Statistical Analysis Plan

Protocol number:	Sobi.emapalumab-102
Title:	A randomized, double-blinded, placebo-controlled, single center, phase I study to evaluate pharmacokinetics, pharmacodynamics and safety of emapalumab after a single intravenous dose in Japanese healthy volunteers.
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SAP version:	1.0 (Seiko Yamazaki) 2.0 (Hiroo Shimoda)

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1 Abbreviations and definition of terms

ADA	Anti-drug antibodies
ADR	Adverse drug reaction
AE	Adverse event
BMI	Body mass index
CSR	Clinical study report
CRO	Contract research organization
CXCL9	CXC chemokine ligand 9
DBL	Database lock
FSI	First subject in
IFNγ	Interferon-gamma
IMP	Investigational medicinal product
i.v.	Intravenous
LLOQ	Lower limit of quantification
mITT	Modified intention-to-treat population
nAbs	Neutralizing antibodies
PCR	Polymerase chain reaction
PD	Pharmacodynamics
PT	Preferred Term
PK	Pharmacokinetics
SADR	Serious adverse drug reaction
SAE	Serious adverse event
SAP	Statistical analysis plan
SARS-CoV-19	Severe acute respiratory syndrome coronavirus 19
sIL2R	Soluble interleukin-2 receptor
Sobi	Swedish Orphan Biovitrum

SOC	System Organ Class
TEAE	Treatment-emergent adverse event

2 Introduction

This Statistical Analysis Plan (SAP) describes the planned analysis and reporting for the Sobi protocol Sobi.emapalumab-102 (A randomized, double-blinded, placebo-controlled, single center, phase I study to evaluate pharmacokinetics, pharmacodynamics and safety of emapalumab after a single intravenous dose in Japanese healthy volunteers.).

This phase I study is being completed to assess the pharmacokinetics, pharmacodynamics and safety of emapalumab in healthy Japanese subjects following a single i.v. dose of emapalumab.

The purpose of this SAP is to outline the planned analyses to be completed to support the Clinical Study Report (CSR) for protocol Sobi.emapalumab-102. The planned analyses identified in this SAP will be included in regulatory submissions and/or future manuscripts. Also, exploratory analyses not necessarily identified in this SAP may be performed to support the clinical development program. Any post-hoc, or unplanned, analyses not identified in this SAP will be clearly identified in the respective CSR.

The structure and content of this SAP provides sufficient detail to meet the requirements identified by the FDA and International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH): Guidance on Statistical Principles in Clinical Trials. All work planned and reported for this SAP will follow internationally accepted guidelines, published by the American Statistical Association and the Royal Statistical Society, for statistical practice.

3 Study objectives and endpoints

3.1 Primary objective

The primary objective is to evaluate the pharmacokinetics (PK) and pharmacodynamics (PD) of emapalumab in healthy Japanese subjects following a single intravenous (i.v) dose of emapalumab.

3.2 Secondary objectives

The secondary objectives are as follows:

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

3.3 Study endpoints

3.3.1 Primary endpoints

The primary endpoints are as follows:

- PK parameters: C_{max}, t_{max}, CEOI, AUC_{last}, AUC_{inf}, %AUCextr, λ_z, $t_{½}$, CL, V_{ss}, MRT_{last} and MRT_{inf}.
- PD biomarkers:
  - Pre-dose circulating IFNγ concentration
  - Total IFNγ concentrations
  - CXCL9 concentration
  - sIL2R concentration

3.3.2 Secondary endpoints supporting the secondary objectives

The study has the following secondary endpoints:

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

4 Study methods

4.1 Overall study design and plan

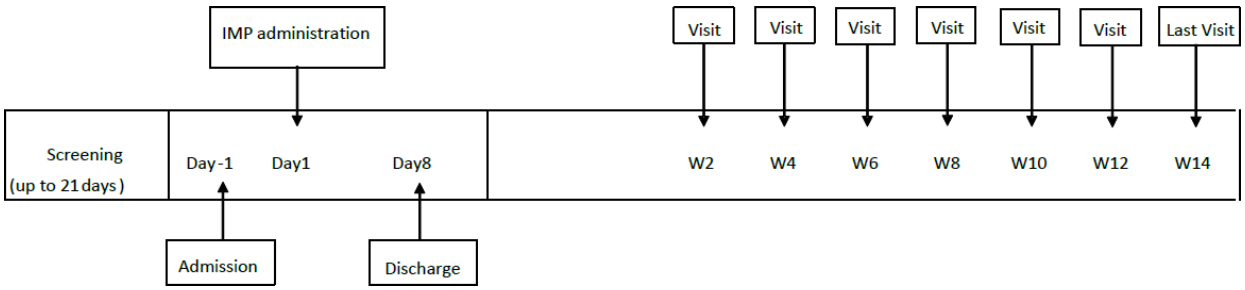
This is a randomized, placebo-controlled and double-blinded study to evaluate the PK, PD and safety of a single i.v. dose (1 mg/kg) of emapalumab in adult healthy Japanese subjects, performed in Japan. 8 subjects will be randomized to receive either emapalumab or matching placebo in a 3:1 ratio (emapalumab: placebo). The investigator, study subjects and sponsor will be blinded to treatment allocation (placebo and active) to avoid reporting, assessment and allocation biases. It is considered sufficient with 6 subjects randomized to emapalumab, considering the inter-subject variability in the PK results in the NI-0501-03 study.

Figure 1 shows the study design.

