
HLH	hemophagocytic lymphohistiocytosis
HLT	high level term
HSCT	hematopoietic stem cell transplantation
ICH	international council for harmonization
IFNγ	interferon gamma
IRR	infusion related reactions
IV	intravenous
LLOQ	lower limit of quantitation
MedDRA	medical dictionary for regulatory activities
n	number of patients
PD	pharmacodynamic

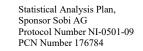
AD-ST-33.06 Effective date: 12-Nov-2020

Version 2.0 | Date 24-Oct-2022 | AD-PR-109.02 Effective date: 17-Aug-2020





Abbreviation	Definition
PedsQL	Pediatric quality of life inventory
pHLH	primary hemophagocytic lymphohistiocytosis
РК	pharmacokinetic
РО	per os – by mouth in Latin
PT	preferred term
QOL	quality of life
SAE	serious adverse event
SAP	statistical analysis plan
SAS®	a software system used for data analysis
SD	study day
SOC	system organ class
ТВ	tuberculosis
TEAE	treatment-emergent adverse event
TLFs	tables, listings, and figures
ULOQ	upper limit of quantitation
US	United States of America
WHO-DD	world health organization drug dictionary





1. Overview

This statistical analysis plan (SAP) describes the planned analysis and reporting for Sobi protocol number NI-0501-09 (An Open-label, Single Arm, Multicenter Study to Broaden Access to Emapalumab, an Anti-Interferon Gamma [Anti-IFNγ] Monoclonal Antibody, and to Assess its Efficacy, Safety, Impact on Quality of Life, and Long-term Outcome in Pediatric Patients with Primary Hemophagocytic Lymphohistiocytosis), dated 31-Mar-2020 version 4.0.

Reference materials for this statistical plan include the protocol and the accompanying sample data collection documents (e.g. case report forms, guidelines for completion of CRF, etc.). Operational aspects related to collection and timing of planned clinical assessments are not repeated in this SAP unless relevant to the planned analysis.

The structure and content of this SAP meets the requirements identified by the Food and Drug Administration (FDA), European Medicines Agency (EMA), and International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use: Guidance on Statistical Principles in Clinical Trials¹. All work planned and reported for this SAP will follow internationally accepted guidelines, published by the American Statistical Association³ and the Royal Statistical Society¹, for statistical practice.

The planned analyses identified in this SAP may be included in clinical study reports (CSRs), 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 database lock of Sobi's study NI-0501-09.

2. Study Objectives and Endpoints

2.1. Study Objectives

- To gather additional safety and efficacy data on emapalumab (previously referred to as NI-0501) in primary hemophagocytic lymphohistiocytosis (pHLH) patients.
- To assess a starting dose of emapalumab of 3 mg/kg.
- To assess the impact of emapalumab on Quality of Life (QOL).
- To gather additional evidence on the long-term outcome of pHLH patients treated with emapalumab.
- To further evaluate the pharmacokinetic (PK) profile of emapalumab in pHLH patients.
- To further evaluate the pharmacodynamic (PD) effects (levels of circulating total IFNγ and biomarkers of its neutralization, namely CXCL9 and CXCL10).
- To assess the profile of other relevant HLH biomarkers, e.g., soluble IL-2 receptor



(sCD25) and other exploratory biomarkers.

• To monitor for potential occurrence of anti-drug antibodies (ADAs).

2.2. Study Endpoints

2.2.1. Efficacy Endpoints

2.2.1.1. Primary Efficacy Endpoint

The primary efficacy endpoint of this study is Overall Response, i.e., achievement of either Complete or Partial Response or HLH Improvement, at end of treatment (EOT) or Week 8 (whichever occurs earlier).

2.2.1.2. Secondary Efficacy Endpoint(s)

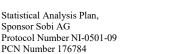
The secondary efficacy endpoints of this study include the following:

- Overall Survival, including survival to hematopoietic stem cell transplantation (HSCT) and survival after either HSCT or last emapalumab infusion (if HSCT is not performed).
- Event-free survival.
- Overall Response, i.e., achievement of either Complete or Partial Response or HLH Improvement, at start of conditioning (or at last emapalumab infusion if HSCT is not performed).
- Duration of Response, i.e., maintenance of the response achieved any time during the study (with censoring time at start of conditioning for patients with no event).
- Time to Response at any time during the study.
- Number of patients able to reduce glucocorticoids by 50% or more of the baseline dose at any time during emapalumab treatment.
- Number of patients able to proceed to HSCT, when deemed indicated.
- Quality of Life assessed through PedsQLTM, Pediatric Quality of Life InventoryTM.⁴
- Quality of Life assessed through BASES, The Behavioral, Affective and Somatic Experiences questionnaires.

2.2.2. Safety Endpoints

Safety and tolerability of emapalumab will be assessed as follows:

• Incidence, severity, causality and outcomes of adverse events (AEs) (serious and non-serious).





- Evolution of relevant laboratory parameters, e.g., complete blood cell (CBC) count, liver and renal function tests, and coagulation parameters.
- Number of patients who discontinued emapalumab treatment for safety reasons.

2.2.3. Pharmacokinetic/Pharmacodynamic Variable(s)

In the present SAP, the following PK/PD parameters are considered for the purpose of descriptive statistics only:

- Serum concentration of emapalumab.
- Levels of circulating total IFN γ (free + bound) at any time point.
- Markers of IFNy neutralization, namely CXCL9 and CXCL10.
- Other relevant HLH biomarkers, e.g., sCD25 and other exploratory biomarkers.
- Level (if any) of circulating antibodies against emapalumab (ADAs).

Measurement of emapalumab concentrations and PD parameters in other matrices, e.g., cerebrospinal fluid (CSF), bronchoalveolar lavage (BAL), if clinically appropriate, will be used in an exploratory fashion.

3. Overall Study Design and Plan

3.1. Overall Design

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

The study enrols pediatric patients with confirmed or suspected pHLH who are treatment-naïve, have failed conventional HLH therapy, or have shown intolerance to it.

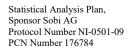
Patients will be in the treating unit the day before the first administration of emapalumab (study day minus 1, SD-1).

Patients are required to receive dexamethasone from SD-1. In treatment-naïve patients, a background therapy of 10 mg/m² dexamethasone will be required. In patients who failed previous HLH therapy, dexamethasone is to be administered at a dose of at least 5 mg/m² or at the dose administered prior to Screening if higher.

Lower dexamethasone doses are allowed in case of documented intolerance to glucocorticoids. During the study, dexamethasone can be tapered depending on the patient's condition, according to the judgment of the treating physician.

The study is divided into three parts:

• Screening period. Screening will be carried out within 2 weeks prior to first administration of emapalumab (SD0) to enable confirmation of patient eligibility and





following the signature of the Informed Consent Form.

- **Treatment period.** The duration of treatment is foreseen until the start of conditioning for HSCT but must not exceed 6 months. The minimum treatment duration is 4 weeks, if the patient's conditions and donor availability allow for HSCT. No washout period is required between the last administration of emapalumab and the start of conditioning.
- Follow-up period. After treatment completion or treatment discontinuation (for any reason), patients will continue in the study for long-term follow-up until 1 year after either HSCT or last emapalumab infusion (if HSCT is not performed). A patient who experiences HLH reactivation during the follow-up period, may be re-treated with emapalumab. Re-treated patients will follow the same schedule of assessments as applicable during the initial treatment and will enter follow-up period after completion of re-treatment.

The end of the study is defined as last patient last visit at 1 year after either HSCT or last emapalumab infusion (as applicable). In case of an ongoing serious adverse event (SAE) the patient will continue to be monitored until resolution or until the outcome of the event is known and stable, beyond the defined study end as necessary.

3.2. Sample Size and Power

The sample size calculation is based on the primary efficacy endpoint of Overall Response. Assuming an Overall Response Rate of 65%, a minimum of 34 treated patients is required to show a significant improvement above 40% with 85% power using an exact binomial test at a one-sided significance level of 2.5%. A drop-out rate of 20% may be expected, hence a total maximum of 41 patients may be enrolled. Due to the rarity of pHLH, recruitment is competitive across all European and North American sites in order to gather data in a reasonable timeframe.

3.3. Study Population

The study population comprises pHLH patients of both genders, from birth up to and including 18 years at diagnosis of HLH. Patients in this study can be naïve to HLH treatment or may have already received conventional HLH therapy without having obtained a satisfactory response according to the treating physician or shown signs of intolerance to HLH therapy.

3.4. Treatments Administered

This is an open-label, single-arm study and no randomization is being performed. Emapalumab will be administered by intravenous (IV) infusion over a period of 1 to 2 hours depending on the volume to infuse, at a dose of 3 mg/kg. Infusions will be performed twice weekly (not more than 4 days apart), except for the second infusion which must be administered on SD-3. The 3 mg/kg dose will be maintained unless the Investigator, guided by the clinical and laboratory response in each patient, deems that a dose increase is appropriate; at any time during the study, it will be possible to increase the emapalumab dose to 6 mg/kg. The dose of emapalumab may be further increased to 10 mg/kg per Investigator's decision based on the patient's clinical and laboratory response.



Upon achievement of Complete Response (i.e., normalization of all clinical and laboratory HLH parameters), the dose of emapalumab will be lowered to achieve 1 mg/kg twice a week and maintained until conditioning for transplant, as long as the patient's clinical conditions are satisfactory. Given the unpredictable course of the disease, in case of reactivation (e.g. triggered by intercurrent infections), subsequent dose increases to 3 mg/kg (and up to 6 or 10 mg/kg, as appropriate) may need to be considered and will be guided by the same clinical and laboratory parameters. Upon obtaining again a Complete Response, the dose of emapalumab will be lowered again to achieve 1 mg/kg twice a week. Should hematopoietic stem cell transplantation (HSCT) be scheduled beyond 12 weeks from emapalumab initiation for reasons unrelated to the administration of emapalumab (e.g., lack of donor availability) and provided Complete Response is maintained, the treatment with emapalumab may continue at the dose of 1 mg/kg once a week.

3.5. Method of Assigning Subjects 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

Not applicable.

3.7. Schedule of Events

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

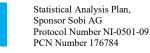
4. Statistical Analysis and Reporting

4.1. Introduction

Data processing, tabulation of descriptive statistics, calculation of inferential statistics, and graphical representations will be performed primarily using SAS (release 9.4 or higher). If the use of other software is warranted, the final statistical methodology report will detail what software was used for what purposes.

Continuous (quantitative) variable summaries will include the number of patients (n) with non-missing values, mean, standard deviation, median, minimum, and maximum. 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. Mean, standard deviation and median will be reported to 1 degree of precision more than the observed data.

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. Percentages will be rounded to 1 decimal place, unless otherwise





specified. Therefore, there may be cases where for instance the total of the percentages does not exactly equal 100%. In case confidence intervals are provided, they will be shown with 1 decimal place.

The number of missing values will be calculated as difference of the total number of subjects in the study population minus the number of non-missing values.

All p-values will be displayed to four decimals and rounded using standard scientific notation (e.g., 0.XXXX). If a p-value less than 0.0001 occurs it will be shown in tables as <0.0001.

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 will be included only in the data listings.

4.2. Interim Analysis and Data Monitoring

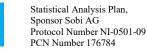
No interim analyses are planned.

An Independent Data Monitoring Committee (iDMC) has overall responsibility for safeguarding the interests of subjects by monitoring relevant data obtained in the study and making appropriate recommendations based on the reported data, thus ensuring that the study is being conducted with the highest scientific and ethical standards.

5. Analysis Sets

The following analysis populations are planned for this study:

- **Enrolled Analysis Set:** The Enrolled Population Analysis Set includes all patients who sign the informed consent form including screen failures. This population will be used only for the purpose of describing patient disposition and for protocol deviations (note: screen failures will be excluded in protocol deviation outputs).
- All Treated Analysis Set: The All Treated Analysis Set includes all patients who receive any part of an infusion of study drug. The All Treated Analysis Set will be the primary population for efficacy endpoints, and will be used for safety and PK/PD endpoints.
- Evaluable Analysis Set: The Evaluable Analysis Set includes all patients in the All Treated Analysis Set who have
 - Received a minimum of 3 consecutive infusions of emapalumab, not more than 6 days between infusions,
 - Not had a diagnosis of secondary HLH subsequent to the initiation of emapalumab treatment.
- Evaluable Analysis Set Without Major Protocol Deviations: The Evaluable Analysis Set Without Major Protocol Deviations includes all patients in the Evaluable analysis set who do not have a major protocol deviation that is deemed to have an impact on the statistical analysis.





Inclusion in the analysis sets defined above will be determined at a data review meeting before database lock.

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

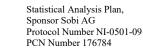
While all possible efforts will be made to ensure that patients stay in the study and all data is collected as scheduled, the occurrence of missing data cannot be completely eliminated.

