Statistical Analysis Plan

Protocol number:	NI-0501-14
Title:	A two-cohort, open-label, single arm, multicenter study to evaluate efficacy, safety and tolerability, pharmacokinetics and pharmacodynamics, of emapalumab in children and adults with macrophage activation syndrome (MAS) in Still's disease (including systemic juvenile idiopathic arthritis and Adult onset Still's disease) or with MAS in Systemic lupus erythematous
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SAP version:	4.0

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1 Abbreviations and definition of terms

AE	Adverse Event
ADA	Anti-drug antibodies
ALT	Alanine aminotransferase
AOSD	Adult-onset Still's disease
AST	Aspartate Transaminase
ATC	Anatomical Therapeutic Chemical
AxMP	Auxiliary medicinal product
BCG	Bacillus Calmette–Guérin
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
CNS	Central Nervous System
CR	Complete Response
CRA	Clinical research associate
CRF	Case Report Form
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CXCL9	Chemokine (C-X-C Motif) ligand 9
CXCL10	Chemokine (C-X-C Motif) ligand 10
EDC	Electronic data capture
EOT	End of treatment
EOS	End of study
FDA	Food and Drug Administration
FUP	Follow-UP
G-CSF	Granulocyte-colony stimulating factor
GC	GlucoCorticoid
HIV	Human Immunodeficiency Virus
HLGT	High-Level Group Terms
HLH	Hemophagocytic LymphoHistiocytosis
ICH	International Council for Harmonisation

IFNγ	Interferon gamma
IMP	Investigational Medicinal Product
IRR	Infusion Related Reaction
JAK	JAnus Kinase
KM	Kaplan Meier
LLN	Lower Limit of Normality
mAB	Monoclonal antibody
MAS	Macrophage Activation Syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
NA	Not Applicable
Nab	Neutralizing antibodies
PCR	Polymerase chain reaction
PD	Pharmacodynamic
PDN	Prednisolone
PedsQL	Pediatric Quality of Life Inventory
PK	Pharmacokinetic
PR	Partial Response
PT	Preferred Term
Q1	First Quartile
Q3	Third Quartile
RI	Run-in phase
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
sCD25	Soluble CD25 (i.e., soluble IL-2 receptor)
SD	Study Day
SDTM	Study Data Tabulation Model
SLE	Systemic Lupus Erythematosus
sJIA	Systemic Juvenile Idiopathic Arthritis

Sobi	Swedish Orphan Biovitrum
SOC	System Organ Class
TM	Trademark
TNF	Tumor Necrosis Factor
ULN	Upper limit of normality
US	United States
VAS	Visual analog scale
WBC	White blood cell
WHO DD	WHO Drug Dictionary

2 Introduction

This Statistical Analysis Plan (SAP) describes the planned analysis and reporting for Study NI-0501-14 (*a two-cohort, open-label, single arm, multicenter study to evaluate efficacy, safety and tolerability, pharmacokinetics and pharmacodynamics, of emapalumab in children and adults with macrophage activation syndrome (MAS) in Still's disease (including systemic juvenile idiopathic arthritis and adult onset Still's disease) or with MAS in systemic lupus erythematous*).

Study NI-0501-14 is a two-cohort trial that enrolls patients who are diagnosed with MAS and who are presenting an inadequate response to high doses of glucocorticoids (GCs). These patients will be enrolled in 2 cohorts as per their background disease. The cohorts are defined as follows:

- Cohort 1: MAS in Still's disease including sJIA and AOSD.
- Cohort 2: MAS in pediatric and adult SLE.

The study has the objectives to investigate the efficacy, safety and tolerability, PK and PD, and immunogenicity of emapalumab (an anti-interferon-γ monoclonal antibody [mAb]) in these 2 cohorts.

The purpose of this SAP is to outline the planned analyses to be completed to support the Clinical Study Report (CSR) for protocol NI-0501-14. 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 Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH): Guidance on Statistical Principles in Clinical Trials (1). All work planned and reported for this SAP will follow internationally accepted guidelines, published by the American Statistical Association and the Royal Statistical Society, for statistical practice.

3 Study objectives and endpoints

3.1 Primary objective

The primary objective of the study is to demonstrate efficacy of emapalumab in the treatment of patients in:

- Cohort 1: MAS in Still's disease.
- Cohort 2: MAS in pediatric and adult SLE.

3.2 Secondary objectives

The secondary objectives of the study are:

- To demonstrate efficacy of emapalumab with respect to tapering of GCs.
- To evaluate the time to onset of response to emapalumab treatment.
- To evaluate efficacy of emapalumab with respect to overall response.
- To evaluate the sustained efficacy of emapalumab treatment.
- To evaluate the patient's survival after treatment of emapalumab.
- To evaluate the safety and tolerability of emapalumab.
- To evaluate patient reported outcome of MAS in patients treated with emapalumab.
- To determine the pharmacokinetic (PK) profile of emapalumab.
- To determine the pharmacodynamic (PD) profile of emapalumab.
- To determine the immunogenicity of emapalumab.

3.3 Exploratory objectives

[redacted]

3.4 Study endpoints

3.4.1 Primary efficacy endpoint

The primary efficacy endpoint is the proportion of patients with complete response (CRTable 11) at Week 8 after first administration of emapalumab.

3.4.2 Secondary efficacy, PK, PD and immunogenicity endpoints

The secondary efficacy objectives with corresponding endpoints are given in Table 1.

Pharmacokinetics analyses, as well as PK/PD characterization will be performed through PK/PD modelling described in a non-study specific and separate analysis plan and report. The population PK and/or PK/PD modeling might be done by combining data from different studies.

Note: The EXIT interview, supportive of PedsQL, is not described in the CSP as an endpoint. Data will be collected outside of the EDC system; a separate analysis plan and report will be prepared by an external vendor.

Table 1 Secondary efficacy, PK, PD and immunogenecity objectives with corresponding endpoints

Objectives	Endpoint(s)
To demonstrate efficacy of emapalumab with respect to tapering of GCs	• GCs tapering to a dose below 50 % of PDN equivalent at the time of emapalumab start or to the same (or lower) dose being administered before the occurrence of MAS (in patients already treated for the underlying condition) whichever occurs first at any time during the study
	• GCs tapering to ≤1 mg/kg/day of PDN equivalent at any time during the study
	• Times to achieve: - GCs tapering to a dose below 50 % of PDN equivalent at the time of emapalumab start or to the same (or lower) dose being administered before the occurrence of MAS (in patients already treated for the underlying condition) whichever occurs first at any time during the study. - GCs tapering to ≤ 1 mg/kg/day of PDN equivalent at any time during the study.
	• Achievement of weekly average prednisolone equivalent daily dose ≤0.5 mg/kg/day • Time to first achievement of weekly average prednisolone equivalent daily dose ≤0.5 mg/kg/day
	• Achievement of weekly average prednisolone equivalent daily dose ≤0.2 mg/kg/day • Time to first achievement of weekly average prednisolone equivalent daily dose ≤0.2 mg/kg/day
To evaluate the time to onset of response to emapalumab treatment	• Time to first CR
	• Time to first normalization of each parameter included in the CR definition.
To evaluate efficacy of emapalumab with respect to overall response	• Overall response as defined by CR or PR
	• Time to first overall response as defined by CR or PR
To evaluate the sustained efficacy of emapalumab treatment	• MAS recurrence at any time after achievement of CR
	• Withdrawal from the study due to lack of response as per Investigator decision
To evaluate the patient's survival after treatment of emapalumab	• Survival time
To evaluate patient reported outcome of MAS in patients treated with emapalumab	• Health-related QoL: Pediatric QoL Inventory (PedsQL™; Generic Core Scales and Infant Scales, Acute versions). Link to examples of questionnaires also applicable to adults is provided in Appendix 1 of the CSP

	• Global Assessment: Patient/Parent Global Impression of Severity. Example is provided in Appendix 1 of CSP
	• Global Assessment: Clinician Global Impression of Severity in Appendix 1 of CSP
To determine the pharmacokinetic (PK) profile of emapalumab	• Serum concentrations of emapalumab
To determine the PD profile of emapalumab	• Levels of circulating free IFN-γ at pre-dose, and total IFNγ (free IFN-γ+bound to emapalumab) after initiation of the study drug
	• Levels of the main IFN-γ-induced chemokines (CXCL9, CXCL10)
	• Levels of MAS markers (soluble CD25)
To determine the immunogenicity of emapalumab	• Occurrence of ADAs, Nab to emapalumab
Abbreviations: ADA, Anti-Drug Antibody; CR, Complete response; CSP, Clinical study protocol; CXCL, C-X-C Motif Chemokine Ligand; CG, Glucocorticoid; IFN, Interferon; MAS, Macrophage activation syndrome; Nab, Neutralizing antibody; PDN, Prednisolone; PR, Partial response; QoL.	

3.4.3 Safety endpoints

The safety objectives with corresponding endpoints are given in Table 2.

Table 2 Secondary safety objectives with corresponding endpoints

Objective	Endpoints
To evaluate the safety and tolerability of emapalumab	• Incidence, severity, causality and outcomes of AEs (serious and non-serious)
	• Withdrawal from the study treatment due to safety reasons
	• Changes from baseline in relevant laboratory parameters, vital signs, physical examinations, ECGs

3.4.4 Exploratory endpoints

4 Study methods

4.1 Overall study design and plan

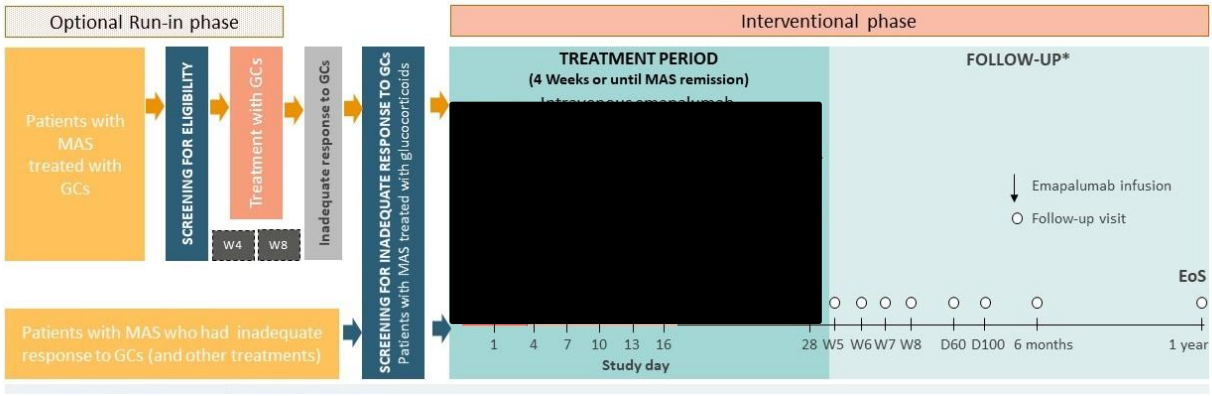
Study NI-0501-14 is a two-cohort, open-label, single arm, multicenter, interventional, phase 2/3 study.

The study enrolls patients between 6 months and 80 years of age with different etiologies of MAS. These patients will be assigned to different cohorts as per the underlying disease:

- Cohort 1: MAS in Still's disease.
- Cohort 2: MAS in pediatric and adult SLE.

Each cohort in this study is designed as a single arm study and will be composed of 2 phases: one optional Run-in phase and one Interventional phase.

Figure 1 Overview of study design for study NI-0501-14



Abbreviations: D, Day; EOS, end of study; EOT, end of treatment; GCs, glucocorticoids ; MAS, macrophage activation syndrome; PD, Pharmacodynamics; PK, Pharmacokinetics; SD, study day; W, Week.
Note: D60 and D100 are 60 days and 100 days after last dose of emapalumab, respectively. Similarly, 6 months and 1 year visits are 6 months and 1 year after last dose of emapalumab respectively.

The patient's participation in the optional Run-in phase of the study comprises 2 parts: screening, and GCs treatment for MAS period as shown in Table 3.

The patient's participation in the Interventional phase of the study comprises 3 parts: screening, treatment period with emapalumab, and follow-up, as shown in Table 4. Re-treatment with emapalumab is allowed during the follow-up period in case of MAS recurrence/reactivation. Re-treated patients should stop their follow-up visits and restart treatment as per schedule of assessment (including follow-up post re-treatment). The end of study for the re-treated patients will be up to the overall end of study (i.e. completion or early termination of all patients as per the

initial schedule of assessment before re-treatment) or at minimum 4 weeks after the end of re-treatment (i.e., follow-up to Week 8).

Note: the Run-in phase is not compulsory, therefore patients can join the study directly in the Interventional phase.

Table 3 Overview of the Run-in phase

Period	**Screening**	**GCs treatment period for MAS[a]**			
Visit	Screening RI visit	Visit 1 RI (start of MAS treatment)	Visit 2 RI (Week 1 from first MAS treatment)	Visit 3 RI (Week 4 from first MAS treatment)	Visit 4 RI (Week 8 from first MAS treatment/EOS/study withdrawal)
Day	RI:SD-7 to RI:SD-1	RI:SD1	RI:SD7	RI:SD28	RI:SD56

Abbreviations: EOS, End of Study; RI, Run-in phase; MAS, Macrophage activation syndrome; GC,glucocorticoid; SD, study day (RI:SD1 is the day of first dose of GCs for MAS treatment).
[a] Patients will be followed until either reaching a CR or until presenting an inadequate response to GCs or up to 12 weeks after the start of GCs treatment for MAS whichever occurs first.

Table 4 Overview of the Interventional phase

Screening Up to 1 week prior to VIP 1	**Treatment period (4 weeks)**		**Follow-up**					
	Initial dose [redacted]	Subsequent doses [redacted]	Follow-up to Week 8 (4 weeks)[b]		Long-term follow-up (after last dose of emapalumab)[c,d]			
	VIP 1 (SD1)	VIP 2 (SD4) and onwards	Weeks 5, 6, 7 visits (SD35-42-49)	Week 8 visit (SD56)	D60	D100	M6	Y1

Abbreviations: CR, Complete response; D, Day; EOS, End of study; M, Month; MAS, Macrophage activation syndrome; SD, Study day; VIP, Visit Interventional phase; Y, Year.
Note: The dose of [redacted] will be administered every 3 days until SD16, and then twice-a-week for an additional 2 weeks, i.e., until SD28. Treatment can be stopped before SD28 if the patient reached a CR.
Note: In the absence of a trend of improvement in key MAS clinical and laboratory parameters suggestive of a lack of response, the emapalumab regimen may be adapted by shortening the interval between the infusions, or by increasing the dose level up to a maximum dose corresponding to [redacted] every 3 days. The treatment could also be prolonged beyond 4 weeks upon Investigator confirmation of a favorable benefit/risk profile in that patient.
Note: D60 and D100 are 60 days and 100 days after last dose of emapalumab, respectively. M6 is 6 months after last dose of emapalumab, and Y1 is 1 year after last dose of emapalumab.
[a]Additional MAS treatments allowed in case of unsatisfactory MAS control after 3 doses of emapalumab. It is expected that VIP 2 will occur on SD4, however if the Investigator chooses to reduce the interval between doses, this visit may occur on another study day, which should be noted in the eCRF.
[b]In the treatment period up to Week 8 the patient will be followed up to SD56. The count starts from SD1.

[c]In the Long-term follow-up (D60 up to EOS) the count starts from last dose of emapalumab.
[d]Patients who relapse during the Long-term follow-up period of the study can be re-treated with emapalumab following the same dosing regimen.

A total of 41 patients are planned to be enrolled in the Interventional phase: 25 patients (of these at least 16 pediatric patients) in cohort 1, and 16 patients (of these at least 6 pediatric patients) in cohort 2.

An interim analysis will be performed after 16 patients in cohort 1 have been treated and reached 8 weeks after first dose of emapalumab. Enrollment in cohort 1 may be closed upon results of this interim. The patient recruitment in cohort 1 will not be on hold while the interim analysis is conducted.

Further interim analyses will be performed once all patients in each cohort have completed the follow-up to Week 8 (i.e., patients who reach the Week 8 Assessment Visit or discontinue the study early). The interim CSRs written based on these interim analyses may be used for regulatory submissions. Finally, a full CSR including the safety follow-up period will be prepared once both cohorts reach the EOS.

4.1.1 Schedule of assessments

Table 5 Schedule of assessment Run-in phase

Assessment		Screening RI visit SD-7 to SD-1	Visit 1 RI (start of MAS treatment) SD1	Visit 2 RI[a] (Week 1 from first MAS treatment) SD7	Visit 3 RI[a] (Week 4 from first MAS treatment) SD28	Visit 4 RI[a] (Week 8 from first MAS treatment) SD56	EOS/study withdrawal or SD84 (Week 12)[b]	UV[c]
Informed consent		x						
Review of inclusion exclusion criteria		x	x					
Demography and medical history		x						
pHLH genetical test, perforin level, and degranulation tests[d]		x						
GCs		x	x	x	x	x	x	x
Previous and concomitant medication including any previous MAS and any underlying disease treatment		x	x	x	x	x	x	x
Clinical assessment	Vital signs[e]	x	x	x	x	x	x	x
	Physical exam[f]	x	x	x	x	x	x	x
	Underlying disease assessment	x	x	x	x	x	x	x
	MAS clinical signs and symptoms including MAS clinical activity[g]	x	x	x	x	x	x	x

Assessment		Screening RI visit SD-7 to SD-1	Visit 1 RI (start of MAS treatment) SD1	Visit 2 RI[a] (Week 1 from first MAS treatment) SD7	Visit 3 RI[a] (Week 4 from first MAS treatment) SD28	Visit 4 RI[a] (Week 8 from first MAS treatment) SD56	EOS/study withdrawal or SD84 (Week 12)[b]	UV[c]
Laboratory assessment	CBC[h]	x	x	x	x	x	x	x
	Biochemistry[h]	x	x	x	x	x	x	x
	Coagulation[h]	x	x	x	x	x	x	x
	Urinalysis[h]	x						
	Pregnancy test (serum or urine) (if applicable)	x						
Infection	CMV	x	x	x	x	x	x	
	Adenovirus, EBV	x		**If clinically indicated**				
	Histoplasma capsulatum, Salmonella leishmania	x		**If clinically indicated**				
	Typical/Atypical mycobacteria	x	**If clinically indicated**					
Current MAS treatment		x	x	x	x	x	x	x
QoL assessment[i]		x				x	x	
AE reporting			x	x	x	x	x	

Abbreviations: AE, Adverse event; ALP, Alkaline phosphatase, ALT, Alanine aminotransferase; aPTT, Activated partial thromboplastin time; AST, Aspartate aminotransferase; CBC, Complete blood cell count; CMV, Cytomegalovirus; CR, Complete response; CRP, C-reactive protein; EBV, Epstein-Barr virus; EOS, End of study; GC, Glucocorticoid; GGT, Gamma-glutamyl transpeptidase; HLH, Hemophagocytic lymphohistiocytosis; LDH, Lactate dehydrogenase; MAS, Macrophage activation syndrome; pHLH, Primary hemophagocytic lymphohistiocytosis; PLT, platelets; QoL, Quality of life; RBC, Red blood cell count; RI, Run-in phase; SD, Study day; UV, Unscheduled visit; VAS: Visual analog scale; WBC, White blood cell count.

Assessment	Screening RI visit SD-7 to SD-1	Visit 1 RI (start of MAS treatment) SD1	Visit 2 RI[a] (Week 1 from first MAS treatment) SD7	Visit 3 RI[a] (Week 4 from first MAS treatment) SD28	Visit 4 RI[a] (Week 8 from first MAS treatment) SD56	EOS/study withdrawal or SD84 (Week 12)[b]	UV[c]

a Visit 2 should occur at SD7 ± 2 days from the MAS treatment with GCs start. Visit 3 should occur at SD28 ± 3 days from the MAS treatment with GCs start. Visit 4 should occur at SD56 ± 3 days from the MAS treatment with GCs start.

b Patients who do not reach MAS remission (as per Investigator assessment), and do not have an inadequate response to GCs by Week 8 will have their EOS Visit 12 weeks after start of GCs. All other patients will combine the Week 8 and EOS Visit.

c UV to be reported when remission or inadequate response to GCs is detected outside of the scheduled assessments. Assessments performed at the UV are per the Investigator's decision.

d The genetical and functional tests relevant to HLH diagnosis are not mandatory. They should be reported if available.

e Vital signs include body temperature, heart rate, blood pressure, and oxygen saturation. More frequent measurements will be done if medically indicated.

f The physical examination should include as a minimum the patient's weight, and should assess the MAS clinical activity as described in Section 7.3.3 of the CSP.

g MAS clinical signs and symptoms will include the evaluation of MAS clinical activity by VAS and the assessment of clinical signs and symptoms as indicated in Section 7.3.3 of the CSP.

h CBC includes hematocrit, hemoglobin, PLT, RBC, and WBC. Hematology differential: lymphocytes, monocytes, neutrophils. Biochemistry includes glucose, CRP, sodium, potassium, calcium, AST, ALT, GGT, ALP, LDH, bilirubin (total, direct and indirect), triglycerides, albumin, creatinine, urea, and ferritin. Coagulation includes aPTT, prothrombin time, D-dimers, and fibrinogen. Urinalysis includes glucose, blood, protein, leukocytes, ketones, and pH (test to be performed at screening visits only).

i Quality of life assessments will be collected at MAS remission (as per Investigator assessment) if it occurs after Week 8.