Study subjects will be screened within 21 days prior to administration of investigational medicinal products (IMP). An additional visit will take place within 96 hours prior to IMP infusion for collection of a PCR test for SAS-CoV-2. Eligible subjects will be admitted to the clinical unit the day before drug administration (Study Day -1). On Day 1 of the admission

period subjects will receive a single dose of emapalumab (1 mg/kg) or placebo administered as a 1-hour infusion. Subjects will be discharged from the unit on Day 8. PK samples will be collected up to Week 14 in order to measure the emapalumab serum levels during at least 3 times the terminal half-life (a total of approximately 3 months). All subjects will be followed-up on regular visits for a minimum of 14 weeks after a single infusion of emapalumab. In addition, any subject with ongoing SAEs at study completion will be followed-up until resolution of the event or until the outcome is known and stable.

Figure 1 Study Design Sobi.emapalumab-102



Abbreviations: IMP, investigational medicinal product W, study week.

4.2 Selection of study population

Refer to protocol section 6.5 Selection of study population for inclusion and exclusion criteria

4.3 Method of treatment assignment and randomization

The different treatment groups are:

Arm A: Emapalumab

Arm B: Placebo (saline)

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

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

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

5 Sequence of planned analysis

5.1 Interim analyses

There is no planned Interim Analysis for this study.

5.2 Analyses and reporting

All final, planned, analyses identified in the protocol and in this SAP will be performed only after the last subject has completed the study. The SAP will be finalized before FSI. If any revision is made, the SAP will be finalized, locked and signed prior to DBL.

6 Sample size determination

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

7 Analysis populations

The analysis sets that will be used in the statistical analyses are described in Section 7.1 (mITT), Section 7.2 (PK/PD population) and Section 7.3 (Safety Analysis population).

7.1 Modified intention-to-treat population (mITT)

The mITT will comprise all randomized subjects who received an infusion of IMP and have at least one blood draw to determine PK and PD. This analysis population will not be used in any statistical analyses.

7.2 PK/PD Analysis population

A PK/PD population will be used for analyzing the primary endpoints. This population comprises all randomized subjects who received an infusion of Emapalumab, without any protocol deviations affecting PK/PD evaluation. All analyses using the PK/PD population will group subjects according to treatment actually received.

7.3 Safety Analysis population

The Safety Analysis population will comprise all subjects who received an infusion of IMP. All analyses using the Safety Analysis population will group subjects according to the treatment actually received.

The Safety Analysis population will be used for the safety analyses.

8 General issues for statistical analysis

No formal statistical hypothesis testing will be performed. All endpoints will be summarized with descriptive statistics and presented individually in listings.

8.1 Statistical Analysis and Tabulation Software

Below are the software and its versions used in this study.

	Software and Versions
OS	Microsoft Windows 10
Statistical Analysis Software	SAS Ver.9.4 or later (SAS Institute Inc., Cary, North Carolina, United States)
Tabulation Software	Microsoft Word 2016 or later
WinNonlin	WinNonlin Ver.8.0 or later

8.2 Dictionaries

Below are the dictionaries used in this study.

Category	Dictionary	Remarks
Adverse Events	MedDRA Version: refer to SDTM define.xml	・The System Organ Class (SOC) for major system organ class name will be applied. ・The Preferred Term (PT) for adverse events name will be applied. ・Adverse events will be sorted by SOC and PT.
Medical History	MedDRA Version: refer to SDTM define.xml	・The System Organ Class (SOC) for major system organ class name will be applied. ・The Preferred Term (PT) for medical histories name will be applied.
Prior/Concomitant Medications	WHO drug dictionary (Version September 2020)	・The generic medication name will be applied. ・Medical history will be displayed by generic medication name.

Abbreviations: WHO, World Health Organization.

8.3 Analysis Methods

8.3.1 Descriptive statistics

Continuous data will be summarized using descriptive statistics: the number of subjects (N), arithmetic mean, standard deviation (SD), median, minimum and maximum.

In PK analysis, geometric mean (geo mean), coefficient of variation (CV %) and 95 % confidence intervals of geo mean are also presented. CV % and Geo mean are calculated using the following formula:

CV = (standard deviation) / (arithmetic mean)*100

Geometric mean = $\exp\left[\frac{\sum_{i=1}^{n}\log X_i}{n}\right] = \sqrt[n]{\prod_{i=1}^{n} X_i}$

8.3.2 Percentages

Percentage is calculated using the following formula (unless otherwise indicated):

$$\text{Percentage (\%)} = \frac{\text{the number of applicable subjects}}{\text{the number of subjects within the treatment group for the population of interest}} \times 100$$

Percentages will be suppressed when the count is zero, however the category will still be displayed.

8.4 Handling of Data

8.4.1 Calculation Method of Number of Days

Number of days is calculated using the following formulas:

- Post-treatment study day: [The date of a respective event] - [The date of IMP administration] +1
- Pre-treatment study day: [The date of a respective event during pre-dosing time] - [The date of IMP administration]

8.4.2 Calculation of Age

Age is calculated using the birth date.

- Age at the time of informed consent will be calculated using the following formula (unless otherwise indicated):

$$\text{Age (Years)} = \frac{(\text{Informed Consent Obtained Date} - \text{Birth Date})}{365.25}$$

8.4.3 Visit Windows

The visit windows for PK and PD assessments are displayed in Table 1, for Vital signs in Table 2 and for other assessments in Table 3. The analysis time points, based on the visit windows, will be used for analysis. In addition, let the IMP administration date be Day 1.

For descriptive statistics, in the case a parameter is not available on the specified analysis timepoint, the visit window is to be applied. Priority will be given to scheduled visits; unscheduled visits will be used if no scheduled visits occurred within the analysis visit window.

If there is more than one observation during the visit window, a value will be selected as follows: the value closest to the actual analysis timepoint in question (eCRF) will be chosen first. In the case that there are 2 values equidistant to the analysis timepoint of interest, the observation that is before the analysis timepoint in question (eCRF) will be selected. In the case of 2 or more measurements on the same date, the earliest measurement will be selected.

