Statistical Analysis Plan

Protocol number: NI-0501-05

Title: A multicentre study for the long-term follow-up of HLH patients who received treatment with NI-0501, an anti-interferon gamma monoclonal antibody

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SAP Version: Version 1.0, 26 March 2021

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1 Abbreviations and definition of terms

ADA	Anti-drug antibodies
ADaM	Analysis Data Model
AE	Adverse event
AKI	Acute Kidney Injury
ALT	Alanine aminotransferase
AOSD	Adult-onset Still's Disease
ARDS	Acute Renal Failure, Unspecified
ASA	American statistical association
AST	Aspartate aminotransferase
ATC	Anatomical therapeutic chemical
CNS	Central Nervous System
CI	Confidence intervals
COVID-19	Coronavirus disease 2019
CRF	Case report form
CSF	Cerebrospinal fluid
CSR	Clinical study report
CU	Compassionate use
CXCL9	Chemokine (C-X-C Motif) ligand 9
CXCL10	Chemokine (C-X-C Motif) ligand 10
ECG	Electrocardiogram
eCRF	Electronic case report form
FDA	Food and Drug Administration
G-CSF	Granulocyte colony stimulating factor
gGT	Gamma-glutamyl transferase
GvHD	Graft versus host disease
HLH	Hemophagocytic lymphohistiocytosis
HSCT	Hematopoietic stem cell transplantation
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IFNγ	Interferon gamma
LDH	Lactate dehydrogenase
LLN	Lower limit of normal
MAS	Macrophage activation syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
PD	Pharmacodynamic
pHLH	Primary hemophagocytic lymphohistiocytosis

PK	Pharmacokinetic
PT	Preferred term
RSS	Royal Statistical Society
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS®	A software system used for data analysis
sCD25	Soluble CD25 (i.e. soluble IL-2 receptor)
SD	Standard deviation
SDTM	Study data tabulation model
sHLH	Secondary hemophagocytic lymphohistiocytosis
sJIA	systemic Juvenile Idiopathic Arthritis
Sobi	Swedish Orphan Biovitrum
SOC	System organ class
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal
VAS	Visual Analog Scale
WBC	White blood cell
WHO-DD	World Health Organization Drug Dictionary

2 Introduction

This statistical analysis plan (SAP) describes the planned analysis and reporting for Sobi AG protocol number NI-0501-05 ("A multicentre study for the long-term follow-up of HLH patients who received treatment with NI-0501, an anti-interferon gamma monoclonal antibody"). This study has been conducted in North America and Europe according to twin protocols (NI-0501-05-P-IND #111015 and NI-0501-05-EudraCT #2012-005753-23), one for each region, both dated 31-Oct-2019 version 4.0.

This long-term follow-up study is being completed to assess the long-term efficacy and safety of emapalumab for the treatment of hemophagocytic lymphohistiocytosis (HLH) in male and female patients who have received at least one dose of emapalumab in the context of a previous emapalumab clinical study, including patients receiving emapalumab under compassionate use (CU). The research name of emapalumab was NI-0501 and both terms are used interchangeably in this document.

The purpose of this SAP is to outline the planned analyses to be completed to support the Clinical Study Report (CSR) for protocol NI-0501-05. The planned analyses identified in this SAP may be included in regulatory submissions and/or future manuscripts. 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 CSR.

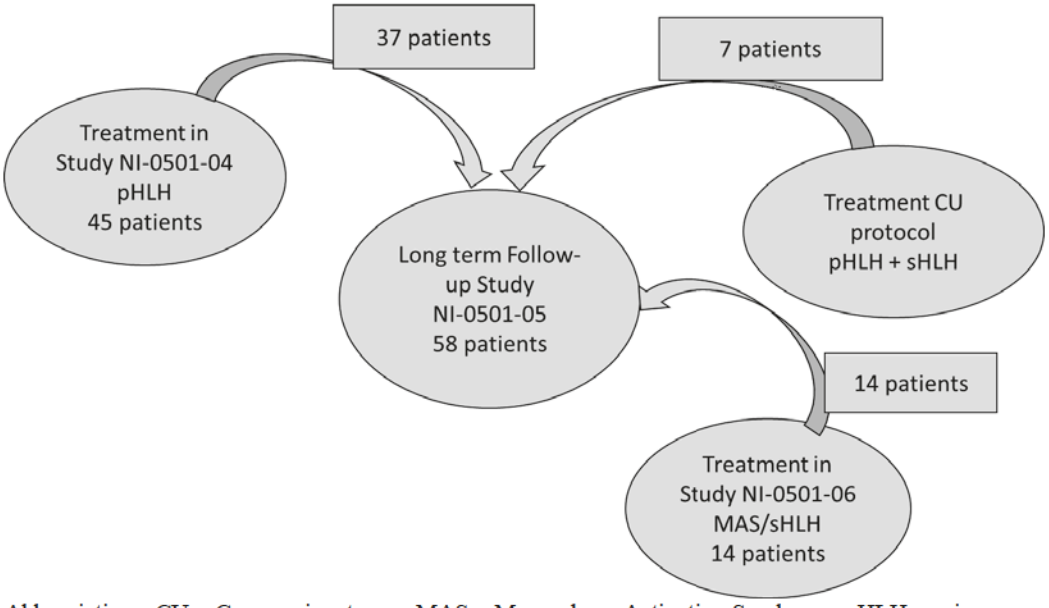
This SAP includes analysis plans for all patients enrolled in the NI-0501-05 follow-up study. These patients are separated into cohorts based on the parent emapalumab clinical study. These cohorts are described below and outlined in Figure 1:

- Enrolled-04: This cohort includes patients previously enrolled in the NI-0501-04 study, a phase 2/3 open-label, single arm, multicenter study to assess safety, tolerability, pharmacokinetics, and efficacy of intravenous multiple administrations of emapalumab, in the treatment of male and female pediatric patients (≤18 years of age at the time of HLH diagnosis) with suspected or confirmed primary HLH (pHLH).
- Enrolled-06: This cohort includes patients previously enrolled in the NI-0501-06 study, a pilot, open-label, single arm, multicenter study to evaluate safety, tolerability, pharmacokinetics, and efficacy of intravenous administrations of emapalumab, an anti-interferon gamma (anti-IFNγ) monoclonal antibody, in patients with systemic Juvenile Idiopathic Arthritis (sJIA) or Adult-onset Still's Disease (AOSD) developing Macrophage Activation Syndrome/secondary HLH (MAS/sHLH).
- Enrolled-CU: This cohort includes patients who were treated under CU and not treated under either of the above clinical studies (NI-0501-04 or NI-0501-06). Compassionate use treatment was granted to pHLH and sHLH patients having exhausted all possible treatment options and who could not be enrolled in a clinical study.