Table 6 Schedule of assessment Interventional phase: screening, emapalumab treatment and follow-up to Week 8 (from SD-1 to SD56)

Visit	**Screening for Interventional phase**	**Interventional phase (emapalumab treatment period)**				**Follow-up to Week 8**	
		Week 1 and Week 2 (SD2 to SD16)[a]		**Week 3 to Week 4 (SD17 to SD27)[a,b]**	**Week 4 (SD28)/EOT visit[c]**	**Weekly follow-up visits**	
	Screening visit (SD-7 to SD-1)	**VIP 1 (SD1)**	**VIP 2 VIP 3 VIP 4 VIP 5 VIP 6**	**VIP 7 VIP 8 VIP 9**	**VIP 10**	**Week 5-6-7 (SD35-42-49) (± 2 days) VIP Week 5, VIP Week 6, VIP Week 7**	**Week 8 Follow-up Visit SD56[d] VIP Week 8**
Informed consent	x						
Review of inclusion exclusion criteria	x	x					
Demography and medical history	x						
pHLH genetical tests, perforin level and degranulation tests[f]	x						
GCs	x	x	x	x	x	x	x
Previous and concomitant medication including any previous MAS and any underlying disease treatment[g]	x	x	x	x	x	x	x
Emapalumab infusion		x	x	x	x (if applicable)		

Visit		Screening for Interventional phase	Interventional phase (emapalumab treatment period)				Follow-up to Week 8	
			Week 1 and Week 2 (SD2 to SD16)[a]		Week 3 to Week 4 (SD17 to SD27)[a,b]	Week 4 (SD28)/EOT visit[c]	Weekly follow-up visits Week 5-6-7 (SD35-42-49) (± 2 days) VIP Week 5, VIP Week 6, VIP Week 7	Week 8 Follow-up Visit SD56[d] VIP Week 8
		Screening visit (SD-7 to SD-1)	VIP 1 (SD1)	VIP 2 VIP 3 VIP 4 VIP 5 VIP 6	VIP 7 VIP 8 VIP 9	VIP 10		
Clinical assessment	Vital signs[h]	x	x(pre/postinf.)	x(pre/postinf.)	x(pre/postinf.)	x(pre/postinf.)	x	x
	Physical examination[i]	x	x(pre-inf)	x(pre-inf)	x(pre-inf)	x(pre-inf)	x	x
	Underlying disease assessment	x	x	x	x	x	x	x
	MAS clinical signs and symptoms including MAS clinical activity[j]	x	x	x	x	x	x	x
	Tuberculosis clinical examination[k]	x				x		x
	Clinical monitoring for HZ infection	x	x	x	x	x	x	x
Laboratory assessment	CBC[l]	x	x(pre-inf)	x(pre-inf)	x(pre-inf)	x(pre-inf)	x	x
	Biochemistry[l]	x	x(pre-inf)	x(pre-inf)	x(pre-inf)	x(pre-inf)	x	x
	Coagulation[l]	x	x(pre-inf)	x(pre-inf)	x(pre-inf)	x(pre-inf)	x	x

Visit		Screening for Interventional phase	Interventional phase (emapalumab treatment period)				Follow-up to Week 8	
		Screening visit (SD-7 to SD-1)	Week 1 and Week 2 (SD2 to SD16)[a]		Week 3 to Week 4 (SD17 to SD27)[a,b]	Week 4 (SD28)/EOT visit[c]	Weekly follow-up visits Week 5-6-7 (SD35-42-49) (± 2 days) VIP Week 5, VIP Week 6, VIP Week 7	Week 8 Follow-up Visit SD56[d] VIP Week 8
			VIP 1 (SD1)	VIP 2 VIP 3 VIP 4 VIP 5 VIP 6	VIP 7 VIP 8 VIP 9	VIP 10		
	Urinalysis[l]	x						
	Pregnancy test (serum or urine) if applicable	x				x		
Infection[m]	Adenovirus, EBV	x	If clinically indicated					
	CMV	x	CMV every 2 weeks (± 2 days) if clinically indicated					x
	Atypical mycobacteria Histoplasma Salmonella, leishmania	x	If clinically indicated					
	Tuberculosis	x						x

Visit		Screening for Interventional phase	Interventional phase (emapalumab treatment period)				Follow-up to Week 8	
		Screening visit (SD-7 to SD-1)	Week 1 and Week 2 (SD2 to SD16)[a]		Week 3 to Week 4 (SD17 to SD27)[a,b]	Week 4 (SD28)/EOT visit[c]	Weekly follow-up visits Week 5-6-7 (SD35-42-49) (± 2 days) VIP Week 5, VIP Week 6, VIP Week 7	Week 8 Follow-up Visit SD56[d] VIP Week 8
			VIP 1 (SD1)	VIP 2 VIP 3 VIP 4 VIP 5 VIP 6	VIP 7 VIP 8 VIP 9	VIP 10		
Imaging	Chest X-ray[n]	x	If clinically indicated					x
	Abdominal ultrasound	x				x		x
	Brain MRI	x (if clinically indicated)						x (if brain involvement at baseline)
ECG		x						x
AE reporting			x	x	x	x	x	x
PK[o]			x (pre- and postinf)	x (pre- and postinf)	x (pre- and postinf)	x (pre- and postinf)	x	x
PD[o]			x (pre- and postinf)	x (pre-inf)	x (pre-inf)	x (pre-inf)	x	x
Immunogenicity (ADA and NAb)			x (pre-inf)					x
QoL assessment[p]		x						x

Abbreviations: ADA, Anti-drug antibodies; AE, Adverse event; ALP, Alkaline phosphatase; ALT, Alanine aminotransferase; aPTT, Activated partial thromboplastin time; AST, Aspartate aminotransferase; BMD, Bone mineral density; CBC, Complete blood cell count; CMV, Cytomegalovirus; CRP, C-reactive protein; CXCL9, Chemokine (C-X-C Motif) ligand 9; CXCL10, Chemokine (C-X-C Motif) ligand 10; EBV, Epstein-Barr virus; ECG, Electrocardiogram; eCRF, Electronic case report form; EOT, End of treatment; GC, Glucocorticoid; GGT, Gamma-glutamyl transferase; HLH, Hemophagocytic lymphohistiocytosis; HZ, Herpes zoster; IFN-γ, Interferon-gamma; inf, Infusion; LDH, Lactate dehydrogenase; MAS, Macrophage activation syndrome; MRI, Magnetic resonance imaging; NAb, Neutralizing antibodies; PCR, Polymerase chain reaction; PD, Pharmacodynamics; pHLH, Primary hemophagocytic lymphohistiocytosis; PK, Pharmacokinetics; PLT, platelets; QoL, Quality of life; RBC, Red blood cell count; sCD25, Soluble CD25 (i.e., soluble IL-2 receptor); SD, Study day; TB, Tuberculosis; VAS, Visual analog scale; VIP, Visit interventional phase; WBC, White blood cell count.

a During treatment with emapalumab, visits for infusion will occur concomitantly to emapalumab infusion on SD1 every 3 days until SD16, and twice weekly thereafter (not more than 4 days apart) until Week 4 or until a MAS remission (as per Investigator assessment), is achieved. It is expected that VIP 2 will occur on SD4, VIP 3 will occur on SD7, VIP 4 will occur on SD10, VIP 5 will occur on SD13, and VIP 6 will occur on SD16, however if the Investigator chooses to reduce the interval between doses, these visits may occur on other study days, which should be noted in the eCRF.

b These visits will occur at each emapalumab infusion. If treatment continues above VIP Week 4, VIP 9 assessments should be performed and the visit should be named subsequentially.

c The EOT assessment should be performed 3 days (± 1 day) after the last emapalumab infusion. If emapalumab treatment is shortened, an EOT Visit must be performed 3 days (± 1 day) after the last emapalumab infusion. If emapalumab treatment continues beyond the Week 4 assessment visit, an additional EOT Visit must be performed 3 days (± 1 day) after the last emapalumab infusion.

d Patients that complete their study treatment earlier than SD28 should complete an EOT visit 3 days (±1 days) after the last emapalumab infusion. After the EOT visit, three weekly follow-up visits should be completed with the assessments outlined for week 5, 6 and 7. Following the third weekly follow-up visit, the patient will complete the week 8 visit at SD56 (±3 days).

e The Week 8 assessment should be performed at SD56 (± 3 days) from first emapalumab infusion. This assessment should be performed in all patients regardless of when they complete the study treatment.

f The genetical and functional tests relevant to HLH diagnosis are not mandatory. They should be reported if available. In case a patient enrolled in the Run-in phase agrees to continue in the Interventional phase, genetic and functional testing do not have to be repeated.

g Previous and concomitant medication including any previous MAS and any underlying disease treatment.

h Vital signs include body temperature, heart rate, blood pressure, and oxygen saturation. To be measured pre-infusion, at the end of the infusion, and 1 and 2 hours after the end of the infusion, except for body temperature, which is to be taken only pre-infusion. More frequent measurements will be done if medically indicated (Section 7.3.4.3 of the CSP).

i Physical examination should include as a minimum the patient's height at Screening, weight before each emapalumab infusion then every 2 weeks, the assessment of MAS clinical activity as described in Section 7.3.3 of the CSP and footnote h, and the guided TB clinical exam as described in Section 7.3.4.2.2 of the CSP and footnote i.

j MAS clinical signs and symptoms will include the evaluation of MAS clinical activity by VAS and the assessment of clinical signs and symptoms as indicated in Section 7.3.3 of the CSP. Assessment of MAS clinical signs and symptoms including activity by VAS should be performed pre-infusion.

k A TB guided clinical examination should be performed at the baseline visit then every 4 weeks. If a patient is presenting any unexplained fever, cough, a skin lesion suggestive of TB or any other clinical signs and symptoms suggestive of TB infection as per Investigator discretion, a PCR testing should be performed.

l **CBC** includes hematocrit, hemoglobin, PLT, RBC, and WBC. Hematology differential: lymphocytes, monocytes, neutrophils. **Biochemistry** includes glucose, CRP, sodium, potassium, calcium, AST, ALT, GGT, ALP, LDH, bilirubin (total, direct and indirect), triglycerides, albumin, creatinine, urea, and ferritin. **Coagulation** includes aPTT, prothrombin time, D-dimers, and fibrinogen. **Urinalysis** includes glucose, blood, protein, leukocytes, ketones, and pH (test to be performed at Screening only).

m If a patient's medical condition warrants rapid treatment initiation, availability of the results for infection screening is not required prior to initiation of emapalumab, provided that there are no clinical findings suggestive of any of the infections which represent exclusion criteria. However, samples for infection screening need to be collected for analysis prior to first administration of emapalumab according to the protocol requirements. Only patients who have been in regions where leishmania is endemic during the 6 months prior to screening, or are living in an endemic country at the time of screening, are required to be actively screened for leishmania. The search for infections will be repeated if was done more than 30 days prior to the presumed emapalumab treatment start or if any clinical symptoms suggestive of infection. CMV testing is mandated every 2 weeks during the treatment phase of the study: the number of samples collected will take into consideration the weight and health status of the patient.

n Chest X-ray will be performed as a measure for detection of pulmonary infections, or to check for MAS lung involvement at Screening and at Week 8. Chest X-ray should be done more frequently in case of clinical suspicion of a pulmonary infection.

o PK will serve to measure the emapalumab concentration and PD to test sCD25, total IFN-γ, CXCL9, and CXCL10. PK samples should be taken preferably within 30-60 min post-infusion, but not earlier than 30 min. If the post-infusion sample must be collected from the same line as emapalumab has been administered through, the line must be flushed with 0.9% saline before the sample collection. In case of children weighing < 12 kg, the Investigator has the possibility to reduce the PK/PD sampling to every second visit between VIP 3 and VIP 9.

p In some countries QoL will also be assessed in an Exit interview (see Appendix 2 of the CSP). The Exit Interview will be performed separately by phone a few weeks (2-4 weeks) after the EOT.

Table 7 Schedule of assessment long-term follow-up

Assessment		**Long-term follow-up up to 1 year from last dose of emapalumab**				
		Day +60 visit (± 1 week)	**Day +100 visit (± 1 week)**	**6-month visit (± 2 weeks)**	**1-year visit/EOS Visit/WD visit (± 2 weeks)[a]**	**UV[b]**
GCs		x	x	x	x	
Concomitant medication including treatment of underlying disease and any additional MAS treatment (if applicable)		x	x	x	x	
Clinical assessment	Vital signs[c]	x	x	x	x	
	Physical exam[d]	x	x	x	x	
	Underlying disease assessment	x	x	x	x	
	Survival	x	x	x	x	
	MAS clinical signs and symptoms including MAS clinical activity[e]	x	x	x	x	

Assessment		Long-term follow-up up to 1 year from last dose of emapalumab				
		Day +60 visit (± 1 week)	**Day +100 visit (± 1 week)**	**6-month visit (± 2 weeks)**	**1-year visit/EOS Visit/WD visit (± 2 weeks)[a]**	**UV[b]**
	TB clinical exam[f]	x	x	x	x	
	Clinical monitoring of HZ infection	x	x	x	x	x
Laboratory assessment[h]	CBC[g]	x	x	x	x	
	Biochemistry[g]	x	x	x	x	
	Coagulation[g]	x	x	x	x	
	Pregnancy test (serum or urine) if applicable	If indicated			x	
Infection	Other infection as clinically indicated[h]	x	x	x	x	
	Mycobacterium TB[i]				x	
Imaging	Abdominal ultrasound			x	x	
	Chest X-ray	When clinically indicated				
	Brain MRI				x (if brain involvement at baseline)	
AE reporting		x	x	x	x	x
PK[j]		x	x	x	x	x
PD[j]		x	x	x	x	x
Immunogenicity (ADA and NAb)				x	x	
QoL assessment				x	x	

Abbreviations: ADA, Anti-drug-antibodies AE, Adverse event; ALP, Alkaline phosphatase; ALT, Alanine aminotransferase; aPTT, Activated partial thromboplastin time; AST, Asparate aminotransferase; BMD, Bone mineral density; CBC, Complete blood cell count; CMV, Cytomegalovirus; CXCL9, Chemokine (C-X-C Motif) ligand 9; CXCL10, Chemokine (C-X-C Motif) ligand 10; EBV, Epstein-Barr virus; EOS, End of study; GC, Glucocorticoid; GGT, Gamma-glutamyl transferase; HZ, Herpes zoster; IFN-γ, Interferon-gamma; LDH, Lactate dehydrogenase; MAS, Macrophage activation syndrome; MRI, Magnetic resonance imaging; NAb, Neutralizing antibodies; PCR, Polymerase chain reaction; PD, Pharmacodynamics; PK, Pharmacokinetics; PLT, platelets; QoL, Quality of life; RBC, Red blood cell count; sCD25, Soluble CD25 (i.e., soluble IL-2 receptor); TB, Tuberculosis; UV, Unscheduled visit; VAS, Visual analog scale; WBC, White blood cell count; WD, Withdrawal.

a The EOS Visit could be combined to the 1-year Follow-up Visit or to the Withdrawal Visit as applicable.

b A UV should be performed whenever it is clinically indicated throughout the study, the assessments to be performed during these visits should be as clinically indicated. Assessments performed at the UV are per the Investigator's decision.

c Vital signs include body temperature, heart rate, blood pressure, and oxygen saturation. More frequent measurements will be done if medically indicated, as described in Section 7.3.4.3 of the CSP.

d The physical examination should include as a minimum the patient's height at Month 6 visit and 1-year visit, and the assessment of MAS clinical activity as described in Section 7.3.3 of the CSP.

e MAS clinical signs and symptoms will include the evaluation of MAS clinical activity by VAS and the assessment of clinical signs and symptoms as indicated in Section 7.3.3 of the CSP.

f A TB guided clinical examination should be performed at the baseline visit then every 4 weeks. If a patient is presenting any unexplained fever, cough, a skin lesion suggestive of TB or any other clinical signs and symptoms suggestive of TB infection, as per Investigator discretion, a PCR should be performed.

g CBC includes hematocrit, hemoglobin, PLT, RBC, and WBC. Hematology differential: lymphocytes, monocytes, and neutrophils. Biochemistry includes glucose, C-reactive protein (CRP), sodium, potassium, calcium, AST, ALT, GGT, ALP, LDH, bilirubin (total, direct and indirect), triglycerides, albumin, creatinine, urea, and ferritin. Coagulation includes aPTT, prothrombin time, D-dimers, and fibrinogen.

h CMV, EBV, and adenovirus as clinically indicated.

i The mycobacterium TB search to be performed by PCR testing.

j PK will serve to measure the emapalumab concentration and PD to test sCD25, total IFN-γ, CXCL9, and CXCL10.

4.2 Selection of study population

Patients eligible in this study are males and females, pediatric and adult patients diagnosed with either Still's disease (including sJIA and AOSD) or SLE and developing MAS as per the MAS diagnosis criteria.

These patients should have been treated with GCs for MAS and should be presenting an inadequate response to GCs before starting treatment with emapalumab.

Patients will be included in the study if they meet all the inclusion criteria and none of the exclusion criteria listed in section 7.1.3.1 and section 7.1.3.2, respectively, in the CSP.

4.3 Method of treatment assignment and randomization

Not applicable as single arm study.

5 Sequence of planned analysis

5.1 Interim analyses

Interim Analysis 1

A first interim analysis, assessing efficacy, will be performed for cohort 1 (MAS in Still's disease including sJIA and AOSD) after enrollment of 16 treated patients who reached Week 8 or early discontinued the study. The purpose of the first interim analysis is to terminate enrollment in cohort 1 if efficacy is shown.. If the efficacy is demonstrated at the time of the interim analysis, then the enrolment in this cohort will be stopped by the Sponsor; otherwise the enrollment will continue up to 25 patients.

The formal stopping efficacy boundary will be determined by a one-sided exact binomial test at a significance level of 0.5 % to test if the CR rate is significantly above 40 % (see Section 13.1). With 16 treated patients at the time of the interim analysis, the threshold for the stopping for efficacy will be 12 out of 16 patients (corresponding to a CR rate of 75 %, i.e., 99 % exact confidence interval: [0.4009; 0.9545] with lower limit above 40 %). A CR rate of ≥50 % (≥8 of 16 patients) will be sufficient to conclude that there is evidence for efficacy in aggregation with another study and support regulatory submission but will not trigger a stop for efficacy unless a CR rate of 75 % is observed. The overall type 1 error rate for the group sequential design for cohort 1 will be controlled to be less than 2.5% as shown by clinical trial simulations (Appendix 6).

Note that the patient recruitment will not be on hold in this cohort while the first interim analysis is conducted.

5.2 Interim Analysis 2

A second interim analysis will be performed for Cohort 1 after enrollment of 25 patients treated with emapalumab who have reached the Week 8 Assessment Visit or have discontinued the study early. The second interim analysis may be used for regulatory submission. The null hypothesis (i.e., CR rate ≤ 40 %) will be rejected if a 2-sided 96 % CI is above the alternative hypothesis (i.e., CR rate > 40 %). Analyses and reporting

All planned analyses identified in the CSP and in this SAP, will be performed, as applicable, for

- The first interim CSR, at the time of the planned interim analysis: once 16 treated patients in the cohort 1 [MAS in Still's disease including sJIA and AOSD] underwent the Week 8 visit or early discontinued the study.
- The second interim CSR, once all patients in cohort 1 have completed the Week 8 Assessment Visit (i.e. Week 8 visit or early discontinued the study).
- The full CSR including the safety follow-up period, once all patients in both cohorts reach the end of the study.

Data reviews will be held prior to each cut-off date and database lock to check the validity of statistical assumptions. The SAP will be finalized, locked and signed prior to each cut-off date and database lock.

Any post-hoc analyses included in the CSR, which were not identified in this SAP, will be clearly identified as such in the relevant section of the CSR.

6 Sample size determination

The 2 cohorts will be analyzed separately, a sample size for the Interventional phase has been calculated for each cohort as described below. More details could be found in the sample size report (Appendix 6).

Cohort 1: In patients with MAS in Still's disease, patients intolerant or with inadequate response to GCs will receive other treatments, which occur in 60 to 70 % (2, 3); a successful treatment with GCs, when patients achieve response, can be expected in a proportion of patients up to 40 %. For a fixed study design, the sample size required for the cohort 1 (MAS in Still's disease) to achieve a power of 80 % using an one-sided exact binomial test at significance level of 2.5 % to test null hypothesis: proportion of CR is ≤40 % versus alternative hypothesis: proportion of CR is >40 % if the truth is 70 % complete responders, is 25 patients (nQuery 8, Version 8.6.0.0). The study design is a group sequential design that includes an interim analysis assessing efficacy after the enrollment of 16 patients into cohort 1. If efficacy is demonstrated at the time of the interim analysis, then the enrolment in this cohort will be stopped by the Sponsor; otherwise the enrollment will continue up to 25 patients. Using clinical trial simulations, the overall type 1 error rate for the group sequential design described above is less than 2.5 % and the power is estimated to 81.7 %. The type 1 error rate spent in the efficacy interim analysis (N=16 patients) is 0.5 % based on the

one-sided exact binomial test. The probability of type 1 error in the final efficacy analysis (N=25 patients), given that the study continues after the interim analysis, is 2.0 %.

Cohort 2: An article by Liu et al, 2018 (4), demonstrated that 21.9 % of SLE patients with MAS received GCs alone and did not require any other treatments. The assumption was made that patients in this cohort responded less frequently than in the other cohort: expected CR rate of at least 30 %. An exact binomial test at a one-sided significance level of 2.5 % will have 82 % power to reject the one-sided null hypothesis that the CR rate is at most 30 %, if the truth is 70 % complete responders, when the sample size is 16 (nQuery 8, Version 8.6.0.0).

7 Analysis populations

7.1 All Treated analysis set

The All Treated analysis set will include all enrolled patients (who signed an informed consent and who meet all eligibility criteria) in the Interventional phase who receive any part of an infusion of emapalumab and will be used to evaluate efficacy, safety, PK and PD, immunogenicity and exploratory endpoints. This population will be used as the primary population for the efficacy and safety analyses.

7.2 Evaluable analysis set

Evaluable analysis set will be a subset of the All Treated analysis set patients

- Who received a minimum of 3 consecutive infusions of emapalumab,
- For whom the diagnosis of background disease sJIA and AOSD (i.e., cohort 1) or SLE (i.e., cohort 2) is confirmed (e.g., no evidence for malignancy-related HLH or primary HLH has emerged after enrollment),
- And excluding protocol violations (deviations impacting primary efficacy analysis and leading to exclusion of the impacted patients).
  The criteria for identifying deviations impacting primary efficacy analysis and leading to exclusion of patients from the evaluable analysis set will be described in Section 7.2.1 in this SAP.

This population will be used as a sensitivity analysis of the primary efficacy endpoint.

7.2.1 Protocol deviations

The study specific Protocol Deviation Guidance document defines all protocol deviations considering operational aspect of the study conduct, including deviations as a result of the COVID-19 pandemic.

The CRO, in charge of the monitoring, will be responsible for producing the protocol deviations file and for updating it periodically. The protocol deviations file will be a consolidated file between

protocol deviations reported by the CRA and programmable protocol deviations as described in the Protocol Deviation Guidance.

The CRO and the Sponsor will perform regular reviews of the protocol deviations data throughout the study and prior to each planned and final analyses during the clinical data review meetings (before cut-off dates or database lock), updating the Protocol Deviation Guidance as appropriate. The file will clearly identify whether or not each deviation warrants an exclusion of the patient from a population (statistical assessment: Exclusion from the evaluable analysis set [Yes/No]), as well as the classification from a study conduct perspective (Non-important/Important) and the relationship to COVID-19; and will be used as source data for SDTM DV domain.

The following non-exhaustive list of protocol deviations are considered to potentially significantly impact the statistical primary efficacy analysis and may therefore lead to an exclusion of patients from the Evaluable analysis set after review by the Sponsor medical responsible.