Rules for handling missing or partial AEs or birth dates are described in Section 6.1.10

For defining the primary efficacy endpoint (Overall Response, see Section 6.1.9.4 for definition), values of some parameters may be missing, thus impacting the response assessment. Imputation rules for assessing disease response at EOT or Week 8 (whichever occurs earlier) and throughout the study have been pre-defined as follows. Note: Imputed values will be flagged in the listings for all endpoints where applicable.

Response at EOT or Week 8 (whichever occurs earlier):

- Missing data at EOT/Week 8 for the parameters relevant to assessment of Overall Response will be imputed by the closest available value from the EOT/Week 8 target day (as per Table 1 and Table 2) up to 8 days, provided upper window limit is before start of conditioning. For body temperature, in the event of repeated measures recorded on the same study day, the highest value will be selected.
- No imputation will be applied if no value is available within the time of the EOT/Week 8 target day up to 8 days. That parameter will be viewed as missing and complete response will not be assigned, even if all other parameters are normal.
- Values recorded at both scheduled and unscheduled visits will be considered.





• If all parameters are unable to be imputed then the overall response assessment will be recorded as missing.

Response throughout the study:

- For secondary time to event analyses (e.g., duration of response, time to response), both scheduled and unscheduled visits will be used for assessment of response.
- If a numerical parameter (i.e. Body Temperature, D-Dimer, Fibrinogen, Ferritin, Platelets, Neutrophils) needed for the response assessment is missing, the midpoint approach will be used to estimate the missing value i.e., the last observed value before the missing period will be averaged with the first value available after the missing period. This rule will be applied to parameter values missing for a period of up to a maximum of 7 consecutive days.

If a character parameter needed for the response assessment (i.e. Spleen Assessment, CNS) is missing, last observation carried forward method will be used to estimate the missing value - i.e., the last observed value within a maximum of 7 consecutive days before the missing period will be used.

In case that, after imputation, data is still missing in any of the criteria considered for the definition of response, a Complete Response cannot be adjudicated.

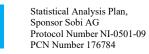
- If the maintenance of response (of at least 4 days) cannot be confirmed due to missing data, the response will be assumed to be lost. In case of calculation of duration of response (i.e. durability of first response) the next response period will be considered. If none of the subject's responses could have been confirmed to last for at least 4 days or only one response was documented which could not have been confirmed to last for at least 4 days, the duration of response will be set to 1 day applying a conservative imputation strategy.
- Since data relevant to CNS assessment has been collected at irregular time-points (based on individual patient conditions), the investigators assessment of CNS status will be carried-forward until the time-points of relevance for response analysis

For descriptive statistics on the evolution over time of clinical signs characterizing HLH disease, the time windows listed in Table 1 and Table 2 will be applied in the case that a parameter is not available on the specified study day.

For any assessment, if there is more than one observation during the visit window, the closest value (within the visit window) to the target day will be chosen first. In the case that there are 2 equidistant values to the study day of interest, the observation that is after the study day in question will be selected.

6.1.5. Analysis Visit Windows

Statistical analyses will be based on the windowing displayed in Table 1 (patients with a





treatment duration less than 8 weeks, i.e. < 56 days) and Table 2 (patients with a treatment duration of 8 weeks or more, i.e. >= 56 days).

However, imputation of missing data will be applied as described in Section 6.1.4.

Visit Name		Tougot dou	Analysis visit window			
		Target day	From SD	To SD		
Baseline				ded prior to the first dose apalumab		
Study Day 0 (free mapal		1	1	1		
Study	Day 3	4	2	5		
Study Day x		Study Day x + 1 day	Target day – 1 day	Target day + 1 day		
	Study Day n-1	Study Day x +1 day	Target day – 1 day	Day of last infusion of emapalumab		
a) EOT visit available	EOT / Week 8	EOT visit	Day of last infusion of emapalumab +1	EOT visit		
	EOT	EOT visit	EOT visit	EOT visit		
	Study Day n-1	Study Day x +1 day	Target day – 1 day	Day of last infusion of emapalumab – 1 day		
b) no EOT visit available	EOT / Week 8	Start day of last infusion *	Start day of last infusion *	End day of last infusion *		
	EOT	Start day of last infusion *	Start day of last infusion *	End day of last infusion *		

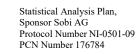
* Start and End date of infusion are in most of the cases the same date.

- a) If an EOT visit was performed and treatment duration was < 8 weeks (i.e. < 56 days), the day of EOT visit will be assigned as EOT/Week 8 analysis visit and as EOT visit prior to start of conditioning.
- b) If no EOT visit was performed and treatment duration was < 8 weeks (i.e. < 56 days), the day of last infusion will be assigned as EOT/Week 8 analysis visit and as EOT visit prior to start of conditioning.



		-	Analysis visit window			
Visit Name		Target day				
			From SD	To SD		
Baseli	ne		Last observation recorded prior to the first dose of emapalumab			
Study Day 0 (firs	t infusion of	1	1	1		
emapalur		1	1	1		
Study D	ć	4	2	5		
Study D	•	7	6	8		
Study D	•	10	9	11		
Study Da	2	13	12	14		
Study Da	2	16	15	17		
Study Da		19	18	20		
Study Da	•	22	21	23		
Study Da		25	24	26		
Study Da		28	27	29		
Study Da		31	30	32		
Study Da		34	33	35		
Study Da	•	37	36	38		
Study Da	2	40	39	41		
Study Day 37 Study Day 42		43	42	44		
Study Da	•	46	45	47		
Study Day 49 Study Day 48		49	48	50		
Week 8 is the last week prio			_	20		
	Study Day 51	52	51	Day of last infusion of emapalumab		
a) EOT visit available	EOT / Week 8	EOT visit	Day of last infusion of emapalumab + 1 day	EOT visit		
	EOT	EOT visit	EOT visit	EOT visit		
	Study Day 51	52	51	Day of last infusion of emapalumab - 1 day		
b) no EOT visit available	EOT / Week 8	57	Day of last infusion of emapalumab	Day of last infusion of emapalumab + 6 days		
	ЕОТ	Start day of last infusion *	Start day of last infusion *	End day of last infusion *		

Table 2: Treatment Visit Windows, treatment duration >= 8 weeks





Visit Name		Torget day	Analysis visit window				
		Target day	From SD	To SD			
Week 8 is not th	Week 8 is not the last week prior to EOT visit or last infusion (subsequent weeks (x to n))						
	Week x	Week (x*7) +1	Target day – 3 days	EOT visit – 1 day			
a) EOT visit available	EOT / Week 8	57	54	60			
EOT		EOT visit	EOT visit	EOT visit			
	Week x	Week (x*7) +1	Target day – 3 days	Day of last infusion of emapalumab – 1 day			
b) no EOT visit available	EOT / Week 8	57	54	60			
ЕОТ		Start day of last infusion *	Start day of last infusion *	End day of last infusion *			

* Start and End date of infusion are in most of the cases the same date.

If treatment duration was ≥ 8 weeks (i.e. ≥ 56 days) the visit within the analysis visit window of 54 and 60 days and closest to the target day will be assigned as EOT/Week 8 analysis visit.

- a) If an EOT visit was performed the day of EOT visit will be assigned as EOT visit prior to start of conditioning.
- b) If no EOT visit was performed the day of last infusion will be assigned as EOT visit prior to start of conditioning.

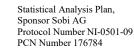
6.1.6. Treatment naïve / experienced patients

Treatment naïve (First Line) patients:

Patients who have not received any conventional treatment for pHLH. In treatment-naïve patients, an initial background therapy of 10 mg/m2 dexamethasone will be required. Dexamethasone not more than 7 days or Methylprednisolone pulses for less than 3 consecutive days until emapalumab treatment start (SD0).

Treatment experienced (Second line) patients:

Patients who have received conventional HLH therapy (as per site standard of care), e.g., any of the following alone or in combination (Etoposide, ATG, Alemtuzumab and Cyclosporine A) and Dexamethasone at 10 mg/m2 for more than 7 days or methylprednisolone pulses for 3 or more consecutive days before emapalumab treatment start (SD0).





The following derivation to identify second line patients will be done:

• Yes to Question: Was any HLH treatment administered at diagnosis [History of HLH treatments]

and

- Medication that:
 - Contains text 'HLH 2004'.

or

- Medication recorded in eCRF with a start date prior to emapalumab first infusion as follows: (priorities need to be followed as below list, check first condition first if not met then check second condition, if not met then the third and so on).

o Etoposide [ATC04ID L01CB - Preferred code 00511901001], any dose, any duration o Antithymocyte immunoglobulin [ATC04ID L04AA - Preferred code 00575401001], any dose, any duration

o Alemtuzumab [ATC04ID L04AA - Preferred code 01268601001], any dose, any duration

o Cyclosporin A [ATC04ID L04AD - Preferred code 00549701001], any dose, any duration

o Anakinra [ATC04ID L04AC - Preferred code 01345101001], any dose, any duration o Tocilizumab [ATC04ID L04AC - Preferred code 01759101001], any dose, any duration

o Dexamethasone [ATC04ID H02AB - Preferred code 00016001001], dose ≥ 10 mg/m² for at least 7 days

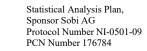
o Methylprednisolone [ATC04ID H02AB - Preferred code 00049601001], with a verbatim indicating "pulses" or "high dose", or any dose for more than 7 days or 30 mg/kg for 3 consecutive days

and any of the following

- Having not achieved a satisfactory response (Unsatisfactory response)
- Having not responded or worsened (No response or worsening)
- Showing intolerance to previous conventional treatment of HLH.
- Having reactivated after satisfactory response based on investigator assessment at screening.

6.1.7. Subgroup Analyses

All data will be presented for the following subgroups, with the relevant analysis sets described in Table 3:





- **Treatment-naïve:** Patients in the All Treated Analysis Set who are naïve to HLH treatment (according to section 6.1.6).
- **Treatment-experienced:** Patients in the All Treated Analysis Set who have received conventional HLH therapy (as per site standard of care) without having obtained a satisfactory response according to the treating physician or having shown signs of intolerance to previous HLH therapy.

Conventional HLH therapy is defined as per site standard-of-care, e.g., any of the following, alone or in combination (etoposide, ATG, alemtuzumab and cyclosporine A) or glucocorticoids, namely dexamethasone at 10 mg/m^2 for at least 7 days or methylprednisolone pulses for 3 consecutive days.



Table 3: Patient Populations for Each Analysis/Summary

	Patient Populations						
	Enrolled	All Treated Analysis Set			Evaluable Analysis Set		
Analyses	Population Analysis Set	Treatment naïve	Treatment experienced	Total	Treatment naïve	Treatment experienced	Total
Patient Disposition	Х	Х	Х	Х	Х	Х	Х
Protocol Deviations	X*						
Demographics, Baseline		X	Х	Х			
Prior and Concomitant Therapies		X	Х	Х			
Primary Efficacy Endpoint		X	Х	Х	Х	Х	Х
Secondary Efficacy Endpoints		X	X	Х	Х	Х	Х
Sensitivity analysis 1: Overall Response at EOT or Week 8 (whichever occurs earlier) with deaths considered as non-responders		X	X	Х			
Sensitivity analysis 2: Overall Response at EOT or Week 8 (whichever occurs earlier) with early withdrawal considered as non- responders					Х	Х	Х
Sensitivity analysis 3: Overall Response at EOT or Week 8 (whichever occurs earlier) with patients who receive concomitant administration of other HLH treatments considered as non-responders		Х	Х	Х			



			Patient Populations				
	Enrolled	All Treated Analysis Set			Evaluable Analysis Set		
Analyses	Population Analysis Set	Treatment naïve	Treatment experienced	Total	Treatment naïve	Treatment experienced	Total
Sensitivity analysis 4: Overall Response at EOT or Week 8 (whichever occurs earlier) with deaths, early withdrawals, and patients who receive concomitant administration of other HLH treatment considered as non- responders		Х	Х	Х			
Sensitivity analysis 5: Overall Response at EOT or Week 8 (whichever occurs earlier) with patients deemed as having a major protocol deviation impacting statistical analysis removed from the Analysis Set					X^	X^	X^
Supplementary analysis: Overall Response at EOT or Week 8 (whichever occurs earlier) - Modified Definition		Х	Х	Х			
Exposure		Х	Х	Х			
Quality of life: PedsQL [™] , BASES		Х	Х	Х			
Safety: AEs, SAEs, Lab tests		Х	Х	Х			
Safety: Vital Signs, Physical Examination, ECG		Х	Х	Х			

* Excluding Screening failures ^ Evaluable Analysis Set Without Major Protocol Deviations



6.1.8. Pooling of Sites

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

6.1.9. Derived Variables

6.1.9.1. General

• Sponsor defined study day = date of interest – date of first emapalumab infusion

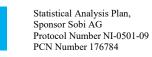
Note: This study day will be used in the analysis visit windowing and displayed on listings if required. Study Day 0 (SD0) is the day when first emapalumab infusion is performed.