Table 1 Visit Window of pharmacokinetic and pharmacodynamic assessment

Analysis time point		Visit Window	Pharmacokinetics	Pharmacodynamics
Day 1	Preinfusion	Before IMP administration	X	X
	1 hr	55 min to < 65 min	X [a)]	X
	2 hr	1 hr 55 min to < 2 hrs 5 min	X	X
	4 hr	3.75 hr to <4.25 hr	X	X
	8 hr	7.5 hr to <8.5 hr	X	X
	10 hr	9.5 hr to <10.5 hr	X	X
Day 2		Day 2	X	X
Day 3		Within Day 3	X	X
Day 5		Within Day 5	X	X
Day 8		Within Day 8	X	X
Follow-up Week 2		Day 12 to Day 16	X	X
Follow-up Week 4		Day 26 to Day 30	X	X
Follow-up Week 6		Day 40 to Day 44	X	X
Follow-up Week 8		Day 54 to Day 58	X	
Follow-up Week 10		Day 68 to Day 72	X	
Follow-up Week 12		Day 82 to Day 86	X	
Study Completion Visit (Week 14)		Day 96 to Day 100	X	X
Withdrawal (WD)		When the subject is withdrawn	X	X

a) At end of infusion.

Table 2 Visit Window of Vital Signs[b)]

Analysis time point		Visit Window
Screening		Within 21 days prior to IMP administration
Day -1		Within Day -1
Day1	1 hr	0.75 hr to <1.25 hr
	1.5 hr	1.25 hr to <1.75 hr
	2 hr	1.75 hr to <2.25 hr
	2.5 hr	2.25 hr to <2.75 hr
	3 hr	2.75 hr to <3.25 hr
	3.5 hr	3.25 hr to <3.75 hr
	4 hr	3.75 hr to <4.5 hr
	5 hr	4.5 hr to <5.5 hr
	6 hr	5.5 hr to <6.5 hr
	7 hr	6.5 hr to <7.5 hr
	8 hr	7.5 hr to <8.5 hr
	9 hr	8.5 hr to <9.5 hr
	10 hr	9.5 hr to <11 hr
	12 hr	11 hr to <13 hr
Day 2		Within Day 2
Day 3		Within Day 3
Day 5		Within Day 5
Day 8		Within Day 8
Follow-up Week 2		Day 12 to Day 16
Follow-up Week 4		Day 26 to Day 30
Follow-up Week 6		Day 40 to Day 44
Study Completion Visit (Week 14) / Withdrawal (WD)		Day 96 to Day 100 or when the subject is withdrawn

b) Body weight and height will be collected at Screening, and body weight at Study Day -1 and Study Completion Visit (Week 14)/ Withdrawal (WD).

Table 3 Visit window of the other items

Analysis time point		Visit Window	Laboratory[a)]	ADA	Physical Examination[c)]	12-lead ECG	Pregnancy Test[d)]
Screening		Within 21 days prior to IMP administration	X		X	X	
Day -1		Within Day -1	X		X		
Day 1	Preinfusion	Before IMP administration within Day 1		X		X	

Analysis time point		Visit Window	Laboratory[a)]	ADA	Physical Examination[c)]	12-lead ECG	Pregnancy Test[d)]
	1 hr	0.75 hr to <1.25 hr					
	2 hr	1.75 hr to <2.25 hr					
	4 hr	3.5 hr to <4.5 hr	X			X	
	8 hr	7.5 hr to <8.5 hr					
	10 hr	9 hr to <11 hr					
	12 hr	11 hr to 13 hr					
Day 2		Within Day 2	X				
Day 3		Within Day 3	X				
Day 5		Within Day 5	X				
Day 8		Within Day 8	X				
Follow-up Week 2		Day 12 to Day 16	X				
Follow-up Week 4		Day 26 to Day 30	X				X
Follow-up Week 6		Day 40 to Day 44	X				
Follow-up Week 8		Day 54 to Day 58					X
Follow-up Week 10		Day 68 to Day 72	X [b)]				
Follow-up Week 12		Day 82 to Day 86					X
Study Completion Visit (Week 14) / Withdrawal (WD)		Day 96 to Day 100 or when the subject is withdrawn	X	X	X	X	X

a) Laboratory includes hematology, chemistry, and urine and hematology measurements, taken under fasting condition except from screening.

b) Only hematology and chemistry.

c) A full physical examination will be performed at screening and at Week 4 visit. At all other visits brief physical examinations will be performed, only if indicated.

d) Urine pregnancy test is to be performed with a dipstick at week 4, 8, 12 and study completion.

8.4.4 Baseline

Baseline is defined as the last non-missing value taken before the study drug administration.

8.5 Rounding digits

8.5.1 Displaying of Descriptive Statistics

- Mean, Median and Geometric Mean

  Round to one more significant digit than what was used to collect the variable.

- Standard Deviation

  Round to two more significant digit than what was used to collect the variable.

- Minimum and Maximum

  Round to the same number of significant digits used to collect the variable.

8.5.2 Rounding Digits for Percentages (including CV%)

Round to the nearest tenths (0.1).

8.6 Handling of Missing Data and Outliers

8.6.1 Handling the Date of Adverse Events

8.6.1.1 TEAE

In the case of partially or completely missing AE start date/time, the AE will be considered treatment emergent, unless the available date/time information clearly indicates that the AE started prior to start of the IMP infusion as follows:

- If the start time is missing, but start date is before start date of IMP infusion.
- If the day of the AE is missing, but the year/month are before the year/month of the start of IMP infusion.
- If the day and month of the AE are missing, but the year is before the year of the start of IMP infusion.
- If the stop date of the AE is before the start date of the IMP infusion.

