AMENDED STATISTICAL ANALYSIS PLAN 01

Protocol title:	**Open-label, Single-arm Trial to Evaluate Antitumor Activity, Safety, and Pharmacokinetics of Isatuximab Used in Combination With Chemotherapy in Pediatric Patients From 28 Days to Less Than 18 Years of Age With Relapsed/Refractory B or T Acute Lymphoblastic Leukemia or Acute Myeloid Leukemia In First or Second Relapse**
Protocol number:	**ACT15378**
Compound number (INN/Trademark):	**SAR650984** **Isatuximab**
Study phase:	**2**
Short title:	**Isatuximab in Combination with Chemotherapy in Pediatric Patients with Relapsed/Refractory Acute Lymphoblastic Leukemia or Acute Myeloid Leukemia (ISAKIDS)**
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VERSION HISTORY

This statistical analysis plan (SAP) for study ACT15378 is based on the protocol amendment V5.0 dated 14-Oct-2021.

Table 1 - Major changes in statistical analysis plan

Document	Approval Date	Changes	Rationale
Original SAP	07-Dec-2020	Not Applicable	Original version
Amended SAP 01	02-May-2022	Section 3 Analysis population: The evaluation population has been changed to: The evaluable population will include participants from the AT population who received at least 1 full dose of isatuximab in Cycle 1 and who had at least one valid response value that is evaluable.	Updated according to Amended Protocol 05
		Section 4.3.5: Subgroup analyses Add one more column to provide derivation algorithms for those that are not retrieved directly for CRF data.	To provide derivation algorithms.
		Section 4.3.5: Subgroup analyses 1, Removed MRD 2, Added 4 more subgroup categories: Immunophenotyping, Prior lines, Prior cell therapy, and Prior transplant.	1, This becomes redundancy because it is actually the secondary efficacy endpoint. 2, To provide more supplemental subgroup analyses on primary efficacy endpoint.
		Section 4.7.6.2 Analyses of laboratory variables: Add modified baseline for lab results as: Baseline for laboratory analysis is defined as the last assessment prior to the first administration of isatuximab	For clarification.

1 INTRODUCTION

1.1 STUDY DESIGN

This is a Phase 2 single arm, multicenter, open-label study evaluating the antitumor activity, safety, and pharmacokinetic (PK) of isatuximab in combination with standard salvage chemotherapies in participants with Relapsed/Refractory Acute Lymphoblastic Leukemia (R/R ALL) (including both T- and B-ALL) and Acute Myeloid Leukemia (AML) conducted in 3 separate cohorts. Male and female children from 28 days to less than 18 years of age with R/R B- or T-ALL or AML in first or second relapse will be eligible.

1.1.1 Study participants and cohorts

Three cohorts of study participants will be treated:

- B-ALL
- T-ALL
- AML

Approximately 128 participants will be screened (32, 48, and 48 for the T-ALL, B-ALL, and AML cohorts, respectively) to achieve 104 participants assigned to study treatment (approximately 26, 39, and 39 in the T-ALL, B-ALL, and AML cohorts, respectively) and 96 evaluable participants for an estimated total of 24, 36, and 36 evaluable participants in the T-ALL, B-ALL, and AML cohorts, respectively.

For an assessment of the dose for children younger than 2 years of age, 20 participants of 2 years of age or more (at least 5 participants in the age group of 2 to 10 years, including approximately 3 patients between 2 and 5 years old) will be enrolled first to check the isatuximab exposure.

In addition, for each cohort, at the end of the trial, at least 5 participants should be recruited for each of the following age groups: 28 days to 4 years of age, 5 to 11 years of age, and 12 to 18 years of age.

1.1.1.1 Screening

The screening assessments are to be performed within 3 weeks prior to the first study intervention administration (Day 1), unless indicated otherwise. The screening assessment data obtained prior to the informed consent may be accepted if performed within 1 month prior to Day 1.

All of the inclusion criteria (and none of the exclusion criteria) must be met, and informed consent must be signed by the legally acceptable representative of the participant before any study-specific procedure is performed.