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

6.1.9.2. Demography and Baseline Parameters

- 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
- Age at diagnosis in years = date of diagnosis date of birth +1.
- Age in days = date of informed consent date of birth +1.
- Age in years = Age in days / 365.25.
- Age categories: The following groups will be used for categorizing age:

Age Group	Definition
Newborns (0-27 days)	$0 \le (Date of informed consent - Date of Birth +1) \le 27$
Infant and toddlers (28 days - 23 months)	$28 \le$ (Date of informed consent – Date of Birth +1) and age in years = 1
Children (2-11 years)	2 <= age in years <= 11
Adolescents (12-18 years)	12 <= age in years <= 18





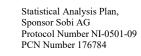
6.1.9.3. Safety Parameters

Table 4: Definition of Drug Administration Variables

Statistics for Exposure (dosing)	Derivation
Duration of exposure (days)	Date of last infusion of emapalumab – date of first infusion of emapalumab + 1
Duration of exposure (weeks)	Duration of exposure (days)/7
Maximum dose prescribed	Maximum of all doses prescribed (mg/kg)
Cumulative dose (mg/kg)	Sum of total actual dose per kg administered from first infusion date until last infusion date
Average dose frequency (days)	Duration of exposure (days)/ total number of infusions
Average dose of emapalumab per day (mg/kg)	Cumulative dose (mg/kg)/ duration of exposure (days)
Percentage of dose increases from baseline dose	(Number of dose increases from baseline dose / number of total doses) multiplied by 100.
Percentage of dose decreases from baseline dose	(Number of dose decreases from baseline dose / number of total doses) multiplied by 100.

Table 5: Definition of Adverse Events

Variable	Definition
Adverse Event (AE)	All recorded AEs (collection of AEs starts after ICF signature).
Treatment-Emergent Adverse Event (TEAE)	Any AE (serious and non-serious) with an onset date after the start of the first emapalumab infusion.
Pre-conditioning AE	Any AE (serious and non-serious) with start date before the start of conditioning for HSCT*.

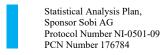




Variable	Definition			
Post-conditioning AE	Any AE (serious and non-serious) with start date after the start of conditioning for HSCT*.			
TEAEs related to the study drug	Any AEs with an onset date after the start of the first emapalumab infusion with "Relationship to Study Drug" of "Related".			
Serious TEAEs	Any AEs with an onset date after the start of the first emapalumab infusion with "Serious" of "Yes".			
TEAEs leading to withdrawal of study drug	Any AEs with an onset date after the start of the first emapalumab infusion with "Action taken with study drug" of "Drug Withdrawn".			
TEAEs resulting in death	Any AEs with an onset date after the start of the first emapalumab infusion with "Results in death" of "Yes".			
TEAE with infections	Any AE with an onset date after the start of the first emapalumab infusion with system organ class (SOC) 'Infections and Infestations' or in the HLGT 'Microbiology and serology investigations'.			
TEAE with infusion-related reactions (IRRs)	Any AE reported to have occurred within 24 hours after the start of infusion and reported as related to study treatment by the Investigator, excluding the following 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, unless the available information clearly indicates the AE was not treatment-emergent.			

*Note: The start date of conditioning is captured in the HSCT module of the eCRF or CM module. For more information of HSCT medications see Appendix 16.2.

AD-ST-33.06 Effective date: 12-Nov-2020



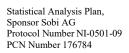


6.1.9.4. Efficacy Parameters

- Overall Response at EOT or Week 8 = achievement (yes/no) of either Complete or Partial Response or HLH improvement at EOT or the Week 8 assessment, whichever occurs earlier.
- Overall Response at start of conditioning for HSCT = achievement (yes/no) of either Complete or Partial Response or HLH improvement at start of conditioning of HSCT (date of start of conditioning) or last emapalumab if HSCT is not performed.

The definition of the Overall Response for the primary endpoint is detailed in Table 6 along with additional clarifications.

The definition of the Overall Response used in the supplementary analysis is detailed in Table 7.





Response for Primary Endpoint	Definition	Additional Clarifications
Complete Response	Complete Response is adjudicated if: - No fever = body temperature < 37.5 °C - Normal spleen size - No cytopenia = Absolute Neutrophil Counts $\geq 1.0 \times 10^{9}$ /L and platelet count $\geq 100 \times 10^{9}$ /L [absence of G-CSF and transfusion support must be documented for at least 4 days to report no cytopenia] - No hyperferritinemia = serum ferritin level is < 2000 µg/L - No evidence of coagulopathy, i.e., normal D-Dimer and/or normal (> 150 mg/dL) fibrinogen levels - No neurological and CSF abnormalities attributed to HLH - No sustained worsening of sCD25 (as indicated by at least two consecutive measurements that are > 2-fold higher than baseline)	 All HLH parameters that were abnormal at baseline must be normalized No AEs relating to organ failure All other parameters that were normal at baseline must still meet the definition of normalized Normal spleen size confirmed by abdominal ultrasound (US) whenever possible based on the splenomegaly not present; if US not performed physical examination will be used Normal D-Dimer levels are <= 500 ug/L No neurological abnormalities attributed to HLH = "normal" neurological assessment by investigator in the neurological examination page (without findings in brain imaging (Brain MRI/Brain CT/cranial ultrasound) or AEs indicative of "CNS involvement" (Appendix 15.3) No CSF abnormalities = no AE indicative of "CSF abnormalities" (Appendix 15.3)



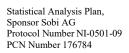
Response for Primary Endpoint	Definition	Additional Clarifications
Partial Response	 Partial Response is adjudicated if: At least 3 of the HLH clinical and laboratory abnormalities (including CNS abnormalities) meet the above mentioned criteria for "Complete Response" In the case of "reactivated patients" who enter the study with 3 abnormal HLH features, Partial Response is adjudicated if at least 2 parameters normalize 	If a patient is not considered as "reactivated" or a patient is considered "reactivated" with 4 or more abnormal HLH features upon entry to the study and at least 3 of the HLH clinical and laboratory abnormalities (including CNS abnormalities) meet the above-mentioned criteria for "Complete Response" Partial Response is adjudicated.
	 In case of reactivated patients who enter the study with 2 abnormal HLH clinical and laboratory parameters only, Partial Response is adjudicated if one of the 2 parameters normalizes There is no progression of other aspects of HLH disease pathology 	For all patients: no progression of other aspects of HLH disease pathology is assessed by absence of AEs indicating organ failure including no worsening of sCD25 levels.



Response for Primary Endpoint	Definition	Additional Clarifications
HLH Improvement	 HLH Improvement is adjudicated if: Improvement (>50% change from baseline or normalization) of at least 3 HLH clinical and laboratory abnormalities (including CNS abnormalities). In the case of "reactivated patients" who enter the study with only 2 abnormal HLH features, a change from baseline greater than 50% for both will define HLH as improved. 	 Definition of 50% improvement from baseline: Spleen size decreased by 50%, as recorded in cm from costal margin at physical examination. Absolute Neutrophil Count increased by 50%, if G-CSF has not been administered in the previous 4 days and Platelet count increased by 50%, if no platelet transfusion has been administered in the previous 4 days Ferritin decreased by 50% Fibrinogen increased by 50% or D-Dimer decreased by 50% Normalization of CNS abnormalities = normal neurological assessment by investigator without findings in brain imaging (Brain MRI/Brain CT/cranial ultrasound), CSF analysis or AEs indicative of "CNS involvement" or "CSF abnormalities"
No Response	If a subject does not meet the criteria for at least HLH improvement, response is categorized as "No Response"	
Abbreviations: CNS, c lymphohistiocytosis	entral nervous system; CSF, cerebrospinal fluid; G-CSF, gr	anulocyte-colony-stimulating factor; HLH, hemophagocytic

AD-ST-33.06 Effective date: 12-Nov-2020

Version 2.0 | Date 24-Oct-2022 | AD-PR-109.02 Effective date: 17-Aug-2020





Response for Supplementary Analysis	Definition	Additional Clarifications
Complete Response	Complete Response is adjudicated if: - No fever = body temperature < 37.5 °C - Normal spleen size - No cytopenia = Absolute Neutrophil Counts $\geq 1.0 \times 10^9/L$ and platelet count $\geq 100 \times 10^9/L$ [absence of G-CSF and transfusion support must be documented for at least 4 days to report no cytopenia] - No hyperferritinemia = serum ferritin level is < 2000 µg/L - No evidence of coagulopathy, i.e., normal D-Dimer and/or normal (> 150 mg/dL) fibrinogen levels - No neurological and CSF abnormalities attributed to HLH - No sustained worsening of sCD25 (as indicated by at least two consecutive measurements that are > 2-fold higher than baseline)	 All HLH parameters that were abnormal at baseline must be normalized No AEs relating to organ failure All other parameters that were normal at baseline must still meet the definition of normalized Normal spleen size confirmed by abdominal ultrasound (US) whenever possible based on the splenomegaly not present; if US not performed physical examination will be used Normal D-Dimer levels are <= 500 ug/L No neurological abnormalities attributed to HLH = "normal" neurological assessment by investigator in the neurological examination page (without findings in brain imaging (Brain MRI/Brain CT/cranial ultrasound) or AEs indicative of "CNS involvement" (Appendix 15.3) No CSF abnormalities = no AE indicative of "CSF abnormalities" (Appendix 15.3)

Table 7: Definition of Response for Supplementary Analysis



Response for Supplementary Analysis	Definition	Additional Clarifications
Partial Response	 Partial Response is adjudicated if: A patient has more than 3 abnormal HLH features at baseline and at least 3 parameters normalize. The remaining may be the same or worse as baseline (unless 2 or more parameters no longer meet the definition of normality) In the case where a patient has only 3 abnormal HLH features at baseline, Partial Response is adjudicated if at least 2 parameters normalize. The remaining may be the same or worse as baseline (unless 2 or more parameters no longer meet the definition of normality) In the case where a patient has only 3 abnormal HLH features at baseline, Partial Response is adjudicated if at least 2 parameters normalize. The remaining may be the same or worse as baseline (unless 2 or more parameters no longer meet the definition of normality) In the case where a patient has only 2 abnormal HLH features at baseline, Partial Response is adjudicated if one of the 2 parameters normalizes. The remaining may be the same or worse as baseline (unless 2 or more parameters normalizes. The remaining may be the same or worse as baseline (unless 2 or more parameters normalizes. The remaining may be the same or worse as baseline (unless 2 or more parameters normalizes. The remaining may be the same or worse as baseline (unless 2 or more parameters no longer meet the definition of normality) There is no progression of other aspects of HLH disease pathology 	If a patient is not considered as "reactivated" or a patient is considered "reactivated" with 4 or more abnormal HLH features upon entry to the study and at least 3 of the HLH clinical and laboratory abnormalities (including CNS abnormalities) meet the above-mentioned criteria for "Complete Response" Partial Response is adjudicated. For all patients: no progression of other aspects of HLH disease pathology is assessed by absence of AEs indicating organ failure including no worsening of sCD25 levels.



Response for Supplementary Analysis	Definition	Additional Clarifications	
HLH Improvement	 At least 3 of the HLH parameters that were abnormal at baseline must be normalized or improved (i.e., >=50% change from baseline). The remaining may be the same or worse as baseline (unless 2 or more parameters no longer meet the definition of normality) In the case where a patient has only 2 abnormal HLH features at baseline, a change from baseline greater than 50% for both will define HLH as improved. 	 Definition of 50% improvement from baseline: Spleen size decreased by 50%, as recorded in cm from costal margin at physical examination. Absolute Neutrophil Count increased by 50%, if G- CSF has not been administered in the previous 4 days and Platelet count increased by 50%, if no platelet transfusion has been administered in the previous 4 days Ferritin decreased by 50% Fibrinogen increased by 50% or D-Dimer decreased by 50% Normalization of CNS abnormalities = normal neurological assessment by investigator without findings in brain imaging (Brain MRI/Brain CT/cranial ultrasound), CSF analysis or AEs indicative of "CNS involvement" or "CSF abnormalities" 	
No Response	If a subject does not meet the criteria for at least HLH improvement, response is categorized as "No Response"		
Abbreviations: CNS, central nervous system; CSF, cerebrospinal fluid; G-CSF, granulocyte-colony-stimulating factor; HLH, hemophagocytic lymphohistiocytosis			

AD-ST-33.06 Effective date: 12-Nov-2020

Version 2.0 | Date 24-Oct-2022 | AD-PR-109.02 Effective date: 17-Aug-2020



- Statistical Analysis Plan, Sponsor Sobi AG Protocol Number NI-0501-09 PCN Number 176784
- Overall Survival, defined as the time from the date of first dose to the date of death. Patients without an event will be censored at date of last contact. The analysis start and end dates and the censoring rules are described in the following scheme:

Table 8: Overall Survival

Situation	Outcome (event or censored)	Analysis start date	Analysis end date
No assessments after first infusion	Censored	Start of treatment	Start of treatment + 1
Death for any cause	Event	Start of treatment	Death
Alive at the end of the observation period*	Censored	Start of treatment	Last known alive
* end of study, or premature end of study for the patient (including withdrawal of consent)			