8.6.1.2 IRR

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 the infusion date or infusion date + 1 will be considered for the assessment of Infusion Related Reactions (IRRs), unless the available information clearly indicates that the AE was not treatment-emergent.

If the onset date/time of the AE is completely missing, the AE will be considered as IRR.

8.6.1.3 Severity and Relationship

The relationship to study drug and severity of AEs are assessed by the Investigator and recorded in eCRF.

If the relationship of an AE is missing, it will be assumed as related to study drug for presentation in summary tables, unless the AE is not treatment-emergent.

If severity of an AE is missing, it will be considered as severe for presentation in summary tables.

8.7 Multicenter Studies

Not applicable. This is a single center study.

8.8 Multiple Comparisons and Multiplicity

As no formal hypothesis testing will be performed, adjustment for multiple comparisons is not applicable.

9 Subject Disposition

9.1 Subject Disposition

Population: Consented Subjects

Group: Emapalumab, Placebo

Contents:

- Calculate the number of subjects by groups for the following items:

Informed consent
Screened
Screen failure
Primary reason for screen failure
- Did not meet all eligibility criteria
- The trial was prematurely terminated
- Subjects wishes to withdraw from the trial
- Investigator's decision
- Withdrawn due to an adverse event
- Reserved subject
- Death
- Lost to follow-up
- Other

Randomized subject
Randomized, but not treated
Receiving IMP
Completed study
Discontinued study
Primary reason for discontinuation
- The trial was prematurely terminated
- Subjects wishes to withdraw from the trial

  - Investigator's decision
  - Withdrawn due to an adverse event
  - Reserved subject
  - Death
  - Lost to follow-up
  - Other
- Denominator for Screened, Screen Failure will be the Consented Subjects.
- Denominator for Primary reason for screen failure will be the number of Screen failure.
- Denominator for Randomized, but not treated, Treated investigational product, Completed study and Discontinued study will be the number of Randomized subjects in each group.
- Denominator for Primary reason for discontinuation will be the number of Discontinued study in each group.

9.2 Protocol Deviations

Population: Randomized Subjects

Group: Emapalumab, Placebo

Contents:
- Calculate the number of subjects and the percentages of those with and without deviations from the protocol with their deviation contents by groups (Refer to protocol section 9.4 Protocol Deviations).
- Denominator to calculate the percentage will be the number of subjects from the population in each group.
- Subjects with more than one protocol deviations will be counted once for each category.
- Both major and minor protocol deviation will be presented.

9.3 Analysis Dataset

Population: Randomized Subjects

Group: Emapalumab, Placebo

Contents:
- Calculate the number and percentages of subjects by groups in the following population:

- Randomized Subjects
- Safety Analysis population (Qualified/Unqualified)
- PK/PD population (Qualified/Unqualified)

- Calculate the number of unqualified subjects by reasons in PK/PD and Safety Analysis population.

10 Demographics and baseline characteristics

10.1 Demographics and Other Baseline Characteristics

Population: Safety Analysis population, PK/PD Analysis population
Group: Emapalumab, Placebo
Contents:
- For categorical data and ordinal data, calculate the number of subjects and percentages.
- For continuous data, calculate the descriptive statistics.

Definitions:
- BMI
  BMI at screening will be calculated using the following formula:

$$BMI = \frac{\text{Weight [kg]}}{(\text{Height [m]})^2}$$

- Unknown and Missing values
  If unknown or missing values are observed, add "Unknown" category and only calculate the number of subjects. Remove "Unknown" category from the denominator for percentages.

- Race is only displayed in the listing.

[Background Factors]

Classification [Unit]	**Category**
Age [Year]	<30, 30≤ <40, 40≤
	Descriptive statistics
Sex	Male, Female
Height [cm]	Descriptive statistics
Weight [kg]	Descriptive statistics
BMI [kg/m^2]	Descriptive statistics

10.2 Medical History

Population: Safety Analysis population

Group:	Emapalumab, Placebo
Contents:	• Calculate the number of subjects and percentages for each PT by groups.
Definitions:	• Denominator to calculate the percentage: The number of subjects from the population in each group. • Subjects who have same PTs are counted only once for each PT.

11 Prior and Concomitant Medication

Population:	Safety Analysis population
Group:	Emapalumab, Placebo
Contents:	• Calculate the number of subjects and percentages for each prior/concomitant medications by groups, using the entered codes. • Subjects using at least one prior/concomitant medications with each effect will be counted.
Definitions:	• Prior Medications: Any medication which ended before the day of IMP administration. • Concomitant Medications: Any medication which started on or after the day of IMP administration or any medication taken prior to the day of IMP administration and continued after IMP administration. • Denominator to calculate the percentage: The number of subjects from the population in each group. • Subjects who take multiple drugs with the same generic names are counted only once for each drug. Subjects who take multiple drugs in the same drug effects are counted only once at each drug effects.

12 Treatment compliance

Not applicable.

13 Efficacy analyses

Efficacy analyses will not be conducted.

14 Pharmacokinetic and pharmacodynamic assessment

14.1 Pharmacokinetic assessment

PK parameters will be calculated using the actual time and actual dose of study drug of collected samples. Sample collected before administration will be analyzed as time point 0 hours. Linear Trapezoidal Linear Interpolation will be used to calculate AUC and AUMC, by using actual elapsed time values. Data points BLOQ in the end of the serum concentration time curve will be omitted from estimation of AUC and AUMC using Phoenix WinNonlin.

The list of pharmacokinetic parameters derived in this study are presented in Table 4.