Screening procedures are to be performed/assessed in accordance with the Schedule of Activities (SOA) in the protocol.

In order to have rapid control of the tumor burden, in addition to dexamethasone pre-dose mandatory in ALL cohorts, the administration of following cytoreductive therapies are proposed (these are examples):

- cyclophosphamide up to 1g/m² PO or IV for 1 day before isatuximab treatment for ALL
- hydroxyurea 50-75 mg/kg/day PO for 4-5 days before isatuximab treatment for AML
- cytarabine up to 1g/m² IV every 12 hours for up to 2-3 days before isatuximab treatment for AML

Dexamethasone 10 mg/m²/day (or equivalent) before the first study intervention administration (at least 3 times, on Days -3, -2, and -1) is (mandatory for ALL cohorts as a part of study treatment and optional for AML cohort). Administration of dexamethasone on Day 1 is mandatory in both cohorts as part of isatuximab premedication.

1.1.2 Study treatment period

In all 3 disease cohorts, participants will receive 1 administration of single agent isatuximab on Day 1. Starting on Day 8, combination chemotherapy will be added. In case of rapid degradation of patient's status during this week, chemotherapy could be started earlier than Day 8.

A bone marrow (BM) aspiration will be performed at screening (including minimal residual disease [MRD] screening sample, only for ALL cohorts), between Days 8 and 15 (optional; between second and third isatuximab infusion), between 36 and 43 days for the ALL cohorts, for the AML cohort either between Days 22 and 29 or at the time of hematological recovery (at least 48 hours after last injection of G-CSF, when neutrophils will reach 1 G/L and platelet count 100 G/L); this last sample is recommended but not mandatory if peripheral blood blasts are present. The MRD will be done at the time of hematological recovery and/or at the time of each BM aspirate for disease assessment if complete response (CR) or complete response with incomplete peripheral recovery (CRi) is achieved.

1.1.3 Post-study treatment period

After completion of these treatment periods, participants will be treated following Investigator's and site's standard of care.

1.1.4 Study duration

The duration of the study for an individual participant will include:

- The screening period of up to 3 weeks prior to the first study treatment administration
- The on-treatment period
- The period of aplasia followed by recovery period
- An EOT visit within 30 days after hematological recovery
- Follow-up period.

Participants with documented disease progression at the EOT visit will be followed for survival every 4 months until death or final analysis cut-off date, whichever comes first.

Participants without documented disease progression at the EOT visit and who have not yet started treatment with another anticancer therapy will receive follow-up visits every 2 months until initiation of another anticancer therapy, disease progression, death or final analysis cut-off date, whichever comes first. After disease progression or initiation of a new anticancer treatment, participants will be followed every 4 months for survival until death or the cut-off date.

Also, during the follow-up period, women of childbearing potential will perform pregnancy assessments every month, until 6 months after the last dose of isatuximab, or 12 months after the last dose of cyclophosphamide and at least 6 months after other IMPs discontinuation (vincristine, pegaspargase, L-asparaginase (Erwinase), methotrexate, etoposide, doxorubicin, mitoxantrone, fludarabine, cytarabine), whatever occurs last and with the longest recommended period of contraception.

In case the participant or the LAR withdraws consent for any reason or following the Investigator's opinion that the participant will not follow the planned treatment, no follow-up will be done after these decision dates.

The final analysis cut-off date will be approximately 12 months after first study treatment administration in the last participant enrolled in the study. After the final analysis cut-off date, only new related AEs (serious or not), all ongoing SAE (related or not) and all ongoing related non-serious AEs and related concomitant medications will continue to be collected.

1.2 OBJECTIVE AND ENDPOINTS

The objectives and their corresponding endpoints are presented in the table below.

Table 2 - Objectives and endpoints

Objectives	Endpoints
Primary	
To evaluate the anti-leukemic activity of isatuximab in combination with chemotherapies in pediatric participants of ages 28 days to 18 years with R/R ALL or AML as measured by CR + CRi	Morphological CR rate defined as the proportion of participants with CR+CRi, in each cohort. **For AML:** • CR: bone marrow blasts lower than 5%; No blasts with Auer rods or persistence of extramedullary disease; absolute ANC higher than 1000/mm^3, platelets higher than 100 000/mm^3; transfusion independence. • CRi: same criteria as for CR, except neutrophils and/or platelets recovery. **For ALL:** • CR: bone marrow blasts lower than 5%, no circulating blasts or lymphoblasts in CSF or extramedullary disease; ANC higher than 1000/mm^3, platelets higher than 100 000/mm^3.