• Survival to HSCT, defined as the time from the date of first dose to the date of death. Patients who receive a HSCT will be censored at that date. Patients who did not receive HSCT will be censored at date of last contact. The analysis start and end dates and the censoring rules are described in the following scheme:

Table 9: Survival to HSCT

Situation	Outcome (event or censored)	Analysis start date	Analysis end date
No assessments after first infusion	Censored	Start of treatment	Start of treatment + 1
Death for any cause	Event	Start of treatment	Death
Alive at HSCT	Censored	Start of treatment	HSCT date
Alive without having received HSCT	Censored	Start of treatment	Last known alive date



Protocol Number NI-0501-09 PCN Number 176784

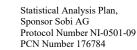
Statistical Analysis Plan, Sponsor Sobi AG

• Survival post HSCT, defined as the time from date of HSCT to the date of death. Patients without an event will be censored at date of last contact. Patients who do not proceed to HSCT will be excluded from this analysis. The analysis start and end dates and the censoring rules are described in the following scheme:

Table 10: Survival post HSCT

Situation	Outcome (event or censored)	Analysis start date	Analysis end date
Death for any cause	Event	Date of HSCT	Death
Alive at the end of the observation period* Censored Date of HSCT Last known alive date			
* end of study, or any time during follow-up period (including withdrawal of consent)			

- HLH Reactivation = any adverse event in the following preferred term (PT) (PT code):
 - Condition Aggravated (10010264)
- Graft failure = any adverse event in at least one of the following PTs (PT code):
 - Transplant failure (10060872)
 - Engraft failure (10068081)
 - Bone marrow transplant rejection (10048396)
 - Transplant rejection (10044439)
 - Complications of bone marrow transplant (10010162)
 - Graft loss (10048748)
- Event-free survival = time from HSCT to date of (whichever occurs first): death from any cause, graft failure, HLH reactivation. The analysis start and end dates and the censoring rules are described in the following scheme:





Situation	Outcome (event or censored)	Analysis start date	Analysis end date	
At least one event, i.e. graft failure, HLH reactivation, death for any cause	Event	Date of HSCT	Date of first event	
None of the events at the end of the observation period*	Censored	Date of HSCT	Last known alive	
* end of study, or any time during follow-up period (including withdrawal of consent)				

Table 11: Event-Free Survival

• Duration of Response (i.e. maintenance of response achieved at any time during the study until EOT) is defined as the total elapsed time from achievement of first Overall Response to first loss of response, pending the duration of this response is at least 4 days. If the first observed response does not last for at least 4 days, then the next response period will be considered. Similarly, loss of response should persist for at least 4 days, otherwise the next loss of response period will be considered. Patients who are in response at EOT will be censored at that date. Patients who do not achieve at least HLH improvement once between the date of first dose and EOT will be excluded from the analysis.

The analysis start and end dates and the censoring rules for calculation of duration of response are described in the following scheme:

Situation	Outcome (event or censored)	Analysis start date	Analysis end date
Maintained loss of overall response	Event	Date of first response ²	Date of loss of overall response ²
Death for any cause	Event	Date of first response ²	Date of death
In response at the end of the observation period ¹	Censored	Date of first response ²	Last known response

Table 12: Duration of Response

AD-ST-33.06 Effective date: 12-Nov-2020





¹ end of treatment without conditioning, or start of conditioning for HSCT, or early termination (including withdrawal of consent);

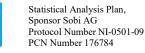
² last for at least 4 days

- Cumulative Duration of Response = Total time in response from the first achievement of an Overall Response until HSCT conditioning (or EOT if the patient did not have HSCT performed). Considering patients who achieve a response, lost that response, and then achieve it subsequently, the total time in response will be calculated by adding together these separate periods in response. Patients who do not achieve response at least once between the date of first dose and the time of conditioning start are excluded from the analysis.
- Percent days in response = Cumulative response duration divided by number of days from first infusion until HSCT conditioning (or EOT if the patient did not have HSCT performed).
- Time to Response (i.e. time to first maintained response) is defined as elapse time from start of treatment to first achievement of a response maintained for at least 4 days prior to or at EOT. Patients with no post-baseline assessments (assessment after the first infusion) will be censored at the first dose date. The analysis start and end dates and the censoring rules are described in the following scheme:

Situation	Outcome (event or censored)	Analysis start date	Analysis end date
No assessments after first infusion	Censored	Start of treatment	Start of treatment + 1
At least 1 event i.e. complete or partial response or HLH improvement	Censored	Start of treatment	Date of first response which lasted for at least 4 days
Death for any cause	Censored	Start of treatment	Death
Alive at the end of the observation period*	Censored	Start of treatment	Last known alive
* end of study, or premature end of study for the patient (including withdrawal of			

Table 13: Time to Response

consent)





Medication Parameters

The definition of treatment naïve and treatment experienced patients are described in detail in section 6.1.6.

Table 14: Derivations for Medications

Dexamethasone daily dose

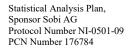
The dose of dexamethasone is to be expressed as $mg/m^2/day$ in order to give homogeneous metrics across patients.

The 'Systemic Steroids Administration' module of the eCRF also collects other glucocorticoids that need to be converted to dexamethasone equivalent using the following assumptions:

- The equivalent dose will include only glucocorticoids administered IV or per os (PO)
- IV and PO route of administration are equivalent, which means 1 mg of IV dexamethasone is equivalent to 1 mg of PO dexamethasone, and 1 mg of IV methylprednisolone is equivalent to 1 mg of PO methylprednisolone.
- Conversion factor:
 - \circ 1 for dexamethasone
 - \circ 1/5.3 for methylprednisolone
 - \circ 1/6.7 for prednisolone
 - \circ 1/6.7 for prednisone
 - \circ 1/5.3 for triamcinolone
 - \circ 1/26.6 for hydrocortisone
 - \circ 1/33.3 for cortisone
- Dose unit: If the dose unit is not mg, then the following conversion will be done:
 - \circ 1 g = 1000 mg
 - \circ 1 mcg = 0.001 mg

Given the possibility of having dexamethasone doses recorded differently in the eCRF or conversions from other glucocorticoids required the following calculation will be performed:

- Daily dose = Conversion factor* Dose of dexamethasone in mg * number of administrations per day
- BSA Surface Area (BSA) [VS]
- Equivalent dose $(mg/m^2/day) = Daily dose / BSA$





Glucocorticoid tapering

For the reduction of glucocorticoid dose by 50% or more of baseline dose, the use of glucocorticoid for systemic use during the study period will be obtained by the CM (ATC04ID H02AB) or medications captured on the SSA module of the eCRF. Drug names on the SSA page are standardized (Dexamethasone, Hydrocortisone, Methylprednisolone, Prednisolone, Prednisolone, not coded. The calculation of reduction of glucocorticoid dose by 50% or more of baseline dose will take into consideration the following:

- Dexamethasone (H02AB PREFERRED CODE 00016001001) dose expressed as mg/m2/day at
 - \circ Baseline = SD-1 or closest day to SD0
 - The lowest dose received during the study and the corresponding SD,
 - The dose received at EOT

provided that:

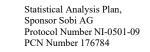
- No other glucocorticoids have been received by oral or IV route on the SD of interest with reference to:
 - Methylprednisolone (CM page: H02AB PREFERRED CODE 00049601001)
 - Prednisolone (CM page: H02AB PREFERRED CODE 00016201001)
 - Prednisone (CM page: H02AB PREFERRED CODE 00044701001)
 - Hydrocortisone (CM page: H02AB PREFERRED CODE 00028601001, 00028603001,00028602001)
 - Triamcinolone (CM page: H02AB PREFERRED CODE 00031901001 if single ingredient medication; in case of multiple ingredients medications or salt derivates every entry need to be checked manually for Triamcinolone)
 - Cortisone (CM page: H02AB PREFERRED CODE 00014601001 if single ingredient medication; in case of multiple ingredients medications or salt derivates every entry need to be checked manually for Cortisone)

In that case, the dose of the other glucocorticoids has to be summed up, taking into consideration glucocorticoid conversion.

• Glucocorticoids reduction until EOT

A patient will achieve a glucocorticoids reduction by 50% or more of the baseline dose if the equivalent dose of dexamethasone at any post-baseline time until EOT is less than or equal to (\leq) ¹/₂ the equivalent dose of dexamethasone at baseline. This reduction has to be maintained for at least one week.

• Patients proceeding to HSCT = patient with HSCT (date of HSCT non missing in the HSCT module of the eCRF).





Quality of Life Parameters

- The Pediatric Quality of Life Inventory (PedsQL) is a brief measure of health-related quality of life in children and adults. PedsQLTM 4.0 generic core scales (ages 2 to over 26) and PedsQLTM infant scales (ages 1 to 24 months) are used in the study. The PedsQLTM 4.0 generic core scales can be completed by parents (Parent Proxy-Report from 2 years old) as well as children and adults (Child/Adult Self-Report from 5 years old). The PedsQL generic core scales are composed of four scales grouped together in one questionnaire:
 - Physical functioning
 - Emotional functioning
 - Social functioning
 - School functioning

The PedsQL Infant Scales, specific for healthy and ill infants ages 1-24 months, are completed by parents and composed of five scales grouped together in one questionnaire:

- Physical functioning
- Physical symptoms
- Emotional functioning
- Social functioning
- Cognitive functioning

Scales are estimated using the following 2-step process as described in the 'Scaling and Scoring of the Pediatric Quality of Life Inventory PedsQL' version 17, dated May 2017 and available online https://www.pedsql.org/PedsQL-Scoring.pdf.

Response Choices	Never	Almost Never	Sometimes	Often	Almost Always
Raw scores	0	1	2	3	4
Reversed score	100	75	50	25	0

1) Calculate reversed scored items transforming the 0-4 scale item to 0-100 as follows:

Notes:

- Higher scale scores indicate better HRQOL (Health-Related Quality of Life).

2) Calculate the average as sum of the items divided by the number of items answered. If more than 50% of the items in the scale are missing, the Scale Score should not be computed.

³⁻point scales: 0 (Not at all), 2 (Sometimes) and 4 (A lot) applicable for the young child (ages 5-7) self-report.



- Functioning scale scores as average of the transformed functioning scale items
 - Physical Functioning Scale Score = average of transformed physical functioning scale items; up to 6 items for infants (1-12 months), 9 items for infants (13-24 months), and 8 items for toddlers, young children, children, teens, and young adults.
 - Physical Symptoms Scale Score = average of transformed physical symptoms scale items; up to 10 items for infants (1-12 months) and infants (13-24 months). This scale score is not available for toddlers, young children, children, teens, and young adults.
 - Emotional Functioning Scale Score = average of the transformed emotional functioning scale items; up to 12 items for infants (1-12 months) and infants (13-24 months) and 5 items for toddlers, young children, children, teens, and young adults.
 - Social Functioning Scale Score = average of the transformed social functioning scale items; up to 4 items for infants (1-12 months) and 5 items for infants (13-24 months), toddlers, young children, children, teens, and young adults.
 - Work/Study Functioning Scale Score = average of the transformed school functioning scale items; up to 3 items for toddler and 5 items for young children, children, teens, and young adults. This scale was not collected for infants (1-12 months) or infants (13-24 months).
 - Cognitive Functioning Scale Score = average of the transformed cognitive functioning scale items; up to 4 items for infants (1-12 months) and 9 items for infants (13-24 months). This scale score is not available for toddlers, young children, children, teens, and young adults.
- Health summary scores
 - Physical Health Summary Score = Physical Functioning Scale Score for toddlers, young children, children, teens, and young adults. For infants (1-12 months) and infants (13-24 months), it is the sum of transformed items over the number of items answered in physical functioning and physical symptoms scales.
 - Psychosocial Health Summary Score = sum of transformed items over the number of items answered in Emotional, Social, and Work/Study Functioning Scales for toddlers, young children, children, teens, and young adults. It is the sum of transformed items over the number of items answered in Emotional, Social, and Cognitive Functioning Scales for infants (1-12 months) and infants (13-24 months).



- Total Scale Score = sum of all the transformed items over the number of items answered on all the scales. (i.e. average as sum of the items divided by the number of items answered).
- The BASES questionnaire is a validated 38 item questionnaire. In this study a reduced nonvalidated 22 item version is used in an exploratory nature for the secondary endpoint. BASES subscale scores will be calculated using a 5-point Likert scale from 1 to 5 for all items and they will be weighted equally to calculate subscale scores. for the following domains:
 - Physical Discomfort, items 1 to 5 (5 items where 1 is considered best response for all items)
 - Cooperation/Compliance, items 6 to 10 (5 items where 1 is considered best response for all items)
 - Mood/Behavior, items 11 to 17 (7 items where 5 is considered best response for all items)
 - Quality of Interactions, items 18 to 20 (3 items where 1 is considered best response for all items)
 - Activity/Sleep, items 21 to 22 (2 items where 5 is considered best response for patient's activity level and 1 is considered best response for patient's sleeping)

6.1.10. Data Adjustments/Handling/Conventions

Medical history and AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 21.0 (or later) thesaurus.