Table 8 Deviations impacting primary efficacy analysis - Unmet inclusion or met exclusion criteria

Inclusion/Exclusion criteria	Phase	Cohort	Description
Inclusion	Run-in phase	Cohort 1 and 2	3. MAS defined as per the criteria defined below (see inclusion criteria #4) for each cohort and requiring treatment with GCs.
	Interventional phase	Cohorts 1 and 2	1. Informed consent provided by the patient or by the patient's legally authorized representative(s) with the assent of patients who are legally capable of providing it, as required by local law.
			3. Patients who have shown an inadequate response to high dose intravenous (i.v.) GCs administered for at least 3 days according to local standard clinical practice, including but not limited to pulses of 30 mg/kg prednisolone on 3 consecutive days. High i.v. GCs dose is recommended not to be lower than 2 mg/kg/ day prednisolone equivalent (or at least 60 mg/day in pediatric patients of 30 kg or more, and at least 1g/day in adult MAS patients). In case of rapid worsening of the patient's condition and/or laboratory parameters, as per Investigator judgment, inclusion may occur within less than 3 days from starting high dose GCs.
			4. Diagnosis of active MAS confirmed by the treating rheumatologist, having ascertained the followings: a. Febrile patients presenting with ferritin > 684 ng/mL. b. and any 2 of: i. Platelet count ≤ 181 x10^9/L ii. AST-level > 48 U/L iii. Triglycerides > 156 mg/dL iv. Fibrinogen level ≤ 360 mg/dL

		Cohort 1	Specific inclusion criteria for Cohort 1 1. Cohort 1 a. Confirmed sJIA diagnosis. For patients presenting with MAS in the context of the onset of sJIA, high presumption of sJIA will suffice for eligibility. b. Confirmed diagnosis of AOSD as per Yamaguchi criteria.
		Cohort 2	Specific inclusion criteria for Cohort 2 2. Cohort 2: a. Confirmed diagnosis of SLE as per SLICC'12 criteria.
Exclusion	Run-in and Interventional phases	Cohorts 1 and 2	1. pHLH documented by either the presence of a known causative genetic mutation or abnormal perforin expression or CD107a degranulation assay as described with primary hemophagocytic lymphohistiocytosis or by the presence of family history.
			2. Confirmed malignancy. Note: patients with a suspected malignancy should have mononuclaear cells typed by flow cytometry and/or tissue biopsy, as applicable, to rule out malignancy.
			3. Treatment with canakinumab, JAK inhibitors, TNF inhibitors, and tocilizumab at the time of emapalumab initiation.
			4. Ongoing treatment with anakinra at a dose above 4 mg/kg at time of emapalumab initiation.
			5. Patients treated with etoposide for MAS in the last 1 month.
			9. Evidence of leishmania infection.

Abbreviations: AOSD, Adult-onset Still's disease ; GC, GlucoCorticoid ; SLICC, Systemic Lupus International Collaborating Clinics; JAK, JAnus Kinase; SLE, Systemic Lupus Erythematosus; HLH, Hemophagocytic LymphoHistiocytosis; TNF: Tumor Necrosis Factor; MAS, Macrophage Activation Syndrome; sJIA, Systemic Juvenile Idiopathic Arthritis.
Note: Relevant Inclusion/Exclusion criteria are copied from CSP (i.e. numbering is the same as in the CSP).

7.3 All screened analysis set

All screened analysis set will include all patients who signed an informed consent form.

Note: Only patients having signed a run-in phase informed consent could have a run-in phase period. Similarly, only patients having signed an interventional phase informed consent could have an interventional phase period.

7.4 Run-in phase analysis set

Run-in phase analysis set will include all patients enrolled (who signed an informed consent and who meet all eligibility criteria) in the Run-in phase.

8 General issues for statistical analysis

For measurements of continuous endpoints, summary statistics will include n, mean, median, standard deviation, minimum, lower quartile (Q1), upper quartile (Q3) and maximum values. Minimum and maximum will be presented to the same number of decimal places as the raw data. The mean, median and quartiles will be presented to one more decimal place than the raw data. The standard deviation will be presented to two more decimals places than the raw data.

For binary data (proportions of patients showing a defined variable) the counts and percentages will be tabulated. Percentages will be suppressed when the count is zero, however the category will still be displayed. The denominator for all percentages will be the number of patients for the population of interest with available results (i.e. excluding missing), unless otherwise indicated. Missing will be presented but not considered in the percentage calculation, unless otherwise indicated. In the shift tables, missing will be presented under "Not reported" and percentage will be calculated. Percentages will be presented to one decimal place.

P-values from statistical analyses (only applicable to the primary efficacy endpoint analysis) will be presented to three decimal places with values below 0.001 displayed as <0.001 and confidence intervals will be presented to one more decimal places than the raw data.

The analysis of the Run-in phase will be purely descriptive using the Run-in phase analysis set. Descriptive statistics for the Run-in phase will be summarized by

- Patients with inadequate response to high dose intravenous GCs for the treatment of MAS (i.e. status at the end of the Run-in phase equals to Inadequate response, 12 weeks without response or prematurely discontinued).
- Patients with adequate response to GCs (i.e. status at the end of the Run-in phase equals to complete response).
- And overall.

All analyses will be presented separately for each cohort. Safety, PD, PK, ADA and QoL data will also be displayed overall when applicable.

All data will be listed in individual patient data listings. The data listings will display nominal and analysis visits where applicable. Data used in summary statistics or for statistical analyses based on visit windowing rules will be flagged. Data recorded as "Other" with additional information specified will be presented as "Other: *specified text*" in the listings. Separate listing for the Run-in phase and the All Treated analysis sets will be provided, as appropriate.

Statistical analyses will be performed using SAS software Version 9.4 or later (SAS Institute Inc, Cary, North Carolina, United States).

8.1 Handling of missing data and outliers

All available data will be used in the statistical analysis. A patient who withdraws prior to the last planned visit in the study will be included in the analyses up to the time of discontinuation.

Rules for derivation of variables with missing input parameters are described for each variable in section 8.4.

8.2 Multiple comparisons and multiplicity

The efficacy analyses of the 2 cohorts will be performed and presented separately (i.e., independent populations). As there is only one primary endpoint in this study, complete response at Week 8, no adjustment for multiple comparisons is needed.

The efficacy in cohort 1 is evaluated using a group sequential design that includes an interim analysis assessing efficacy after 16 patients have been treated and reached Week 8 or early discontinued the study. The overall type I error rate for the group sequential design is less than 2.5% as shown by clinical trial simulations in Appendix 6.

8.3 Analysis visit windows

As a general rule for summaries by visit, if not otherwise stated, the below approach and the analysis visit windows given in Table 9 are to be applied to determine which value will be associated to which analysis visit.

For post-baseline visits, one or more results may fall in the same visit window; in that case the scheduled assessment will prevail over the unscheduled ones, i.e., the assessments during the scheduled visit will be used to summarize the analysis visit if there is one scheduled assessment and any unscheduled assessments performed with the visit window for the visit.

In case there are two (or more) assessments from a patient within the visit window where prioritization of scheduled visits is not enough to select which assessment should be used for the visit, the assessment with the date closest to the visit date as per protocol will be used for the efficacy and safety analysis. In the event that two assessments are available and equidistant from the visit date, the result from earliest assessment will be used. If there are still two or more assessments recorded during the same day, the earliest measurement before the emapalumab infusion (applicable for the Interventional phase) will be used. If there are no treatment on the selected day, the earliest assessment of the selected day will be selected. If there is no possibility to identify the earliest assessment, the assessment with the earliest sequence number will be used.

Table 9 Time Windows for Endpoint Assessment at Pre-defined Time-Points

Protocol visit	Analysis visit	Time window used to define valid datapoints in the analyses
Run-in phase		
	RI:Baseline	Last value before GCs treatment start for MAS
Visit 1 RI (start of MAS treatment with GCs)	RI:SD1*	

Visit 2 RI	RI:Week 1	RI:SD7 ±3 days (RI:SD4 – RI:SD10)
Visit 3 RI	RI:Week 4	RI:SD28 ±7 days (RI:SD21 – RI:SD35)
Visit 4 RI	RI:Week 8	RI:SD56 ±7 days (RI:SD49 – RI:SD63)
	RI: At the time of remission	Assign to visit occurring Completion/Discontinuation Date ± 3 days
Interventional phase		
	Baseline	Last value pre-infusion of emapalumab
Treatment period timepoints		
VIP 2	Study Day 4**	Study Day§ 1$ - 5
VIP 3	Study Day 7	Study Day§ 7 ±1 day
VIP 4	Study Day 10	Study Day§ 10 ±1 day
VIP 5	Study Day 13	Study Day§ 13 ±1 day
VIP 6	Study Day 16	Study Day§ 16 ±1 day
Treatment period timepoints (twice-a-week emapalumab infusion)		
VIP 7	Study Day 19	Study Day§ 19 ±1 day
VIP 8	Study Day 22	Study Day§ 22 ±1 day
VIP 9	Study Day 25	Study Day§ 25 ±1 day
VIP Week 4	Week 4 (Study Day 28)	Study Day§ 28 -1 day +3 days (i.e. Study Day 27 – 31)
EOT visit***	End of Treatment	From EOT date to EOT date +8 days.
Follow-up to Week 8 timepoints		
VIP Week 5	Week 5 (Study day 35)	Study Day§ 35 ±3 days (i.e. Study Day 32 – 38)
VIP Week 6	Week 6 (Study day 42)	Study Day§ 42 ±3 days (i.e. Study Day 39 – 45)
VIP Week 7	Week 7 (Study day 49)	Study Day§ 49 ±3 days (i.e. Study Day 46 – 52)
VIP Week 8	Week 8 (Study day 56)	Study Day§ 56 ±3 days (i.e. Study Day 53 – 59)
	Week 8 efficacy assessment§§	Study day§ 56 ±5 days (i.e. Study Day 51 – 61)

	At the time of remission[$$]	Assign to Week 8 visit if MAS remission occurred before Week 8; otherwise unscheduled visit occurring Treatment completion/discontinuation date ± 3 days where MAS remission occurred (primary reason for end of treatment equals to "MAS remission") if after Week 8 (i.e. after study day 59)
		Time window if treatment continues beyond week 8 will be ±3 days.
Long-term follow-up timepoints		
Last infusion day +60 days visit	Follow-up Day + 60 days	Day 60[#] ±14 days
Last infusion day +100 days visit	Follow-up Day + 100 days	Day 100[#] ±14 days
6 months visit	Follow-up Day + 6 months	Day 182[#] ±30 days
One year visit/EOS visit[##]	Follow-up Day + 1 year	Day 365[#] ±30 days
One year visit/EOS visit[##]	End of Study	Assign to the End of Study visit

CR: Complete response; EOT: End of Treatment; EOS: End of Study; MAS: Macrophage activation syndrome; VIP: Visit Interventional Phase; RI: Run-in

[*] RI:SD1 is the day when GCs treatment for MAS starts. RI:SD4 is 3 days after the day of the first dose of GCs treatment for MAS.

[**] SD1 is the day of the first dose of emapalumab. SD4 is 3 days after the day of the first dose of emapalumab.

[§] The study day is the day from the first dose of emapalumab (i.e. Study day 1).

[$] Post-infusion of emapalumab. Not applicable for vital signs (heart rate, blood pressure and oxygen saturation collected pre and post dose) and pharmacokinetic sampling (pre/post) summary tables; except for body temperature only collected pre-infusion.

[§§] Timepoint for the assessment of the primary efficacy endpoint.

[#] The Follow-up day is the day from the last dose of emapalumab (i.e. Follow-up Day 1 is the day after the last dose of emapalumab).

[##] The EOS visit could be combined to the one-year follow-up visit or to the withdrawal visit as applicable.

[***] The EOT visit is defined as EOT assessment at the Week 4 Assessment Visit, 3 days after the last Week 4 infusion of emapalumab. In case treatment is shortened, an EOT visit shall be performed 3 days after the last administration of emapalumab. Whenever a patient receives treatment beyond Week 4, both a Week 4 Assessment Visit and an EOT visit shall be performed.

In case the EOT visit is the last visit of the study (i.e. No end of study visit) and performed later than EOT date + 8 days, no additional analysis visit beyond EOT is created and the EOT visit as per EDC is reported under the analysis visit EOT (i.e., not visit widows is applied in that case).

[$$] Applicable for PedsQL and_Clinical and Patient/Parent Global Impression of Severity which are assessed as per protocol (Section 7.3.5): in the Run-in phase at screening, Week 8 and at the time of remission if the remission is achieved after Week 8; in the Interventional phase at screening, Week 8, visit Month 6, the EOS visit and at the time of remission if remission is achieved after Week 8.

In case a patient is re-treated with emapalumab during the follow-up period, the treatment and follow-up timepoints as described in Table 9 will be followed and analysis visits will start by "Re-treatment", e.g. "Re-treatment Study day 1", "Re-treatment Study day x",... As described in Section 8.4.1, baseline is the last observed value prior to first infusion of the first emapalumab treatment (i.e. no baseline defined for the re-treatment period).

For vital signs (heart rate, blood pressure and oxygen saturation) and, pharmacodynamic and pharmacokinetic sampling data collected pre and post emapalumab infusion during the Interventional phase, analysis visits starts from study day 1 and then use the analysis visits as described in the above table, concatenated with PRE-DOSE, END OF INFUSION, POST-DOSE 1 HOUR, POST-DOSE 2 HOURS when applicable.

8.4 Derived and computed variables

8.4.1 Baseline

There are two different baseline defined, one for the Run-in phase and one for the Interventional phase:

Run-in phase:

Run-in (RI) baseline is defined as the last observation prior to the start of MAS treatment with GCs. GCs are defined in Section 8.4.19.

Interventional phase:

Interventional baseline, also called baseline, is defined as last observed value prior to first emapalumab infusion.

Note: For the re-treated patients with emapalumab, baseline is still the last observed value prior to first infusion of the first emapalumab treatment.

8.4.2 Change from baseline

The change from baseline is defined as follows for the Run-in phase and the Interventional phase:

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

8.4.3 Study day

Study day is defined as follows for the Run-in phase and the Interventional phase:

Run-in phase:

Study day x in the Run-in phase (RI:SDx) is defined as x = date of interest – date of first MAS treatment with GCs + 1 when date of interest is on or after date of first MAS treatment with GCs. x = date of interest – date of first MAS treatment with GCs when date of interest is before date of first MAS treatment with GCs.

Study day 1 in the Run-in phase is the date of first MAS treatment with GCs.

Interventional phase:

Study day x in the Interventional phase (SDx) is defined as x = date of interest – date of first emapalumab infusion + 1 when date of interest is on or after date of first emapalumab infusion. x = date of interest – date of first emapalumab infusion when date of interest is before date of first emapalumab infusion.

Study day 1 in the Interventional phase is the date of first infusion of emapalumab.

8.4.4 Time and temperature conversions

The following conversion factors will be used to convert days to months, weeks or years, or Fahrenheit to Celsius, where applicable:

- 1 month = 30.4375 days
- 6 months = 182.625 days
- 1 year = 365.25 days
- 1 week = 7 days
- °C = (°F - 32)/1.8

The following corrections will further be applied for body temperature measurements in °C, depending on the location of measurement:

- Orally: value (°C) + 0.5
- Axillary: value (°C) + 0.5
- Rectal: no correction
- Temporal: value (°C) + 0.5
- Tympanic: no correction

8.4.5 Age

Age in years or months at informed consent for both the Run-in and Interventional phases is collected from the electronic CRF (eCRF).

The year of birth is collected in the eCRF, not the date of birth.

Age at time of event (e.g. diagnosis) in years, for example, will defined using the following steps:

1. Estimation of date of birth

    - Date of birth = Date of informed consent – Age at informed consent

        - If age at informed consent is in years, e.g. patient of 7 years old at 19SEP2021 (informed consent date), estimated date of birth is 19SEP2014.

        - If age at informed consent is in months, e.g. patient of 10 months old at 31AUG2021 (informed consent date), estimated date of birth is 30NOV2020.

2. Age at time of event will be defined as (date of event – estimated date of birth)/365.25 rounded down to a value with no decimals.

In case of partial date of event:

- If only month and year are available, age at time of event is derived as above using 15th of the month and year as date of event.

- If only year is available, age at time of event is derived as above using 1st of January and year as date of event.

8.4.6 Number of emapalumab doses

The number of doses of emapalumab received is defined as the sum of all emapalumab administrations recorded on the eCRF where the actual dose infused > 0, regardless of whether the infusion is completely administered or not.

8.4.7 Emapalumab infused dose

- The emapalumab infused dose (mg/kg) at each visit will be defined as the total dose infused (mg) at the visit adjusted for the patient's weight as

$$Infused\ dose\ (mg/kg) = \frac{Total\ Dose\ Infused\ (mg)}{Weight\ (kg)}$$

  The patient's weight recorded at the timepoint closest, but prior, to the infusion date is used for the calculation.

- The minimum/maximum emapalumab dose infused (mg/kg) for each patient will be defined as the minimum/maximum infused dose (mg/kg) per patient administered throughout the study.

8.4.8 Auxiliary medicinal product (AxMP)

Herpes zoster virus prophylaxis drugs are considered as auxiliary medicinal product (AxMP) in the study according to protocol version 1.0 in which Herpes zoster prophylaxis was mandatory.

During the Interventional phase, patients with Herpes zoster virus prophylaxis treatments are defined as patients who received medications listed in Appendix 2 – Herpes zoster virus prophylaxis treatments

The final list should be reviewed and provided before database lock or cut-off dates by the clinical science team using the latest version of the WHO DD dictionary.

Patients vaccinated against Herpes zoster at screening are counted as patients with Herpes zoster virus prophylaxis treatments. As per Section 7.2.8.2 of the CSP version 1.0 (19MAR2021): "*Unless a subject has been previously vaccinated, prophylaxis against Herpes zoster virus infection must be in place on SD-1 (or, at the latest, before initiation of emapalumab treatment) and must be maintained for 2 half-lives (i.e., 44 days) after the last administration of emapalumab.* »

Patients with Herpes zoster virus prophylaxis treatments will also be identified through the eCRF form Herpes Zoster (HZ) Prophylaxis Check where the answer is "Yes" to the question "Has the Prophylaxis treatment been given to the patient at the treating physicians discretion?"

Following protocol amendment, Herpes zoster virus prophylaxis was no longer mandated in protocol version 2.0 and the relevant drugs therefore no longer considered as AxMP.

8.4.9 Cumulative GCs dose from MAS diagnosis to first overall response

The cumulative GCs dose is defined as the sum of the GCs doses received, expressed as "equivalent dose of prednisolone", from the date of MAS diagnosis (current episode of MAS) to the first overall response (CR or PR) during the Run-in phase for each patient. The translation into equivalent dose of prednisolone (mg/kg/day) is described in Section 8.4.22.

8.4.10 Last study contact date

The last study contact date is defined as follows for the Run-in phase and the Interventional phase:

<u>Run-in phase:</u>

The last study contact date in the Run-in phase is defined as the maximum of the following: last visit date or Run-in completion/discontinuation date or the day before the date of Interventional phase informed consent (i.e. for patients enrolled in the Interventional phase) but no later than the day before the date of Interventional phase informed consent. In case of death during the Run-in phase, the death date will be used.

Interventional phase:

The last study contact date in the Interventional phase, also called “last contact date”, is defined as the maximum of the following: last visit date or completion/discontinuation date. In case of death, the death date will be used. All dates used must not be imputed.

8.4.11 Last study contact date before re-treatment with emapalumab

For patients re-treated with emapalumab during the Interventional phase, the last study contact date before re-treatment is defined as the minimum of the following:

- Last visit date before re-treatment study day 1.
- Last visit date before MAS recurrence/reactivation start date (from the AE page, see Section 8.4.28) that occurs after CR achievement.

This definition is used in the times to events definition (Section 8.4.27).

8.4.12 Last study participation date

The last study participation date in the Interventional phase is defined as the maximum of the following: last visit date or last AE start/stop date or last medication start/stop date or completion/discontinuation date. In case of death, the death date will be used.

8.4.13 Study duration

Study duration is defined overall, as well as for the Run-in and Interventional phases.

- The overall study duration (days) is defined from the date of informed consent (using the earliest informed consent date from Run-in phase or Interventional phase) to the last contact date:

Overall study duration (days) = Last study contact date – Date of first informed consent (Run-in or Interventional phase) + 1.

- The Run-in (RI) phase duration (days) is defined from the date of Run-in phase informed consent till the last contact date in the Run-in phase (Section 8.4.10).

Run-in phase duration (days) = Last study contact date in the Run-in phase – Date of Run-in phase informed consent + 1.

- The Interventional phase duration (days) is defined from the date of Interventional phase informed consent till the last contact date (Section 8.4.10).

Interventional phase duration (days) = Last study contact date– Date of Interventional phase informed consent + 1.

8.4.14 Treatment duration

Definitions of treatments durations (emapalumab and GCs [defined in Section 8.4.19]) are as follows:

Emapalumab duration

- Emapalumab duration (days) during the Interventional phase is defined, from the Exposure - IV/Infusion Administration: Emapalumab eCRF form, as

  Emapalumab duration (days) = Date of last emapalumab dosing – Date of first emapalumab dosing + 1

GCs durations

- Duration (days) of GCs treatment for MAS during the Run-in phase is defined, from the Concomitant Medications (including GCs) eCRF form, as

  RI GCs duration (days) = Date of last MAS treatment with GCs during Run-in phase – date of first MAS treatment with GCs + 1

  Where:

  - The date of last MAS treatment with GCs during Run-in phase is the last GCs treatment date prior to the date of Interventional phase informed consent for patients enrolled in the Interventional phase or the last GCs treatment date for patients not enrolled in the Interventional phase.

- Duration (days) of GCs treatment for MAS during the Interventional phase is defined, from the Concomitant Medications (including GCs) eCRF form, as

  Interventional GCs duration (days) = Date of last MAS treatment with GCs – date of first MAS treatment with GCs on or after date of Interventional phase informed consent + 1

- Overall duration (days) of GCs treatment for MAS, on both Run-in and Interventional phases from the Concomitant Medications (including GCs) eCRF form, is defined as

  Overall GCs duration (days) = Date of last MAS treatment with GCs – date of first MAS treatment with GCs + 1

  Where:

  - The last date of MAS treatment with GCs is the last GCs treatment date irrespective of the study phases.

- The first date of MAS treatment with GCs is the first GCs treatment date irrespective of the study phases.

8.4.15 Treatment-emergent adverse event

Treatment-emergent AE (TEAE) is defined as any adverse event with an onset date/time on or after the start of the first emapalumab administration in the Interventional phase of the study.

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 first emapalumab infusion as follows:

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

8.4.16 Infusion-related reaction (IRR)

Infusion-related reactions (IRRs) is defined as any TEAE that is reported to have occurred within 24 hours after start of infusion and assessed as related to study treatment by the Investigator, excluding the following system organ classes (SOCs):

- “Infections and infestations”
- “Congenital, familial and genetic disorders”
- “Neoplasms benign, malignant and unspecified (incl. cysts and polyps)”
- “Product issues”
- “Social circumstances”
- “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 the infusion date or equal to the infusion date + 1 will be considered for the assessment of IRRs. If the onset date of the AE is completely missing, the AE will be considered as IRR.