Objectives	Endpoints
	• CRi: same criteria as for CR, except neutrophils and/or platelets recovery. • Extramedullary disease: complete resolution of lymphomatous enlargement by computed CT. For participants with a previous positive PET scan, a post-treatment residual mass of any size is considered a CR as long as it is PET negative.
Secondary	
• Safety and tolerability assessments	• Safety assessment, in terms of AEs/SAEs, laboratory parameters, vital signs, and physical examination.
• Assessment of IRs	• Incidence and severity of IRs.
• PK of isatuximab	• PK parameters of isatuximab calculated using a population PK approach including at least C_{max}, C_{trough}, and AUC.
• Minimal residual disease	• Estimation of minimal residual disease in participants achieving CR or CRi.
• Overall response rate	• The overall response rate is defined as the proportion of participants with CR or CRi for blood and bone marrow disease; PR based on the NCCN guideline will be considered
• Overall survival	• Overall survival is defined as the time interval from the date of first study treatment administration to death from any cause.
• Event free survival	• Event free survival is defined as the time interval from the date of first study treatment administration to the date of the first of: completion or going off protocol induction/consolidation therapy without CR, relapse from CR, or death due to any cause.
• Duration of response	• Duration of reponse is defined as the time from the date of the first response to the date of first disease progression or death from any cause, whichever happens first.
• Relationship between clinical effects and CD38 receptor density and occupancy	• CD38 receptor density will be assessed at baseline and CD38 receptor occupancy at Day 15 and correlated with clinical endpoints.
Tertiary/exploratory	
• Immunogenicity of isatuximab	• Immunogenicity of isatuximab assessed throughout the study by detecting the presence of antidrug antibodies.
• PK/ PD relationships with regards to safety and efficacy endpoints.	• PK/PD parameters estimated as prognostic factors for clinical outcomes including safety and efficacy endpoints, if possible

AE = adverse event; ALL = acute lymphoblastic leukemia; AML = acute myeloid leukemia; ANC = absolute neutrophil count; AUC = area under the curve; B-ALL = B-cell acute lymphoblastic leukemia; Cmax = maximum serum concentration; CR = complete response; CRi = complete response with incomplete peripheral recovery; CSF = cerebrospinal fluid; CT = computed tomography; Ctrough = lowest serum concentration reached by a drug before the next dose is administered; IR = infusion reaction; NCCN = National Comprehensive Cancer Network; PD = pharmacodynamics; PET = positron emission tomography; PK = pharmacokinetics; PR = partial response; R/R = relapsed or refractory; SAE = serious adverse event; T-ALL = T-cell acute lymphoblastic leukemia.

2 SAMPLE SIZE DETERMINATION

A 2 stage Simon's Min/Max design was used for sample size calculations in 3 cohorts (T-ALL, B-ALL, and AML).

T-ALL cohort: a maximum of 24 evaluable participants will be enrolled in this cohort. This sample size will provide 80% power to reject the null hypothesis that the CR rate is ≤60% if the complete response (CR + CRi) rate is ≥80%, based on a 1-sided exact binomial test at a significance level of 0.1:

- Stage 1: 11 evaluable participants. Proceed to Stage 2 if more than 6 responses are observed
- Stage 2: 24 evaluable participants (13 additional participants). If more than 17 responses are observed among the 24 participants evaluable for efficacy, the null hypothesis will be rejected.

B-ALL cohort and AML cohort: a maximum of 36 evaluable participants will be enrolled in each cohort. This sample size will provide 80% power to reject the null hypothesis that the CR rate is ≤70% if the complete response (CR + CRi) rate is ≥85%, based on a 1-sided exact binomial test at a significance level of 0.1:

- Stage 1: 23 evaluable participants. Proceed to Stage 2 if more than 17 responses are observed
- Stage 2: 36 evaluable participants (13 additional participants). If more than 28 responses are observed among the 36 participants evaluable for efficacy, the null hypothesis will be rejected.