Medications will be coded using World Health Organization Drug Dictionary (WHO-DD) B2 Enhanced v. March 2018 (or later).

Tables describing AEs will show SOCs by descending number of patients and preferred terms within SOC also by descending number of patients. Tables describing prior and concomitant medication will show Anatomical Therapeutic Chemical (ATC) level 1 by descending number of patients and ATC level 2 term also by descending number of patients.

A treatment-related AE is any AE with a relationship to the study drug of 'related'. If a particular event is missing the relationship, the strongest possible relationship will be assumed for analysis (relationship = related).

Adverse events will also be described by intensity (mild, moderate, severe). If a particular event is missing the intensity, the strongest possible intensity will be assumed for analysis (intensity=severe).



Partially missing dates for AEs will be imputed as follows. Note, imputation of missing/partial AE date will be performed only to identify treatment emergent AEs.

AE onset dates

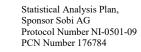
- Partially missing onset dates will be imputed as follows:
 - When only day is missing:
 - If month and year of the onset date_are the same as month and year of the first infusion date, the imputed onset date will be imputed as the minimum of the first infusion date and the AE resolution date (imputed if needed).
 - Otherwise, the missing day will be replaced as the first day of the month.
 - When day and month are missing:
 - If year of the onset date is the same as year of the first infusion date, the imputed onset date will be imputed as the minimum of the first infusion date and the AE end date (imputed if needed).
 - Otherwise, the missing day and month will be replaced by "01JAN".
- Complete missing onset dates for AEs will be imputed by the first infusion date and the AE will be considered as treatment emergent unless, the end date of the AE (imputed if needed) or the end year of the AE (if day and month are missing) is entered and is before the first infusion date.

AE end dates (for non-ongoing events)

- If only day is missing, incomplete end dates will be replaced by the last day of the month, if not resulting in a date later than the date of patient's death. In the latter case the date of death will be used to impute the incomplete end date.
- If day and month are missing, day and month will be replaced by "31DEC", if not resulting in a date later than the date of patient's death. In the latter case the date of death will be used to impute the incomplete end date.
- In all other cases the incomplete end date will not be imputed.

Medication dates

Partially or missing dates for medications will be imputed as follows. Note, imputation of missing/partial medication dates will be performed for differentiating between prior vs





concomitant medications and used in the derivation of equivalent daily dose of dexamethasone.

- If the start date of the medication is unknown (i.e., complete missing date) and there is no end date or any evidence to suggest the medication is ongoing, the worst-case scenario will be assumed. The medication will be considered as both a prior and concomitant medication.
- If the month and the day of the start date of the medication are missing, the month and day will be imputed as "01JAN" of the year specified.
- If the day of the start date of the medication is missing and there is no end date, the day will be imputed as the first day of the month specified.
- If the month and the day of the end date of the medication are missing, the month and day will be imputed as "31DEC" of the year specified, unless there is evidence that the medication is not ongoing in the NI-0501-09 study (although complete end date is unknown). In such circumstances the medication will be considered as prior to enrolment.
- If the day of the end of the medication is missing, the day will be imputed to the last day of the month specified, unless there is evidence that the medication is not ongoing in the NI-0501-09 study (although complete end date is unknown). In such circumstances the medication will be considered as prior to enrolment.

No other dates will be imputed, unless otherwise specified. In data listings, the original incomplete, missing or partial dates (not the imputed dates) will be presented.

Laboratory parameters

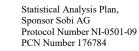
For laboratory results, as well as pharmacokinetic and pharmacodynamic results, with values below the lower limit of quantitation (i.e. < LLOQ), values will be imputed to zeros when summarizing for descriptive statistics and presented as "Below LLOQ" in listings. Values above the upper limit of quantitation (i.e. > ULOQ) for individual values will be imputed to ULOQ values when summarizing for descriptive statistics and presented as "Above ULOQ" in listings.

Pharmacokinetic/Pharmacodynamic/Immunogenicity parameters

For PK, PD and ADA the primary samples should be used in analyses, unless there is a reason (e.g., sample mishandling or bioanalytical reason) for the primary data to be considered invalid, in which case the back-up sample will be utilized. All results will be listed.

6.1.11. COVID-19

A Coronavirus Disease 2019 (COVID-19) Continuity Plan will be 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 trial and trial participants will be extensively described both in the tables, listings, figures (TLFs) 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

The situation is rapidly evolving and further updates to the COVID-19 Continuity Plan and to this SAP are possible and likely.

7. Study Patients/Subjects and Demographics

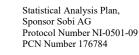
7.1. Disposition of Patients/Subjects and Withdrawals

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

- Patients screened (i.e. Enrolled Population Analysis Set)
- Patients as screen failures and reason for screen failures
- Treated patients
 - Treatment naïve patients
 - Treatment experienced patients
- All Treated Analysis Set
- Evaluable Analysis Set
- Patients who completed the study
- Patients who stopped treatment and reason for stopping treatment
- Patients who prematurely terminated the study and primary reason for early study termination

Percentages will be calculated using the number of patients in the All Treated Analysis Set as the denominator unless otherwise specified.

A separate tabulation of re-treated patients will be provided, outlining the number of re-treated patients and number of re-treated periods per patient.





7.2. Protocol Violations and Deviations

Protocol deviations will be identified and classified as important/non-important during the study in line with ICH guidelines after a medical review.

Important protocol deviations: are a subset of protocol deviations that may significantly impact the completeness, accuracy, and/or reliability of key study data, or that may significantly affect a subject's rights, safety or well-being.

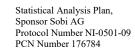
Major protocol deviations: are defined as protocol deviations that have an impact on efficacy.

Classification of important and major protocol deviations will be assessed at ongoing PD review meetings and the blinded data review meeting prior to data base lock.

Any major deviations will lead to an individual being excluded from the Evaluable Analysis Set Without Major Protocol Deviations in a sensitivity analysis as outlined in Section 8.1.

Important deviations will be summarized by category and relationship to COVID-19 in a table considering at minimum the following categories:

- Eligibility: patients entering the study who do not meet all eligibility criteria
- Co-medication: non-adherence to protocol with regard to administration of concomitant medications
 - Patients are required to receive dexamethasone from not later than SD-1. Treatment-naïve patients: 10 mg/m2 of dexamethasone will be required. In patients who failed previous HLH therapy (second line patients): At least 5 mg/m2, or at the dose administered prior to Screening if higher. Lower dexamethasone doses at study entry are allowed in case of documented intolerance to glucocorticoids
 - Biologic drugs (for other indications than HLH) during emapalumab administration. The following are allowed: Granulocyte-colony-stimulating factor (G-CSF), in case of prolonged neutropenia and Rituximab, in case of documented EBV infection.
 - Cyclosporin A (CsA) can be continued, if already administered prior to Screening. CsA is not to be introduced (or re-introduced) during the course of the study once emapalumab administration has started.
 - o Janus kinase (JAK) inhibitors used concomitantly with emapalumab
 - IVIG at doses expected to produce immunomodulatory effect (IVIG is only allowed as replacement therapy)
- Study drug:
 - Patients receiving less than 3 consecutive infusions (i.e. an infusion will be considered as missed If infusions are given more than 6 days apart) of emapalumab and major deviations to treatment dose assessed as impacting efficacy by the study team.





- Assessments: deviations re. schedule of assessments (e.g., missing examinations assessed as impacting the efficacy evaluation)
- Other protocol deviations impacting on patient evaluability (e.g. GCP incompliance)

Important protocol deviations by category, statistical major and minor classification and those due to COVID-19 will be listed by patient.

An assessment of the potential impact on study data analysis and subject's well-being (e.g. major, minor) will also be included.

7.3. Demographics and Other Baseline Characteristics

Demographics and baseline data will be summarized as outlined in Table 3.

• Summary of patient demographics

Summary statistics for age at informed consent (as continuous and categorical variables), body weight (kg), height (cm), body surface area (m²), gender (including childbearing potential), race, ethnicity, and country of origin will be presented.

Patients reporting more than 1 race will be counted in a 'More than one race' category for purposes of tabulating summary statistics race.

• Summary of HLH disease characteristics at diagnosis

The following will be summarized:

- Age at HLH diagnosis (years)
- Number of patients meeting each HLH criteria
- o Number of patients with genetic mutations identified and which mutations

• Summary of medical history other than HLH disease

The number and percentage of patients reporting various medical histories, grouped by MedDRA system organ class and preferred term will be tabulated.

• Summary of HLH disease characteristics at Screening and Baseline

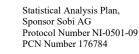
- Number of patients meeting each HLH criteria at screening and baseline
- Number of patients presenting with CNS involvement at screening and baseline (as defined in Appendix 15.4)

• Summary of steroid use prior to first emapalumab infusion

• Summary of previous HLH treatments

• Number of patients who received HLH treatment including type of drug will be tabulated grouped by ATC level 1 and level 2.

All demographic and baseline characteristic data will be presented in patient listings.





7.4. Exposure and Compliance

Investigational product administration will be listed at patient level including all dose adjustments over time and summarized in terms of the number of doses administered, maximum dose, equivalent dose of dexamethasone, duration of exposure from the first dose to the last dose of treatment, cumulative dose, average dose frequency and average dose per day.

The emapalumab dose change from the baseline dose will be summarized showing the number of patients with a dose increase or a dose decrease at each visit. Moreover, the percentage of dose increases and decreases for each patient will be summarized using a descriptive table.

A listing outlining dose increases along with dose level increased to and reasons for the increase, as well as dose decreases over the study will be provided.

This analysis will be conducted as outlined in Table 3.

8. Efficacy Analysis

The evolution of clinical signs (fever, liver and spleen size) characterizing HLH disease, will be presented per visit using descriptive statistics.

All efficacy data will be presented in patient listings.

8.1. Primary Efficacy Analysis

The primary efficacy endpoint is Overall Response at EOT or Week 8 (whichever occurs earlier) (Section 6.1.9.4) with imputation of missing values. The primary efficacy endpoint and its components (Complete Response, Partial Response, and HLH Improvement) will be summarized using descriptive statistics. The analysis of the primary endpoint will utilize an exact binomial test to evaluate the following hypotheses:

Ho: $R \le 40\%$ H1: R > 40%

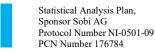
where R is the percentage of the number of patients that achieved Overall Response in the All Treated Analysis Set divided by the total number of patients in the All Treated Analysis Set. The test will be undertaken at the one-sided 0.025 level. The 2-sided exact 95% confidence interval will be provided as well as the 95% confidence interval calculated via the Wilson score method as supportive.

This evaluation will be presented as described in Table 3.

The components of the primary efficacy endpoint (Complete Response, Partial Response, HLH Improvement and No response) will be summarized using counts and percentages at Week 8 or EOT (whichever occurs first).

Sensitivity analyses will be performed on the primary efficacy endpoint using the same test, and displayed as outlined in Table 3:

Version 2.0 Date 24-Oct-2022	AD-PR-109.02 Effective date: 17-Aug-2020)
--------------------------------	--	---





Sensitivity analysis 1: Overall Response at EOT or Week 8 (whichever occurs earlier) with deaths considered as non-responders.

Sensitivity analysis 2: Overall Response at EOT or Week 8 (whichever occurs earlier) with early withdrawal considered as non-responders.

Sensitivity analysis 3: Overall Response at EOT or Week 8 (whichever occurs earlier) with patients who receive concomitant administration of other HLH treatments considered as non-responders.

Sensitivity analysis 4: Overall Response at EOT or Week 8 (whichever occurs earlier) with deaths, early withdrawals, and patients who receive concomitant administration of other HLH treatment considered as non-responders.

Sensitivity analysis 5: Overall Response at EOT or Week 8 (whichever occurs earlier) with patients deemed as having a major protocol deviation impacting statistical analysis removed from the Evaluable Analysis Set.

8.2. Secondary Efficacy Analysis

All secondary efficacy endpoints are viewed as supportive for the primary endpoint and therefore no formal hierarchy of endpoint will be declared.

The evaluations will be performed as outlined in Table 3.

The secondary efficacy endpoints of this study are included in the following sections.

8.2.1. Overall Survival

Overall Survival, Survival to HSCT and Survival post HSCT (Section 6.1.9.4) will be analysed using a descriptive time-to-event approach including Kaplan-Meier curves.

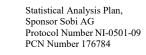
Summaries will include the number and rates of patients experiencing the event and the number of censored observations; the median and 95% confidence interval, and lower quartile and upper quartile estimates of time-to-event; survival estimates at specified timepoints; and the median, minimum and maximum follow-up time in months.

8.2.2. Event-free Survival

Event-free survival (Section 6.1.9.4) will be analysed using the same methods described in Section 8.2.1.