Table 4 List of pharmacokinetic parameters

Parameter	Description	Unit	Display Digits
C_{max}	Maximum observed serum concentration	ug/L	3 significant figures
t_{max}	Time to C_{max}	h	2 decimal places
CEOI	Observed concentration at end of infusion	ug/L	3 significant figures
AUC_{last}	Area under the serum concentration-time curve from time 0 to the time corresponding to the last quantifiable serum concentration $\mathrm{AUC} = \int_0^t C$	ug*h/L	3 significant figures
AUC_{inf_calc}	Area under the serum concentration-time curve extrapolated to infinity, calculated using the formula: $AUC_{inf,\ calc} = AUC_{last} + Ct/\lambda z$, where Ct is the predicted concentration at tlast and λz is the apparent terminal phase rate constant. Values of $AUC_{inf,calc}$ will only be deemed reliable if □z is reliably estimated and if % AUCextr is less than 20%.	ug*h/L	3 significant figures
%AUCextr	Percentage of extrapolated AUC from T last to infinity time $= \frac{\mathrm{AUCINF\_calc} - \mathrm{AUClast}}{\mathrm{AUCINF\_calc}} \times 100$	%	1 decimal place
$AUMC_{last}$	Area under the first moment curve from the time of dosing to the last measureable concentration. $\mathrm{AUMC}_{last} = \sum_{i=1}^{last}(t_{(i+1)} - t_i) \cdot \frac{t_i \cdot C_i + t_{(i+1)} \cdot C_{(i+1)}}{2}$ i=timepoint(1,2,⋯, last)	ug*h*h/L	3 significant figures
$AUMC_{inf\_calc}$	Area under the first moment curve (AUMC) extrapolated to infinity, based in the last predicted concentration. $=\mathrm{AUMC}_{last} + \frac{\mathrm{Tlast} - \mathrm{Clast}_{pred}}{\lambda z} + \frac{\mathrm{Clast}_{pred}}{\lambda z \hat{} 2}$	ug*h*h /L	3 significant figures
λz	Terminal rate constant The first-order rate constant for the terminal phase (log-linear) part of the curve. Estimated by linear regression of time-logarithmic concentration. If the number of measurement results with a value greater than 0 and less than 3 points measured after Cmax is not calculated by WinNonlin. The associated R^2 of the estimate is required to be >0.8 in order to be reliably estimated.	1/h	2 decimal places
$t_{1/2}$	Terminal half-life, where t½ = ln(2)/ λz	h	3 significant figures
CL	Total systemic clearance $= \frac{\mathrm{Dose}}{\mathrm{AUCINF\_calc}}$	L/h	3 significant figures

	CL is calculated using dose level (mg/kg) and actual dose (mg).		
Vss	Steady state volume of distribution Calculate from the following formula in subjects whose λz can be calculated. Vss = CL ×MRTinf Vss is calculated using dose level (mg/kg) and actual dose (mg).	L	3 significant figures
MRT_{last}	Average residence time from the start of infusion to the final blood collection time $= \frac{AUMClast}{AUClast} - \frac{TI}{2}$ TI :Duration of infusion	h	3 significant figures
MRT_{inf}	Average residence time from start of infusion to infinite time $= \frac{AUMCinf\_calc}{AUCINF\_calc} - \frac{TI}{2}$ TI :Duration of infusion	h	3 significant figures

Subjects will be excluded from the PK analysis if their data do not allow for accurate assessment of the PK (e.g. incomplete administration of the study drug; subject vomited after receiving study drug; missing information of dosing and sampling times; concentration data not sufficient for PK parameter calculation).Following rules will be applied for descriptive statistics.

- Lower Limit of Quantification (LLOQ) will be substituted with 0.
- The number of subject displayed as "N" on summary tables will be the number of subject whose serum concentrations are measured (include LLOQ) or PK parameters are calculated.
- When the time of blood collection is outside the time windows, the relevant serum concentration will be listed but excluded from the calculation of summary statistics.

Table 5 List of compound and lower limit of quantification

Compound	Unit	Lower Limit of Quantification	Rounding Digit
Emapalumab	ug/L	62.5 ug/L	0.01

14.1.1 IMP Concentration

Population: PK/PD population

Group: Emapalumab

Contents:
- Calculate the descriptive statistics of IMP Concentration at each analysis time point (defined in Table 1 in Section 8.4.3 Visit Windows) by groups.

14.1.2 Figure of Mean ± SD of IMP Concentration Versus Time Curves

Population: PK/PD population

Group: Emapalumab

Contents:
- Create XY plots of Mean ± SD of IMP Concentration from before IMP administration and at each analysis time point (defined in Table 1 in 8.4.3 Visit Windows) by groups.
- X axis: Analysis visits defined in Table 1 in Section 8.4.3 Visit Windows
- Y axis: IMP Concentration [ug/L]
- Create the same XY plots with Y axis of log-transformed IMP Concentration.
- When Y axis is log-transformed, its scale will be log base 10 of 10^{-1}, 10^{0}, 10^{1}, 10^{2}, 10^{3}, 10^{4}.
- When the Y axis is log-transformed, eliminate LLOQ from the plot.

14.1.3 Figure of IMP Concentration Versus Time Curves of Individual Subjects

Population: PK/PD population

Group: Emapalumab

Contents:
- Create XY plots of IMP Concentration at actual time points by individual subjects.
- X axis: Actual time points observed
- Y axis: IMP Concentration [ug/L]
- Create the same XY plots with Y axis of log-transformed IMP Concentration.
- When Y axis is log-transformed, its scale will be log base 10 of 10^{-1}, 10^{0}, 10^{1}, 10^{2}, 10^{3}, 10^{4}.
- When the Y axis is log-transformed, eliminate LLOQ from the plot.
- For individual concentration-time profiles, concentrations used for the determination of the terminal half-life will be presented.

14.1.4 Pharmacokinetic Parameters

Population: PK/PD population

Group: Emapalumab

Contents:
- Calculate the descriptive statistics of pharmacokinetic parameters defined in Table 4 in Section 14.1 Pharmacokinetic assessment by groups.