3 ANALYSIS POPULATIONS

The following populations for analyses are defined:

Table 3 - Populations for analyses

Population	Description
All-treated	The AT population will include all participants who received at least 1 dose (even incomplete) of study intervention. This population is the primary population for the analyses of safety parameters.
Evaluable population	The evaluable population will include evaluable participants from the AT population who received at least 1 full dose of isatuximab in Cycle 1 and who had at least one valid response value that is evaluable. This population is the primary population for the analyses of efficacy parameters.
PK	The PK population will include all participants from the AT population with at least 1 PK parameter available.
ADA evaluable	The ADA evaluable population will include all participants from the AT population with at least 1 non-missing ADA result during the on-study observation period.

ADA = antidrug antibody; ALL = acute lymphoblastic leukemia; AML = acute myeloid leukemia; AT = all-treated; PK = pharmacokinetic.

4 STATISTICAL ANALYSES

4.1 GENERAL CONSIDERATIONS

The following are general considerations for statistical analysis.

- Data from participants enrolled in 3 cohorts (T-ALL, B-ALL, and AML) will be analyzed separately.
- Unless otherwise specified, analyses will be descriptive and performed on the AT population, except for the analyses of efficacy endpoints that will utilize the evaluable population.
- The baseline for a given parameter is defined as the last assessment for this parameter before the first study intervention administration unless otherwise specified.
- Continuous data will be summarized using the number of available observations, mean, SD, median, minimum, and maximum by cohort and overall (where applicable).
- Categorical and ordinal data will be summarized using the number and percentage of participants by cohort and overall (where applicable).
- All efficacy analysis will be performed using the evaluable population for each ALL and AML cohort.
- The database will be locked when clinical review of the database has been completed and all critical queries have been resolved.
- All summaries and statistical analyses will be generated using SAS® version 9.4 or higher.

Planned date for analysis cut-off

For each cohort, the cut-off date for interim analysis (Stage 1) will be approximately 2 months after the last participant is treated in Stage 1.

For each cohort, the cut-off date for the primary analysis of complete response (CR + CRi) and other secondary endpoints will be approximately 6 months after the last participant has had their first study intervention administration. The final analysis cut-off date for the analysis of OS and other secondary endpoints will be approximately 12 months after the last participant has had their first study intervention administration.

4.2 PARTICIPANT DISPOSITIONS

Participant disposition will be summarized by cohort based on the analysis populations defined in Section 3.

For participant study status, the total number of participants for each of the following categories will be presented in the clinical study report using a flow-chart diagram or a summary table:

- Screened patients

- Enrolled patients
- Enrolled and not treated patients
- Enrolled and treated patients
- Patients still on treatment
- Patients completed treatment
- Patients who discontinued the study treatments period and reasons for permanent discontinuation.

The number and percentage of participants in analysis populations (defined in Section 3) will be provided in a summary table.

A summary of the reasons for definitive and premature treatment discontinuation for either treatment will be provided. Definitive treatment discontinuation is defined as the discontinuation of all the study treatments. Premature treatment discontinuation is defined as the discontinuation of one of the study treatments but the other one continued. Listing of the reasons for treatment discontinuation will be provided.

The number (%) of participants treated by country and center will be summarized using the all-treated population (defined in Section 3).

All critical or major deviations potentially impacting efficacy and safety analyses will be summarized by cohort separately. Critical or major protocol deviations will be listed.

Protocol deviations

Critical and major protocol deviations (automatic or manual) will be summarized in the all-treated population.

4.3 PRIMARY EFFICACY ENDPOINT(S) ANALYSIS

4.3.1 Definition of primary efficacy endpoint

The primary efficacy endpoint of the study is the complete response rate (CR + CRi), which is defined as the proportion of participants achieving complete response (CR + CRi) assessed by the investigator per NCCN Guidelines version 1.2018 criteria, relative to the total number of patients in the analysis population.