The structure and content of this SAP provides sufficient detail to meet the requirements identified by the Food and Drug Administration (FDA) and International Council for Harmonisation (ICH): Guidance on Statistical Principles in Clinical Trials[1]. All analyses planned

and reported for this SAP will follow internationally accepted guidelines, published by the American Statistical Association (ASA)[2] and the Royal Statistical Society (RSS)[3], for statistical practice.

Figure 1 Overview of the patient cohorts in the NI-0501-05 study



Abbreviations: CU = Compassionate use; MAS = Macrophage Activation Syndrome; pHLH = primary Haemophagocytic lymphohistiocytosis; sHLH = secondary Haemophagocytic lymphohistiocytosis.

Note: There are four patients who entered study NI-0501-05 twice and were assigned separate patient IDs upon re-entry into the study (including 1 patient that received a new ID upon transfer to a different study site). Details are included in Appendix 17.1.

3 Study objectives and endpoints

3.1 Study objectives

The study objectives for the NI-0501-05 are as follows:

- To monitor the long-term safety profile of emapalumab
- To assess HLH patients' survival after emapalumab treatment
- To assess duration of response to emapalumab treatment (ie, maintenance of HLH control)
- To assess post-Hematopoietic Stem Cell Transplantation (HSCT) outcome measures, if applicable

- To assess background disease activity, in patients with secondary forms of HLH
- To study the elimination profile of emapalumab
- To evaluate the pharmacodynamic (PD) effects (levels of circulating total interferon gamma [IFNγ], chemokine (C-X-C Motif) ligand 9 [CXCL9], chemokine (C-X-C Motif) ligand 10 [CXCL10])
- To assess the profile of relevant HLH biomarkers, e.g., sCD25 (soluble CD25)
- To assess the immunogenicity of emapalumab

3.2 Study endpoints

The study objectives and endpoints are presented in Table 1, including an indicator for which cohort will be assessed for each endpoint.

The safety endpoints of this study are the following:

- Incidence, seriousness, intensity, relationship to emapalumab and outcome of adverse events (AEs)
- Evolution over time of vital signs, physical examination, and laboratory values

The efficacy endpoints are the following:

- Duration of Response after completion of emapalumab treatment (assessed according to the definitions set in the parent study, NI-0501-04 or NI-0501-06).
- Survival time up to one-year post-HSCT (including survival to HSCT and survival post-HSCT) or one year after last emapalumab infusion (if transplant is not performed), calculated from the date of last emapalumab infusion.
- Overall survival calculated as time from the date of last emapalumab infusion to the date of death.
- Post-HSCT outcome indices (applicable only to patients who receive HSCT):
    - Engraftment rate, based on the number of patients experiencing primary or secondary graft failure, as reported as an AE
    - Donor chimerism achieved, based on donor chimerism in peripheral blood completed (i.e., doner cells > 95%)
    - Incidence of acute and chronic graft versus host disease (GvHD), based on occurrence of GvHD, as reported as an AE
- Monitoring of background disease activity (applicable only to patients with sHLH), as assessed by a visual analogue scale (VAS) of MAS activity.

The pharmacokinetics (PK) endpoint is:

- The emapalumab elimination profile, as assessed by levels of circulating emapalumab.

The pharmacodynamics (PD) endpoints include:

- Levels of IFNγ total.
- Exploratory PD parameters/disease markers, including sCD25, CXCL9, CXCL10.

The immunogenicity endpoint is:

- Presence of anti-drug antibodies (ADAs).

Table 1 Study Objectives and Endpoints

Objective	Endpoints	Population[1]
To monitor the long-term safety profile of emapalumab	Incidence, seriousness, intensity, relationship to emapalumab and outcome of AEs Evolution over time of vital signs, physical examination, and laboratory values	Enrolled-04 Enrolled-06 Enrolled-CU
To assess pHLH patients' survival after emapalumab treatment	Survival time up to one-year post-HSCT (including survival to HSCT and survival post-HSCT) or one year after last emapalumab infusion (if transplant is not performed or planned) calculated from the date of last emapalumab infusion	Enrolled-04
To assess sHLH patients' survival after emapalumab treatment	Overall survival time up to one year after last emapalumab infusion	Enrolled-06
To assess duration of response to emapalumab treatment (ie. maintenance of HLH control)	Duration of Response after completion of emapalumab treatment (assessed according to the definitions set in the parent study)	Enrolled-04 Enrolled-06
To assess post-HSCT outcome measures, if applicable	Post-HSCT outcome indices, e.g., engraftment rate, donor chimerism achieved, incidence of acute and chronic Graft versus Host Disease (GvHD) (it applies to patients who receive HSCT)	Enrolled-04
To assess background disease activity, in patients with secondary forms of HLH	Monitoring of background disease activity (applicable only to patients with sHLH)	Enrolled-06
To study the elimination profile emapalumab	Emapalumab elimination profile	Enrolled-04 Enrolled-06 Enrolled-CU
To evaluate the pharmacodynamic (PD) effects (levels of circulating total IFNγ, CXCL9, CXCL10)	IFNγ total Exploratory PD parameters/disease markers such as sCD25, CXCL9, CXCL10	Enrolled-04 Enrolled-06 Enrolled-CU
To assess the profile of relevant HLH biomarkers, e.g., sCD25	Exploratory PD parameters/disease markers such as sCD25, CXCL9, CXCL10	Enrolled-04 Enrolled-06 Enrolled-CU
To assess the immunogenicity of NI-0501	Presence of ADAs	Enrolled-04 Enrolled-06 Enrolled-CU

[1]. Enrolled-04, Enrolled-06, and Enrolled-CU populations are defined in Section 7.
Abbreviations: AE = adverse event; CXCL9 = chemokine (C-X-C Motif) ligand 9; CXCL1 = chemokine (C-X-C Motif) ligand 10; HSCT = hematopoietic stem cell transplantation; PD = pharmacodynamics; sCD25 = soluble CD25 (ie, soluble IL-2 receptor).