8.4.17 Relationship and severity of adverse event

The relationship to emapalumab or AxMP (when applicable, described in Section 8.4.8) and severity of AEs are assessed by the Investigator and recorded in the eCRF.

If the relationship to study drug 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.

8.4.18 Infection

Infection is defined as any AEs in the SOC "Infections and infestations" or in the HLGT "Microbiology and serology investigations".

8.4.19 Glucocorticoids

Glucocorticoids (GCs) will be defined as all medications under the ATC level 4 code H02AB (Glucocorticoids) and will be expressed in equivalent dose of prednisolone as defined in Section 8.4.22. Only Glucocorticoids and GC application methods with systemic bioavailability will be considered and selected under the ATC level 4 code H02AB.

Systemic use is defined by looking at routes:

- SC
- Nasal
- Intra-thecal
- IV
- Oral
- Sublingual
- Rectal
- Intramuscular

8.4.20 JAK inhibitors

JAK inhibitors include the all medications under the ATC level 4 code L01EJ (JAK Inhibitors) and the below preferred names under the ATC level 4 code L04AA (Selective immunosuppressant):

- UPADACITINIB
- AZD 0449
- BARICITINIB
- BREPOCITINIB
- BREPOCITINIB TOSYLATE
- DECERNOTINIB
- FILGOTINIB
- FILGOTINIB HYDROCHLORIDE TRIHYDRATE
- FILGOTINIB MALEATE

- ITACITINIB
- ITACITINIB ADIPATE
- JANEX 1
- PEFICITINIB
- PEFICITINIB HYDROBROMIDE
- RITLECITINIB
- SOLCITINIB
- TOFACITINIB
- TOFACITINIB CITRATE
- UPADACITINIB

8.4.21 TNF inhibitors

TNF inhibitors are defined as all medications under the ATC level 4 code L04AB (Tumor necrosis factor alpha [TNF-alpha] inhibitors) and the preferred name "NERELIMOMAB" under the ATC level 4 code L04AA (Selective immunosuppressant).

8.4.22 Equivalent dose of prednisolone

Equivalent dose of prednisolone (mg/kg/day) is calculated using the following steps:

- Select glucocorticoids (see section 8.4.19)
- Calculate the frequency per day using below table (not exhaustive list)

Table 10 Frequency in number of daily dose

Frequency	Description	Number of doses per day
OB, QD	Once a day	1
BID	Twice a day	2
TID	Three times a day	3
QID	Four times a day	4
QW	Every week	1/7
2xW	Twice per week	2/7
3xW	Three times per week	3/7
NxW	N times per weeks	N/7
EVERY 2 WEEKS	Every two weeks	1/14
QM	Every month	1/30.4375

QAD, QOD	Every other day	0.5
Once	Single intake	1/(stop date – start date +1)
PRN	As needed	0
Other	Other	0
UNK	Unknown	0
	Missing	0

Note: Administration of GCs with 'as needed', 'other', missing or 'unknown' frequency will not be included in the calculation of the equivalent dose of prednisolone.

- Convert the dose in mg using the following conversions:
  - 1 g = 1000 mg,
  - 1 mcg = 0.001 mg.
- Select the weight in kg from the visit closest to the GCs administration date. If there are 2 such observations that are equidistant from the GCs administration date, the first observation will be selected.
- Calculate the daily equivalent dose of prednisolone using the following formula:

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

where the conversion factor is:

- Prednisone/prednisolone: 1
- Methylprednisolone: 1.25
-
- Dexamethasone: 6
- Triamcinolone:1.25
- Deflazacort: 0.67
- Hydrocortisone 0.25

-

If the equivalent daily dose of prednisolone is not reported during some periods from ICF start date in the medication page, then equivalent daily dose of prednisolone will be assumed to be 0 (i.e., GCs treatment will be considered as not taken).

8.4.23 Glucocorticoids tapering

Multiple definitions of GCs tapering will be used for the Interventional phase:

First definition:

Glucocorticoids tapered

- to the same (or lower) equivalent dose of prednisolone being administered before the occurrence of MAS in patients already on treatment for sJIA/AOSD or SLE; i.e. patients enrolled based on a confirmed diagnosis

Note: The equivalent daily dose of prednisolone (mg/kg/day) being administered before the occurrence of MAS will be defined as the average equivalent daily dose of prednisolone during the last week prior to the current MAS diagnosis date. If the previous MAS episode end date is available and within the last week prior to the current MAS episode, then the average will be derived from the day after the previous MAS episode end date until the day prior the current MAS diagnosis date. The weekly average prednisolone equivalent daily dose (mg/kg/day) post emapalumab start will be compared with the weekly average prednisolone equivalent daily dose prior to the current MAS diagnosis as defined above.

or

- by at least 50% of the equivalent dose of prednisolone administered at emapalumab start in patients who present MAS at sJIA/AOSD or SLE onset, i.e. patients enrolled based on high presumption of sJIA or not confirmed SLE diagnosis.

Note: The weekly average prednisolone equivalent daily dose (mg/kg/day) post emapalumab start will be compared with the average equivalent daily dose of prednisolone administered at Week –1 (study day -7 to study day -1, see Section 8.4.3).

If it is not possible to establish if a patient has been treated with GCs or not before study start (i.e. Interventional phase), or if it is not possible to retrieve GCs dose administered before the occurrence of MAS for all patients who are already treated for sJIA/AOSD or SLE, the glucocorticoids tapering endpoint will be changed. In this case the endpoint will be: "glucocorticoids tapered at any time during the study by at least 50% of the average equivalent daily dose of prednisolone administered at Week –1 (study day -7 to study day -1)".

Second definition: Glucocorticoids tapered to ≤ 1 mg/kg/day of weekly average prednisolone equivalent daily dose, starting at Week 1 (study day 1 to 7) at any time during the study (i.e. Interventional phase).

Third definition: Glucocorticoids tapered to weekly average prednisolone equivalent daily dose ≤0.5 mg/kg/day, starting at Week 1 (study day 1 to 7).

Fourth definition: Glucocorticoids tapered to weekly average equivalent dose of prednisolone ≤0.2 mg/kg/day, starting at Week 1 (study day 1 to 7).

For all definitions above, the weekly average prednisolone equivalent daily dose administered will be used to assess the GCs tapering throughout the study and defined using the below periods:

- Week -1 (study day -7 to -1), i.e. weekly pre-infusion of emapalumab.
- Week 1 (study day 1 to 7)
- Week 2 (study day 8 to 14)
- Week 3 (study day 15 to 21)
- Week 4 (study day 22 to 28)

- Week 5 (study day 29 to 35)
- Week 6 (study day 36 to 42)
- Week 7 (study day 43 to 49)
- Week 8 (study day 50 to 56)
- …
- Week 52 (study day 358 to 364)
- …

In addition, the weekly average prednisolone equivalent daily dose will be derived at EOT and EOS.

- EOT (Last week prior to EOT date: last treatment date -7 days to last treatment date -1 day)
- EOS (Last week prior to EOS visit date: EOS visit date -7 days to EOS visit date -1 day)

The time to first achievement of GCs tapering, defined later in the document, will be expressed in week. For example, if a patient tapers GCs at Week 2 for the first time based on the weekly average prednisolone equivalent daily dose as described above, then the time to first achievement of GCs tapering will be Week 2 for that patient. More details could be found in the Section 8.4.27.

Daily dose of GCs will be calculated as equivalent dose of prednisolone in mg/kg/day (see Section 8.4.22).

Only data collected before re-treatment with emapalumab will be used for emapalumab re-treated patients.

8.4.24 Complete response (CR)

The proportion of patients with complete Response (CR) at Week 8 efficacy assessment in the Interventional phase is the primary efficacy endpoint.

A patient is defined CR at a visit (e.g. Week 8 efficacy) if the MAS clinical signs and symptoms score (assessed using the VAS scale) and the laboratory values associated with that particular visit fulfill the criteria for CR in Table 11, regardless the time of first CR. The MAS Clinical signs and symptoms score and the laboratory values associated with the particular visit are selected using the principles described in Section 8.3.

If the MAS clinical signs and symptoms score (assessed using the VAS scale) or any individual laboratory parameter value is missing, rules for assessing CR at the visit of interest have been pre-defined as follows:

- Missing data for the parameters relevant to the assessment of CR will be imputed by the closest available value within the visit window following the principles in Section 8.3.
- No imputation will be applied if no value is available within the analysis visit window; parameter(s) will be viewed as missing and CR will not be achieved even if all other parameters are normal.

A patient is classified as ‘CR’ or ‘No CR’ at Week 8 efficacy assessment:

- ‘CR’ if criteria in Table 11 are fulfilled
- ‘No CR’ otherwise, i.e. if any of the criteria in Table 11 are not fulfilled or if any parameter value used to determine CR is missing after applying the imputation rules above.

A patient is classified as ‘CR’, ‘no CR’ or ‘Not evaluable’ at all visits except Week 8 efficacy assessment:

- ‘CR’ if all criteria in Table 11 are fulfilled
- ‘No CR’ if any of the criteria in Table 11 are not fulfilled
- ‘Not evaluable’ if all parameter values used to determine CR are missing even after applying the imputation rules described above.

Data from different dates may contribute to the assessment of response. Therefore, the date of response, or non-response, is defined as the latest date among the dates with data contributing to the derivation of the response variable for the particular visit.

Only data collected before re-treatment with emapalumab, will be used for emapalumab re-treated patients.

Table 11 Complete Response criteria definition cohort 1 and cohort 2

CR	Resolution of clinical signs and symptoms present at baseline*: The MAS clinical activity will be measured on a 10 cm VAS. Clinical signs will be considered as resolved if VAS is below or equal to 1/10. And Normalization of laboratory parameters relevant to MAS, as follows: • WBC > LLN • Platelet count > LLN • LDH < 1.5 ULN • ALT < 1.5 ULN • AST < 1.5 ULN • Fibrinogen> 100 mg/dL (1 g/L) • Ferritin levels decreased by at least 80 % from values at screening or baseline* (whichever is higher) or < 2000 ng/ml, whichever is lower.

Abbreviations: ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; CNS, Central nervous system; CR, Complete response;CSF, Cerebrospinal fluid; LLN, Lower limit of normal; MAS, Macrophage activation syndrome; ULN, Upper limit of normal;VAS, Visual analog scale; WBC, White blood cell.

* The Run-in baseline (see section 8.4.1) is used as baseline when determining CR/PR in the Run-in phase whereas the (Interventional) baseline (see section 8.4.1) is used as baseline when deriving CR/PR during the Interventional phase (i.e. used for primary efficacy endpoint assessment).

8.4.25 Partial response (PR)

Partial Response (PR) at a study visit is defined as patients who do not meet the criteria for CR but the PR criteria as per Table 12 are met for that particular study visit. PR is used for the definition of the overall response (Section 8.4.26).

The same pre-defined imputation rules as for CR will be applied if the MAS clinical signs and symptoms score (assessed using the VAS scale) or any individual laboratory parameter value is missing at that particular study visit.

A patient is classified as having 'CR', 'PR', 'No CR nor PR' or 'Not evaluable' at each visit based on the MAS clinical signs and symptoms score (assessed using the VAS scale) and individual laboratory parameter values associated with that particular visit:

- 'CR' if criteria for CR as per Table 11 are met for the visit.
- If 'No CR' then
    - 'PR' if criteria for CR not are met but the criteria for PR as per Table 12 are met for parameters not missing within the time window for the visit.
    - 'No CR nor PR' if criteria for PR as per Table 12 are not met and not all parameters are missing within the time window for the visit (e.g. a patient having a visit with only MAS clinical signs and symptoms score available or only two laboratory parameter values available will be considered as 'No CR nor PR').
- 'Not evaluable' if all parameter values used to determine CR/PR are missing even after applying the pre-defined imputation rules for the visit.

Only data collected before re-treatment with emapalumab will be used for emapalumab re-treated patients.

Table 12 Partial Response criteria definition cohort 1 and cohort 2

PR	Resolution or improvement in clinical signs and symptoms measured by the MAS clinical activity on the VAS. The patient will be classified as PR if he or she presents a VAS scale < 4/10. And Normalization of at least 3 of the abnormal baseline laboratory parameters relevant to MAS, as defined above.

8.4.26 Overall response (complete response [CR] or partial response [PR])

A patient is classified at each visit based on the classification of CR/PR as follows:

- 'Overall response' if CR or PR is achieved for the visit (Sections 8.4.24 and 8.4.25).
- 'No CR nor PR' if patient is classified as 'no CR nor PR' for the visit (Section 8.4.25).
- 'No CR, not applicable PR' for patients with no CR and less than 3 abnormal laboratory parameters at baseline. (For ferritin, there is no threshold for abnormality in the definition of response. Therefore, the inclusion criteria of ferritin > 684 ng/mL will be used to define abnormality at baseline.).
- 'Not evaluable' if all parameter values used to determine CR/PR are missing even after applying the pre-defined imputation rules for the visit.

Data from different dates may contribute to the assessment of response. Therefore, the date of response, or non-response, is defined as the latest date among the dates with data contributing to the derivation of the response variable for the particular visit.

Only data collected before re-treatment with emapalumab will be used for emapalumab re-treated patients..

8.4.27 Time to events

The times to events, including time to first CR, time to first overall response, time to first achievement of GCs tapering, time to death, and times to first normalization of parameters included in the CR definition, for the Interventional phase and Run-in phase (when applicable) will be defined as:

Time to event (day) = event date - start date + 1

The event date, start date and censored date are defined for each phase in the Table 13 below.

Only data collected before re-treatment with emapalumab will be used for emapalumab re-treated patients.

Table 13 Time to events description

Event	Dates	Run-in phase	Interventional phase
Time to first CR	*Start date*	GCs treatment start date	Emapalumab treatment start date
	Event date	First CR date	First CR date
	*Censored date**	Last study contact date	Last study contact date or Last study contact date before re-treatment with emapalumab (applicable for emapalumab re-treated patients)
Notes: -Event date will exclude Week 8 efficacy assessment visit -A visit with missing CR means that it is not known if the patient is CR or no CR at that visit. In case a patient has all CR results missing, the time to first CR is defined as missing. - Time to first CR analysis will not consider data collected after re-treatment with emapalumab (i.e. after MAS recurrence/reactivation).			
Time to first overall response (CR or PR)	*Start date*	GCs treatment start date	Emapalumab treatment start date
	Event date	First CR or PR date	First CR or PR date

	*Censored date**	Last study contact date	Last study contact date or Last study contact date before re-treatment with emapalumab (applicable for emapalumab re-treated patients)
Notes: -Event date will exclude Week 8 efficacy assessment visit -In case a patient has no assessment of overall response, i.e. all overall response results are missing, the time to first overall response is defined as missing. - Time to first overall response analysis will not consider data collected after re-treatment with emapalumab (i.e. after MAS recurrence/reactivation).			
Time to first achievement of GCs tapering	*Start date*	Not an endpoint/Not applicable	Emapalumab treatment start date
	Event time		Week of achievement of first GCs tapering
	*Censored date**		Last study participation date or last study contact date before re-treatment with emapalumab (applicable for emapalumab re-treated patients) converted in week
Notes: -Assessment of first GCs tapering will be based on the weekly average equivalent dose of prednisolone derived as defined in Section 8.4.23. The week of first achievement of GCs tapering will be selected as the time to event. -Censoring time (week) will be derived (Censored date – emapalumab treatment start date +1) /7 rounded up to a value with no decimals. -Event time will exclude EOT and EOS (see Section 8.4.23). -Time to first achievement of GCs tapering analysis will not consider data collected after re-treatment with emapalumab (i.e. after MAS recurrence/reactivation).			
Time to death	*Start date*	Not an endpoint/Not applicable	Emapalumab treatment start date
	Event date		Death date
	*Censored date**		Last study participation date
Times to first normalization	*Start date*	Not an exploratory endpoint/Not applicable	Emapalumab treatment start date
	Event date		First achievement date
	*Censored date**		Last study contact date or Last study contact date before re-treatment with emapalumab (applicable for emapalumab re-treated patients)

Notes :
-Time to first normalization will be derived for each criteria included in the complete response definition:
- MAS clinical activity ≤ 1
- White blood cell above LLN
- Platelet count above LLN
- Lactate dehydrogenase below 1.5 ULN
- Alanine transaminase below 1.5 ULN
- Aspartate aminotransferase below 1.5 ULN
- Fibrinogen higher than 100 mg/dL (1 g/L)
- Ferritin levels decreased by at least 80 % from values at screening or baseline (whichever is higher) or below 2000 ng/ml (2000 µg/L), whichever is lower.

-Event date will exclude Week 8 efficacy assessment visit
- Time to first normalization analysis will not consider data collected after re-treatment with emapalumab (i.e. after MAS recurrence/reactivation).

* In case the event does not occur.

8.4.28 MAS recurrence at any time after achievement of CR

Patients with a MAS recurrence at any time after achievement of CR will be derived from the AE CRF form, by search of specific terms in the adverse event description (e.g. “MAS” and “recurrence” or “recurred” or “relapse” or “reactivation” or “reactivated” or “flare”, or “new episode”) or if the patient was diagnosed with a MAS recurrence since the last visit (see eCRF). In the latter case, the date of the MAS recurrence will be compared with the date of CR. Based on this preliminary check, a medical review for each of the terms will be performed to confirm the status of MAS recurrence. Only data collected before re-treatment with emapalumab will be used for emapalumab re-treated patients.

8.4.29 Medication dates

Medication dates are captured from the CRF form. The below imputations of partial/missing medication start, and end dates will be performed for all medications reported on the eCRF and will be used to derive the equivalent dose of prednisolone or total daily dose of anakinra, canakinumab, ciclosporin, etoposide, methotrexate, tocilizumab, JAK inhibitors, and TNF inhibitors, and to derive medications duration.

- Partial medication start date
  - If only the day is missing, the day will be imputed to the 1st day of the corresponding month/year.
  - If only the day and month are missing, the day/month will be imputed to the 1st January of the corresponding year.
  - If, after imputation of partial medication start date, the medication start date < MAS diagnosis date, the date will be set to the MAS diagnosis date. This rule should be applied only if 1) only year part is available, and this year is equal to MAS diagnosis year or 2) Year and Month are available and these are equal to MAS diagnosis year/month. If there is a partial date, which can be shown to be on prior year/month compared to MAS diagnosis date, then the imputation rules will remain
- Partial medication end date

  - If only the day is missing, the day will be imputed to the last day of the corresponding month.
  - If only the day and month are missing, the day/month will be imputed to the 31st December of the corresponding year.
  - If, after imputation of partial medication end date, the medication end date > date of last contact, the date will be set to date of last contact.
- Missing medication start date will be set to the current MAS diagnosis date.
- Missing medication end date will be set to the last date of contact of the corresponding patient (regardless of "ongoing" ticked).
    - If, after imputation, the medication end date < study day - 365, the record of the medication will not be considered in tables.

Notes:

- If medication end date is available and ongoing flag is ticked, the medication end date will be used.
- As per CSP, previous treatment of the underlying disease must be collected in the last 12 months prior to enrollment.
- Derivation rules before first infusion of emapalumab (study day 1) or GCs treatment start for MAS (RI:study day 1) will be used for the creation of patient profiles (Section 15).

8.4.30 Total daily dose of anakinra, canakinumab, cyclosporin, etoposide, methotrexate, tocilizumab, JAK inhibitors, and TNF inhibitors

The total daily dose of anakinra, canakinumab, cyclosporin, etoposide, methotrexate, tocilizumab, JAK inhibitors, and TNF inhibitors will be defined for each patient using the following unit of measurement and formula:

- Anakinra, canakinumab, cyclosporin, methotrexate, and tocilizumab in mg/kg/day
- Etoposide in $mg/m^2/day$
- TNF inhibitors and JAK inhibitors in mg/kg/day

Total daily dose = Dose * Number of doses per day

where the number of doses per day will be derived by phase (Run-in phase and Interventional phase) using the same approach for the calculation of the equivalent dose of prednisolone (Table 10).

8.4.31 Prior and Concomitant Medications

Prior and concomitant medications for the Run-in phase and the Interventional phase are defined as follows:

- Medications that start prior to GCs treatment for MAS start/first infusion of emapalumab will be considered prior medications for the Run-in phase/Interventional phase, respectively, whether or not they were stopped prior to the first dose of treatment.
- Any medications that are continuing or start post GCs treatment for MAS/first infusion of emapalumab will be considered concomitant for the Run-in phase/Interventional phase, respectively.
- Medications that start prior to first dose of GCs treatment for MAS/first infusion of emapalumab and continue post GCs treatment for MAS start/first infusion of emapalumab will be considered both prior and concomitant for the Run-in phase/Interventional phase, respectively.
- If the start/stop dates of a medication are partially or completely missing, then the imputation rules defined in section 8.4.29 will be applied.

8.4.32 Patients underwent wash-out of biologics before study entry

Patients who have undergone wash-out of biologics before study entry (i.e. Interventional phase) are defined as patients who had not taken any of the below biologics prior start of treatment with emapalumab, more specifically during 5 half-lives of the biologic prior to first infusion of emapalumab (study day 1).

- Anakinra: 5 half-lives=1 day (one half-life ~ 4 hours).
- Canakinumab: 5 half-lives=115 days (one half-life ~ 23 days).
- Tocilizumab: 5 half-lives=80 days (one half-life ~ 16 days).

Note: Minimum half-lives were used according to the package insert, in consideration of the fact that MAS is characterized by hyperinflammation impacting on the half-life of the biologic.

8.4.33 Patients with lung or/and hepatic involvement at baseline of the Interventional phase

Patients with organ involvement (lung and/or hepatic involvements) at baseline of the Interventional phase are derived from the eCRF page “MAS Clinical Signs and Symptoms” by selecting MAS organ involvement: lung involvement (interstitial lung disease) and/or hepatic involvement.

8.4.34 Patients with dialysis/hemofiltration at screening

Patients with dialysis or hemofiltration at screening are defined as patients with Ultrafiltration/dialysis equals to “Yes” from the eCRF page “MAS Clinical Signs and Symptoms” at screening.

8.4.35 Patients with concomitant G-CSF treatment

Patients who received G-CSF treatment defined as patients with ATC 4 level L03AA (Colony stimulating factors) medications taken after emapalumab treatment start and up to Week 8 efficacy assessment, i.e., SD61

8.4.36 Withdrawal from the study due to lack of efficacy

Patients who withdrew from the study due to lack of efficacy are derived from the End of Study eCRF form, from the tick box "Lack of Efficacy" in the primary reason for study discontinuation field. Only data collected during the first treatment with emapalumab will be used for emapalumab re-treated patients.