4.3.2 Main analytical approach

The complete response (CR + CRi) rate will be summarized with descriptive statistics on the all evaluable population. An 80% confidence interval will be computed using the Clopper Pearson method.

4.3.3 Sensitivity analysis

There is no sensitivity analysis planned to perform on the primary efficacy endpoint.

4.3.4 Supplementary analyses

Analysis will be performed based on the all-treated participants with valid response assessment for the primary efficacy endpoint as supplementary analysis.

4.3.5 Subgroup analyses

Subgroup analyses will be performed as supplemental to support the primary efficacy. The subgroup categories are specified in Table 4 below.

Additional subgroup analysis may be produced as appropriate upon the study team's request.

Table 4 - List of variables for subgroup analyses

Subgroup Category	Description	Derivation if applicable
Extramedullary	Yes vs No	Derived upon 'Disease Involvement Location' in Leukemia / Lymphoma Diagnosis. 'Yes' if any location is checked except bone marrow. 'No' otherwise.
Refractory to prior treatment	Yes vs No	
Hyperleucocytosis prior to Isatuximab	Yes vs No	'Yes' if WBC >20 prior to isatuximab administration. 'No' otherwise.
Selected observed cytogenetics	negative vs positive	Select the following: 11q23, t(12;21), t(9;22), and under 'Other' - IAMP21, T(1;19)
Selected immunophenotyping	negative vs positive	Select the following: CD19, CD22 for B-ALL; CD33 for AML.
Number of prior lines	1 vs 2 vs >2	
Prior cell therapy	Yes vs No	'Yes' if any therapy of Blinatumomab, Gemtuzumab, or CAR T cell received. 'No' otherwise.
Prior allogeneic transplant	Yes vs No	
Age	28 days to 4, 5 to 11, and equal or greater than 12 years old	

Subgroup analyses will be conducted when at least 10 patients are included in a subgroup.

4.4 SECONDARY EFFICACY ENDPOINT(S) ANALYSIS

4.4.1 Definition of secondary endpoints

The secondary efficacy endpoints are specified in the subsequent sections.

4.4.1.1 Minimal residual disease (MRD)

Proportion of participants with CR or CRi who have achieved negative MRD will be analyzed.

4.4.1.2 Overall response rate (ORR)

ORR is defined as the proportion of participants with CR, CRi, or PR.

4.4.1.3 Overall survival (OS)

OS is defined as the time interval from the date of first study treatment administration to death from any cause.

If patient did not die prior to the analysis cut-off date or the study completion date, OS will be censored at the last date the patient was known to be alive or the cut-off date, whichever comes first.

4.4.1.4 Event free survival (EFS)

EFS is defined as the time interval from the date of first study treatment administration to the date of the first of: completion or going off protocol induction/consolidation therapy without complete response, relapse from complete response or death due to any cause.

In absence of the above events, EFS will be censored at the cutoff date or the last date the patient was known to be alive, whichever comes first.

4.4.1.5 Duration of response

The DOR is defined as the time from the date of the first response to the date of first disease progression or death from any cause, whichever happens first. In absence of disease progression or death before the cutoff date or the date of the last valid response assessment, DOR will be censored at the date of the last valid response assessment not showing disease progression or the analysis cut-off date, whichever is earlier. DOR will not be calculated for patients who do not achieve a response.

4.4.1.6 CD38 Receptor density and occupancy

CD38 receptor density (RD) at baseline and receptor occupancy (RO) at Day 15 in blood will be assessed.

4.4.2 Main analytical approach

The analyses of secondary efficacy endpoints will be performed as described:

- Minimal residual disease: The number and percentage of participants by MRD status (negative and positive) will be provided.