4 Study methods

4.1 Overall study design and plan

This is an international multicentre long-term follow-up study of HLH patients who have received at least one dose of emapalumab in the context of a previous emapalumab clinical study in which no long-term follow-up was already planned. Patients who have received emapalumab under CU treatment protocol may also be considered for enrolment, whenever appropriate.

Patients will enter the NI-0501-05 study either after the last emapalumab infusion or at the end of the short-term follow-up in the parent study, depending on the design of the parent study. Given the fact that patients with different forms of HLH (pHLH or sHLH) can be enrolled in this study, the schedule of assessments differs based on HSCT status: patients who underwent or will undergo HSCT vs. patients for whom HSCT is not planned. Only patients with pHLH are considered for HSCT.

Emapalumab treatment can be continued in the NI-0501-05 study, upon the request of the Investigator in case of the need to delay the schedule for HSCT for reasons unrelated to the administration of emapalumab, provided that a favorable benefit/risk has been established for the patient.

The schedule of assessments for patients enrolled in this study is described in the study protocol, Table 1 for patients who underwent or will undergo HSCT and Table 2 for patients for whom HSCT is not planned. Further assessments for patients continuing emapalumab treatment during the study are described in Appendix A of the study protocol.

4.2 Selection of study population

The study population comprises male and female HLH patients who have received at least one dose of emapalumab in a previous emapalumab clinical study in which no long-term follow-up was planned. An Informed Consent Form (ICF) was signed by the patient or the patient's legal representative(s), as applicable, with the assent of patients who are legally capable of providing it. Patients having received emapalumab under CU were also included where appropriate.

There are no exclusion criteria.

4.3 Method of treatment assignment and randomization

Not applicable.

5 Sequence of planned analysis

5.1 Interim analyses

As described in the protocol, data collected in this study may be analyzed on multiple occasions as the study proceeds, in order to facilitate the development programme for emapalumab and to optimize the dissemination of information which may help patient care. These analyses were described in the parent study (NI-0501-04) analysis plan (NI-0501-04 SAP V4 03NOV2017; V5 20SEP2019).

5.2 Analyses and reporting

Data for this long-term follow-up study is collected in two separate databases: one for Enrolled-04 and Enrolled-CU, and one for Enrolled-06. Data for each study cohort will be presented separately as described in this SAP.

All final, planned analyses identified in the protocol and in this SAP will be performed only after the last patient has completed the study (last patient last visit) for that cohort, and a data review will be held prior to database lock. The SAP will be finalized and signed prior to the first database lock.

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

6 Sample size determination

A formal sample size calculation was not performed for this long-term, follow-up study. The number of patients enrolled in this study is based on the sample size of the parent studies and under CU.

7 Analysis populations

The following analysis populations are planned for this study, separated by cohort as described in Section 2:

- Enrolled-04 includes all consented patients who were previously treated in the NI-0501-04 study.
- Enrolled-06 includes all consented patients who were previously treated in the NI-0501-06 study.
- Enrolled-CU includes all consented patients who have been previously treated in CU and were not otherwise treated in a clinical study (NI-0501-04 or NI-0501-06).

7.1 Protocol deviations

Protocol deviations are medically reviewed and categorized as major, minor and exception on an ongoing basis. The final log will be confirmed during a data review meeting, which will be conducted prior to database lock for that cohort. Individual major, minor and exception protocol deviations will be listed by patient.

7.2 COVID-19

A coronavirus disease 2019 (COVID-19) continuity plan has been written to mitigate the negative effects of the COVID-19 pandemic on the conduct of this clinical trial, maintain continuity of study delivery, and, most importantly, ensuring patient safety and wellbeing for patients in the NI-0501-05 study.

The impact of COVID-19 on this clinical trial and trial participants will be included in the listings presenting protocol deviations.

8 General issues for statistical analysis

Tabulations will be produced for appropriate demographic, baseline, efficacy, PK, PD, and safety parameters.

Continuous data will be summarized using descriptive statistics: n, mean, standard deviation (SD), median, minimum, and maximum, unless otherwise indicated. Minimum and maximum will be presented to the same number of decimal places as the raw data and mean, standard deviation, standard error of the mean and median will be presented to one more decimal place than the raw data.

Categorical data will be summarized using counts and percentages. 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 within the group of the population of interest, unless otherwise indicated. Percentages will be presented to one decimal place.

Time-to-event data will be summarized using Kaplan-Meier methodology using 25th, 50th (median), and 75th percentiles with associated 2-sided 95% confidence intervals (CIs), as well as count and percentage of events and censored observations. Endpoints based on binary outcomes, including post-HSCT outcome efficacy measures, will be converted to proportions and associated 95% CIs calculated.

All data will be listed in individual patient data listings. Dates will include a relative study day, presenting the number of days from enrollment (ie, date of consent) in the NI-0501-05 study. Select dates will include a study day, presenting the number of days from date of first dose in the parent study.

Data for each study cohort will be presented separately. For the Enrolled-CU cohort, only listings will be presented, data will not be further summarized in any tables or figures.

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

The immortal time is when subjects cannot experience an event of interest during some period of follow-up time, which can lead to bias if not adequately analyzed. In this study the immortal time is the period between the date of the last visit in the parent study and the date of enrollment in the NI-0501-05 study, thus there is no immortal time for these cohorts by study design.

8.1 Handling of missing data and outliers

There will be no imputation for missing or partial dates for AEs or concomitant medications.

For the duration of response efficacy endpoint, imputation methods for missing parameters in assessment of response are described in Section 8.5.1 for the Enrolled-04 cohort and Section 8.5.2 for the Enrolled-06 cohort.

No other imputations of missing data are planned.

8.2 Multicenter studies

As relatively few patients are included in the study, the study sites will not be taken into account in the analyses, and data for each cohort will be pooled across sites.

8.3 Multiple comparisons and multiplicity

No multiplicity adjustment will be considered, since all analyses are descriptive and no formal hypothesis tests are planned for this long-term, follow-up study.

8.4 Analysis visit windows

All statistical analyses will be based on scheduled or unscheduled visits as collected in the Case Report Form (CRF) or as mapped in the source SDTM (study data tabulation model) data. The first visit in NI-0501-05 study will be labeled as "First study-05 visit."