14.2 Pharmacodynamic Biomarkers

The list of pharmacodynamic biomarkers evaluated in this study are presented in Table 6.

Table 6 List of pharmacodynamic biomarkers

Biomarkers	Unit	Lower Limit of Quantification	Rounding Digit
Pre-dose circulating IFNγ concentration	pg/mL	50.00 pg/mL	0.01
Total IFNγ concentrations	pg/mL	50.00 pg/mL	0.01
CXCL9 concentration	pg/mL	80.00 pg/mL	0.01
sIL2R concentration	pg/mL	50.00 pg/mL	0.01

Following rule will be applied for descriptive statistics.

- Lower Limit of Quantification (LLOQ) will be substituted with 0.

14.2.1 Pharmacodynamic Biomarkers Concentration

Population: PK/PD population

Group: Emapalumab

Contents:
- Calculate the descriptive statistics of pharmacodynamic biomarkers concentration in those parameters described in Table 6 in Section 14.2 Pharmacodynamic biomarkers at each analysis time point (defined in Table 1 in Section 8.4.3 Visit Windows) by groups.

14.2.2 Figure of Mean ± SD of Pharmacodynamic Biomarkers Concentration Versus Time Curves

Population: PK/PD population

Group: Emapalumab

Contents:
- Create XY plots of Mean ± SD of pharmacodynamic biomarkers concentration in those parameters described in Table 6 in Section 14.2 Pharmacodynamic biomarkers at each analysis time point (defined in Table 1 in Section 8.4.3 Visit Windows) by groups.
- X axis: Analysis visits defined in Table 1 in Section 8.4.2 Visit Windows
- Y axis: Biomarkers parameter name [unit]

14.2.3 Figure of Pharmacodynamic Biomarkers Concentration Versus Time Curves of Individual Subjects

Population: PK/PD population

Group: Emapalumab

Contents:
- Create XY plots of pharmacodynamic biomarkers concentration in those parameters described in Table 6 in 14.2 Pharmacodynamic biomarkers at actual time points by groups.
- X axis: Actual time points observed
- Y axis: Biomarkers parameter name [unit]

15 Safety analyses

15.1 Drug exposure

Summaries of total dose of IMP will be presented in a listing.

15.2 Adverse events

Term	Definition
AE	Any unfavorable and unintended sign, (including an abnormal laboratory findings) symptom or disease, whether or not considered related to the IMP.
ADR	An adverse event whose causal relationship to the IMP cannot be ruled out.
Serious AE	Any AE occurring at any dose that in the opinion of either the investigator or sponsor results in any of the following outcomes: 1) Death, 2) Life-threatening adverse drug experience, 3) Inpatient hospitalization or prolongation of existing hospitalization (for > 24 hours), 4) Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, 5) Congenital anomaly/birth defect, 6) Important Medical Event (IME) that may not result in death, be life threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon medical judgment, it may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.
Serious ADR	A serious adverse event whose causal relationship to the IMP cannot be ruled out.
TEAE	All reported AEs that occurred after the administration of IMP up till the end of study, and those that worsened after administration of IMP.
IRR	All reported TEAEs which occured within 24 hours from the infusion starting date/time unless the available information clearly indicates that the AE is not treatment-emergent.

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

15.2.1 Adverse Events/Adverse Drug Reactions

Population: Safety Analysis population

Group: Emapalumab, Placebo

Contents:
- Calculate the number of subjects with TEAEs and percentages by groups for the following items:
  - All TEAEs
  - ADRs
  - Serious TEAEs
  - Serious ADRs
  - TEAEs leading to drug withdrawn
  - ADRs leading to drug withdrawn
  - TEAEs leading to dose reduced
  - ADRs leading to dose reduced
  - TEAEs leading to drug interrupted
  - ADRs leading to drug interrupted
  - TEAEs leading to death
  - ADRs leading to death
- Denominator to calculate the percentage: The number of subjects from the population in each group.
- Each subject will contribute at most one count per summarization category.

15.2.2 Adverse Events/Adverse Drug Reactions by SOC and PT

Population: Safety Analysis population

Group: Emapalumab, Placebo

Contents:
- Calculate the number of subjects and the percentages of TEAEs according to SOC/PT by groups.
- Contents will be sorted by SOC and PT.
- Denominator to calculate the percentages: The number of subjects from the population in each group.
- Each subject with more than one TEAE in the same SOC/PT will be counted once.
- Conduct the same analysis for ADRs, serious TEAEs and non-serious TEAEs.

15.2.3 Adverse Events/Adverse Drug Reactions by Intensity

Population: Safety Analysis population

Group: Emapalumab, Placebo

Contents:
- Calculate the number of subjects and percentages of TEAEs according to SOC/PT by groups and intensity (Mild/Moderate/Severe).
- Denominator to calculate the percentages: The number of subjects from the population in each group.
- Each subject with more than one TEAE in the same SOC/PT will be counted once by using the maximum intensity.
- Conduct the same analysis for ADRs and serious TEAEs.

15.2.4 Adverse Events/Adverse Drug Reactions by Causal Relationship

Population: Safety Analysis population

Group: Emapalumab, Placebo

Contents:
- Calculate the number of subjects and percentages of TEAEs according to SOC/PT by groups and causal relationship to the IMP ("Not related" and "Related").
- Each subject with multiple causal relationship to IMP in the same SOC/PT will be counted once by using the "Related" in each category.
- Denominator to calculate the percentages: The number of subjects from the population in each group.
- Conduct the same analysis for serious TEAEs.