- Overall response rate: ORR will be summarized with descriptive statistics. A 80% confidence interval will be computed using Clopper-Pearson method.
- Overall survival (OS) will be analyzed using the Kaplan-Meier method. The Kaplan-Meier estimates of the 25th, 50th and 75th percentiles and the 95% confidence intervals of median will also be computed. The Kaplan-Meier curves will be plotted.
- Event free survival (EFS) will be analyzed using the Kaplan-Meier method. The analyses will be provided by for patient with bridging to transplant vs patients without bridging to transplant. The Kaplan-Meier estimates of the 25th, 50th and 75th percentiles and the 95% confidence intervals of median will also be computed. The Kaplan-Meier curves will be plotted. The analyses will be provided by patients with bridging to transplant vs patients without bridging to transplant.
- Duration of response (DOR) will be analyzed using the Kaplan-Meier method. The Kaplan-Meier estimates of the 25th, 50th and 75th percentiles and the 95% confidence intervals of median will also be computed. The Kaplan-Meier curves will be plotted.
- CD38 receptor density (RD) at baseline and receptor occupancy (RO) at Day 15 will be summarized with descriptive statistics across the efficacy responses.

4.4.3 Subgroup anaslysis for selected secondary efficacy endpoints

A subgroup analysis for selected secondary efficacy endpoints (eg, DOR, EFS and OS) may be performed using subgroups specified in Table 4 if considered necessary.

4.5 TERTIARY/EXPLORATORY ENDPOINT(S) ANALYSIS

Additional exploratory endpoints can be added if considered appropriate.

Exploratory analysis will be descriptive unless otherwise specified.

4.6 MULTIPLICITY ISSUES

There is no formal statistical test to be performed for this study. Multiplicity is not an applicable issue.

4.7 SAFETY ANALYSES

All safety analyses will be performed based on the AT population (Section 3) for each ALL and AML cohort, and overall, unless otherwise specified.

The analysis of the safety variables will be essentially descriptive, and no testing is planned. Table 5 provides a brief list of safety endpoints and their corresponding analysis methodology.

Table 5 - Safety analyses

Endpoint	Statistical Analysis Methods
Secondary	
AEs/SAEs	Descriptive statistics
Laboratory parameters, vital signs, and physical examination	Descriptive statistics
Incidence and severity of IRs	Descriptive statistics
Incidence of seizures graded >=3 as AESI	Descriptive statistics
Tertiary/Exploratory	
ADA against isatuximab	Descriptive statistics
	If needed, other tertiary/exploratory analyses will be described in the statistical analysis plan finalized before database lock

ADA = antidrug antibody; AE = adverse event; IR = infusion reaction; SAE = serious adverse event.

4.7.1 Extent of exposure

The extent of study treatment exposure will be assessed and summarized on the all-treated population.

4.7.1.1 Extent of investigational medicinal product exposure

The overall extent of exposure will be assessed as:

- Overall number of cycles started
- Duration of overall exposure (weeks): defined as Min[(last day of last cycle, date of death) – first day of first cycle]/7. The first day of first cycle is defined as the date of the first dose of study treatments. The last day of last cycle is defined as the later date of the following:
  - Day of the last dose of isatuximab +7 days
  - Day of the last dose of any other IMPs.

Total number of cycles started, number of cycles started by patient by category (ie, number [%] of patients receiving 1 cycle or 2 cycles), duration of overall exposure will be summarized using descriptive statistics.

4.7.1.2 Isatuximab or other study treatment exposure

The following variable will be described to summarize each IMP exposure (ie, isatuximab, Dexamethasone, Fludarabine, Cytarabine Anthracycline, G-CSF, Mitoxantrone and Doxorubicin etc):

- Total number of cycles started
- Number of cycles started by patient by category (C1, C2)

- Duration of exposure (weeks) is defined as
  - For isatuximab:
    - Min[(Date of the last dose of isatuximab + 7 days, date of death) – date of the first dose of isatuximab]/7 if the frequency of infusion is QW
    - Min[(Date of the last dose of isatuximab + 14 days, date of death) – date of the first dose of isatuximab]/7 if the frequency of infusion is Q2W (only in consolidation period for ALL cohorts).
  - For others:
    - Min[(Date of last dose of other, date of death) - first dose of other + 1 day]/7.
- Actual dose (mg/kg): is defined as the actual dose (mg) administered divided by the body weight at the time.
- Cumulative dose (mg/kg): the cumulative dose is the sum of all actual doses (mg/kg) of isatuximab given from the first to the last administration.
- Actual dose intensity (ADI, mg/kg/week): is defined as the cumulative dose (mg/kg) divided by the duration of isatuximab exposure (weeks).
- Relative dose intensity (RDI, %):

  $$100 \times \frac{\text{ADI (mg/kg/week)}}{\text{Planned Dose Intensity (mg/kg/week)}}.$$