Further details on the mapping of visit labels from the CRF will be documented in the ADaM (analysis data model) define.XML file.

'Baseline' will be used for the baseline visit in the parent study as defined in Section 8.5. These observations will be integrated from the parent study source data in the analysis datasets. For Enrolled-CU not all parameters were collected, therefore baseline from parent study does not apply.

8.5 Derived and computed variables

The following derived variables will be calculated:

- Age (years) at time of consent for the NI-0501-05 study:
  Age (years) = (Date of Informed consent – date of birth+1)/365.25
  - Note: The age variable will be calculated to 1 decimal place, to account for patients less than a year old.
- Baseline: the last observation occurring prior to the first treatment administration of emapalumab from the parent study
  - Note: observations occurring on the same day as first treatment administration may be the baseline assessment only if the time of assessment occurs prior to the time of treatment. If this cannot be determined, the observation will be assumed to have occurred after dosing.
- Change from baseline = value at current time point – value at baseline
- Relative day (calculated as study day relative to informed consent in study NI-0501-05) = Event date – date of informed consent +1
- Day (calculated as number of days from the first dose in the parent study) = Event date - date of the first dose in the parent study + 1
- Patients who completed the NI-0501-05 study = patients that completed the 1 year visit (i.e., 1 year post HSCT or after last emapalumab infusion)
- Pre-conditioning AEs = any AE with an onset date before the start date of conditioning for HSCT*
- Post-conditioning AEs = any AE with an onset date on or after the start date of conditioning for HSCT*, applicable only to those patients with an HSCT conditioning start date. If the patient received HSCT prior to enrollment (either in NI-0501-04 or CU), all AEs in the NI-0501-05 study will be considered as having occurred after HSCT conditioning.
- Infection: any AEs from the System Organ Class (SOC) 'Infections and infestations'
- Concomitant medication: any medications that are continuing or start after enrollment (i.e., date of informed consent in NI-0501-05). If an end date is missing or the medication is ongoing at the time of study treatment, the medication will be considered concomitant.

*Note: The start date of conditioning will be derived based on the start date of the first medication administered for HSCT conditioning, as described in Appendix 17.5.

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

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

Not all patients will receive treatment under the NI-0501-05 protocol. For those who receive treatment, the definitions of drug administration variables are provided in Table 2, and will be derived using the dosing data from the NI-0501-05 study only.

Table 2: Definition of Drug Administration Variables

Statistics for Exposure (dosing)	NI-0501-04 and CU
Duration of dosing (days and weeks) in NI-0501-05	Last infusion date - first infusion date+1 (days) (Last infusion date - first infusion date+1)/7 (weeks)
Cumulative dose per kg in NI-0501-05 study	Sum of total dose per kg administered from first infusion date until last infusion date in the NI-0501-05 study.
Average dose frequency (in days) in NI-0501-05	Duration of dosing (days) / total number of infusions
Average dose (mg/kg) per day in NI-0501-05	Cumulative dose (mg/kg) / duration of dosing (days)

8.5.1 Efficacy variables: Enrolled-04 cohort

Overall response in the Enrolled-04 cohort is defined as achievement of Complete Response, Partial Response, or HLH Improvement. Criteria for the definition of response are presented in Table 3 and are according to the definitions set in the parent study, Study NI-0501-04. A more detailed specification for implementation of these criteria to derive Overall Response is presented in Appendix 17.3.

Table 3: Definition of Response

Complete Response	Complete Response is adjudicated if: • No fever = body temperature < 37.5°C • Normal spleen size confirmed by abdominal ultrasound whenever possible • No cytopenia = Absolute Neutrophil Counts ≥ $1.0x10^9$/L and platelet count ≥ $100x10^9$/L [absence of G-CSF and transfusion support must be documented for at least 4 days to report no cytopenia] • No hyperferritinemia = serum ferritin level is < 2000 µg/L • No evidence of coagulopathy, i.e., normal D-Dimer and/or normal (> 150 mg/dL) fibrinogen levels • No neurological and CSF abnormalities attributed to HLH • No sustained worsening of sCD25 (as indicated by at least two consecutive measurements that are > 2-fold higher than baseline)
Partial Response	Partial Response is adjudicated if: • At least 3 of the HLH clinical and laboratory abnormalities (including Central Nervous System [CNS] abnormalities) meet the above-mentioned criteria for "Complete Response." In the case of "reactivated patients" who enter the study with 3 abnormal HLH features, at least 2 criteria should meet the definition given • There is no progression of other aspects of HLH disease pathology (e.g., jaundice, liver size, oedema, CNS clinical alterations)
HLH improvement	• Normalization or Improvement (>50% change from baseline) of at least 3 HLH clinical and laboratory abnormalities (including CNS involvement). In the case of "reactivated patients" who enter the study with 2 abnormal HLH features, a change from baseline greater than 50% for both will define HLH as improved.

Abbreviations: CSF = cerebrospinal fluid; CNS = central nervous system; HLH = hemophagocytic lymphohistiocytosis; G-CSF = granulocyte colony stimulating factor; sCD25 = soluble CD25 (ie, soluble IL-2 receptor).

For defining Overall Response, values of some parameters may be missing, thus impacting the response assessment. Imputation rules for assessing disease response throughout the study have been pre-defined as follows:

- For calculation of duration of response, both scheduled and unscheduled visits will be used for assessment of response.
- If a parameter needed for the response assessment is missing, the midpoint approach will be used to estimate the missing value – i.e., the last observed value before the missing period will be averaged with the first value available after the missing period. Imputed values will be flagged in the listings. This rule will be applied to parameter values missing for a period of up to a maximum of 7 consecutive days. In case that, after imputation, data is still missing in any of the criteria considered for the definition of response, a Complete Response cannot be adjudicated.
- Since data relevant to CNS assessment has been collected at irregular time-points (based on individual patient conditions), the most recent experts' assessment of CNS status will be carried-forward for subsequent time-points.