8.4.37 Patients with concomitant use of biologics and other targeted therapies during the long term follow-up period

Patients with concomitant use of biologics and other targeted therapies during the long-term follow-up period are defined as patients from Cohort 1 who receive e.g., tocilizumab, canakinumab, TNF inhibitors, or JAK inhibitors (as approved in the applicable country for the treatment of the underlying disease [sJIA or AOSD], non-exhaustive list) 44 days after the last dose of emapalumab (i.e., after 2 half-lives of emapalumab have elapsed) but not before Week 8 visit (i.e., SD61 being the upper limit for the visit windows to assess complete response at Week 8).

Belimumab is available for the treatment of SLE. When used as a treatment for SLE, belimumab can be continued if administered at a stable dose as per Section 7.2.8.5 of the CSP. Therefore, patients with concomitant use of biologics during the long-term follow-up period will not be defined for Cohort 2.

As new drugs for the treatment of the underlying diseases could be made available in different countries during the study, a final list should be provided before database lock or cut-off dates by the clinical science team.

Considering the long-term follow-up period after emapalumab re-treatment, only the follow-up period between emapalumab treatment and Re-treatment is considered when searching for concomitant use of biologics.

9 Patient disposition

For the Run-in phase,

- Patients screened.
- Patients who failed screening.

- Reason for screen failure.
- Patients enrolled.
- Status at the end of the Run-in phase.
- Reason for Run-in phase discontinuation.

will be summarized (number and percentage) for each cohort and overall on the Run-in phase analysis set, except for the number and percentage of screened patients, which will be based on the All Screened analysis set.

In addition, the Run-in phase duration (weeks), as defined in Section 8.4.13, will be summarized as continuous and categorical (<1 week, 1 to<4 weeks, 4 to<8 weeks, ≥ 8 weeks) variables by cohort and overall.

For the Interventional phase,

- Patients enrolled in the Run-in phase.
- Patients screened.
- Patients who failed screening.
- Reason for screen failure.
- Patients enrolled.
- Patients not treated with emapalumab.
- Patients treated with emapalumab.
- Patients who completed treatment with emapalumab as per protocol.
- Patients who prematurely discontinued emapalumab treatment.
- Primary reason for emapalumab discontinuation.
- Patients re-treated with emapalumab.
- Number of re-treated periods
- Patients who completed re-treatment with emapalumab as per protocol.
- Patients who prematurely discontinued emapalumab re-treatment.
- Primary reason for re-treatment with emapalumab discontinuation.
- Patients who completed the Interventional phase.
- Patients who prematurely discontinued the Interventional phase.
- Primary reason for Interventional phase discontinuation.

will be presented (number and percentage) for each cohort and overall on the All Treated analysis set, except for the number and percentage of screened patients, patients not receiving treatment and patients treated, which will be based on the All Screened analysis set.

In addition, the Interventional phase duration and study duration (weeks), as defined in Section 8.4.13, will be summarized as continuous and categorical (<4 weeks, 4 to<8 weeks, 8 to<24 weeks, ≥24 weeks) variables by cohort and overall on the All Treated analysis set.

All screen failure data, including reason for screen failure will be listed for the Run-in and Interventional phases. Run-in and Interventional phases completion data, including reason for discontinuation phase will be listed respectively for the Run-in phase analysis set and All Treated analysis set. The listing on the Interventional phase will include emapalumab completion data and the reason for emapalumab discontinuation.

The number and percentage of patients in the analysis sets, defined in Section 7, will be summarized on the All Screened analysis set. The reasons for exclusions from the analysis sets will also be listed.

10 Protocol deviations

The frequency and percentage of patients with at least one important protocol deviations related to the study conduct (i.e. assessment performed from a clinical operation perspective) and the number of deviations by category as well as those occurring as a result of COVID-19 (Yes/No/Overall) will be presented in separate summary tables on the All Treated analysis set and the Run-in phase analysis set.

Listings of all protocol deviations will be presented by patient as follows:

- All deviations including flags of important deviations (i.e. related to study conduct), deviations related to statistical analysis (i.e., leading to exclusion of a patient from the evaluable analysis set) and deviations due to COVID-19 will be produced on the All Treated analysis set.
- All deviations including flags on important deviations (i.e. related to study conduct) and deviations due to COVID-19 will be produced on the Run-in phase analysis set.

11 Demographics and baseline characteristics

11.1 Demographics

Demographic characteristics will be summarized for the Run-in phase analysis set, All Treated analysis set and the Evaluable analysis set:

- Age (years) and age categories (described below) at respective informed consent (Run-in phase informed consent for the Run-in phase analysis set and Interventional phase informed consent for the All Treated analysis set and the Evaluable analysis set).
    - <2 years, 2 to<12 years, 12 to<17 years, <17 years, ≥17 years.
    - <2 years, 2 to<17 years, ≥17 years.

  - Neonates (birth to<1 month), infants (1 month to<2 years), children (2 to<12years), adolescents (12 to<17 years), 17 to<65 years, 65 to<85 years, ≥85 years.

- Sex (Male/Female).
- Ethnicity (Hispanic or Latino/not Hispanic or Latino).
- Race as defined in the eCRF (if allowed locally).
- Country of investigational site.
- Weight (kg) at baseline (Section 8.4.1).
- Height (cm) at baseline (Section 8.4.1).

Covariates of subgroup analyses, listed below, will be summarized

- Age categories (<2 years old, 2 to<12 years old, 12 to<17 years old, <17 years old, ≥17 years old) at Interventional phase informed consent.
- Sex (Male/Female).
- Race categories (White, Asian, Black or African American, Other [including Other, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander], Not reported [including unknown, not reported, not collected and missing]).
- Region (North America [including US and Canada], EU, Japan, China, Russia).
- Patients who have undergone wash-out of biologics before entry in the Interventional phase (defined in Section 8.4.32).
- Patients with lung or/and hepatic involvements at baseline of the Interventional phase (defined in Section 8.4.33).
- Patients with concomitant G-CSF treatment up to Week 8 efficacy assessment (defined in Section 8.4.35 8.4.34).
- Patients with dialysis/hemofiltration at screening (defined in Section 8.4.34).
- Patients with use of concomitant biologics during the long-term follow-up period (defined in Section 8.4.37).
- Patients with Herpes zoster virus prophylaxis treatments (defined in Section 8.4.8).

Demographic characteristics data, including covariates for subgroup analyses when applicable, will be listed for patients in the Run-in phase analysis set and the All Treated analysis set.

11.2 Underlying disease and MAS history

Underlying disease history and underlying disease assessment data will be listed for patients in the Run-in phase analysis set and the All Treated analysis set and the following information will be summarized:

- Underlying disease (sJIA, AOSD, SLE).
- Age (years) at onset of the underlying disease symptoms.
- Confirmed diagnosis (Yes/No).
  Note: For highly presumed sJIA patients, patients with highly presumed sJIA not confirmed, will be displayed under "No".
- Age (years) at diagnosis.
- Inactive disease during the last 12 months (Yes/No).
- Any underlying disease treatment(s) within the last 12 months (Yes/No).
- Any underlying disease flare(s) within the last 12 months (Yes/No).
- Annual underlying disease flare rate (over the last 12 months prior study entry). The flare rate over the last 12 months will be taken directly from CRF. Annual flare rate during study will be calculated as number of events from time period starting from Interventional phase IC date and ending Interventional IC date +365 days. Patients with time interval shorter than 12 months and patients <1 year old at the IC date will be set to missing value.
- Annual underlying disease flare rate during the study as per investigator assessment (i.e. Underlying disease assessment form).

MAS characteristics, including MAS history data, will be listed for patients in the Run-in phase analysis set and the All Treated analysis set, and the following information will be summarized:

- Type of MAS at screening (Classic MAS, Relapsing/recurring MAS, MAS diagnosed at onset of the underlying disease).
- Annual MAS rate (over the last 12 months) in patients with MAS recurrence (i.e. type of MAS at screening equals to MAS recurrence).
- Annual MAS rate during the study (considering information from the AE form as described in Section 8.4.28 irrespective of the CR achievement); only applicable for the Interventional phase (i.e. All Treated analysis set).
- Duration (days) of last MAS episode in patients with MAS recurrence (i.e. type of MAS at screening equals to MAS recurrence).
- Age (years) at diagnosis of the current MAS episode.
- Receiving treatment(s) for the current MAS episode (Yes/No)
- Failing treatment with high GCs as per standard of care at screening (Yes/No).
- Failing other treatments than GCs at screening (Yes/No).

Prophylaxis treatment for Herpes zoster virus data will be listed on the All Treated analysis set, and the following information will be summarized:

- Vaccination for Herpes zoster before study entry (Yes/No).

Underlying disease, MAS characteristics and vaccination for Herpes zoster data will also be summarized on the Evaluable analysis set.

Primary HLH genetic perforin level and degranulation tests data will be listed on the Run-in phase analysis set and the All Treated analysis set.

11.3 Medical history

All medical history data will be coded using the latest version of Medical Dictionary for Regulatory Activities (MedDRA).

Summary tables will be prepared by system organ class (SOC) and preferred term (PT) for each cohort and in total, separately on the Run-in phase analysis set and the All Treated analysis set. These tables will include number and percentages of patients and will be sorted by descending frequency SOC of the total column. Within a SOC, PTs are sorted in decreasing frequency within the total column. A patient will only be counted once within a particular class even if he/she has multiple conditions/symptoms. Medical history data will be listed on the Run-in phase analysis set and the All Treated analysis set.

11.4 Prior and concomitant medication, and procedures

All prior and concomitant medications and procedures will be coded using the latest version of World Health Organization drug dictionary (WHO-DD).

Summary tables, presenting the number and percentage of patients by Anatomical Therapeutical Class (ATC) level 4 and PT for each cohort and in total, sorted in decreasing frequency of the ATC level 4 total column and decreasing PT total column (within ATC level 4), will be produced based on:

- The Run-in phase analysis set on:
    - Prior/Concomitant/All medications
    - Prior/Concomitant/All medications related to MAS
    - Prior/Concomitant/All medications related to Underlying Condition (AOSD/sJIA/SLE)
    - Prior/Concomitant/All medications related to Flare of Underlying Condition
    - Prior/Concomitant/All medications related to Other (including Other Medical History, Adverse event, Herpes zoster virus Prophylaxis, and Other)
- The All Treated analysis set on:
    - Prior/Concomitant/All medications
    - Prior/Concomitant/All medications related to MAS
    - Prior/Concomitant (Before/After Week 8/overall)/All medications related to Underlying Condition (AOSD/sJIA/SLE)
    - Prior/Concomitant/All medications related to Flare of Underlying Condition
    - Prior/Concomitant/All medications related to Other (including Other Medical History, Adverse events, Herpes zoster virus Prophylaxis, and Other)

Prior and concomitant medications are defined in Section 8.4.31.

If a patient reports taking 2 drugs belonging to the same class, he/she will only be counted once within that class.

All prior and concomitant medications data from the Run-in and Interventional phases will be presented in listings including prior/concomitant assessments on each phase, reason for use category (MAS, Underlying condition…), ATC levels 2 and 4, and PT, on the Run-in phase analysis set and the All Treated analysis set.

All procedures data will be listed on the Run-in phase analysis set and the All Treated analysis set.

12 Treatment compliance

Emapalumab will be administered as intravenous infusion at the site under medical supervision, during the study; therefore, patient compliance will not be presented.

Emapalumab infusions for the Interventional Phase (date of administration, start and stop time,prescribed dose and total dose infused, infusion rate, infusion interruptions along with reasons, change in dosing regimen along with reasons, new start and stop time, and new rate of infusion, and whether the infusion was completed as planned) will be listed as described in Section 14.1.

13 Efficacy analyses

All efficacy analyses, will not consider data collected after re-treatment with emapalumab (i.e. after MAS recurrence/reactivation) except for the survival time analysis (see Section 8.4.27).

Efficacy analyses will be performed for each cohort separately (not overall) on the All Treated analysis set, unless otherwise specified.

13.1 Primary efficacy endpoint

The primary objective of the study will be evaluated on the All Treated analysis set, for cohort 1 only, by statistically testing the null hypothesis (H_0) versus the alternative hypothesis (H_1) defined as follows:

H_0: $p \leq 0.4$ H_1: $p > 0.4$, where p is the proportion of patients with CR (defined in Section 8.4.24) in cohort 1.

The primary endpoint, CR at Week 8 efficacy assessment after first administration of emapalumab, will be analyzed using an exact binomial test for cohort 1 only.

For cohort 1:

- At the first interim analysis: if a two-sided 99 % CI is above the alternative hypothesis (i.e., CR rate > 40 %), the null hypothesis (i.e., CR rate ≤ 40 %) will be rejected.

- At the final efficacy analysis (second interim analysis and final analysis) (if no stop for efficacy at the interim analysis): if a two-sided 96 % CI is above the alternative hypothesis (i.e. CR rate > 40 %), the null hypothesis (i.e., CR rate ≤ 40 %) will be rejected.

The proportion CR will be calculated as the number of patients achieving CR divided by the number of patients in the population assessed. The number and percentage of patients achieving CR, the two-sided Clopper-Pearson CI for the proportion CR in cohort 1 (99 % CI at the interim analysis and 96 % at the final analysis) together with the associated p-value for the one-sided exact binomial test will be presented.

CR at Week 8 efficacy assessment data will be listed by patient on the All Treated analysis set.

See below example of SAS code for confidence interval and p-value of each cohort:

```
proc freq data=DATASET (where=(paramcd="PARAMETER")) ;
    tables AVAL / exact binomial (level=2) alpha=0.01 /* e.g. for 99% confidence
interval at the time of the 1st interim analysis, to be updated to 0.04 once all
patients will be enrolled */;
    exact binomial;
run;
```

13.1.1 Supplementary analysis of the primary endpoint

The primary analysis will be conducted using the Evaluable analysis set as a supplementary analysis to evaluate the robustness of the analysis of the primary endpoint.

13.2 Secondary endpoints

All secondary efficacy endpoints are viewed as exploratory and therefore no formal testing of secondary endpoints will be undertaken.

13.2.1 Glucocorticoids tapering

For each of the definitions of GCs tapering as defined in Section 8.4.23, the number, percentage and two-sided 95 % Clopper-Pearson CI of the percentage of patients achieving GCs tapering during the Interventional phase will be presented for each cohort

- at any time during the study.
- at Week 4 (study day 22 to 28).
- at Week 8 (study day 50 to 56).
- at Week 12 (study day 78 to 84).
- at Week 24 (study day 162 to 168).
- at Week 52 (study day 358 to 364).
- at EOT (Last week prior to EOT date).
- and at EOS (Last week prior to EOS visit date).

In addition, weekly average prednisolone equivalent daily dose (see Section 8.4.22 for the definition of equivalent daily dose of prednisolone) in mg/kg/day will be derived for the periods described in Section 8.4.23 including EOT, EOS and presented by cohort for the Interventional phase in the All Treated analysis set as absolute value and percent change from weekly pre-infusion of emapalumab over time using descriptive statistics as described in Section 8 for continuous variables.

Glucocorticoid tapering data, including level of weekly average prednisolone equivalent daily dose, will be listed by patient on the All Treated analysis set.

13.2.2 Time to achieve GCs tapering

The time to first achievement of GCs tapering is defined in Section 8.4.27. For each definition of GCs tapering, the number and percentage of patients experiencing the event as well as patients censored will be summarized. Kaplan-Meier (KM) estimates of median time to first achievement of GCs tapering and corresponding 95 % CI will be provided along with the 25th and 75th percentiles. In addition, the percentage of patients having achieved GCs tapering at Week 8, Week 24 and Week 52 (corresponding to study days 56, 168 and 365 when applicable) will be estimated together with corresponding two-sided 95 % CI using the KM estimator. An additional table presenting the estimate rate, number of patients at risk and number of censored patients by time will be produced for each definition of GCs tapering.

Time to first achievement of GCs tapering data will be listed by patient on the All Treated analysis set.

For these analyses, KM failure curve will be provided together with number of patients at risk through time.

See below SAS codes:

```
ODS OUTPUT QUARTILES=QUARTILES ; /* KM estimates of median time as well as 25% and 75%
percentiles */
PROC LIFETEST DATA= DATASET (where=(paramcd="PARAMETER"))
       OUTSURV=TIMELIST_ESTIMATES /* Cumulative incidence at specific study days  */
       BANDMINTIME=0

       TIMELIST =8 24 52 /* When Study days are applicable (e.g. Time to first CR,
Time to first overall response…), replace by TIMELIST =56 168 365 */
       REDUCEOUT /* Specifies that only INTERVAL= or TIMELIST= observations be listed
in the OUTSURV= data set */
       STDERR;
       TIME AVAL*CNSR(1);
RUN; QUIT;


ODS OUTPUT PRODUCTLIMITESTIMATES=KM_ESTIMATES; /* Estimate rate, number of patients at
risk, … */
PROC LIFETEST DATA= DATASET (where=(paramcd="PARAMETER"))
       OUTSURV=SURVIVAL
       BANDMINTIME=0

       STDERR;
```

```
      TIME AVAL*CNSR(1);
RUN; QUIT;
```

13.2.3 Achievement of weekly average prednisolone equivalent daily dose ≤0.5 mg/kg/day

The number, percentage and two-sided 95 % Clopper-Pearson CI of patients achieving a weekly average prednisolone equivalent daily dose ≤ 0.5 mg/kg/day

- at any time during the study
- at Week 4 (study day 22 to 28)
- at Week 8 (study day 50 to 56)
- at Week 12 (study day 78 to 84)
- at Week 24 (study day 162 et 168)
- at Week 52 (study day 358 to 364)
- at EOT (Last week prior to EOT date)
- and at EOS (Last week prior to EOS visit date)

will be presented by cohort using data collected during the Interventional phase on the All treated analysis set.

13.2.4 Time to first achievement of weekly average prednisolone equivalent daily dose ≤0.5 mg/kg/day

The time to first achievement of weekly average prednisolone equivalent daily dose ≤0.5 mg/kg/day, defined in Section 8.4.27 as the time from the date of first emapalumab infusion to the first achievement of GCs tapering (i.e., weekly average prednisolone equivalent daily dose ≤0.5 mg/kg/day), will be analyzed using time-to-event methodology in the same way as the time to first achievement of GCs tapering described in Section 13.2.2.

13.2.5 Achievement of weekly average prednisolone equivalent daily dose ≤0.2 mg/kg/day

The number, percentage and two-sided 95 % Clopper-Pearson CI of patients achieving a weekly average prednisolone equivalent daily dose ≤0.2 mg/kg/day

- at any time during the study
- at Week 4 (study day 22 to 28)
- at Week 8 (study day 50 to 56)
- at Week 12 (study day 78 to 84)
- at Week 24 (study day 162 et 168)
- at Week 52 (study day 358 to 364)
- at EOT (Last week prior to EOT date)
- and at EOS (Last week prior to EOS visit date)

will be presented by cohort using data collected during the Interventional phase on the All treated analysis set.

13.2.6 Time to first achievement of weekly average prednisolone equivalent daily dose ≤0.2 mg/kg/day

The time to first achievement of weekly average prednisolone equivalent daily dose ≤0.2 mg/kg/day, defined in Section 8.4.27 as the time from the date of first emapalumab infusion to the first achievement of GCs tapering (i.e., weekly average prednisolone equivalent daily dose ≤0.2 mg/kg/day), will be analyzed using time-to-event methodology in the same way as the time to first achievement of GCs tapering described in Section 13.2.2.

13.2.7 Time to first normalization of each parameter included in the Complete Response definition

The time to first normalization is defined in Section 8.4.27. For each criteria included in the complete response definition (MAS clinical activity score ≤1; White blood cell above LLN; Platelet count above LLN; Lactate dehydrogenase below 1.5 ULN; Alanine transaminase below 1.5 ULN; Aspartate aminotransferase below 1.5 ULN; Fibrinogen higher than 100 mg/dL [1 g/L]; Ferritin levels decreased by at least 80 % from values at screening or baseline [whichever is higher] or below 2000 ng/ml [2000 µg/L], whichever is lower), the number and percentage of patients experiencing the event as well as patients censored will be summarized by cohort on the All Treated analysis set. KM estimates of median time to first normalization and corresponding 95 % CI will be provided along with the 25th and 75th percentiles. An additional table presenting the estimate rate, number of patients at risk and number of censored patients by study day will be produced.

For these analyses, KM failure curve will be provided together with number of patients at risk through time.

The time to first normalization data of each criterion of the CR will be listed by patient on the All Treated analysis set.

13.2.8 Time to first CR

The time to first CR, defined as the time from the date of first emapalumab infusion to the first achievement of CR (Section 8.4.27), will be analyzed using time-to-event methodology in the same way as the time to first achievement of GCs tapering as described in Section 13.2.2.

In addition, this analysis will be performed using the Run-in phase data on the Run-in phase analysis set (only the percentage of patients achieving CR at Week 8 [study day 56] will be presented using KM estimator, i.e. no KM failure curve nor estimate rate over time).

13.2.9 Overall response (CR or PR)

The number, percentage and two-sided 95 % Clopper-Pearson CI of patients achieving an overall response (CR or PR) will be provided by visit.

In addition, assessments of the individual criteria of response will be presented for each visit (including Week 8 efficacy assessment) in a data listing using the All Treated analysis set:

- MAS clinical activity score according to the investigator (measured via the VAS scale ranging from 0 to 10 by 0.5 cm): 1-10.
- White blood cell count (WBC) above the lower limit of normal (LLN): Yes/No.
- Platelet count above the LLN: Yes/No.
- Lactate dehydrogenase (LDH) below 1.5 upper limit of normal (ULN): Yes/No.
- Alanine aminotransferase (ALT) below 1.5 ULN: Yes/No.
- Aspartate aminotransferase (AST) below 1.5 ULN: Yes/No.
- Fibrinogen higher than 100 mg/dL (1 g/L): Yes/No.
- Ferritin level decreased by at least 80 % from values at screening or baseline (whichever is higher; e.g. post-baseline value <0.2 × highest ferritin value prior to the first emapalumab infusion) or below 2000 ng/mL (2000 µg/L), whichever is lower: Yes/No.
- MAS status: CR/PR/No CR nor PR/Not evaluable.

Similar table and listing, as described above, will be produced for the Run-in phase data on the Run-in phase analysis set.

13.2.10 Time to first overall response

The time to first overall response, defined in Section 8.4.27 as the time from the date of first emapalumab infusion to the first achievement of CR or PR, will be analyzed using time-to-event methodology in the same way as the time to first achievement of GCs tapering as described in Section 13.2.2.

In addition, this analysis will be performed using the Run-in phase data on the Run-in phase analysis set (only the percentage of patients achieving overall response at Week 8 [study day 56] will be presented using KM estimator, i.e. no KM failure curve nor estimate rate over time).