  Planned dose intensity (mg/kg/week) corresponds to the planned dose (mg/kg) multiplied by the theoretical total number of doses during the started cycles and divided by the theoretical cycle duration (weeks).
- The total number of cycles started, number of cycles started by patients by category (ie, number [%] of patients receiving at least 1 cycle, at least 2 cycles), duration of isatuximab exposure, cumulative dose, ADI and RDI will be summarized by descriptive statistics.

The following variables will be derived to describe dose modification:

- Infusion interruption: an infusion is considered to be interrupted (as collected on eCRF) if the isatuximab administration is stopped during an infusion before it is completed regardless of whether it is further restarted or not.
- Dose omission: a dose is considered omitted if the dose is not administered for the scheduled visit and there are dose(s) administered afterwards at the planned dates.

Dose modification will be summarized at the patient and infusion levels as follows:

- Patient level:
  - Number (%) of patients with at least 1 dose omission
  - Number (%) of patients with at least 1 infusion interrupted

  - Number (%) of patients with at least 1 infusion interrupted and re-started
  - Number (%) of patients with at least 1 infusion interrupted and not re-started.
- Infusion level:
  - Number of isatuximab infusions
  - Number (%) of infusions interrupted
    - Number (%) of infusions interrupted and re-started
    - Number (%) of infusions interrupted and not re-started
  - Number (%) of infusions interrupted more than once
  - Number (%) of infusions interrupted at 1st infusion, 2nd infusion, subsequent infusions
  - Time from infusion start to first interruption in minutes summarized as a continuous variable and by category (<5 minutes, 5-10 minutes, etc.).

4.7.2 Analysis of adverse events

4.7.2.1 Adverse events

The observation periods, screening period, treatment-emergent AE period, and post-treatment period, are defined as follows:

- The screening period is defined as the time informed consent is signed until the first IMP administration.
- The treatment-emergent adverse event (TEAE) period is defined as from the time of the first IMP administration until the time of hematological recovery or new anticancer therapy is started or 30 days after the last IMP, whichever is first.
- The post-treatment period is defined as the period from the end of the treatment-emergent period.

Pre-treatment AEs are defined as any AE during the screening period. Treatment-emergent AEs (TEAEs) are defined as AEs that develop, worsen (according to the Investigator opinion) or become serious during the treatment-emergent AE period. Post-treatment AEs are defined as AEs that are reported during the post-treatment period. The primary focus of AE reporting will be on TEAEs.

The TEAEs will be coded according to the MedDRA dictionary. AEs will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0. The grade will be taken into account in the summary. For participants with multiple occurrences of the same PT within an observation period, the maximum grade will be used.

4.7.2.2 Analysis of adverse events

The primary focus of adverse event reporting will be on treatment-emergent adverse events. Pre-treatment and post-treatment adverse events will be described separately.

If an AE date of onset (occurrence, worsening, or becoming serious) is incomplete, an imputation algorithm will be used to classify the AE as pretreatment, treatment-emergent, or post-treatment. The algorithm for imputing date of onset will be conservative and will classify an AE as treatment emergent unless there is definitive information to determine it is pretreatment or post-treatment. Details on classification of adverse events with missing or partial onset dates are provided in Section 5.4.

Regarding treatment discontinuation, following definitions will be used:

- **Premature** treatment discontinuation is defined when 1 of the IMPs is permanently discontinued, subjects will continue receiving the other IMP until study treatment permanent discontinuation.
- **Definitive** treatment discontinuation is defined as the discontinuation of all the study drugs.

The severity grade will be taken into account in the summary. For patients with multiple occurrences of the same AE, the maximum (worst) severity grade by period of observation will be used. Summaries will be provided for all grades and for grade ≥3 (including Grade 5). Missing grades handling is provided in Section 5.4.