Cumulative duration of response will be calculated as follows:

- The time in response will be calculated from the first achievement of an Overall Response until start of HSCT conditioning (or end of treatment if the patient did not have HSCT performed). Considering patients may achieve a response, lose that response, and then achieve it subsequently, the total time in response will be calculated by adding together these separate periods in response. Patients who are in response at the time of HSCT conditioning start will be censored at that date. Patients who do not achieve response at least once between the date of first dose and the time of conditioning start are excluded from the analysis.
- Each response duration is defined as the total elapsed time from achievement of response to subsequent loss of response, pending the duration of each is at least 4 days. If the observed response or loss of response does not last for at least 4 days, then the next response period will be considered.
- The start date of conditioning is derived based on the start date of the first medication administered for HSCT conditioning, as described in Appendix 17.5.
- The percentage of days in response will be derived as cumulative response duration divided by number of days from first infusion until HSCT conditioning (or end of treatment if the patient did not have HSCT performed).

Survival:

Survival up to HSCT, up to one year post HSCT, and overall survival will be calculated for the Enrolled-04 cohort as follows:

- Survival pre HSCT is defined as the time from the date of last dose to the date of death.

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

  Patients who receive an HSCT will be censored at that date. Patients who did not receive HSCT will be censored at last of contact date or 365 days after last dose (whichever comes first).

- Survival post HSCT is defined as the time from the date of HSCT (the last HSCT if a patient has more than one HSCT) to the date of death.

  Time to death = date of death – date of HSCT + 1

  Patients without an event will be censored at last of contact date or 365 days after last dose (whichever comes first).

  Patients who do not proceed to HSCT will be excluded from this analysis.

- Overall survival is defined as time from the date of last dose to the date of death. Patients without an event will be censored the time of last contact or 365 days after last dose (whichever comes first).

8.5.2 Efficacy variables: Enrolled-06 cohort

Response and duration of response will be derived for the Enrolled-06 cohort as follows:

- Response (MAS remission) after completion of emapalumab treatment (assessed according to the definitions set in the parent study NI-0501-06 (NI-0501-06 SAP V2.0 29OCT20 Section 6.1.7 Derived variables).

  MAS remission = resolution of clinical signs and symptoms according to the Investigator (defined as a MAS clinical signs and symptoms score ≤ 1) AND normalization of laboratory parameter relevant to MAS as follows:

  - White blood cell count (WBC) and platelet count above the lower limit of normal (LLN)
  - Lactate dehydrogenase (LDH) below 1.5 times the upper limit of normal (ULN)
  - Alanine aminotransferase/aspartate aminotransferase (ALT/AST) below 1.5×ULN
  - Fibrogen higher than 100 mg/dL
  - Ferritin level decreased by at least 80% from values at screening or baseline (whichever is higher) or below 2000 ng/mL, whichever is lower

  If one or more laboratory data are unavailable, MAS remission cannot be evaluated.

- MAS recurrence is defined as not meeting the above criteria for remission.

  Duration of response will be calculated in the subgroup of patient showing MAS remission during the parent study NI-0501-06, defined as the time from date of first MAS remission during the parent study until the first date of MAS recurrence or death.

  date of MAS recurrence/death – date of first MAS remission + 1

Patients who meet the criteria of MAS remission at the end of the study will be censored at the date of last disease assessment (ie, date last known to be in MAS remission).

The MAS remission evaluation is based on a combination of assessments, including Investigator assessment and laboratory findings. The latest date of assessments, within the visit label, will be used for the calculation of the duration of response.

Survival: Overall survival time up to one year after last emapalumab infusion will be calculated as follows:

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

Patients who survive to the end of the study (i.e., beyond 365 days after date of last infusion) will be censored at the date of last contact or 365 days after last dose (whichever comes first). Patients who withdrew consent will be censored at the date of withdrawal of consent.

9 Patient disposition

A tabulation of patient disposition will be provided for the Enrolled-04 and Enrolled-06 cohorts (presented separately). For each cohort, the number of patients for each of the following categories will be presented:

- Number of patients enrolled (i.e., the enrolled population for that cohort)
- Number of patients who received treatment in the NI-0501-05 study
- Number of patients who completed the NI-0501-05 study
- Number of patients who withdrew from the NI-0501-05 study
- Reason for not completing the NI-0501-05 study

Percentages will be calculated using the number of patients in the enrolled population for that cohort.

All disposition data, including the study completion status and the reason for not completing the study will be listed for all cohorts (Enrolled-04, Enrolled-06, and Enrolled-CU). The date of first and last dose received (in either the parent study or NI-0501-05 study) will also be included in the listings.

A by-patient listing of protocol deviations and relationship to COVID-19, as described in Sections 7.1 and 7.2, will be also presented.

10 Demographics and medical history

10.1 Demographics

Summary statistics for age at time of consent in the NI-0501-05 study, sex, and race will be tabulated separately for the Enrolled-04 and Enrolled-06 cohorts. A by-patient listing of age, sex,

and race will be presented for all cohorts (Enrolled-04, Enrolled-06, and Enrolled-CU), including height and weight data at first study 05 visit.

10.2 Medical history

All medical history data will be coded using the latest version of Medical Dictionary for Regulatory Activities (MedDRA) version 23.0. Medical history collected in NI-0501-05 study will be presented in listings only for the Enrolled-04 and Enrolled-CU cohorts.

11 Concomitant medication

All concomitant medications will be coded using World Health Organization drug dictionary (WHO-DD) 2019 version or later.

Concomitant medications will be summarized descriptively by Anatomical Therapeutic Chemical (ATC) level 2 and preferred term (PT) using counts and percentages for the Enrolled-04 and Enrolled-06 cohorts.

Any medications that are continuing or start after the enrollment will be considered concomitant. If an end date is missing or the medication is ongoing at the time of study treatment, the medication will be considered concomitant.

Concomitant medications and procedures (including transfusions) will be presented in listings for all cohorts, including a flag for HSCT conditioning medications as applicable. A separate listing for HSCT procedures will be presented for the Enrolled-04 and Enrolled-CU cohorts only.

12 Efficacy analyses

12.1.1 Efficacy analyses: Enrolled-04 cohort

Cumulative duration of response will be presented using descriptive statistics, both overall and as a percentage of days in response.

The survival endpoints (overall survival, survival pre HSCT, and survival post HSCT) will be analyzed descriptively using Kaplan-Meier methodology. The 25th, 50th (median), and 75th percentiles with associated 2-sided 95% CIs, Month 3, 100 days, Month 6, and Month 12 survival probability estimates with associated 95% CIs, as well as count and percentage of events and censored observations will be summarized. A Kaplan–Meier curve will also be presented for each time-to-event endpoint.