13.2.11 MAS recurrence at any time after achievement of CR

The number, percentage and two-sided 95 % Clopper-Pearson CI of patients who achieved CR at any time during the study and with MAS recurrence at any time after achievement of CR (defined

in Section 8.4.28) will be presented in the subset of the All Treated analysis set who achieved CR at any time during the study.

MAS recurrence at any time after achievement of CR data will be listed by patient on the All Treated analysis set.

13.2.12 Withdrawal from the study due to lack of response

The number, percentage and two-sided 95 % Clopper-Pearson CI of the percentage of patients who withdraw from the study due to "lack of efficacy" (i.e. primary reason for study discontinuation, see Section 8.4.36) will be presented on the All Treated analysis set.

Withdrawal from study due to lack of response data will be listed by patient on the All Treated analysis set.

13.2.13 Survival time

Survival time is defined as the time from the date of first infusion of emapalumab to the date of death from any cause (Section 8.4.27), and will be analyzed using time-to-event methodology in the same way as the time to first achievement of GC tapering as described in Section 13.2.2. In contrast to the other time-to-event endpoints, the results will be presented in terms of survival time and survival rate instead of time to event and event rate (e.g. KM curve instead of KM failure curve).

13.3 Exploratory endpoints

13.4 Subgroup analyses

Subgroup efficacy analysis of the Interventional phase, to explore the uniformity of emapalumab treatment effect across subgroups, will be conducted for the following subgroups:

- Sex (Male, Female).
- Age at informed consent categorized into: (<2 years, 2 to<12 years, 12 to<17 years, <17 years and ≥17 years).
- Race (White, Asian, Black or African American and Other [including Other, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander]).
  Note: Multiple races could be selected. In case a patient is White/Other, then a "White/Other" subgroup will be created.
- Geographical regions (North America [including US and Canada], EU [including UK], Japan, China, Russia).
- Patients who have undergone wash-out of biologics before study entry (Yes, No) as defined in Section 8.4.32.
- Patients with organ involvement (lung and/or hepatic involvements) at baseline of the Interventional phase (Yes, No) as defined in Section 8.4.33.
- Patients with concomitant G-CSF treatment (Yes, No) as defined in Section 8.4.35..
- Patients with dialysis/hemofiltration at screening (Yes, No) as defined in Section 8.4.34.
- Patients with use of concomitant biologics during the long-term follow-up period (Yes/No) as defined in Section 8.4.37.

The subgroups for each of the (primary and secondary) efficacy endpoints will be analyzed in the same way as the corresponding original analysis (as defined in Section 13.1 and Section 13.2) for each subgroup, with the following exceptions:

- No significance tests are performed.
- Subgroup analysis may be performed at the time of the interim.
- Two-sided 95 % CI (instead of 99 % CI in the interim analysis and 96 % CI in the final analysis for the primary efficacy endpoint).
- Time-to-event endpoints are reported as Kaplan Meier curves with estimate of median survival and two-sided 95 % CI by cohort (no other analyses are reported for the time-to-event endpoints or estimate rate over time).

The analyses will be based on the All Treated analysis set. If a subgroup contains less than 3 patients, only patient counts will be presented for that subgroup, i.e. no summarized data (e.g. mean, standard deviation, confidence intervals) will be reported for such subgroups.

Note: Patients with missing, unknown, not collected or not reported information about subgroup will not be part of the analysis of that subgroup.

The tables concerned will be flagged in the list of tables/figures (

Appendix 3 - List of Tables, Appendix 5 - List of Figures).

14 Safety analyses

All data relating to safety will be summarized using descriptive statistics by cohort and in total based on the Run-in phase analysis set and the All Treated analysis set, as appropriate.

The Run-in phase analysis set will be used for the analysis of the Run-in phase and the All treated analysis set for will be used for the analysis of the Interventional phase.

Safety patient-level data will be displayed in listings: both Run-in phase data and Interventional phase data will be presented on the Run-in phase analysis set and the All Treated analysis set (i.e. complete overview for patients), unless otherwise specified.

14.1 Emapalumab exposure and re-exposure

Emapalumab exposure and re-exposure will be presented separately on the All Treated analysis set. Emapalumab exposure will include first treatment with emapalumab. Emapalumab re-exposure (second treatment with emapalumab) will include data collected after re-treatment with emapalumab (i.e. after MAS recurrence/reactivation) during the follow-up period.

The following summaries of emapalumab exposure and re-exposure will be provided:

- Number of doses received will be summarized as a continuous variable and by category (<3 doses; ≥3 and <11 doses; ≥11 doses)
- Maximum dose prescribed and administered will be summarized by category ([redacted]
- Minimum dose prescribed and administered will be summarized by category [redacted]
- Cumulative prescribed and administered doses in mg/kg will be summarized as continuous variables
- Average prescribed and administered doses in mg/kg will be summarized as continuous variables
- Emapalumab treatment duration will be summarized as a continuous variable in days and by category in weeks (<1 week; 1 to<4 weeks; 4 to<8 weeks; ≥8 weeks)
- Number of patients with at least one dose regimen modification
- Type of dose regimen modification
    - Number of patients with at least one change in dosing interval (Interval reduced/Interval prolongated)
    - Number of patients with at least one change to study drug dose (Dose increased/Dose decreased)
- Reason for dose regimen modification

- Number of patients with at least one “abnormal laboratory parameters”
- Number of patients with at least one “abnormal clinical parameters”
- Number of patients with at least one “adverse events”
- Number of patients with at least one “other”

The time (days) between two doses of the first treatment with emapalumab will be summarized for each dose from the 2nd dose to the last infused dose; e.g. for the 2nd dose, duration in days between 1st dose (using infusion start date; date of $dose_n$ – date of $dose_{n-1}$) and 2nd dose (using infusion start date), for the 3rd dose, duration in days between 2nd dose and 3rd dose, … will be presented. The time (days) between two doses during the re-treatment with emapalumab will also be summarized for each dose from the 2nd dose to the last infused dose on the patients re-treated with emapalumab (subset of the All Treated analysis set).

Emapalumab administration, infusion details (for both treatment periods in case a patient is re-treated with emapalumab during the follow-up period), exposure and re-exposure data will be listed by patient.

14.2 GCs exposure

GCs exposure will be presented on the Run-in phase analysis set (presenting data collected during the Run-in phase, see Section 8.4.10 for Run-in phase duration) and the All treated analysis set (presenting data collected during the Run-in phase, the Interventional phase, and during both phases if applicable, see Section 8.4.10).

The following summaries will be provided:

<u>For the Run-in phase, Interventional phase and overall separately</u>

- Average daily dose (expressed as equivalent dose of prednisolone in mg/kg/day) will be summarized as a continuous variable.
- Maximum equivalent dose of prednisolone (mg/kg/day) will be summarized as continuous and categorical (≤1, >1 to<10, ≥10 to<20, ≥20 to<30, ≥30) variables.
- GCs treatment duration, defined in Section 8.4.14, will be summarized as a continuous variable in days and by category in weeks (<1 week; 1 to<4 weeks; 4 to<8 weeks; ≥8 weeks).
- Number of patients with at least one dose increased due to the underlying disease flare.

  Note: using primary reason for stopping medication from the eCRF form “Prior/Concomitant Medications - Including Glucocorticoids”).
- Number of patients with at least one tapering dose reduction.

  Note: using primary reason for stopping medication from the eCRF form “Prior/Concomitant Medications - Including Glucocorticoids”).
- Number of patients with at least one inefficacy/inadequate response of MAS.

Note: using primary reason for stopping medication from the eCRF form "Prior/Concomitant Medications - Including Glucocorticoids").

For the Interventional phase only

- Number of patients with an average equivalent daily dose of prednisolone ≤1 mg/kg/day at the end of study (defined in Sections 8.4.22 and 8.4.23).
- Number of patients with an average equivalent daily dose of prednisolone ≤0.5 mg/kg/day at the end of study (defined in Sections 8.4.22 and 8.4.23).
- Number of patients with an average equivalent daily dose of prednisolone ≤0.2 mg/kg/day at the end of study (defined in Sections 8.4.22 and 8.4.23).

For the Run-in phase only

- Cumulative GCs dose from MAS diagnosis to first overall response (only applicable for the Run-in phase; Section 8.4.9).

GCs exposure data will be listed by patient on the Run-in phase analysis set (presenting GCs data taken during the Run-in phase) and the All treated analysis set (presenting GCs data taken during each phase and overall).

14.3 Adverse events

All AEs will be coded using the latest version of MedDRA.

A treatment emergent AE is any AE temporally associated with the use of study treatment (from study treatment [i.e., emapalumab] initiation) whether or not considered by the Investigator as related to the study treatment. Derivation of TEAEs are described in section 8.4.15.

For the Run-in phase:

All AEs with a start date up to the day before the date of Interventional phase informed consent will be summarized.

A summary table will be provided that includes number and percentage of patients with at least one event, and number of events for the following:

- All AEs
- All serious AEs
- All non-serious AEs
- All AEs leading to death

In addition, summary table of all AEs categorized by SOC and PT and presenting the number, percentage of patients, and the number of events will be presented.
All AEs recorded (from Run-in and Interventional phases) on the CRFs will be listed.

For the Interventional phase:

All AEs with a start date from the date of Interventional phase informed consent will be flagged under the Interventional phase.

A summary table that includes number and percentage of patients with at least one event, and number of events, for the following will be provided:

- All TEAEs
- TEAEs related to study drug (emapalumab)
- Maximum severity of TEAEs (Mild, Moderate, Severe)
- TEAEs leading to emapalumab withdrawal
- TEAEs resulting in death
- Serious TEAEs
- Serious TEAEs related to emapalumab
- Non-serious TEAEs
- IRRs
- Serious IRRs
- Treatment-emergent infections
- Maximum severity of Treatment-emergent infections (Mild, Moderate, Severe).

In addition, summary tables categorized by SOC and PT showing number and percentage of patients with at least one event, and number of events, will be provided for the following:

- Any TEAE
- Any TEAE by relationship to emapalumab
- Any TEAE by maximum severity
- Any IRR
- Any treatment-emergent infections
- Any non-serious TEAE

The tables categorized by SOC and PT will be presented by SOC in descending order of total frequency of patients and by PT, within SOC, in descending order of total frequency of patients. If the number of patients is the same within one PT or SOC, then these PTs or SOCs will be sorted by descending number of events (if applicable), then alphabetically, (PTs within the SOC).
In the case of multiple occurrences of the same event in the same patient, each patient will only be counted once for each PT/SOC/overall. However, all multiple occurrences will be included in the number of events.

All AEs (from Run-in and Interventional phases) recorded on the CRFs will be listed. In addition, separate by-patient listings will be created on all IRR and infections.

14.3.1 Serious adverse events

For the Run-in phase, summary of the number of events and number and percentage of patients reporting any serious AE (with a start date up to the day before the date of Interventional phase informed consent) will be tabulated by SOC and PT. All SAEs will be presented in a listing.

For the Interventional phase, summaries of the number of events and number and percentage of patients reporting:

- Any serious TEAE
- Any serious TEAE related to emapalumab

will be tabulated by SOC and PT.

All serious AEs (from Run-in and Interventional phases) will be presented in a listing.

14.3.2 Adverse events leading to emapalumab withdrawal

A summary of the number of events and number and percentage of patients reporting any TEAE leading to study drug (emapalumab) withdrawal categorized by SOC and PT will be tabulated on the All Treated analysis set.

All AEs leading to study drug withdrawal will be presented in a separate listing.

14.3.3 Deaths

For the Run-in phase, summary of the number of deaths and number and percentage of patients reporting any AE leading to death will be tabulated by SOC and PT. All AEs leading to death reported in the eCRF will be listed.

For the Interventional phase, summary of the number of deaths and number and percentage of patients reporting any TEAE leading to death will be tabulated by SOC and PT. All AEs leading to death reported in the eCRF will be listed.

14.3.4 Adverse events related to AxMP or leading to AxMP withdrawal

For the Interventional phase, by-patient listings will be created on all AEs related to AxMP and all AEs leading to withdrawal of AxMP (when applicable, described in Section 8.4.8) separately on the All treated analysis set.

14.4 Infections

Infections search (i.e. Cytomegalovirus, Adenovirus, Epstein-Barr virus, Histoplasma capsulatum, Salmonella, Leishmania, Typical mycobacteria, Atypical mycobacteria and Other) and Mycobacterium tuberculosis data will be listed on the Run-in phase analysis set and the All Treated analysis set.

14.5 Laboratory data

The laboratory safety data are being measured locally using appropriate instrument available on the site, and results are recorded on the CRFs. Therefore the ranges of normality could differ and shift tables have been chosen to represent local laboratory results.

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. Shift tables presenting the number and percentage of patients with abnormal low, abnormal high or within the normal range at each post-baseline study visit will be tabulated on the Run-in phase analysis set and the All Treated analysis set.

Shift tables for shift from baseline to worst high and worst low value post-baseline based on low/normal/high classification will be reported for the Run-in phase and the Interventional phase.

In addition, only RI baseline and baseline local laboratory data of white blood cell, platelet count, lactate dehydrogenase, alanine aminotransferase, aspartate aminotransferase, fibrinogen, ferritin, C-reactive protein, triglycerides and D-dimer will be summarized on the Run-in phase analysis set and the All Treated analysis set to help understanding the disease severity.

All laboratory data (including specific laboratory parameters data collected under the Interventional phase) will be listed. Laboratory values outside local reference ranges will be flagged in the listings. Specific laboratory parameters data will be flagged in the listings.

Urinalysis data will be listed as only collected at screening.

Additionally, local laboratory ranges will be listed by site including the parameter, applicable age ranges and gender when applicable.

Laboratory standard units to be displayed in the outputs are detailed in Appendix 1.

14.6 Vital signs, Tuberculosis clinical examination, MAS clinical signs and symptoms, and MAS activity score

14.6.1 Vital signs

Vital signs (corrected body temperature [Celsius] as defined in Section 8.4.4, heart rate [bpm], systolic and diastolic blood pressure [mmHg], and oxygen saturation [%]) will be presented for the Run-in phase as absolute values over time (i.e. analysis visit) and for Interventional phase as absolute and change from pre-dose values (for all parameters except corrected body temperature) over time (i.e. analysis visit) using descriptive statistics as described in Section 8 for continuous endpoints, as appropriate.

Listings will include data at scheduled and unscheduled assessments. Any reduction greater than or equal to 30% from baseline in systolic blood pressure will be presented/flagged in the listings.

14.6.2 Tuberculosis clinical examination

Tuberculosis clinical examination data, collected during the Interventional phase, will be listed on the All Treated analysis set.

14.6.3 MAS clinical signs and symptoms, and activity score

Baseline is defined as last observed value prior to first emapalumab infusion. Any assessment performed on Study day 1 will be assumed to have occurred pre-dose and will be used as baseline.

14.6.3.1 MAS clinical activity score

Summary statistics (including the change from baseline), as described in section 8 for continuous endpoints, of the MAS clinical activity score according to the investigator (measured via the VAS scale ranging from 0 to 10 cm by 0.5) will be presented by visit for the Run-in phase analysis set and the All Treated analysis set.

Patient-level data will be displayed in listings.

14.6.3.2 MAS clinical signs and symptoms

Pre-defined individual items in MAS clinical signs and symptoms, supporting the MAS clinical activity score, will be summarized using descriptive statistics, as described in section 8, by visit and will be structured by domain (fever [temperature > 38 °C], skin rash, hemorrhagic manifestations, CNS, respiratory function treatment, cardiac, kidney, other, MAS organ involvement), for the Run-in phase analysis set and the All Treated analysis set.

Patient-level data will be displayed in listings.

14.7 Electrocardiogram (ECG)

An ECG (6 Lead Standard or 12 Lead Continuous ECG or Holter Monitoring) will be performed at screening, at Week 8 and EOS visit in the Interventional phase.

Patient-level data of ECG results, including abnormal findings, will be displayed for the All Treated analysis set.

14.8 Imaging

Patient-level data of abdominal ultrasound, chest X-ray and brain MRI data, collected during the Interventional phase, will be displayed in listing on the All Treated analysis set.

14.9 PK/PD analysis

PD parameters are defined as: CXCL9, total IFNg, sIL2ra and CXCL10

PK and PK/PD analyses will be conducted separately and are not included in this SAP. A detailed description of the PK/PD analysis will be provided in a separate non study specific PK and PD modelling analysis plan. This analysis plan and report can combine data from different studies.

However, descriptive summaries (including the change from pre-dose or baseline when applicable) of emapalumab concentration and PD parameters, including marker levels, will be tabulated by visit on the All Treated analysis set. Patient-level data of emapalumab concentration, PD parameters, and marker levels will be listed on the All Treated analysis set. Graphical presentations of mean and individual PK and PD parameters will be provided based on the descriptive statistics mentioned above.

14.10 Immunogenicity analyses

Occurrence of anti-drug antibodies (ADA) and neutralizing antibodies (Nab) to emapalumab will be tabulated descriptively and listed using the All Treated analysis set.

ADA Assay is composed of several tiers: 1- Screening 2- Confirmatory 3- Titration 4- NAb. Any positive sample at screening will be tested in the confirmatory tier. All samples positive in the confirmatory tier will be titrated and assayed for Nab. All results will be reported as Positive/Negative, except for the titer that will be a numeric value or "titer too low to be determined". Confirmatory results will be presented in the summary table.

14.11 Patient report outcomes

14.11.1 PedsQL

The Pediatric Quality of Life Inventory (PedsQL) is a brief measure of health-related quality of life in children and adults. PedsQL^{TM} 4.0 generic core scales (ages 2 to over 26) and PedsQL^{TM} infant scales (ages 1 to 24 months) are used in the study.

The PedsQL^{TM} 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 (5).

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

Table 14 PedsQL reversed score

Response Choices	Never/Not at all	Almost Never	Sometimes	Often	Almost Always/A lot
Raw scores	0	1	2	3	4
0-100 Scale scores	100	75	50	25	0

Notes:

- Higher scale scores indicate better HRQOL (Health-Related Quality of Life).
- 3-point scales: 0 (Not at all), 2 (Sometimes) and 4 (A lot) applicable for the young child (ages 5-7) self-report.

2) Calculate scores

- Functionning scale scores as average of the transformed functioning scale items
  - Physical (applicable to infant [1-12 months, 13-24 months old], toddlers [2-4 years old], young [5-7 years old], children [8-13 years old], teen [13-18 years old], young adult [18-25 years old], adult [≥26 years old])
  - Physical symptoms (applicable to infant only)
  - Emotional (applicable to infant, toddlers, young, children, teen, young adult, adult)
  - Social (applicable to infant, toddlers, young, children, teen, young adult, adult)
  - School (applicable to toddlers, young, children, teen, young adult, adult)
  - Cognitive (applicable to infant only)
- Health summary scores
  - Psychosocial health summary score
    - Infant: average (i.e. sum of the transformed functioning scale items over the number of items answered) of the emotional, social, and cognitive functioning scales.
    - Toddler, young, children, teen, young adults, adult: average (sum of the transformed functioning scale items over the number of

items answered) of the emotional, social, and school functioning scales.

- Physical health summary score
  - Infant: average (sum of the transformed functioning scale items over the number of items answered) of the physical functioning and physical symptoms scales
  - Toddler, young, children, teen, young adults, adult: physical functioning scale score
- Total score: sum of all the transformed functioning scale items over the number of items answered on all functioning scales. (i.e. 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.

Descriptive summaries of absolute score and change from baseline will be presented for the PedsQL total scale score, the health summary scores, and the functioning scale scores by visit using the time windows defined in Section 8.3.

PedsQL parent and child/adult reports as well as parent report for infants will be presented separately on both the Run-in phase analysis set and the All Treated analysis set.

Similar analysis as above, with the exception of the infant questionnaires, will be repeated and stratified on the following age groups: 2 to<17 years and ≥17 years. If a subgroup contains less than 3 patients, only patient counts will be presented for that subgroup, i.e. no summarized data (e.g. mean, standard deviation, confidence intervals) will be reported for such subgroups.

PedsQL patient-data, including derived scores, will be listed on the Run-in phase analysis set and the All Treated analysis set.

14.11.2 Clinical and Patient/Parent Global Impression of Severity

PedsQL will be supported by clinician and patient/parent global impression of severity questionnaires on both Run-in and Interventional phases regarding the overall severity over the past week. In the Run-in phase these will be collected at screening, Week 8 and at the time of CR if the CR is achieved after Week 8. In the Interventional phase, these will be collected at screening, Week 8, follow-up visit Month 6, the EOS visit and at the time of CR if CR is achieved after Week 8.

- Clinical Global Impression of Severity

On the Run-in phase analysis set (presenting data collected during the Run-in phase, see Section 8.4.10) and All Treated analysis set (presenting data collected during the Interventional phase, see Section 8.4.10), shift tables will be created for clinical global impression of severity (none, mild, moderate, severe) presenting the shift in number and percentage of patients with ‘None’/’Mild’/’Moderate’/’Severe’ at each post-baseline visit using the time windows defined in Section 8.3, compared to baseline.

- Patient/Parent Global Impression of Severity

On the Run-in phase analysis set (presenting data collected during the Run-in phase, see Section 8.4.10) and All Treated analysis set (presenting data collected during the Interventional phase, see Section 8.4.10), shift tables will be created separately for the patient/parent global impression of severity (none, mild, moderate, severe) presenting the shift in number and percentage of patients with 'None'/'Mild'/'Moderate'/'Severe' at each post-baseline visit using the time windows defined in Section 8.3, compared to baseline.

Similar analyses as above will be repeated and stratified on the following age groups: <2 years, 2 to<17 years and ≥17 years. If a subgroup contains less than 3 patients, only patient counts will be presented for that subgroup, i.e. no summarized data (e.g. mean, standard deviation, confidence intervals) will be reported for such subgroups.

Clinical and patient/parent global impression of severity patient-data will be listed on the Run-in phase analysis set and the All Treated analysis set.

14.12 Subgroup analyses

Subgroup analysis of the data collected during the Interventional phase will be conducted for the following subgroups:

- Sex (Male, Female).
- Age at informed consent categorized into: (<2 years, 2 to<12 years, 12 to<17years, <17 years and ≥17 years).
- Race (White, Asian, Black or African American and Other [including Other, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander]).
  Note: Multiple races could be selected. In case a patient is White/Other, then a "White/Other" subgroup will be created.
- Geographical regions (North America [including US and Canada], EU, Japan, China, Russia).
- Patients who have undergone wash-out of biologics before study entry (Yes, No) as defined in Section 8.4.32.
- Patients with organ involvement (lung and/or hepatic involvement) at baseline of the Interventional phase (Yes, No) as defined in Section 8.4.33.
- Patients with concomitant G-CSF treatment (Yes, No) as defined in Section 8.4.35.
- Patients with use of concomitant biologics during the long-term follow-up period (Yes/No) as defined in Section 8.4.37.
- Patients with Herpes zoster virus prophylaxis treatments (Yes/No) as defined in Section 8.4.8.