8.2.3. Overall Response at Start of Conditioning

Overall Response (Section 6.1.9.4) at the start of conditioning will be analysed using the same methods described for the primary efficacy endpoint in Section.





8.2.4. Duration of Response

The Duration of Response (Section 6.1.9.4) will be calculated only for patients showing confirmed overall response and will be analysed using the same methods described in Section 8.2.1. The Cumulative Duration of Response will be analysed in absolute days and percent days in response using descriptive summaries.

Swimmer plots will be presented to show response progression and duration of response by patient.

8.2.5. Time to Response

The Time to Response will be analysed using comparable methods described in Section 8.2.1. However, the survival function will be plotted based on the complement of the Kaplan-Meier estimates (1-KM) to provide an estimate of the cumulative incidence of response over time.

8.2.6. Clinical Response

Assessment of Clinical Response using the response categories seen in Table 6, will be described using counts and percentages at each visit.

8.2.7. Glucocorticoids Reduction

Number of patients able to reduce glucocorticoids by 50% or more of the baseline dose during emapalumab treatment (Section 6.1.9.4) will be described using counts and percentages.

8.2.8. Number of Patients Proceeding to HSCT

The number of patients proceeding to HSCT (Section 6.1.9.4) will be described using counts and percentages.

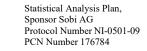
8.2.9. Quality of Life Assessed Through PedsQL[™], Pediatric Quality of Life Inventory

Descriptive summaries of absolute score and change from baseline will be calculated for the PedsQL total scale score, the health summary scores, and the functioning scale scores (Section 6.1.9.4) for all visits where the questionnaire was completed (Baseline, Visit 3 post-infusion, EOT and follow-up visits D+30, D+100, 6 months and 1 year). PedsQL parent and child/adult reports as well as parent report for infants will be presented separately as outlined in Table 3.

PedsQL subject-data, including derived scores, will be listed.

8.2.10. Quality of Life Assessed Through BASES Questionnaires

The BASES questionnaire scores for the 6 domains (note: activity and sleep subscales will be split into two separate domains due to differing best responses and exploratory nature of questionnaire) at the EOT and follow-up visits D+30, D+100, 6 months and 1 year will be





described using descriptive summaries of absolute values. BASES nurse and parent reports will be presented separately. Only patients with HSCT planned and/or performed will be analysed. Note: HSCT planned is defined as patients captured on the HSCT module of the eCRF with a start of conditioning date or on the CM module with HSCT conditioning medications as indicated in Appendix 15.3.

9. Supplementary Analysis

A supplementary analysis for Overall Response at EOT or Week 8 (whichever occurs earlier) using the definition of Overall Response in Table 7 will be performed. This will be evaluated using an exact binomial test as outlined in Section 8.1 and with the components of the overall response (Complete Response, Partial Response, HLH Improvement and No response) summarized using counts and percentages at Week 8 or EOT (whichever occurs first).

10. Safety and Tolerability Analysis

All safety analyses will be performed as specified in Table 3. All data relating to safety will be listed and summarized using descriptive statistics. No inferential statistical tests will be performed.

The analysis of safety assessments in this study will include summaries of the following categories of safety and tolerability data collected for each patient:

- Adverse events, treatment-emergent AEs (TEAEs), non-TEAEs, serious AEs (SAEs) and non-serious TEAEs
- Clinical laboratory parameters
- Vital signs

Where applicable, analyses will be performed separately for the pre and post-conditioning time periods and by treatment naïve/experienced (unless otherwise specified).

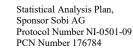
Data of patients who have not undergone HSCT will be analyzed in the pre-conditioning period.

10.1. Adverse Events

All AEs, non-TEAEs, TEAEs, and SAEs will be coded using the MedDRA v. 21.0 (or later). For definitions of AEs see Table 5.

A summary table will present:

- All AEs
- Non-TEAEs
- TEAEs





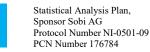
- TEAEs related to study drug
- Mild TEAEs
- Moderate TEAEs
- Severe TEAEs
- TEAEs leading to withdrawal of study drug
- TEAEs resulting in death
- Serious TEAEs
- Treatment emergent SAEs related to study drug
- TEAEs with IRRs
- TEAEs with Infections
- Mild infections
- Moderate infections
- Severe infections

For summary tables the incidence of the safety event of interest (i.e. AE, TEAE, non-SAE) and the number of patients with at least one safety event of interest will be given. A patient with more than one occurrence of the same safety event of interest will be counted only once in the total of those experiencing this safety event.

Information grouped by severity (mild, moderate, severe) will be presented by the worst severity per patient. Any AEs with a missing severity will be reported in the "missing" category grade.

The following safety events of interest will be provided in summary tables grouped by MedDRA system organ class and preferred term (coded using MedDRA v. 21.0 or later):

- AEs
 - overall
 - by severity
- TEAEs
 - overall
 - by severity
 - by relationship to the study drug
- Non-TEAEs
 - overall
- Non-SAEs
- overall
- pre-conditioning TEAEs
 - overall
 - by severity
 - by relationship to the study drug
- post-conditioning TEAEs





- overall
- by severity
- by relationship to the study drug

In the AE data listings, all AEs will be displayed. AEs that are treatment-emergent will be flagged. Additional listings for pre-conditioning and post-conditioning AE will be displayed.

10.1.1. Adverse Events Leading to Study Drug Withdrawal

A summary of incidence rates (percentages) of TEAEs leading to study drug withdrawal and preferred term will be displayed as specified in Table 3.

A data listing of AEs leading to withdrawal of study drug will also be provided, displaying details of the event(s) captured on the CRF.

10.1.2. Deaths and Serious Adverse Events

TEAEs resulting in death will be listed and tabulated by preferred term.

Serious TEAEs will be tabulated by system organ class and preferred term separately for overall, by pre-conditioning and post-conditioning.

10.1.3. Treatment-Emergent Adverse Events with Infections

The number and percentage of patients reporting infections, by SOC and preferred term, and by severity will be tabulated separately for pre-conditioning and post-conditioning infections.

10.1.4. Infusion-related reactions

Infusion-related reactions will be tabulated by system organ class and preferred term.

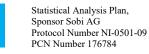
10.2. Clinical Laboratory Evaluations

10.2.1. Hematology, Coagulation and Clinical Chemistry

The number of patients with clinical laboratory values below, within, or above the normal range by visit 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 Analysis Set. Clinical chemistry, hematology, and coagulation results will be presented in separate tables.

Box and whisker plots for each parameter under clinical chemistry, hematology and coagulation will be produced to display absolute values over time.

All laboratory data will be provided in data listings. Laboratory data will be listed by patient





number and visit, and flagged according to pre/post-conditioning. Laboratory values that are outside the normal range will be flagged in the data listings.

10.2.2. Urinalysis

Urinalysis results will be listed only.

10.2.3. Cerebrospinal Fluid Data

The following information has been collected during the study with regard to CSF analysis:

- Protein
- RBC
- WBC
- Neopterin

All CSF data will be provided in data listings including comments on the results and reasons if not performed.

10.3. Vital Signs

Vital signs results will be presented in listings by patient number and visit. Values outside the normal range (+/-10%) and body temperature >= 37.5 Celsius will be flagged.

10.4. Physical examination

A by-patient listing will be provided for physical examination results by patient number and visit.

10.5. Electrocardiograms

ECG results will be presented in listings.

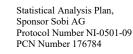
10.6. Imaging Test Results

A by-patient listing will be provided separately for abdominal ultrasound, chest examinations (including x-ray and CT) and brain examinations (including MRI and CT).

10.7. Systematic Search for Infections

Abnormal results of TB search as well as adenovirus, CMV, EBV and other specific infections assessed as medically relevant were to be recorded as AEs and will be presented in AE tables.

A by-patient listing will be provided with results from each infection search.





10.8. Hematopoietic Stem Cell Transplantation (HSCT)

A by-patient listing will be provided including patients undergoing HSCT with regards to:

- Date of start of conditioning / HSCT
- Stem cell source
- Graft manipulation
- Donor type.

10.9. Concomitant Medications and Procedures

Prior medication/therapy is defined as any medication/therapy with an end date prior to the first emapalumab infusion date or recorded with ongoing = 'No', if the end date is unknown. A concomitant medication is defined as a medication taken on or after the first dose of study drug (start date/time is on or after the first dose of study medication, end date/time is after the first dose of study drug), or recorded with ongoing = 'Yes', if the end date is unknown. If a medication starts prior to the date of first dose and continues after the date of first dose it will be considered both prior and concomitant.

Prior and concomitant medications will be summarized descriptively using counts and percentages as specified in Table 3. Summary tables of concomitant steroid use and concomitant HLH treatment (from the time of the first emapalumab infusion) will be provided.

Prior medications will be presented separately from concomitant medications. Prior medications will be split by previous HLH treatment and previous medications other than HLH treatment. Concomitant medications will be split by concomitant medications for HLH treatment and concomitant medications other than HLH treatment.

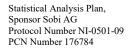
The frequency and percentage of medications will be summarized by ATC level 2 within level 1 by treatment groups, unless otherwise specified.

Prior and concomitant medications will be presented in listings. Prior and concomitant procedures will be listed separately and defined similarly as specified for prior and concomitant medications.

11. Changes from Planned Analysis

A summary of the changes with respect to analyses described in the study protocol is given below:

- Protocol Violations and Deviations terminology of major protocol deviations is used in the protocol. Due to an update in regulations ICH E3 Q&A R1 and ICH GCP E6 R2 terminology of important and non-important will be used when referring to protocol deviation classification from a study conduct perspective.
- Pharmacokinetic endpoints- population PK analysis will not be conducted as part of this





study. However, data from this study might be used in combination with data from other studies to refine existing population PK models.

- Pharmacodynamic endpoints- Population PK/PD analysis using non-linear mixed effects modelling will not be conducted as part of this study. However, data from this study might be used in combination with data from other studies to refine existing population PK/PD models. As part of the SAP, only PD parameters (i.e., concentrations) will be reported descriptively.
- Secondary efficacy endpoint: cumulative duration of response has been added to protocol specified endpoints.
- 'Evaluable Analysis Set Without Major Protocol Deviations' added which contains patients in the Evaluable analysis set who do not have a major protocol deviation that is deemed to have an impact on the statistical analysis.
- Sensitivity analysis 5 added where the overall response at EOT or Week 8 (whichever occurs earlier) is displayed based on patients in the 'Evaluable Analysis Set Without Major Protocol Deviations'.
- Supplementary analysis added where the overall response at EOT or Week 8 (whichever occurs earlier) is derived checking the number of abnormalities at baseline and the number of HLH criteria which worsen from baseline.

12. Other Planned Analysis

12.1. Pharmacokinetic/Pharmacodynamic/Immunogenicity Analysis

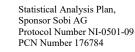
Descriptive summaries per timepoint of the serum concentration of emapalumab, PD parameters and ADAs (if any), as well as corresponding listings including CSF analysis or other matrices as applicable, will be provided in TLFs of this SAP.

Descriptive summaries of the following results will be presented in appropriate graphical analysis and tables for the All Treated Analysis Set:

- Levels of circulating total IFNγ (free IFNγ + bound to emapalumab) after initiation of emapalumab treatment.
- Levels of the main IFNγ-induced chemokines (CXCL9, CXCL10).
- Levels of other potential disease biomarkers.
- Level (if any) of circulating antibodies against emapalumab (ADAs).
- Serum concentration of emapalumab.
- Levels of serum sCD25

13. References

 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.
- 4. Varni, J.W., Seid, M., Rode, C.A (1999). The PedsQL[™]: Measurement Model for the Pediatric Quality of Life Inventory. Medical Care, 37(2), 126-139.
- 5. Phipps, S., Hinds, P. S., Channell, S., & Bell, G. L. (1994). Measurement of Behavioral, Affective, and Somatic Responses to Pediatric Bone Marrow Transplantation: Development of the BASES Scale. Journal of Pediatric Oncology Nursing, 11(3), 109–117.
- Phipps, S., Dunavant, M., Lensing, S., Rai, S.N. (2002). Acute health-related quality of life in children undergoing stem cell transplant: II. Medical and demographic determinants. Bone Marrow Transplantation, 29 (5) 435-442.

14. Tables, Listings, and Figures

All listings, tables, 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-0501-09. The table numbers and page numbers are place holders only and will be determined when the tables are produced.