Binary endpoints:

- **Post HSCT engraftment rates:** based on the number of patients experiencing primary or secondary graft failure, as reported in the AE module of eCRF (electronic CRF), Appendix 17.1.
- **Post HSCT acute and chronic GvHD incidence:** based on occurrence of GvHD, as reported in the AE module of eCRF, Appendix 17.2.
- **Donor chimerism:** based on donor chimerism in peripheral blood completed (ie, donor cells > 95%) as reported in Chimerism Update module of eCRF.

For these binary secondary endpoints, the number and proportion of patients will be provided with two-sided 95% CIs.

All efficacy data will be provided in data listings.

12.1.2 Efficacy analyses: Enrolled-06 Cohort

The numeric level of background disease activity will be tabulated using descriptive statistics by visit. MAS activity is monitored using a VAS ranging from 0 to 10 by steps of 0.5 (as collected on the CRF).

Duration of response and overall survival will be analyzed descriptively using Kaplan-Meier methodology. The 25th, 50th (median), and 75th percentiles with associated 2-sided 95% CIs, Month 3, 100 days, Month 6, and Month 12 survival probability estimates with associated 95% CIs, as well as count and percentage of events and censored observations will be summarized. A Kaplan–Meier curve will also be presented for each time-to-event endpoint.

All efficacy data, including the parameters used to derive response over time (with baseline values from the parent NI-0501-06 study), will be provided in data listings.

12.1.3 Efficacy analyses: Enrolled-CU cohort

The survival variable (date os death) in the Enrolled-CU cohort will be listed only.

13 Safety analyses

Safety will be evaluated from reported AEs, clinical laboratory findings, changes in vital signs, 12-lead electrocardiograms (ECGs), physical examination results, and emergence of ADAs.

These analyses will be conducted for the Enrolled-04 and Enrolled-06 cohorts separately, with the data from the Enrolled-CU cohort presented in listings only.

13.1 Drug exposure

Not all patients are expected to receive treatment during this long-term, follow-up study. None of the Enrolled-06 patients will receive treatment during the NI-0501-05 study, thus drug exposure will be presented for the Enrolled-04 and Enrolled-CU cohorts only.

13.1.1 Enrolled-04 cohort

The number of patients who received treatment during the NI-0501-05 study will be summarized. Duration of dosing (in days and weeks), cumulative dose per kg, average dose frequency (in days), and average dose (mg/kg) per day will be summarized for those patients who received treatment, using dosing data from the NI-0501-05 study only.

All dosing data will be provided in a data listing.

13.1.2 Enrolled-06 cohort

Study drug exposure is not applicable during the conduct of the NI-0501-05 study.

13.1.3 Enrolled-CU cohort

All dosing data will be provided in data listings, including the derived variables of duration of dosing (in days and weeks), cumulative dose per kg, average dose frequency (in days), and average dose (mg/kg) per day will be listed for those patients who received treatment, using dosing data from the NI-0501-05 study only.

13.2 Adverse events

All AEs and serious AEs (SAEs) will be coded using MedDRA version 23.0. Summaries will be presented separately for the Enrolled-04 and Enrolled-06 cohorts.

For the Enrolled-04 and Enrolled-CU cohorts, AEs will be flagged as occurring pre- or post-HSCT conditioning start, as defined in Section 8.5.

A summary table will present the number and percent of patients reporting as least one of the following:

- AE (overall and by maximum severity)
- Treatment-related AE
- Serious AE
- Treatment-related serious AE
- AE resulting in death

- AE leading to study drug withdrawal (Enrolled-04 and Enrolled-CU cohorts only)
- AE classified as an infection

For the Enrolled-04 cohort, this summary table will be presented for those events occurring pre-HSCT conditioning, post-HSCT conditioning, and overall.

Summaries of the incidence of AEs will be displayed by:

- System Organ Class (SOC) and Preferred Term (PT)
- SOC, PT and maximum severity
- SOC, PT and maximum relationship to study drug

The AE tables will summarize the incidence of AEs and the number of patients with at least one given AE (sorted in descending order of the total frequency count), including the number of overall events, unless otherwise indicated.

In the case of multiple occurrences of the same AE in the same patient, each patient will only be counted once for each PT. However, all multiple occurrences will be included in the number of events.

In the summary tables by severity and relationship to study drug, the event with the maximum severity or strongest relationship will be reported. If a particular event is missing the severity and/or relationship, then the strongest possible severity or relationship will be assumed for analysis (severity = severe, relationship = related).

By-patient AE data listings with all AEs will be generated.

13.2.1 Serious adverse events

SAEs will be tabulated by:

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

SAEs will be described in a separate data listing.

13.2.2 Adverse events leading to study drug withdrawal

AEs leading to study drug withdrawal will be tabulated by SOC and PT for Enrolled-04 cohort. By-patient data listings of AEs leading to withdrawal will be provided for both Enrolled-04 and Enrolled-CU cohorts.

13.2.3 Deaths

By-patient data listings of AEs with a fatal outcome will be displayed.

13.2.4 Infections

AEs classified as an infection will be tabulated by:

- PT and maximum severity

All events from the SOC "Infections and infestations" will be presented.

A by-patient listing of all infections reported in the infections log (including search for infections and pathogen details) will be displayed with date of sampling, test, specimen, and result.

13.3 Laboratory data

Shift tables will present changes from baseline (as defined in Section 8.5) to worst on-study and last on-study values relative to normal ranges (ie, below, within, above, or missing) for each parameter, except for ALT, AST, gamma-glutamyl transferase (gGT), LDH, and total bilirubin for which a medically relevant multiple of ULN will be presented. The worst on-study values will be presented by highest and lowest values. For ALT, AST, and gGT medically relevant multiples are 2.5xULN, for LDH and total bilirubin medically relevant multiples are 1.5xULN. Missing categories will be included.

Clinical chemistry, hematology, and coagulation results will be presented in separate tables for the Enrolled-04 and Enrolled-06 cohorts.

Urinalysis results will not be tabulated. Abnormalities in urinalysis results assessed as medically relevant will be recorded as AEs and analyzed as described in Section 13.2.

All laboratory values (including individual change from baseline for Enrolled-04 and Enrolled-06 cohorts) will be displayed in the data listings, including cerebrospinal fluid and pregnancy test results, and those that are outside the normal range will be flagged. A separate listing of all abnormal laboratory results will be presented for all cohorts. Data listings will include both standard and original units.