The analyses will be based on the All Treated analysis set. If a subgroup contains less than 3 patients, only patient counts will be presented for that subgroup, i.e. no summarized data (e.g. mean, standard deviation, confidence intervals) will be reported for such subgroups.

The tables concerned will be flagged in the list of tables (

Appendix 3 - List of Tables).

15 Patient Profiles

Two types of patient profiles will be produced on patients who entered the Interventional phase (i.e. All treated analysis set; no patient profile for patients entering and completing only the Run-in phase):

- Overview of emapalumab/MAS treatments administered doses and laboratory parameters during the study, Section 15.1.
- Overview of Rheumatological diseases and/or MAS therapies prior to study initiation, Section 15.2.

Graphs for Emapalumab Serum concentration versus time, VAS and Interferon gamma will be produced.

15.1 Overview of emapalumab/MAS treatments administered doses and laboratory parameters during the study

A graphical display of the MAS therapies administered dose of emapalumab and the evolution of laboratory parameters administered for each patient will be presented, and data from Run-in or/and Interventional phases will be shown in the same figure (for patients participating in both phases). For each patient, a document will display the following data:

- In the header: study, country, study site, patient identifier, diagnosis (sJIA, AOSD, SLE), sex, race, ages (years) at informed consent for Run-in or/and Interventional phases when applicable, MAS diagnosis date of the current episode, Underlying disease diagnosis date, emapalumab treatment start/stop dates.
- Administered dose (mg/kg) of emapalumab by study day.
- Equivalent dose of prednisolone (mg/kg/day) by RI:SD and study day.
  In addition, pulses, defined as equivalent dose of prednisolone ≥20 mg/kg/day, will be presented using symbol.
- Daily total dose of anakinra, canakinumab, cyclosporin, etoposide, methotrexate, tocilizumab, TNF inhibitors, and JAK inhibitors by RI:SD and study day.
  Notes:
  - Anakinra, canakinumab, cyclosporin, methotrexate, and tocilizumab will be presented in mg/kg/day.
  - Etoposide will be presented in mg/m^2/day.
  - TNF inhibitors and JAK inhibitors will be presented in mg/kg/day.
- Laboratory test results by RI:SD and study day:
  - CXCL9 (ng/L) (interventional phase only)
  - C-Reactive protein (mg/L)

- Ferritin (µg/L)
- Triglycerides (mmol/L)
- ALT (IU/L)
- AST (IU/L)
- LDH (IU/L)
- White blood cell (10^9/L)
- Platelets (10^9/L)
- D-Dimer (µg/L)
- Fibrinogen (g/L)

The header, and the graphical display of the administered dose and the equivalent dose of prednisolone will be repeated at the top of each page, when applicable.

The x-axis of plots for all patients will show the Run-in and Interventional phases periods, and the days will range from day -14 based on Run-in phase study day 1 (i.e. RI:SD1) or Interventional study day 1 (i.e. study day 1), whichever occurs first to the last available visit date across all patients. Local laboratory normal ranges will be presented in the patient profile when available.

15.2 Overview of Rheumatological diseases and/or MAS therapies prior to study initiation

A graphical display of the Rheumatological diseases (Still's disease [including sJIA or AOSD], SLE) and/or MAS therapies prior to first informed consent date of the Run-in and Interventional phases for each patient. Each profile will display the following data:

- In the header: study, country, study site, patient identifier, diagnosis (sJIA, AOSD, SLE), sex, race, ages (years) at informed consent for Run-in or/and Interventional phases, when applicable, MAS diagnosis date of the current episode, Underlying disease diagnosis date, emapalumab treatment start date.
- MAS episodes (display as periods).
- Glucocorticoids periods, using definition of equivalent dose of prednisolone as described in Section 8.4.22.
  In addition, pulses, defined as equivalent dose of prednisolone ≥20 mg/kg/day, will be presented using symbol.
- Periods of the following ordered medications: canakinumab, cyclosporin, etoposide, tocilizumab, JAK inhibitors, TNF inhibitors, and anakinra.
- Anakinra daily dose (mg/kg/day).

Data will be presented from study day -365 to Run-in study day 1 (i.e. RI:SD1) or Interventional study day 1 (i.e. study day 1), whichever occurs first.

16 Document history, incl. Changes/Clarifications from clinical study protocol

Version / Date	Brief Summary of Changes

Final 1.0 / 15NOV2021	Initial version -Reference to the EXIT interview is done in the CSP, however it is not defined as a study endpoint. A brief description is detailed in this study SAP (Section 3.4.2). -In the Section 7.3.3 of the CSP, details regarding MAS recurrence/reactivation are given: "The disease would be considered as recurring or reactivating if a deterioration in clinical signs and symptoms as reported in Table 1 is observed, after a previously confirmed PR or a confirmed CR. The deterioration should be documented on 2 repeated clinical and laboratory assessments with an interval of minimum one day and maximum one week. Any new MAS related clinical signs and symptoms are considered as a single criteria for reactivation.". Definition in the study SAP will be based on the AE CRF form, by search of specific terms in the adverse event description and if the patient was diagnosed with a MAS recurrence since the last visit (see CRF). Changes in any of the clinical signs and symptoms or in any of the laboratory parameters could result from intercurrent disease (e.g. infection). Therefore, only the investigators can assess if these changes are related to MAS (i.e. MAS recurrence) or to the infection. -In the CSP, reference to Glucocorticoid Toxicity Index (GTI) is made to assess the GC toxicity. After internal discussion, GTI score (no GTI version 1.0 nor GTI version 2.0) will not be derived; therefore the term GTI was removed or replaced by GC toxicity assessment in this SAP. -Adjudication of the underlying disease flares, mentioned in the Section 7.2.8.3 of the CSP, is not defined as an endpoint and will not be described in this SAP. A scientific steering committee will review each single underlying disease flare, produce an independent and separate report summarizing results of their adjudications. Adjudication results will not be part of the clinical study database. -The footnote under Table 4 (copied from Table 2 of the CSP) was changed from "Additional HLH treatments allowed in case of unsatisfactory HLH control after 3 doses of emapalumab." to "Additional MAS treatments allowed in case of unsatisfactory MAS control after 3 doses of emapalumab." as the body text referred to MAS. -Additional exploratory endpoints were added for the secondary efficacy objectives compared to the CSP.

Version / Date	Brief Summary of Changes
	• Level of average equivalent dose of prednisone and change from weekly pre-infusion of emapalumab over time. • Achievement of weekly average equivalent daily dose of prednisone <0.2 mg/kg/day • Achievement of weekly average equivalent daily dose of prednisone <0.5 mg/kg/day • Time to first normalization of each parameter included in the complete response definition.

Final 2.0 / 30MAY2022	- “Subjects” replaced by “Patients”, “Normalisation” replaced by “Normalization”, -Align endpoints terminology. -Update/Correction (renumbering of the Week for the follow-up to Week 8) of Figure 1 as per protocol amendment version 2.0 (dated: 22FEB2022). -Update Tables 5, 6, 7, 8 and 9 as per CSP amendment version 2.0 (dated: 22FEB2022). -Remove “Major” for protocol deviations and replace by deviations impacting primary efficacy analysis or deviations leading to exclusion of a patient from the evaluable analysis set; to avoid confusion with different terminology. -Add definition, subgroup analyses on patients with/without use of concomitant biologics during the long-term follow-up period as per change in the CSP amendment (version 2.0 dated: 22FEB2022). -Add definition, safety subgroup analysis on patients with/without Herpes zoster virus prophylaxis treatments as per change in the CSP amendment (version 2.0 dated: 22FEB2022). -Clarify the EOT visit windows in case EOT visit is the last visit of the study. -Add definition of withdrawal from the study due to lack of efficacy in the derived variables section. -Clarify calculation of duration between 2 doses (date of $dose_n$ – date of $dose_{n-1}$) and remove time in the calculation (only dates). -Remove “Note: Complete response is equivalent to MAS remission in this context, and the two terms may be used interchangeably in this document.”. The MAS remission is assessed by investigator and may trigger stop of emapalumab treatment. The proportion of patients with complete response is the primary efficacy endpoint that will be derived for interim and final analyses but will not influence investigator judgment. -Equivalent daily dose of prednisolone is assumed to be 0 when no GCs treatment is recorded at any period from ICF start date. -Clarify treatment compliance not presented as emapalumab administered as intravenous infusion at the site under medical supervision. -Remove the exploratory objective [redacted]

	[redacted] - Remove the exploratory objective [redacted] -AxMP: Herpes zoster virus prophylaxis treatments (defined as an AxMP) is no longer mandated and was removed in the CSP amendment (version 2.0 dated: 22FEB2022). - "Prednisone" replaced by "Prednisolone" to align to CSP. -Exploratory endpoints added to the SAP version 1.0 compared to the CSP is considered as secondary endpoints in this SAP: • Level of average equivalent dose of prednisolone and change from weekly pre-infusion of emapalumab over time. • Achievement of weekly average prednisolone equivalent daily dose ≤0.5 mg/kg/day • Achievement weekly average prednisolone equivalent daily dose ≤0.2 mg/kg/day • Time to first normalization of each parameter included in the complete response definition. -Add the following secondary endpoints for the secondary efficacy objective • Time to first achievement of weekly average prednisolone equivalent daily dose ≤0.5 mg/kg/day. • Time to first achievement of weekly average prednisolone equivalent daily dose ≤0.2 mg/kg/day. -Update definitions of weekly average prednisolone equivalent daily dose <0.5 mg/kg/day and <0.2 mg/kg/day to ≤0.5 mg/kg/day and ≤0.2 mg/kg/day -Update age groups to align to FDA Guidance (6) - Appendix 2 - Herpes zoster virus prophylaxis treatments list is updated. - Clarify TNF inhibitors and JAK inhibitors will be presented in mg/kg/day instead of mg/kg -Update imputation rules for medications dates

Version / Date	Brief Summary of Changes
	-Clarify only complete dates (non-imputed) will be used to derive last study contact date -PK/PD: Graphical presentations of mean and individual PK and PD parameters added
Final 3.0 / 29FEB2024	Updates as per CSP amendment: CSP Version 3.0 (dated: 19OCT2023). The reason for the CSP amendment was to accommodate a request from the FDA for additional data and analyses. - Introduction of a third interim analysis and change in timepoint for when the second interim analysis will be performed. -Addition of a footnote to clarify how to manage patients that go into MAS remission earlier than the anticipated 4 weeks of treatment as well as correction of the order of the footnotes in Table 7. -Clarification as to when post-infusion PK-samples are expected to be collected (footnote in table 7). -Clarification that “RI: At the time of remission” should be assigned to Completion/Discontinuation Date ± 3 days. -Definition of Patients with concomitant G-CSF treatment during the interventional phase have been updated to be limited to cover the period from SD1 up to Week 8 efficacy assessment, i.e., SD61. -Clarification in section 8.4.8 that the eCRF form Herpes Zoster (HZ) Prophylaxis Check will be used to identify patients with Herpes zoster virus prophylaxis treatments in addition to medications listed in Appendix 2 and patients vaccinated against Herpes zoster at screening. - Adding a medical review for each of the terms listed in section 8.4.28 to confirm the status of MAS recurrence.
Final v4.0/ date tbd	Updates to incorporate changes specified in “errata” document and further changes arising from dry run discussions with study team

17 References

1 U.S. Department of Health and Human Services Food and Drug Administration (Guidance for Industry E9 Statistical Principles for Clinical Trials)

2 Minoia F, Davì S, Horne A, Demirkaya E, Bovis F, Li C, et al. Clinical features, treatment, and outcome of macrophage activation syndrome complicating systemic juvenile idiopathic arthritis: a multinational, multicenter study of 362 patients. Arthritis & rheumatology (Hoboken, NJ). 2014;66(11):3160-9.

3 Aytaç S, Batu ED, Ünal Ş, Bilginer Y, Çetin M, Tuncer M, et al. Macrophage activation syndrome in children with systemic juvenile idiopathic arthritis and systemic lupus erythematosus. Rheumatology international. 2016;36(10):1421-9.

4 Liu AC, Yang Y, Li MT, Jia Y, Chen S, Ye S, et al. Macrophage activation syndrome in systemic lupus erythematosus: a multicenter, case-control study in China. Clinical rheumatology. 2018;37(1):93-100.

5 https://www.pedsql.org/PedsQL-Scoring.pdf

6 U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) December 2014 (General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products Guidance for Industry)

18 Appendix

Appendix 1 - List of laboratory standard units to be displayed in the outputs

Category	Laboratory parameters	Unit
Hematology	Red blood cells (RBCs)	10^{12}/L
	White blood cells (WBCs)	10^{9}/L
	Neutrophils	10^{9}/L
	Lymphocytes	10^{9}/L
	Monocytes	10^{9}/L
	Platelets	10^{9}/L
	Hemoglobin	g/L
	Hematocrit	%
Biochemistry	Ferritin	µg/L
	Triglycerides	mmol/L
	C-Reactive Protein (CRP)	mg/L
	Aspartate Aminotransferase (AST)	U/L
	Alanine Aminotransferase (ALT)	U/L
	gamma Glutamyl Transferase (γGT)	U/L
	Alkaline Phosphatase (ALP)	U/L
	Lactate Dehydrogenase (LDH)	U/L
	Total Bilirubin	umol/L
	Glucose	mmol/L
	Albumin	g/L
	Creatinine	umol/L
	Blood Urea Nitrogen (BUN)/Urea	mmol/L
	Sodium	mmol/L
	Calcium	mmol/L
	Potassium	mmol/L
Coagulation	Activated partial thromboplastin time (aPTT)	sec
	Prothrombin time (PT)	sec
	D-dimer	mg/L
	Fibrinogen	g/L
Biomarkers	sCD25	ng/L
	IFN γ	ng/L
	CXCL9	ng/L
	CXCL10	ng/L

Appendix 2 – Herpes zoster virus prophylaxis treatments

ATC 4 level	Preferred name	Herpes zoster virus prophylaxis treatments ? (yes/no)
J06BB - Specific immunoglobulins	PALIVIZUMAB	no
	ACETYLTRYPTOPHAN;AMINOMETHYLBENZOIC ACID;ANTI-D IMMUNOGLOBULIN	no
	IMMUNOGLOBULIN ANTIVENOM SCORPIONS	no
	OBILTOXAXIMAB	no
	IMMUNOGLOBULIN ANTI-BACILLUS ANTHRACIS	no
	IMMUNOGLOBULIN ANTIHEPATITIS B	no
	ANTI-D IMMUNOGLOBULIN	no
	IMMUNOGLOBULIN ANTI-CORYNEBACTERI.DIPHT.TOX.	no
	ANTI PSEUDOMONAS IGY	no
	IMMUNOGLOBULIN ANTI-CLOSTRIDIUM TETANI TOXIN	no
	IMMUNOGLOBULIN MEASLES	no
	IMMUNOGLOBULIN HUMAN ANTI-RABIES	no
	IMMUNOGLOBULIN HUMAN ANTI-TETANUS	no
	ATOLTIVIMAB	no
	ATOLTIVIMAB;MAFTIVIMAB;ODESIVIMAB	no
	ATOLTIVIMAB;MAFTIVIMAB;ODESIVIMAB EBGN	no
	TEFIBAZUMAB	no
	BEZLOTOXUMAB	no
	HYPERIMMUNE PLASMA COVID-19	no
	COSFROVIXIMAB	no
	COSFROVIXIMAB;LARCAVIXIMAB;PORGAVIXIMAB	no
	IMMUNOGLOBULIN CYTOMEGALOVIRUS	no
	DOCARAVIMAB	no
	IMMUNOGLOBULIN EQUINE ANTI-RABIES	no
	EXBIVIRUMAB	no
	FORAVIRUMAB	no

	IMMUNOGLOBULIN ANTI-TICKBORNE ENCEPHALITIS	no
	IMMUNOGLOBULIN HUMAN ANTI-RUBELLA	no
	IMMUNOGLOBULIN HUMAN ANTI-SMALLPOX	no
	IMMUNOGLOBULIN VARICELLA-ZOSTER	yes
	IMMUNOGLOBULIN ANTI-HEPATITIS A	no
	IMMUNOGLOBULIN ANTI-STAPHYLOCOCCUS	no
	IMMUNOGLOBULIN ANTI RESPIRATORY SYNCYTIAL VIR	no
	IMMUNOGLOBULIN HUMAN ANTI-PERTUSSIS	no
	IMMUNOGLOBULIN SARS-COV-2	no
	LARCAVIXIMAB	no
	LIBIVIRUMAB	no
	MIROMAVIMAB	no
	MAFTIVIMAB	no
	MEDI 3902	no
	SUVRATOXUMAB	no
	MOTAVIZUMAB	no
	MEDI 557	no
	MEDI 8852	no
	ODESIVIMAB	no
	ODESIVIMAB EBGN	no
	POLYCLONAL HYPERIMMUNE GLOBULIN COVID-19	no
	PORGAVIXIMAB	no
	RAFIVIRUMAB	no
	RAXIBACUMAB	no
	RIVABAZUMAB PEGOL	no
	ROLEDUMAB	no
	ROZROLIMUPAB	no
	SAB 185	no
J05AB - Nucleosides and nucleotides	ACICLOVIR	yes
	ACICLOVIR SODIUM	yes

excl. reverse transcriptase inhibitors	VALACICLOVIR	yes
	ACICLOVIR;GLUCOSE	yes
	VALACICLOVIR HYDROCHLORIDE	yes
	VIDARABINE	yes
	PENCICLOVIR	yes
	GANCICLOVIR	yes
	RIBAVIRIN	no
	VALGANCICLOVIR HYDROCHLORIDE	no
	FAMCICLOVIR	yes
	IDOXURIDINE	yes
	AT 527	no
	RIBAVIRIN;SODIUM CHLORIDE	no
	REMDESIVIR	no
	BRIVUDINE	yes
	BRINCIDOFOVIR	no
	CIDOFOVIR	no
	GANCICLOVIR SODIUM	Yes
	GANCICLOVIR;SODIUM CHLORIDE	yes
	FILOCICLOVIR	No
	GALIDESIVIR	No
	GLUCOSE;RIBAVIRIN	No
	GS 441524	No
	VIDARABINE PHOSPHATE	Yes
	LEVOVIRIN	No
	LOBUCAVIR	Yes
	PENCICLOVIR SODIUM	Yes
	LUMICITABINE	No
	MERICITABINE	No
	NETIVUDINE	Yes

	RUZASVIR	No
	SORIVUDINE	Yes
	TARIBAVIRIN	No
	UPRIFOSBUVIR	No
	VALACICLOVIR HYDROCHLORIDE HYDRATE	Yes
	VALGANCICLOVIR	No
	VALNIVUDINE	Yes
	VALOMACICLOVIR	Yes
	VALOMACICLOVIR STEARATE	Yes
	VIDARABINE SODIUM PHOSPHATE	Yes

Note: Treatments listed as “no” are not used as Herpes zoster virus prophylaxis according to the local label. However, if on the eCRF form Concomitant medications (including GCs) the Primary Reason Medication was taken is ticked “Herpes zoster Prophylaxis”, that medication will be consider in the final list of Herpes zoster Medications prior to database lock.

Appendix 3 - List of Tables

			Subgroups									
Type	**Title**	**Population**	**Sex**	**Age**	**Race**	**Region**	**Wash-out of biologics at study entry**	**Lung and/or hepatic involvements at baseline**	**Concomitant G-CSF treatment**	**Dial / Hemofiltration at screening**	**Concomitant biologics during long term FUP**	**HZ prophylaxis treatments**
Table	Patient disposition - Run-in phase	All screened analysis set										
Table	Patient disposition - Interventional phase	All screened analysis set										
Table	Study populations	All screened analysis set										
Table	Important protocol deviations related to study conduct	Run-in phase analysis set										
Table	Important protocol deviations related to study conduct	All treated analysis set										
Table	Demographics data	Run-in phase analysis set										
Table	Demographics and baseline characteristics	All treated analysis set	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Table	Demographics and baseline characteristics	Evaluable analysis set										
Table	Underlying disease	Run-in phase analysis set										
Table	Underlying disease	All treated analysis set										
Table	Underlying disease	Evaluable analysis set										
Table	MAS Characteristics	Run-in phase analysis set										
Table	MAS Characteristics	All treated analysis set										
Table	MAS Characteristics	Evaluable analysis set										

Table	Vaccination for Herpes zoster before study entry	All treated analysis set
Table	Vaccination for Herpes zoster before study entry	Evaluable analysis set
Table	Medical History by SOC and PT	Run-in phase analysis set
Table	Medical History by SOC and PT	All treated analysis set
Table	All medications by ATC level 4 and PT - Run-in phase	Run-in phase analysis set
Table	Medications related to MAS by ATC level 4 and PT - Run-in phase	Run-in phase analysis set
Table	Medications related to underlying condition by ATC level 4 and PT - Run-in phase	Run-in phase analysis set
Table	Medications related to flare of underlying condition by ATC level 4 and PT - Run-in phase	Run-in phase analysis set
Table	Medications related to other by ATC level 4 and PT - Run-in phase	Run-in phase analysis set
Table	All Medications by ATC level 4 and PT – Interventional phase	All treated analysis set
Table	Medications related to MAS by ATC level 4 and PT – Interventional phase	All treated analysis set
Table	Medications related to underlying condition by ATC level 4 and PT – Interventional phase	All treated analysis set
Table	Medications related to flare of underlying condition by ATC level 4 and PT – Interventional phase	All treated analysis set

Table	Medications related to other by ATC level 4 and PT – Interventional phase	All treated analysis set									
Table	Complete response at Week 8 efficacy assessment	All treated analysis set	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Table	Complete response at Week 8 efficacy assessment	Evaluable analysis set									
Table	Glucocorticoids tapering	All treated analysis set	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Table	Level of weekly average prednisolone equivalent daily dose over time - Interventional phase	All treated analysis set	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Table	Time to first achievement of glucocorticoids tapering	All treated analysis set									
Table	Analysis of Time to first achievement of glucocorticoids tapering - Rate over time	All treated analysis set									
Table	Time to first achievement of weekly average prednisolone equivalent daily dose below or equal 1mg/kg/day	All treated analysis set									
Table	Analysis of time to first achievement of weekly average prednisolone equivalent daily dose below or equal 1mg/kg/day - Rate over time	All treated analysis set									
Table	Time to first complete response	All treated analysis set									
Table	Time to first complete response	Run-in phase analysis set									
Table	Analysis of time to first complete response - Rate over time	All treated analysis set									
Table	Overall response	All treated analysis set	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Table	Overall response - Run-in phase	Run-in phase analysis set									