15.2.5 Infusion Related Reactions

Population: Safety Analysis population

Group: Emapalumab, Placebo

Contents:
- Calculate the number of subjects and percentages of infusion related reactions according to SOC/PT by groups and the need for medication (Yes/No).
- Denominator to calculate the percentages: The number of subjects from the population in each group.
- Conduct the same analysis for serious IRRs.

15.2.6 Deaths

Deaths will be presented in listings.

15.3 Laboratory data

The list of laboratory parameters evaluated in this study is presented in Table 7. Laboratory values will be classified as within range/normal, abnormal high, or abnormal low, based on the local laboratory's normal ranges for the respective parameter.

Table 7 List of Laboratory Assessments

Classification	Examination Component	Unit	Rounding Digit / Categories
Hematology	Hemoglobin	[g/dL]	0.1
	Hematocrit	[%]	0.1
	Platelet Count	[$\times 10^{10}$/L]	0.1
	Red Blood Cells	[$\times 10^{10}$/L]	1
	Leukocyte Total	[/10^{6}/L]	1
	Neutrophils	[%]	0.1
	Lymphocytes	[%]	0.1
	Basophils	[%]	0.1
	Eosinophils	[%]	0.1
	Monocytes	[%]	0.1
	IgG	[mg/dL]	1
	IgA	[mg/dL]	1
	IgM	[mg/dL]	1
	Coagulation Profile (APTT)	[sec]	0.1
Biochemistry	Aspartate Aminotransferase (AST)	[IU/L]	1
	Alanine Aminotransferase (ALT)	[IU/L]	1
	Direct Bilirubin	[mg/dL]	0.1
	Total Bilirubin	[mg/dL]	0.1
	Uric Acid	[mg/dL]	0.1
	Alkaline Phosphatase	[U/L]	1
	Total Protein	[g/dL]	0.1
	Albumin	[g/dL]	0.1
	Prothrombin Time/International Normalized Ratio (PT-INR)	-	0.01
	Fibrinogen	[mg/dL]	1
	Complement C3	[mg/dL]	1

	Complement C4	[mg/dL]	1
	Cardiac Troponin	[ng/L]	0.1
	Creatinine	[mg/dL]	0.01
	C-reactive protein (CRP)	[mg/dL]	0.01
	Sodium	[mEq/L]	1
	Potassium	[mEq/L]	0.1
	Calcium	[mg/dL]	0.1
	Glucose	[mg/dL]	1
	Triglycerides	[mg/dL]	1
	HDL	[mg/dL]	1
	LDL	[mg/dL]	1
	BUN/Urea	[mg/dL]	0.1
Urinalysis	Erythrocytes	-	- , +- , + , 2+ , 3+ , 4+
	Leukocytes	-	- , +- , + , 2+ , 3+ , 4+
	Glucose	-	- , +- , + , 2+ , 3+ , 4+
	Ketones	-	- , +- , + , 2+ , 3+ , 4+
	pH	-	0.1
	Protein	-	- , +- , + , 2+ , 3+ , 4+
	Erythrocytes (Sediment) [a)]	-	
	Leukocytes (Sediment) [a)]	-	
	Protein (Sediment) [a)]		

a) Erythrocytes (Sediment), Leukocytes (Sediment), Protein (Sediment) will be shown only in listings.

15.3.1 Descriptive Statistics of Laboratory Parameters

Population: Safety Analysis population

Group: Emapalumab, Placebo

Contents:
- Calculate the descriptive statistics of quantitative laboratory parameters (in Table 7 in Section 15.3 Laboratory data) at each analysis time point (defined in Table 3 in Section 8.4.3 Visit Windows) by groups.
- Conduct the same analysis by treatment groups and grades (Low/Normal/High).
- Conduct the same analysis for change from baseline.

15.3.2 Figure of Laboratory Parameters Versus Time Curves of Individual Subject

Population: Safety Analysis population

Group: Emapalumab, Placebo

Contents:
- Create XY plots of quantitative laboratory parameters (in Table 7 in Section 15.3 Laboratory data) at actual time points by groups.
- X axis: Actual time points observed
- Y axis: Quantitative laboratory parameters (Show each name of quantitative laboratory parameters in Table 7 in Y axis label)

15.3.3 Contingency Table of Urine Parameters

Population: Safety Analysis population

Group: Emapalumab, Placebo

Contents:
- Create cross tables of qualitative urine parameters (in Table 7 in Section 15.3 Laboratory data) of baseline and at each analysis time point after IMP administration (defined in Table 3 in Section 8.4.3 Visit Windows) by groups.
- Remove data from calculation if both data from before and after IMP administration do not exist.

15.3.4 Contingency Table of Laboratory Parameters

Population: Safety Analysis population

Group: Emapalumab, Placebo

Contents:
- Create cross tables of normal range grading (Low/Normal/High) of quantitative laboratory parameters (in Table 7 in Section 15.3 Laboratory data) of baseline and at each analysis time point after IMP administration (defined in Table 3 in Section 8.4.3 Visit Windows) by groups.
- Remove data from calculation if both data from before and after IMP administration do not exist.

15.4 Anti-drug antibodies

The list of immunogenicity evaluated in this study is presented in Table 8.

Table 8 List of Immunogenicity Assessments

Examination Component	Unit	Rounding Digit / Categories
Anti-drug antibodies (ADAs)	-	Positive, Negative
Neutralizing antibodies (nAbs)	-	Positive, Negative

15.4.1 The presence of ADAs and nAbs

Population: PK/PD population

Group: Emapalumab, Placebo

Contents:
- Calculate the number of subjects with positive with ADA/nAbs in Table 8 in 15.4 Anti-drug antibodies at baseline and at study completion or withdrawal (defined in Table 3 in 8.4.3 Visit Windows) by groups.
- Denominator to calculate the percentages: The number of subjects from the population in each group.