13.4 Vital signs

Descriptive summaries of actual values by visit will be presented for systolic blood pressure (mmHg), diastolic blood pressure (mmHg), heart rate (bpm), respiratory rate, and highest daily body temperature (Celsius) for Enrolled-04 and Enrolled-06 cohorts.

All vital signs will be provided in data listings for all cohorts.

13.5 Physical examination

By-patient listing of all physical exam data will be displayed by body system: skin, ears/nose/ throat, lymphadenopathies, abdominal examination (other than hepato-/spleno-megaly), hepatomegaly, splenomegaly, respiratory, cardiovascular, neurological, and other.

Abnormalities related to physical examination and reported as adverse event will be analyzed as described in Section 13.2.

13.6 Pharmacokinetic/pharmacodynamic analysis

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

However, descriptive summaries for the following parameters will be presented by visit (observed results and change from baseline):

- Levels of circulating emapalumab.
- Levels of circulating IFNγ, main IFNγ-induced chemokines (CXCL9, CXCL10), other potential disease markers (sCD25).

Even when no emapalumab was administered within the NI-0501-05 study, PK and PD samples were collected during the study.

These PK/PD will be presented in data listings.

In addition, population PK analysis is planned to be conducted based on the pooled data from Study NI-0501-04, Study NI-0501-05, Study NI-0501-06 and patients treated under CU. Explorative analysis on the relation between emapalumab concentrations and safety parameters may also be conducted. These analyses will be described in a separate data analysis plan.

13.7 Immunogenicity – anti-drug antibodies (ADAs)

A list of patients who developed ADAs will be presented for each cohort.

13.8 Further safety evaluations

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

The following additional safety data will be included in by-patient listings only:

- 12-lead Electrocardiogram (ECG) results
- Imaging: abdominal ultrasound, chest X-ray, and magnetic resonance imaging (MRI) data
- Hospitalization details

14 Changes to planned analyses

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

- Duration of Response: The protocol (Section 6) states that duration of response after completion of emapalumab treatment will be evaluated. This SAP describes assessment of response throughout the course of participation (either in the parent study or this extension protocol) as follows:
  - Duration of Response for the Enrolled-04 cohort is defined as cumulative response duration, ie, the total number of days in response from the first achievement of response until HSCT conditioning or last treatment date if the patient did not have HSCT performed.
  - Duration of Response for the Enrolled-06 cohort is defined as the number of days between first date of response and first date of loss of response.
- Handling missing data: The protocol (Section 10) stated no imputation of missing data will be applied. In this SAP, for the duration of response efficacy endpoint, imputation methods for missing parameters in assessment of response are described in Section 8.5.1 for the Enrolled-04 cohort and Section 8.5.2 for the Enrolled-06 cohort.

15 Tables, listings, and figures

Table and listing shells are provided as a separate document. No shells are provided for figures.

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

The final statistical tables will be produced in the format of the shells and will additionally include “double” page numbering in the format “page xx of yy.” The first page numbering (‘xx’)

will count all pages of the document continuously and the second numbering ('yy') will count the pages for each table separately.

All output will be incorporated into Microsoft Word, or Adobe Acrobat PDF files, sorted and labeled according to the ICH recommendations, and formatted to the appropriate page size(s).

16 References

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

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

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

17 Appendix

17.1 Flow diagram for patients who entered Study NI-0501-05 more than once

Patient ID for Analysis (enrolled cohort)	Temporal Course of Study Participation			
	1	2	3	4
[redacted] (04 cohort)	NI-0501-04 (pt ID [redacted])	NI-0501-05 (pt ID [redacted])	CU_NI-0501 (pt ID [redacted])	NI-0501-05 (pt ID [redacted])
[redacted] (04 cohort)	NI-0501-04 (pt ID [redacted])	NI-0501-05 (pt ID [redacted])	CU_NI-0501 (pt ID [redacted])	NI-0501-05 (pt ID [redacted])
[redacted] (04 cohort)	NI-0501-04 (pt ID [redacted])	NI-0501-05 (pt ID [redacted])	NI-0501-05 (pt ID [redacted])	N/A
[redacted] (CU cohort)	CU_NI-0501 (pt ID [redacted])	NI-0501-05 (pt ID [redacted])	CU_NI-0501 (pt ID [redacted])	N/A

17.2 Adverse events classification by system organ class and preferred term for acute and chronic GvHD and graft failure

System Organ Class Code	System Organ Class	Preferred Term Code	Preferred Term
Acute and Chronic GvHD			
10021428	Immune system disorders	10066264	Acute graft versus host disease in intestine
10021428	Immune system disorders	10066262	Acute graft versus host disease in skin
10021428	Immune system disorders	10018651	Graft versus host disease
10021428	Immune system disorders	10075160	Graft versus host disease in gastrointestinal tract
10021428	Immune system disorders	10064676	Graft versus host disease in liver
10021428	Immune system disorders	10064675	Graft versus host disease in skin
10021428	Immune system disorders	10051396	Engraftment syndrome
Graft Failure			
10022117	Injury, poisoning and procedural complications	10059032	Blood stem cell transplant failure
10022117	Injury, poisoning and procedural complications	10068081	Engraft failure
10022117	Injury, poisoning and procedural complications	10074860	Transplant dysfunction

17.3 Overall response detailed derivation

The HLH parameters used to assess disease response for the Enrolled-04 cohort, according to the definition of response reported in Table 3, are described in Table 4. Details for deriving the overall response are described in Table 5.