Table 15: Planned Tables

Table Number	Table Title / Summary	Population(s)	Supporting listing			
14.1 Demog	14.1 Demographic Data					
14.1.1.1	Summary of Patient Enrollment and Disposition	Enrolled Pop	16.2.1.1, 16.2.1.2			
14.1.1.2	Summary of Re-Treated Patients	All Treated Pop	16.2.1.1, 16.2.5.1			
14.1.2	Summary of Protocol Deviations	Enrolled Pop Excluding Screen Failures	16.2.2.1			
14.1.3.1	Demographic Characteristics	All Treated Pop	16.2.4.1			
14.1.3.2	Baseline Characteristics	All Treated Pop	16.2.4.1			
14.1.4.1	HLH Disease Characteristics at Diagnosis	All Treated Pop	16.2.4.4, 16.2.4.5			
14.1.4.2	Medical History Other Than HLH Disease by System Organ Class and Preferred Term	All Treated Pop	16.2.4.2			
14.1.4.3	HLH Disease Characteristics at Screening/Baseline	All Treated Pop	16.2.4.11, 16.2.4.12			
14.1.5	Summary of Previous HLH Treatment by ATC Level 1 and Level 2	All Treated Pop	16.2.4.3			
14.1.6	Summary of Systemic Steroid Use Prior to First Emapalumab Infusion	All Treated Pop	16.2.4.3			
14.1.	Summary of Prior Medications Other Than HLH Treatment by ATC Level 1 and Level 2	All Treated Pop	16.2.4.6			
14.2 Efficac	zy Data					
14.2.1.1.1	Statistical Analysis of the Overall Response	All Treated Pop, Evaluable Pop	16.2.6.3			
14.2.1.1.2	Sensitivity Analysis 1: Overall Response at EOT or Week 8 (Whichever Occurs Earlier) With Deaths Considered as Non- Responders	All Treated Pop	16.2.6.3			
14.2.1.1.3	Sensitivity Analysis 2: Overall Response at EOT or Week 8 (Whichever Occurs Earlier) With Early Withdrawal Considered as Non-Responders	All Treated Pop	16.2.6.3			

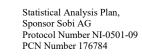
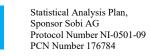




Table Number	Table Title / Summary	Population(s)	Supporting listing
14.2.1.1.4	Sensitivity Analysis 3: Overall Response at EOT or Week 8 (Whichever Occurs Earlier) With Patients Who Receive Concomitant Administration of Other HLH Treatments Considered as Non-Responders	All Treated Pop	16.2.6.3
14.2.1.1.5	Sensitivity Analysis 4: Overall Response at EOT or Week 8 (Whichever Occurs Earlier) With Deaths, Early Withdrawals, and Patients Who Receive Concomitant Administration of Other HLH Treatment Considered as Non- Responders	All Treated Pop	16.2.6.3
14.2.1.1.6	Sensitivity analysis 5: Overall Response at EOT or Week 8 (whichever occurs earlier) with patients deemed as having a protocol deviation impacting statistical analysis removed	Evaluable Pop Without Major PDs	16.2.6.3
14.2.1.1.7	Supplementary Analysis: Overall Response at EOT or Week 8 (whichever occurs earlier) – Modified Definition	All Treated Pop	16.2.6.3
14.2.1.2	Overall Response Components: Complete Response, Partial Response, HLH Improvement, No Response	All Treated Pop, Evaluable Pop	16.2.6.3
14.2.1.3.1	Evolution of Clinical Signs Characterizing HLH Disease - Part 1	All Treated Pop, Evaluable Pop	16.2.6.1.1, 16.2.9.3.
14.2.1.3.2	Evolution of Clinical Signs Characterizing HLH Disease - Part 2	All Treated Pop, Evaluable Pop	16.2.9.4
14.2.2.1	Overall Survival	All Treated Pop, Evaluable Pop	16.2.6.2
14.2.2.2	Survival to HSCT	All Treated Pop, Evaluable Pop	16.2.6.2
14.2.2.3	Survival post HSCT	All Treated Pop, Evaluable Pop	16.2.6.2
14.2.3	Event-free Survival post HSCT	All Treated Pop, Evaluable Pop	16.2.6.2
14.2.4.1	Duration of Response	All Treated Pop, Evaluable Pop	16.2.6.2
14.2.4.2	Cumulative Duration of Response for Patients Achieving Overall Response	All Treated Pop, Evaluable Pop	16.2.6.1.1, 16.2.6.1.2, 16.2.6.1.3, 16.2.6.1.4.



premier research

Table Number	Table Title / Summary	Population(s)	Supporting listing
14.2.5	Time-to-Response	All Treated Pop, Evaluable Pop	16.2.6.2
14.2.6	Investigator Assessment of Clinical Response	All Treated Pop, Evaluable Pop	16.2.6.4
14.2.7.1	Summary of Dexamethasone Daily Dose (mg/m ²) Over Time	All Treated Pop, Evaluable Pop	16.2.5.3
14.2.7.2	Glucocorticoids Reduction	All Treated Pop, Evaluable Pop	16.2.6.3
14.2.7.3	Patients Proceeding to HSCT	All Treated Pop, Evaluable Pop	16.2.6.3
14.2.8.1	Summary of PedsQL Total Scale Score (Parent Reports) and Change from Baseline by Questionnaire Age Group	All Treated Pop, Evaluable Pop	16.2.6.8
14.2.8.2	Summary of PedsQL Physical Health Summary Score (Parent Reports) and Change from Baseline by Questionnaire Age Group	All Treated Pop, Evaluable Pop	16.2.6.8
14.2.8.3	Summary of PedsQL Psychosocial Health Summary Score (Parent Reports) and Change from Baseline by Questionnaire Age Group	All Treated Pop, Evaluable Pop	16.2.6.8
14.2.8.4	Summary of PedsQL Physical Functioning Scale Score (Parent Reports) and Change from Baseline by Questionnaire Age Group	All Treated Pop, Evaluable Pop	16.2.6.8
14.2.8.5	Summary of PedsQL Emotional Functioning Scale Score (Parent Reports) and Change from Baseline by Questionnaire Age Group	All Treated Pop, Evaluable Pop	16.2.6.8
14.2.8.6	Summary of PedsQL Social Functioning Scale Score (Parent Reports) and Change from Baseline by Questionnaire Age Group	All Treated Pop, Evaluable Pop	16.2.6.8
14.2.8.7	Summary of PedsQL Work/Study Functioning Scale Score (Parent Reports for Child >24 months) and Change from Baseline by Questionnaire Age Group	All Treated Pop, Evaluable Pop	16.2.6.8
14.2.8.8	Summary of PedsQL Physical Symptoms Scale Score (Parent Reports for Infants 1-24 months) and Change from Baseline by Questionnaire Age Group	All Treated Pop, Evaluable Pop	16.2.6.8
14.2.8.9	Summary of PedsQL Cognitive Functioning Scale Score (Parent Reports for Infants 1-24 months) and Change from Baseline by Questionnaire Age Group	All Treated Pop, Evaluable Pop	16.2.6.8
14.2.9.1	Summary of PedsQL Total Scale Score (Child Reports) and Change from Baseline by Questionnaire Age Group	All Treated Pop, Evaluable Pop	16.2.6.9

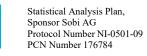




Table Number	Table Title / Summary	Population(s)	Supporting listing
14.2.9.2	Summary of PedsQL Physical Health Summary Score (Child Reports) and Change from Baseline by Questionnaire Age Group	All Treated Pop, Evaluable Pop	16.2.6.9
14.2.9.3	Summary of PedsQL Psychosocial Health Summary Score (Child Reports) and Change from Baseline by Questionnaire Age Group	All Treated Pop, Evaluable Pop	16.2.6.9
14.2.9.4	Summary of PedsQL Physical Functioning Scale Score (Child Reports) and Change from Baseline by Questionnaire Age Group	All Treated Pop, Evaluable Pop	16.2.6.9
14.2.9.5	Summary of PedsQL Emotional Functioning Scale Score (Child Reports) and Change from Baseline by Questionnaire Age Group	All Treated Pop, Evaluable Pop	16.2.6.9
14.2.9.6	Summary of PedsQL Social Functioning Scale Score (Child Reports) and Change from Baseline by Questionnaire Age Group	All Treated Pop, Evaluable Pop	16.2.6.9
14.2.9.7	Summary of PedsQL Work/Study Functioning Scale Score (Child Reports 5-25 years) and Change from Baseline by Questionnaire Age Group	All Treated Pop, Evaluable Pop	16.2.6.9
14.2.10.1	Summary of BASES Questionnaire (Parent Reports)	All Treated Pop, Evaluable Pop	16.2.6.10
14.2.10.2	Summary of BASES Questionnaire (Nurse Reports)	All Treated Pop, Evaluable Pop	16.2.6.11
14.3 Safety	Data		
14.3.1.1.1	Summary of all Adverse Events	All Treated Pop	16.2.7.1.1
14.3.1.1.2	Summary of Adverse Events occurring prior to HSCT conditioning	All Treated Pop	16.2.7.1.2
14.3.1.1.3	Summary of Adverse Events occurring post HSCT conditioning	All Treated Pop	16.2.7.1.3
14.3.1.2.1	Summary of Adverse Events by System Organ Class and Preferred Term	All Treated Pop	16.2.7.1.1
14.3.1.2.2	Summary of non-SAEs by System Organ Class and Preferred Term	All Treated Pop	16.2.7.1.1
14.3.1.3	Summary of Adverse Events by Maximum Severity, System Organ Class and Preferred Term	All Treated Pop	16.2.7.1.1
14.3.1.4.1	Summary of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term	All Treated Pop	16.2.7.1.1
14.3.1.4.2	Summary of Treatment-Emergent Adverse Events by Maximum Severity, System Organ Class and Preferred Term	All Treated Pop	16.2.7.1.1
14.3.1.4.3	Summary of Treatment-Emergent Adverse Events by Relationship to Study Drug, System Organ Class and Preferred Term	All Treated Pop	16.2.7.1.1

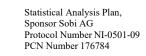




Table Number	Table Title / Summary	Population(s)	Supporting listing
14.3.1.5.1	Summary of Treatment-Emergent Adverse Events occurring prior to HSCT conditioning by System Organ Class and Preferred Term	All Treated Pop	16.2.7.1.2
14.3.1.5.2	Summary of Treatment-Emergent Adverse Events occurring prior to HSCT conditioning by Maximum Severity, System Organ Class and Preferred Term	All Treated Pop	16.2.7.1.2
14.3.1.5.3	Summary of Treatment-Emergent Adverse Events occurring prior to HSCT conditioning by Relationship to Study Drug, System Organ Class and Preferred Term	All Treated Pop	16.2.7.1.2
14.3.1.6.1	Summary of Treatment-Emergent Adverse Events occurring post HSCT conditioning by System Organ Class and Preferred Term	All Treated Pop	16.2.7.1.3
14.3.1.6.2	Summary of Treatment-Emergent Adverse Events occurring post HSCT conditioning by Maximum Severity, System Organ Class and Preferred Term	All Treated Pop	16.2.7.1.3
14.3.1.6.3	Summary of Treatment-Emergent Adverse Events occurring post to HSCT conditioning by Relationship to Study Drug, System Organ Class and Preferred Term	All Treated Pop	16.2.7.1.3
14.3.2.1	Summary of Treatment-Emergent Adverse Events Leading to Study Drug Withdrawal by Preferred Term	All Treated Pop	16.2.7.3
14.3.2.2	Summary of Treatment-Emergent Adverse Events Resulting in Death by Preferred Term	All Treated Pop	16.2.7.4
14.3.2.3.1	Summary of Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term	All Treated Pop	16.2.7.2
14.3.2.3.2	Summary of Serious Treatment-Emergent Adverse Events occurring prior to HSCT conditioning by System Organ Class and Preferred Term	All Treated Pop	16.2.7.1.2 16.2.7.2
14.3.2.3.3	Summary of Serious Treatment-Emergent Adverse Events occurring post HSCT conditioning by System Organ Class and Preferred Term	All Treated Pop	16.2.7.1.3 16.2.7.2
14.3.2.4	Summary of Treatment-Emergent Adverse Events with Infusion-related Reactions by System Organ Class and Preferred Term	All Treated Pop	16.2.7.1.1
14.3.2.5.1	Summary of Treatment-Emergent Adverse Events with Infections occurring prior to HSCT conditioning by Severity, System Organ Class and Preferred Term	All Treated Pop	16.2.7.1.2
14.3.2.5.2	Summary of Treatment-Emergent Adverse Events with Infections occurring post to HSCT conditioning by Severity, System Organ Class and Preferred Term	All Treated Pop (only patients with start date of conditioning for HSCT)	16.2.7.1.3
14.3.5.1.1	Shift Table of Clinical Chemistry Results	All Treated Pop	16.2.8.1
14.3.5.1.2	Shift Table of Clinical Chemistry Results by Treatment Type	All Treated Pop	16.2.8.1



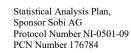


Table Number	Table Title / Summary	Population(s)	Supporting listing
14.3.5.2.1	Shift Table of Hematology Results	All Treated Pop	16.2.8.2
14.3.5.2.2	Shift Table of Hematology Results by Treatment Type	All Treated Pop	16.2.8.2
14.3.5.3.1	Shift Table of Coagulation Results	All Treated Pop	16.2.8.3
14.3.5.3.2	Shift Table of Coagulation Results by Treatment Type	All Treated Pop	16.2.8.3
14.3.6.1	Concomitant Medications for HLH Treatment by ATC Level 1 and Standardized Medication Term	All Treated Pop, Evaluable Pop	16.2.4.8
14.3.6.2	Concomitant Medications other than HLH Treatment by ATC Level 1 and Level 2	All Treated Pop, Evaluable Pop	16.2.4.9
14.3.6.3.1	Summary of Exposure to Emapalumab	All Treated Pop, Evaluable Pop	16.2.5.1 16.2.5.2
14.3.6.3.2	Percentage of Emapalumab Dose Changes from the Baseline Dose	All Treated Pop, Evaluable Pop	16.2.5.1 16.2.5.2
14.3.6.4	Summary of Serum Concentration of Emapalumab Levels	All Treated Pop	16.2.9.8.2
14.3.6.5	Summary of Pharmacodynamic Parameters	All Treated Pop	16.2.9.8.3
14.3.6.6	Summary of ADA Parameters	All Treated Pop	16.2.9.8.4

14.2. Planned Listing Descriptions

The following are planned data and patient data listings for protocol number NI-0501-09.