15.5 Vital Signs

The list of vital signs evaluated in this study is presented in Table 9.

Table 9 List of Vital Signs

Examination Component	Unit	Rounding Digit / Categories
Body Temperature	[°C]	0.1
Semi-Supine Systolic Blood Pressure	[mmHg]	1
Semi-Supine Diastolic Blood Pressure	[mmHg]	1
Heart Rate	[beats/min]	1

15.5.1 Descriptive Statistics of Vital Signs

Population: Safety Analysis population

Group: Emapalumab, Placebo

Contents:
- Calculate the descriptive statistics of vital signs in Table 9 in Section 15.5 Vital Signs in each analysis time point (defined in Table 2 in Section 8.4.3 Visit Windows) by groups.
- Conduct the same analysis for change from baseline.

15.5.2 Figure of Vital Signs Parameters Versus Time Curves of Individual Subject

Population: Safety Analysis population

Group: Emapalumab, Placebo

Contents:
- Create XY plots of quantitative vital sign parameters (in Table 9 in Section 15.5 Vital Signs) at actual time points by groups.
- X axis: Actual time points observed
- Y axis: Quantitative vital sign parameters (Show each name of quantitative vital sign parameters in Table 9 in Y axis label)

15.6 Physical Examination

The list of physical examinations evaluated in this study is presented in Table 10.

Table 10 List of physical examination

Examination Component	Unit	Rounding Digit / Categories
General Appearance	-	Normal / Abnormal
Eyes	-	Normal / Abnormal
Ears	-	Normal / Abnormal
Nose	-	Normal / Abnormal
Throat	-	Normal / Abnormal
Chest/Respiratory	-	Normal / Abnormal
Heart/Cardiovascular	-	Normal / Abnormal
Gastrointestinal/Liver	-	Normal / Abnormal
Musculoskeletal/Extremities	-	Normal / Abnormal
Dermatological/Skin	-	Normal / Abnormal
Thyroid/Neck	-	Normal / Abnormal
Lymph Nodes	-	Normal / Abnormal
Neurological/Psychiatric	-	Normal / Abnormal

15.6.1 Contingency Table of Physical Examination

Population: Safety Analysis population

Group: Emapalumab, Placebo

Contents:
- Create cross tables of physical examination in Table 10 in Section 15.6 Physical Examination at each analysis time point (defined in Table 3 in Section 8.4.3 Visit Windows) by groups and abnormality (Normal/Abnormal).
- Remove data from calculation if both data from before and after IMP administration do not exist.

15.7 Electrocardiogram

The list of electrocardiogram examination evaluated in this study is presented in Table 11.

Table 11 List of electrocardiogram

Examination Component	Unit	Rounding Digit / Categories
12-Lead ECG	-	Normal / Abnormal with no clinical significance / Abnormal with clinical significance

15.7.1 Contingency Table of Electrocardiogram

Population: Safety Analysis population

Group: Emapalumab, Placebo

Contents:
- Create cross tables of electrocardiogram in Table 11 in Section 15.7 Electrocardiogram at each analysis time point (defined in Table 3 in Section 8.4.3 Visit Windows) by groups and abnormality (Normal/Abnormal with no clinical significance/Abnormal with clinical significance).
- Remove data from calculation if both data from before and after IMP administration do not exist.

15.8 Pregnancy

The list of pregnancy test results evaluated in this study is presented in Table 12.

Table 12 List of pregnancy test

Examination Component	Unit	Rounding Digit / Categories
Urine Pregnancy Test	-	Negative / Positive

Pregnancy test results will be presented in a listing with visits and assessment dates.

16 Listings

- Listing of Discontinuations
- Listing of Protocol Deviations
- Listing of Analysis Population Analyzed
- Listing of Demographics and Baseline Characteristics
- Listing of Medical History
- Listing of Prior and Concomitant Medications
- Listing of IMP Administration
- Listing of Emapalumab Concentrations
- Listing of Pharmacokinetic Parameters
- Listing of Pharmacodynamic Biomarkers
- Listing of Treatment-Emergent Adverse Events
- Listing of Adverse Events which Lead to Death
- Listing of Serious Adverse Events which occured between ICF and IMP
- Listing of Laboratory Parameters
- Listing of ADAs and nAbs
- Listing of Vital Signs
- Listing of Physical Examination
- Listing of Electrocardiogram
- Listing of Pregnancy Test

17 References

None.

18 Revision History

Version	Details
1.0	Newly created
2.0	· General change: wording updated, and added some clarificatoin · “Incidence rate” is changed to “percentage” · 8.2 Dictionaries: modified the dictionary version · 8.4.2 Calculation of Age: added · 8.4.3 Visit Windows: added time points for the Vital Signs, added a description for handling the visit window · 8.6 Handling of Missing Data and Outliers: deleted the section “Imputation of Missing Birth Dates to Compute Age” · 8.6.1 Handling the Date of Adverse Events: added a description for handling the dates of adverse events · 15.2 Adverse events: added the definition of IRR · 15.2.2 Adverse Events/Adverse Drug Reactions by SOC and PT: added an analysis for non-serious TEAEs · 15.3 Laboratory data: added to state that Sediment is only displayed in the listing · 15.3.1 Descriptive Statistics of Laboratory Parameters: added to state that same analysis will be conducted by groups and normal range grading · 15.3.2 Figure of Mean ± SD of Laboratory Parameters Versus Time Curves: deleted · 15.5.2 Figure of Mean ± SD of Vital Signs Parameters Versus Time Curves: deleted · Listing of Analysis Population Analyzed (Randomized Subjects): added · Listing of Serious Adverse Events which occured between ICF and IMP: added · Listing of Adverse Events is changed to Listing of Treatment-Emergent Adverse Events