Table 4: HLH Parameters for Assessment

HLH Parameter	Variables Used for Assessment	Definition of Normalization
Parameters that are measured for improvement		
1. Body temperature	SDTM.VS	Below 37.5°C in all measurements performed on that day
2. Spleen as assessed at physical examination	SDTM.PE	Reported as Normal (= 0 cm from costal margin)
3. Absolute Neutrophil Count and G-CSF administration	SDTM.LB; SDTM.CM where ATC code=L03AA	Absolute Neutrophil Count is equal/greater than 1.0 x 109/L, and no G-CSF has been administered in the previous 4 days
4. Platelet count and platelet transfusion	SDTM.LB; SDTM.PR where PRCAT = Transfusions	Platelet count is equal/greater than 100 x 10^9/L, and no platelet transfusion administered in the previous 4 days
5. Ferritin	SDTM.LB	Less than 2000 µg/L
6. Fibrinogen and D-dimers	SDTM.LB	Fibrinogen greater than 1.5 g/L OR D-dimers equal/less than 500 ug/L
7. CNS disease involvement, as assessed by medical team	SDTM.FA	CNS disease ='No' or 'Normalized' means Normal and to be used for CR and PR assessment; CNS= 'Improved' is to be used for HLH improvement assessment
Parameters that are measured for worsening of disease		
HLH Parameter	**Variables Used for Assessment**	**Definition of Worsening**
sCD25 levels	SDTM.PD, where PARAMCD = 'sIL2RA'	Percent Change from Baseline (for the last two sCD25 data points before assessment) is not > 200%
Ongoing AE which indicates presence of organ failure	SDTM.AE, where organ failure is identified by preferred terms selected by the Sobi medical team, listed in Appendix 17.4	No ongoing AE at time of response assessment

Table 5: Derivation of Overall Response

Response	Application of Criteria	Example
Complete Response	– All HLH parameters that were abnormal at baseline must be normalized – All other parameters that were normal at baseline must still meet the definition of normalized – No worsening of disease observed, as assessed by presence of ongoing selected AE or worsening of sCD25 levels	Subject started with 5 abnormal parameters. All 5 improved, and the remaining parameters continue to meet definition of normalized. There are no ongoing AEs that indicate organ failure.
Partial Response	– At least 3 of the HLH parameters that were abnormal at baseline must be normalized. The remaining may be the same or worse as baseline (unless 2 or more parameters no longer meet the definition of normality) Note: If 3 parameters were abnormal at baseline, only 2 need to be normalized. If 2 parameters were abnormal at baseline, only 1 needs to be normalized – No worsening of disease observed, as assessed by presence of ongoing selected AE or worsening of sCD25 levels	Subject started with 4 abnormal parameters. Three (3) of the parameters now meet definition of normalized. The fourth is still abnormal. No more than 1 parameter (normal at baseline) crosses the normality threshold. There are no ongoing AEs that indicate organ failure.

Response	Application of Criteria	Example
HLH Improvement	– At least 3 of the HLH parameters that were abnormal at baseline must be normalized or improved (i.e., >=50% change from baseline). The remaining may be the same or worse as baseline (unless 2 or more parameters no longer meet the definition of normality) Note: If 3 parameters were abnormal at baseline, only 2 need to be at least improved. If 2 parameters were abnormal at baseline, only 1 needs to be improved – No worsening of disease observed, as assessed by presence of ongoing selected AE or worsening of sCD25 levels Definition of 50% improvement from baseline: – Spleen size decreased by 50%, as recorded in cm from costal margin at physical examination. – Absolute Neutrophil Count increased by 50%, if G-CSF has not been administered in the previous 4 days – Platelet count increased by 50%, if no platelet transfusion has been administered in the previous 4 days – Ferritin decreased by 50% – Fibrinogen increased by 50% or D-Dimer decreased by 50% – CNS= 'Improved'	Subject started with 4 abnormal parameters. Two (2) of the parameters now meet definition of normalized. The third improved >50%, but is still abnormal. The fourth is still abnormal and did not improve >50%. No more than 1 parameter (normal at baseline) crosses the normality threshold. There are no ongoing AEs that indicate organ failure.
No Response	If a subject does not meet the criteria for at least HLH improvement, response is categorized as "No Response"	Subject meets the definition of partial response, but has worsening disease as identified by an ongoing AE indicating organ failure at time of assessment.

Abbreviations: AE = adverse event; CNS = central nervous system; HLH = hemophagocytic lymphohistiocytosis; G-CSF = granulocyte colony stimulating factor; sCD25 = soluble CD25 (ie. soluble IL-2 receptor).

17.4 Adverse events indicating organ failure by MedDRA preferred term and code

Preferred Term Code	Preferred Term
10051093	Cardiopulmonary failure
10038695	Respiratory failure
10001053	Acute respiratory failure
10000804	Acute hepatic failure
10038435	Renal failure
10077361	Multiple organ dysfunction syndrome
10010264	Condition aggravated
10001051	ARDS (Acute Renal Failure, Unspecified)
10069339	AKI (Acute Kidney Injury)

17.5 Concomitant medications for HSCT conditioning

HSCT CONDITIONING

Conditioning Agents to Consider [SDTM.CM]

ATC Level 4	Preferred Code	Preferred Text
L01AA	00021101001 00006401001	CYCLOPHOSPHAMIDE MELPHALAN
L01AB	00036801001 00418901001	BUSULFAN TREOSULFAN
L01AC	00053501001	THIOTEPA
L01BB	02122001001 01004601001 01004602001	CLOFARABINE FLUDARABINE FLUDARABINE PHOSPHATE
L01BC	00146201001	CYTARABINE
L01CB	00511901001 00511902001	ETOPOSIDE ETOPOSIDE PHOSPHATE
L01XC	01402501001	RITUXIMAB
L04AA	 01268601001 00575401001 00575402001 02082701001	ALEMTUZUMAB ANTITHYMOCYTE IMMUNOGLOBULIN ANTITHYMOCYTE IMMUNOGLOBULIN (RABBIT) ANTILYMPHOCYTE IMMUNOGLOBULIN

Then:

For Patients with HSCT date [SDTM.PR]

- Med Start Date: >=HSCT date – 16 days (med should start not earlier than 16 days before transplant)

and

- Med End Date: <= HSCT date (med end date should be latest date of transplant)

For Patients without HSCT date [SDTM.PR]

- Med with Indication containing: Conditioning

Start of conditioning is the first start date of any of the selected drugs.

Certificate Of Completion

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Signatures: 2
Certificate Pages: 5
Initials: 0
AutoNav: Enabled
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Witness Events	Signature	Timestamp

Notary Events	Signature	Timestamp

Envelope Summary Events	Status	Timestamps
Envelope Sent	Hashed/Encrypted	3/29/2021 4:59:56 PM
Certified Delivered	Security Checked	3/30/2021 9:22:59 AM
Signing Complete	Security Checked	3/30/2021 9:23:26 AM
Completed	Security Checked	3/30/2021 9:23:26 AM

Payment Events	Status	Timestamps

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