In general, one listing will be produced per CRF domain. All listings will be sorted by treatment, 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 line after line (e.g., repetition of patient number), then only the first occurrence will be displayed.

In data listings, the information for one patient will be kept on one page if at all possible, rather than splitting a patient's information across pages.





Table 16: Planned Listings

Listing Number	Listing Title / Summary	Population(s)
16.2.1.1	Study Completion Status and Assignment to Analysis Populations	All Treated Pop
16.2.1.2	List of Reasons for Screening Failure	Screen Failures
16.2.2.1	Protocol Deviations	Enrolled Pop Excluding Screen Failure
16.2.3.1	Analysis Populations	All Treated Pop
16.2.4.1	Demographic Data	All Treated Pop
16.2.4.2	Medical History	All Treated Pop
16.2.4.3	History of HLH Treatments	All Treated Pop
16.2.4.4	Primary HLH Diagnosis Part 1	All Treated Pop
16.2.4.5	Primary HLH Diagnosis Part 2	All Treated Pop
16.2.4.6	Prior Medications Other Than HLH Treatments	All Treated Pop
16.2.4.7	Prior Procedures	All Treated Pop
16.2.4.8	Concomitant Medications for HLH Treatment	All Treated Pop
16.2.4.9	Concomitant Medications Other Than HLH Treatment	All Treated Pop
16.2.4.10	Concomitant Procedures	All Treated Pop
16.2.4.11	HLH Disease Characteristics at Screening / Baseline - Part 1	All Treated Pop
16.2.4.12	HLH Disease Characteristics at Screening / Baseline - Part 2	All Treated Pop
16.2.5.1	Study Drug Administration	All Treated Pop
16.2.5.2	Study Drug Exposure	All Treated Pop
16.2.5.3	Systemic Glucocorticoids Administration	All Treated Pop
16.2.6.1.1	Response Criteria and Response Status by Visit – Part 1	All Treated Pop
16.2.6.1.2	Response Criteria and Response Status by Visit – Part 2	All Treated Pop
16.2.6.1.3	Response Criteria and Response Status by Visit – Part 3	All Treated Pop

AD-ST-33.06 Effective date: 12-Nov-2020

Version 2.0 | Date 24-Oct-2022 | AD-PR-109.02 Effective date: 17-Aug-2020





Listing Number	Listing Title / Summary	Population(s)
16.2.6.1.4	Response Criteria and Response Status by Visit – Part 4	All Treated Pop
16.2.6.2	Time-to-Event Efficacy Endpoints	All Treated Pop
16.2.6.3	Overall Response, Glucocorticoids Reduction, and Ability to Proceed to HSCT	All Treated Pop
16.2.6.4	Investigator Assessment of Clinical Response	All Treated Pop
16.2.6.5	HSCT	All Treated Pop
16.2.6.6	Post-HSCT Outcome	All Treated Pop
16.2.6.7	Survival Assessment	All Treated Pop
16.2.6.8	PedsQL Parent Reports	All Treated Pop
16.2.6.9	PedsQL Child Reports	All Treated Pop
16.2.6.10	BASES Parent Reports	All Treated Pop
16.2.6.11	BASES Nurse Reports	All Treated Pop
16.2.7.1.1	Adverse Events	All Treated Pop
16.2.7.1.2	Adverse Events occurring prior to HSCT conditioning	All Treated Pop
16.2.7.1.3	Adverse Events occurring post HSCT conditioning	All Treated Pop
16.2.7.2	Serious Adverse Events	All Treated Pop
16.2.7.3	Adverse Events Leading to Withdrawal of Study Drug	All Treated Pop
16.2.7.4	Deaths	All Treated Pop
16.2.7.5	Tuberculosis	All Treated Pop
16.2.7.6	Adenovirus, Epstein-Barr Virus, Cytomegalovirus	All Treated Pop
16.2.7.7	Other Specific Infections	All Treated Pop
16.2.8.1	Clinical Chemistry Results	All Treated Pop
16.2.8.2	Hematology Results	All Treated Pop
16.2.8.3	Coagulation Results	All Treated Pop

AD-ST-33.06 Effective date: 12-Nov-2020

Version 2.0 | Date 24-Oct-2022 | AD-PR-109.02 Effective date: 17-Aug-2020





Listing Number	Listing Title / Summary	Population(s)
16.2.8.4	Urinalysis Results	All Treated Pop
16.2.8.5	Pregnancy Test Results	All Treated Pop
16.2.9.1	Vital Signs	All Treated Pop
16.2.9.2	ECG Results	All Treated Pop
16.2.9.3	Physical Examination Results	All Treated Pop
16.2.9.4	Neurological Examination Results	All Treated Pop
16.2.9.5	Hospitalization	All Treated Pop
16.2.9.6	Abdominal Ultrasound	All Treated Pop
16.2.9.7.1	Chest Examinations	All Treated Pop
16.2.9.7.2	Brain and Cranial Examinations	All Treated Pop
16.2.9.8.1	CSF Analysis Results	All Treated Pop
16.2.9.8.2	Serum Concentration of Emapalumab	All Treated Pop
16.2.9.8.3	Pharmacodynamic Measurements	All Treated Pop
16.2.9.8.4	ADA Findings	All Treated Pop
16.2.9.9	Transfusion	All Treated Pop
16.2.9.10	List of Patients Who Were Affected by COVID-19	All Treated Pop

14.3. Planned Figure Descriptions

The following are planned summary figures for protocol number NI-0501-09. The figure numbers and page numbers are placeholders only and will be determined when the figures are produced.





Table 17: Planned Figures

Figure Number	Figure Title/Summary	Population
14.4.1.1	Kaplan-Meier Graph of Overall Survival	All Treated Pop
14.4.1.2	Kaplan-Meier Graph of Survival to HSCT	All Treated Pop
14.4.1.3	Kaplan-Meier Graph of Survival post HSCT	All Treated Pop
14.4.2	Kaplan-Meier Graph of Event-free Survival	All Treated Pop
14.4.3	Cumulative Incidence Graph of Time to Response	All Treated Pop
14.4.4	Kaplan-Meier Graph of Duration of Response	All Treated Pop
14.4.5.1	Box and Whisker Plots of Clinical Biochemistry Results	All Treated Pop
14.4.5.2	Box and Whisker Plots of Hematology Results	All Treated Pop
14.4.5.3	Box and Whisker Plots of Coagulation Results	All Treated Pop



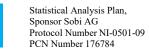
15. Tables, Listings, and Listing Shells

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

The following standard layout will be applied to all Tables, Listings, and Figures in support of this study. Note that programming notes may be added if appropriate after each TLF shell.

Figure 1: Standardized Layout

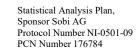
Sobi AG Protocol: NI-0501-09	Page xx of xx Version xxx
1100c01. NE-0501-05	Version XXX
Table, Listing, Figure xx.x.x <title figure="" listing="" of="" or="" table=""><Study Population and if applicable subgroup Description></td><td></td></tr><tr><td></td><td></td></tr><tr><td>Body of Table, Listing or Figure</td><td></td></tr><tr><td></td><td></td></tr><tr><td>Abbreviations: XXXXX</td><td></td></tr><tr><td>Note: XXXXX</td><td></td></tr><tr><td>Source: XXXXX</td><td></td></tr><tr><td>Footnote: Program path and name
Footnote: Executed on DDMMMYYY at HH:MM on data from DDMMMYYYY</td><td></td></tr></tbody></table></title>	





15.2. Planned TFL Shells

Table and listing shells are provided as a separate document. Descriptions are provided for figures.





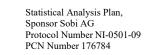
16. **APPENDICES**

16.1. Calculation of Dexamethasone daily dose

Dexamethasone daily dose will be calculated based on the recorded dose frequency as follows:

Table 18: Dexamethasone Daily Dose

Dose frequency	Total daily dose = CMDOSE*factor
QD (once a day)	CMDOSE
BID (twice a day)	CMDOSE*2
TID (three times a day)	CMDOSE*3
QID (four times a day)	CMDOSE*4
PRN (as needed)	0 per day (not included)
QHS (at bedtime)	CMDOSE*1
ONCE (once for the reporting period)	CMDOSE/(end date – start date + 1) per day
WEEKLY	CMDOSE/7 per day
OTHER – Q6HR/Q6HRS	CMDOSE*4
OTHER – Q8HR/Q8HRS	CMDOSE*3
OTHER – EVERY OTHER DAY	CMDOSE/2
OTHER – DAILY CUMULATIVE DOSE	CMDOSE





16.2. Concomitant Medications for HSCT Conditioning

Table 19: Concomitant HSCT Conditioning Medication Preferred Terms

ATC Level 4	Preferred Code	Preferred Text
L01AA	00021101001	CYCLOPHOSPHAMIDE
201121	00006401001	MELPHALAN
L01AB	00036801001	BUSULFAN
	00418901001	TREOSULFAN
L01AC	00053501001	ТНІОТЕРА
L01BB	02122001001	CLOFARABINE
LUIDD	01004601001	FLUDARABINE
	01004602001	FLUDARABINE PHOSPHATE
L01BC	00146201001	CYTARABINE
L01BC	00511901001	ETOPOSIDE
20120	00511902001	ETOPOSIDE PHOSPHATE
L01XC	01402501001	RITUXIMAB
L04AA	01268601001	ALEMTUZUMAB
Lonni	00575401001	ANTITHYMOCYTE IMMUNOGLOBULIN
	00575402001	ANTITHYMOCYTE IMMUNOGLOBULIN (RABBIT)
	02082701001	ANTILYMPHOCYTE IMMUNOGLOBULIN





16.3. Disease Indicating Central Nervous System (CNS) Involvement / CSF abnormalities by Medical History/AE Preferred Term and Code

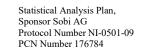
Preferred Term Code	Preferred Term
10029818	Nuclear magnetic resonance imaging brain abnormal
10059703	CSF test abnormal
10053805	CSF white blood cell count increased
10011522	CSF cell count increased
10035551	Pleocytosis
10012559	Developmental delay
10056832	Neurological examination abnormal
10047641	VIth nerve paralysis
10020745	Hyperreflexia
10041962	Status epilepticus
10039906	Seizure
10021118	Hypotonia
10002948	Aphasia
10029202	Nervous system disorder
10017577	Gait disturbance
10048334	Mobility decreased
10008096	Cerebral atrophy
10015037	Epilepsy
10071066	Posterior reversible encephalopathy syndrome
10022840	Intraventricular haemorrhage

The overall response criterion 'No neurological and CSF abnormalities attributed to HLH' is not fulfilled during the time period in which any of the above listed AEs is present or the assessment on neurological examination CRF is 'abnormal' with comment 'CNS involvement'.

AD-ST-33.06 Effective date: 12-Nov-2020

Statistical Analysis Plan, Sponsor Sobi AG

Protocol Number NI-0501-09 PCN Number 176784





16.4. Adverse Events Indicating Organ Failure by MedDRA Preferred Term and Code

Preferred Term Code	Preferred Term
10007554	Cardiac failure
10007556	Cardiac failure acute
10060953	Ventricular failure
10024119	Left ventricular failure
10063081	Acute left ventricular failure
10039163	Right ventricular failure
10063082	Acute right ventricular failure
10051093	Cardiopulmonary failure
10038695	Respiratory failure
10001053	Acute respiratory failure
10019663	Hepatic failure
10000804	Acute hepatic failure
10077305	Acute on chronic liver failure
10019845	Hepatorenal failure
10038435	Renal failure
10077361	Multiple organ dysfunction syndrome
10053159	Organ failure
10010264	Condition aggravated

Table 21: AE Preferred Terms for Organ Failure

Progression of other aspects of HLH disease pathology (i.e. worsening of disease, as assessed by absence of AEs indicating organ failure) is fulfilled during the time period in which any of the above listed AEs is present and partial response cannot be adjudicated even if other criteria were fulfilled.