Table	Time to first overall response	All treated analysis set									
Table	Time to first overall response - Run-in phase	Run-in phase analysis set									
Table	Analysis of time to first overall response - Rate over time	All treated analysis set									
Table	MAS recurrence at any time after achievement of CR	All treated analysis set - Patients who achieved complete response at any time	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Table	Withdrawal from the study due to lack of response	All treated analysis set	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Table	Survival time - Interventional phase	All treated analysis set									
Table	Survival rate over time - Interventional phase	All treated analysis set									
Table	Time to first achievement of weekly average prednisolone equivalent daily dose below or equal 0.5 mg/kg/day	All treated analysis set									
Table	Analysis of time to first achievement of weekly average prednisolone equivalent daily dose below or equal 0.5 mg/kg/day - Rate over time	All treated analysis set									
Table	Time to first achievement of weekly average prednisolone equivalent daily dose below or equal 0.2 mg/kg/day	All treated analysis set									
Table	Analysis of time to first achievement of weekly average prednisolone equivalent daily dose below or equal 0.2 mg/kg/day - Rate over time	All treated analysis set									

Table	Time to first normalization - MAS clinical activity score below or equal to 1cm	All treated analysis set
Table	Analysis of time to first normalization - MAS clinical activity score below or equal to 1cm - Rate over time	All treated analysis set
Table	Time to first normalization - White blood cell above LLN	All treated analysis set
Table	Analysis of time to first normalization - White blood cell above LLN - Rate over time	All treated analysis set
Table	Time to first normalization - Platelet count above LLN	All treated analysis set
Table	Analysis of time to first normalization - Platelet count above LLN - Rate over time	All treated analysis set
Table	Time to first normalization - Lactate dehydrogenase below 1.5 ULN	All treated analysis set
Table	Analysis of time to first normalization - Lactate dehydrogenase below 1.5 ULN - Rate over time	All treated analysis set
Table	Time to first normalization - Alanine transaminase below 1.5 ULN	All treated analysis set
Table	Analysis of time to first normalization - Alanine transaminase below 1.5 ULN - Rate over time	All treated analysis set
Table	Time to first normalization - Aspartate aminotransferase below 1.5 ULN	All treated analysis set
Table	Analysis of time to first normalization - Aspartate aminotransferase below 1.5 ULN - Rate over time	All treated analysis set

Table	Time to first normalization - Fibrinogen higher than 100 mg/dL	All treated analysis set										
Table	Analysis of time to first normalization - Fibrinogen higher than 100 mg/dL - Rate over time	All treated analysis set										
Table	Time to first normalization - Ferritin level decreased by at least 80 % or below 2000 ng/ml	All treated analysis set										
Table	Analysis of time to first normalization - Ferritin level decreased by at least 80 % or below 2000 ng/ml - Rate over time	All treated analysis set										
Table	Emapalumab exposure	All treated analysis set	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Table	Emapalumab re-exposure	All treated analysis set										
Table	Emapalumab treatment - Dosing intervals	All treated analysis set										
Table	Emapalumab re-treatment - Dosing intervals	All treated analysis set										
Table	Glucocorticoids exposure - Run-in phase	Run-in phase analysis set										
Table	Glucocorticoids exposure	All treated analysis set										
Table	Summary of adverse events - Run-in phase	Run-in phase analysis set										
Table	Adverse events by SOC and PT - Run-in phase	Run-in phase analysis set										
Table	Summary of treatment emergent adverse events – Interventional phase	All treated analysis set	Yes	Yes	Yes	Yes	Yes	Yes	Yes		Yes	Yes
Table	Treatment emergent adverse events by SOC and PT – Interventional phase	All treated analysis set	Yes	Yes	Yes	Yes	Yes	Yes	Yes		Yes	Yes
Table	Treatment emergent adverse events related to	All treated analysis set	Yes	Yes	Yes	Yes	Yes	Yes	Yes		Yes	Yes

	emapalumab by SOC and PT – Interventional phase										
Table	Treatment emergent adverse events by relationship to emapalumab and by SOC and PT – Interventional phase	All treated analysis set									
Table	Treatment emergent adverse events by maximum severity and by SOC and PT – Interventional phase	All treated analysis set									
Table	Infusion related reaction by SOC and PT – Interventional phase	All treated analysis set	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Table	Treatment emergent infections by SOC and PT – Interventional phase	All treated analysis set	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Table	Non-serious treatment emergent adverse event by SOC and PT – Interventional phase	All treated analysis set									
Table	Serious adverse events by SOC and PT - Run-in phase	Run-in phase analysis set									
Table	Serious treatment emergent adverse events by SOC and PT – Interventional phase	All treated analysis set	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Table	Serious treatment emergent adverse events related to emapalumab by SOC and PT – Interventional phase	All treated analysis set	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Table	Treatment emergent adverse events leading to emapalumab withdrawal by SOC and PT – Interventional phase	All treated analysis set	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Table	Adverse events leading to death by SOC and PT - Run-in phase	Run-in phase analysis set									
Table	Treatment emergent adverse events leading to death by SOC and PT – Interventional phase	All treated analysis set	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Table	Laboratory results - Hematology: Shift table over time - Run-in phase	Run-in phase analysis set										
Table	Laboratory results - Hematology: Shift table over time – Interventional phase	All treated analysis set	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Table	Laboratory results - Hematology: Shift table from baseline to worst high value - Run-in phase	Run-in phase analysis set										
Table	Laboratory results - Hematology: Shift table from baseline to worst high value – Interventional phase	All treated analysis set	Yes	Yes	Yes	Yes	Yes	Yes	Yes		Yes	Yes
Table	Laboratory results - Hematology: Shift table from baseline to worst low value - Run-in phase	Run-in phase analysis set										
Table	Laboratory results - Hematology: Shift table from baseline to worst low value – Interventional phase	All treated analysis set	Yes	Yes	Yes	Yes	Yes	Yes	Yes		Yes	Yes
Table	Laboratory results - Hematology: Baseline summary - Run-in phase	Run-in phase analysis set										
Table	Laboratory results - Hematology: Baseline summary – Interventional phase	All treated analysis set	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Table	Laboratory results - Biochemistry: Shift table over time - Run-in phase	Run-in phase analysis set										
Table	Laboratory results - Biochemistry: Shift table over time – Interventional phase	All treated analysis set	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Table	Laboratory results - Biochemistry: Shift table from baseline to worst high value - Run-in phase	Run-in phase analysis set										

Table	Laboratory results - Biochemistry: Shift table from baseline to worst high value – Interventional phase	All treated analysis set	Yes	Yes	Yes	Yes	Yes	Yes	Yes		Yes	Yes
Table	Laboratory results - Biochemistry: Shift table from baseline to worst low value - Run-in phase	Run-in phase analysis set										
Table	Laboratory results - Biochemistry: Shift table from baseline to worst low value – Interventional phase	All treated analysis set	Yes	Yes	Yes	Yes	Yes	Yes	Yes		Yes	Yes
Table	Laboratory results - Biochemistry: Baseline summary - Run-in phase	Run-in phase analysis set										
Table	Laboratory results - Biochemistry: Baseline summary – Interventional phase	All treated analysis set	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Table	Laboratory results - Coagulation: Shift table over time - Run-in phase	Run-in phase analysis set										
Table	Laboratory results - Coagulation: Shift table over time – Interventional phase	All treated analysis set	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Table	Laboratory results - Coagulation: Shift table from baseline to worst high value - Run-in phase	Run-in phase analysis set										
Table	Laboratory results - Coagulation: Shift table from baseline to worst high value – Interventional phase	All treated analysis set	Yes	Yes	Yes	Yes	Yes	Yes	Yes		Yes	Yes
Table	Laboratory results - Coagulation: Shift table from baseline to worst low value - Run-in phase	Run-in phase analysis set										
Table	Laboratory results - Coagulation: Shift table from baseline to worst low value – Interventional phase	All treated analysis set	Yes	Yes	Yes	Yes	Yes	Yes	Yes		Yes	Yes

Table	Laboratory results - Coagulation: Baseline summary - Run-in phase	Run-in phase analysis set										
Table	Laboratory results - Coagulation: Baseline summary – Interventional phase	All treated analysis set	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Table	Vital signs over time - Run-in phase	Run-in phase analysis set										
Table	Vital signs over time - Interventional phase	All treated analysis set										
Table	MAS clinical signs and symptoms over time - Run-in phase	Run-in phase analysis set										
Table	MAS clinical signs and symptoms over time - Interventional phase	All treated analysis set	Yes	Yes	Yes	Yes	Yes	Yes	Yes		Yes	Yes
Table	MAS clinical activity over time - Run-in phase	Run-in phase analysis set										
Table	MAS clinical activity over time - Interventional phase	All treated analysis set	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Table	Pharmacodynamic results over time - Interventional phase	All treated analysis set	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Table	Pharmacokinetic results over time - Interventional phase	All treated analysis set	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Table	Immunogenicity results over time - Interventional phase	All treated analysis set	Yes	Yes	Yes	Yes	Yes	Yes				
Table	PedsQL Infant score - Functioning scale scores, Health summary scores and Total scale score over time - Run-in phase	Run-in phase analysis set										
Table	PedsQL Infant - Shift table over time – Run-in phase	Run-in phase analysis set										
Table	PedsQL Infant score - Functioning scale scores, Health summary scores and	All treated analysis set										

	Total scale score over time - Interventional phase	
Table	PedsQL Infant - Shift table over time - Interventional phase	All treated analysis set
Table	PedsQL score (Parent report) - Functioning scale scores, Health summary scores and Total scale score over time – Run-in phase	Run-in phase analysis set
Table	PedsQL (Parent report) - Shift table over time – Run-in phase	Run-in phase analysis set
Table	PedsQL score (Parent report) - Functioning scale scores, Health summary scores and Total scale score over time by age group – Run-in phase	Run-in phase analysis set
Table	PedsQL (Parent report) - Shift table over time by age group – Run-in phase	Run-in phase analysis set
Table	PedsQL score (Parent report) - Functioning scale scores, Health summary score and Total scale score over time - Interventional phase	All treated analysis set
Table	PedsQL (Parent report) - Shift table over time - Interventional phase	All treated analysis set
Table	PedsQL score (Parent report) - Functioning scale scores, Health summary score and Total scale score over time by age group - Interventional phase	All treated analysis set
Table	PedsQL (Parent report) - Shift table over time by age group - Interventional phase	All treated analysis set
Table	PedsQL score (Child/Adult report) - Functioning scale	Run-in phase analysis set

	scores, Health summary scores and Total scale score over time – Run-in phase	
Table	PedsQL (Child/Adult report) - Shift table over time – Run-in phase	Run-in phase analysis set
Table	PedsQL score (Child/Adult report) - Functioning scale scores, Health summary scores and Total scale score over time by age group – Run-in phase	Run-in phase analysis set
Table	PedsQL (Child/Adult report) - Shift table over time by age group – Run-in phase	Run-in phase analysis set
Table	PedsQL score (Child/Adult report) - Functioning scale scores, Health summary score and Total scale score over time - Interventional phase	All treated analysis set
Table	PedsQL (Child/Adult report) - Shift table over time - Interventional phase	All treated analysis set
Table	PedsQL score (Child/Adult report) - Functioning scale scores, Health summary score and Total scale score over time by age group - Interventional phase	All treated analysis set
Table	PedsQL (Child/Adult report) - Shift table over time by age group - Interventional phase	All treated analysis set
Table	Clinical Global Impression of Severity - Shift table over time - Run-in phase	Run-in phase analysis set
Table	Clinical Global Impression of Severity - Shift table over time - Interventional phase	All treated analysis set

Table	Patient/Parent Global Impression of Severity - Shift table over time - Run-in phase	Run-in phase analysis set
Table	Patient/Parent Global Impression of Severity - Shift table over time - Interventional phase	All treated analysis set
Table	Clinical Global Impression of Severity - Shift table over time by age group - Run-in phase	Run-in phase analysis set
Table	Clinical Global Impression of Severity - Shift table over time by age group - Interventional phase	All treated analysis set
Table	Patient/Parent Global Impression of Severity - Shift table over time by age group - Run-in phase	Run-in phase analysis set
Table	Patient/Parent Global Impression of Severity - Shift table over time by age group - Interventional phase	All treated analysis set

Appendix 4 - List of Listings

Type	Title	Population
Listing	Screened failure data	Screened failure patients
Listing	Disposition	All screened analysis set
Listing	Study completion status - Run-in phase	Run-in phase analysis set
Listing	Study and treatment completion status - Interventional phase	All treated analysis set
Listing	Assignment to analysis populations and reasons for exclusion	All screened analysis set
Listing	Protocol deviations - Run-in phase	Run-in phase analysis set
Listing	Protocol deviations - Interventional phase	All treated analysis set
Listing	Demographics data	Run-in phase analysis set
Listing	Demographics data	All treated analysis set
Listing	Subgroup analyses covariates	All treated analysis set
Listing	Underlying disease	Run-in phase analysis set
Listing	Underlying disease	All treated analysis set
Listing	Underlying disease assessment	All treated analysis set
Listing	MAS History collected at Run-in phase screening	Run-in phase analysis set
Listing	MAS History collected at Interventional phase screening	All treated analysis set
Listing	Prophylaxis treatment for Herpes zoster virus data	All treated analysis set
Listing	Primary HLH genetic perforin level and degranulation tests	Run-in phase analysis set
Listing	Primary HLH genetic perforin level and degranulation tests	All treated analysis set
Listing	Medical history	Run-in phase analysis set
Listing	Medical history	All treated analysis set
Listing	Prior/Concomitant medications related to GCs treatment for MAS	Run-in phase analysis set
Listing	Prior/Concomitant medications related to emapalumab treatment	All treated analysis set
Listing	Procedures	Run-in phase analysis set
Listing	Procedures	All treated analysis set
Listing	Emapalumab infusion (first and re-treatment periods) - 1/2	All treated analysis set
Listing	Emapalumab infusion (first and re-treatment periods) - 2/2	All treated analysis set
Listing	Emapalumab exposure	All treated analysis set
Listing	Emapalumab exposure - Time between doses	All treated analysis set
Listing	Glucocorticoids exposure - Run-in phase	Run-in phase analysis set
Listing	Glucocorticoids exposure	All treated analysis set
Listing	Response assessment - Run-in phase	Run-in phase analysis set
Listing	Response assessment	All treated analysis set
Listing	Efficacy events - GC tapering, MAS recurrence and lack of response	All treated analysis set
Listing	Efficacy - Times to first Complete, Partial and Overall responses	Run-in phase analysis set
Listing	Efficacy - Times to first Complete, Partial and Overall responses	All treated analysis set
Listing	Efficacy - Times to first GCs tapering and death	All treated analysis set
Listing	Efficacy - Times to first normalization	All treated analysis set
Listing	Weekly average prednisolone equivalent daily dose over time	All treated analysis set

Listing	Adverse events	Run-in phase analysis set
Listing	Adverse events	All treated analysis set
Listing	Infusion related reactions	All treated analysis set
Listing	Infections	All treated analysis set
Listing	Serious adverse events	Run-in phase analysis set
Listing	Serious adverse events	All treated analysis set
Listing	Adverse events leading to emapalumab withdrawal	All treated analysis set
Listing	Adverse events leading to death	Run-in phase analysis set
Listing	Adverse events leading to death	All treated analysis set
Listing	Adverse events related to AxMP - Interventional phase	All treated analysis set
Listing	Adverse events leading to AxMP withdrawal - Interventional phase	All treated analysis set
Listing	Laboratory results - Hematology	Run-in phase analysis set
Listing	Laboratory results - Hematology	All treated analysis set
Listing	Laboratory results - Biochemistry	Run-in phase analysis set
Listing	Laboratory results - Biochemistry	All treated analysis set
Listing	Laboratory results - Coagulation	Run-in phase analysis set
Listing	Laboratory results - Coagulation	All treated analysis set
Listing	Laboratory results - Urinalysis	Run-in phase analysis set
Listing	Laboratory results - Urinalysis	All treated analysis set
Listing	Laboratory Local lab ranges	Run-in phase analysis set
Listing	Laboratory Local lab ranges	All treated analysis set
Listing	Pregnancy test results	All treated analysis set - Female
Listing	Infection pathogen log	Run-in phase analysis set
Listing	Infection pathogen log	All treated analysis set
Listing	Vital signs	Run-in phase analysis set
Listing	Vital signs	All treated analysis set
Listing	Tuberculosis Infection Surveillance - Screening	All treated analysis set
Listing	Tuberculosis clinical examination	All treated analysis set
Listing	MAS clinical signs and symptoms, and clinical activity score	Run-in phase analysis set
Listing	MAS clinical signs and symptoms, and clinical activity score	All treated analysis set
Listing	Electrocardiogram results	All treated analysis set
Listing	Pharmacodynamic results	All treated analysis set
Listing	Pharmacokinetic results (emapalumab concentrations))	All treated analysis set
Listing	Immunogenicity results	All treated analysis set
Listing	Ultrasound	All treated analysis set
Listing	Chest-x ray	All treated analysis set
Listing	Brain MRI	All treated analysis set
Listing	Glucocorticoid toxicity assessment	Run-in phase analysis set
Listing	Glucocorticoid toxicity assessment	All treated analysis set
Listing	PedsQL dimensions	Run-in phase analysis set
Listing	PedsQL dimensions	All treated analysis set
Listing	PedsQL scores	Run-in phase analysis set

Listing	PedsQL scores	All treated analysis set
Listing	Global Impression of Severity	Run-in phase analysis set
Listing	Global Impression of Severity	All treated analysis set
Listing	Survival status	All treated analysis set
Listing	Death details	Run-in phase analysis set
Listing	Death details	All treated analysis set
Listing	Visit details	Run-in phase analysis set
Listing	Visit details	All treated analysis set

Appendix 5 - List of Figures

				Subgroups									
Type	**Title**	**Population**	**Sub-population (Cohort)**	**Sex**	**Age**	**Race**	**Region**	**Washout Biologic before study entry**	**Organs involvment**	**Concomitant G-CSF treatment**	**Dial/ Hemofiltration at screening**	**Concomitant biologics during long term FUP**	**HZ prophylaxis treatment**
Figure	Time to first complete response	All treated analysis set	Cohort: Still's disease										
Figure	Time to first complete response	All treated analysis set	Cohort: SLE										
Figure	Time to first achievement of glucocorticoid tapering	All treated analysis set	Cohort: Still's disease										
Figure	Time to first achievement of glucocorticoid tapering	All treated analysis set	Cohort: SLE										
Figure	Time to first achievement of weekly average prednisolone equivalent daily dose below or equal 1mg/kg/day	All treated analysis set	Cohort: Still's disease										
Figure	Time to first achievement of weekly average prednisolone equivalent daily dose below or equal 1mg/kg/day	All treated analysis set	Cohort: SLE										
Figure	Time to first achievement of weekly average prednisolone equivalent daily dose below or equal 0.5 mg/kg/day	All treated analysis set	Cohort: Still's disease										
Figure	Time to first achievement of weekly average prednisolone equivalent daily dose below or equal 0.5 mg/kg/day	All treated analysis set	Cohort: SLE										

Figure	Time to first achievement of weekly average prednisolone equivalent daily dose below or equal 0.2 mg/kg/day	All treated analysis set	Cohort: Still's disease									
Figure	Time to first achievement of weekly average prednisolone equivalent daily dose below or equal 0.2 mg/kg/day	All treated analysis set	Cohort: SLE									
Figure	Time to first overall response	All treated analysis set	Cohort: Still's disease									
Figure	Time to first overall response	All treated analysis set	Cohort: SLE									
Figure	Survival time / Time to death	All treated analysis set	Cohort: Still's disease	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Figure	Survival time / Time to death	All treated analysis set	Cohort: SLE	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	
Figure	Time to first normalization - MAS clinical activity score below or equal to 1cm	All treated analysis set	Cohort: Still's disease									
Figure	Time to first normalization - MAS clinical activity score below or equal to 1cm	All treated analysis set	Cohort: SLE									
Figure	Time to first normalization - White blood cell above LLN	All treated analysis set	Cohort: Still's disease									
Figure	Time to first normalization - White blood cell above LLN	All treated analysis set	Cohort : SLE									
Figure	Time to first normalization - Platelet count above LLN	All treated analysis set	Cohort: Still's disease									
Figure	Time to first normalization - Platelet count above LLN	All treated analysis set	Cohort: SLE									

Figure	Time to first normalization - Lactate dehydrogenase below 1.5 ULN	All treated analysis set	Cohort: Still's disease
Figure	Time to first normalization - Lactate dehydrogenase below 1.5 ULN	All treated analysis set	Cohort: SLE
Figure	Time to first normalization - Alanine transaminase below 1.5 ULN	All treated analysis set	Cohort: Still's disease
Figure	Time to first normalization - Alanine transaminase below 1.5 ULN	All treated analysis set	Cohort: SLE
Figure	Time to first normalization - Aspartate aminotransferase below 1.5 ULN	All treated analysis set	Cohort: Still's disease
Figure	Time to first normalization - Aspartate aminotransferase below 1.5 ULN	All treated analysis set	Cohort: SLE
Figure	Time to first normalization - Fibrinogen higher than 100 mg/dL	All treated analysis set	Cohort: Still's disease
Figure	Time to first normalization - Fibrinogen higher than 100 mg/dL	All treated analysis set	Cohort: SLE
Figure	Time to first normalization - Ferritin levels decreased by at least 80 % or below 2000 ng/ml	All treated analysis set	Cohort: Still's disease
Figure	Time to first normalization - Ferritin levels decreased by at least 80 % f or below 2000 ng/ml	All treated analysis set	Cohort: SLE

Figure	Overview of Rheumatological diseases and/or MAS therapies prior to study initiation	All treated analysis set	
Figure	Overview of emapalumab/MAS treatments administered doses and laboratory parameters during the study	All treated analysis set	
Figure	Mean (SD) of Pharmacodynamic results versus Time	All treated analysis set	Cohort: Still's disease
Figure	Mean (SD) of Pharmacodynamic results versus Time	All treated analysis set	Cohort: SLE
Figure	Pharmacodynamic results versus Time of Individual Subjects	All treated analysis set	Cohort: Still's disease
Figure	Pharmacodynamic results versus Time of Individual Subjects	All treated analysis set	Cohort: SLE
Figure	Mean (SD) of Pharmacokinetic results (emapalumab concentrations) versus Time	All treated analysis set	Cohort: Still's disease
Figure	Mean (SD) of Pharmacokinetic results (emapalumab concentrations) versus Time	All treated analysis set	Cohort: SLE

Figure	Pharmacokinetic results (emapalumab concentrations)versus Time of Individual Subjects	All treated analysis set	Cohort: Still's disease
Figure	Pharmacokinetic results (emapalumab concentrations)versus Time of Individual Subjects	All treated analysis set	Cohort: SLE

Appendix 6 - NI-0501-14 Sample size report

The NI-0501-14 Sample size report is included in SAP version 1.0 (23MAR2021)