The AE tables will be sorted as indicated in Table 6.

Table 6 - Sorting of AE tables

AE presentation	Sorting rules
SOC, HLGT, HLT and PT	By the internationally agreed SOC order and by alphabetic order of HLGTs, HLTs and PTs.
SOC, HLT and PT	By the internationally agreed SOC order and by alphabetic order of HLTs and PTs.
SOC and PT	By the internationally agreed SOC order and decreasing frequency of PTs[a, b]
PT	By decreasing frequency of PTs[a]

a Sorting will be based on the overall incidence.
b The table of all TEAEs presented by SOC and PT will define the presentation order for all other tables (eg, treatment-emergent SAE) presented by SOC and PT, unless otherwise specified.

Overall summary of TEAEs

An overall summary of TEAEs will be provided. The number (%) of patients who experience any of the following will be provided:

- TEAE
- TEAE of grade ≥3
- TEAE of Grade 5
- Treatment emergent SAE
- Treatment-related TEAEs (any grade)
- Treatment-related TEAEs of ≥ Grade 3

- Serious treatment related TEAEs
- TEAE leading to definitive study treatment discontinuation
- TEAE leading to premature discontinuation of Isatuximab
- AESI
- Infusion reactions (IR)
- Cytokine-release syndrome (CRS).

Analysis of all TEAEs

The number (%) of patients experiencing TEAEs by primary SOC and PT will be summarized by grade (all grades and Grade ≥3). Similar tables will be presented for treatment related TEAEs, serious TEAEs, and TEAEs leading to definitive/premature discontinuation.

TEAEs with an incidence ≥5% will be summarized by PT for all grades and Grade ≥3.

Listings of serious TEAEs, TEAEs leading to definitive or premature treatment discontinuation will be provided.

4.7.3 Analysis of infusion reactions (IRs)

4.7.3.1 Infusion reactions

IRs typically occur within 24 hours from the start of each isatuximab infusion.

Whenever possible, a diagnosis of the IR will be reported by the investigator in a specific AE page. In addition, symptoms of the IRs will be reported on a separate eCRF form.

IRs will be analyzed based on the investigator reported term collected in the specific AE pages.

4.7.3.2 Analysis of infusion reaction

IR analysis will include all adverse events regardless of relationship to isatuximab. The IRs will be summarized as follow:

- Number (%) of patients experiencing IRs according to investigator reported AEs presented by primary SOC and PT will be summarized
- Number (%) of patients experiencing anaphylaxis according to investigator
- Description of the IR diagnoses (using the diagnosis reported and excluding symptoms)
  - Number (%) of patients with action taken
  - Number (%) of patients with only 1, ≥ 1, ≥ 2, ≥ 3, ≥ 4 and ≥ 5 episodes
  - Number (%) of patients with first occurrence of IR at the first infusion and subsequent infusions

- Number (%) of patients with IR at the first and subsequent infusions
- Number (%) of patients with at least two episodes of IRs at the same infusion
- Day of onset from infusion
- Duration (in days)

Analysis of pre-treatment and post-treatment adverse events

The following analysis will be provided by grade (all grades and Grade ≥3).

- All pre-treatment AEs by primary SOC and PT, showing the number (%) of patients with at least 1 pre-treatment AE, sorted by the internationally agreed SOC order and decreasing incidence of PTs within each SOC.
- All post-treatment AEs by primary SOC and PT, showing the number (%) of patients with at least 1 post-treatment AE, sorted by the internationally agreed SOC order and decreasing incidence of PTs within each SOC.

4.7.4 Analysis of deaths

4.7.4.1 Deaths

The deaths will be summarized as follows:

- Deaths in TEAE period: includes all deaths occurring from the first IMP up to the end of the TEAE period (defined in Section 4.7.2.1).
- Deaths in post-treatment period: includes all deaths occurring after the end of TEAE period up to study closure.

4.7.4.2 Analysis of deaths

The following summaries of deaths will be generated:

- Number (%) of patients who died by study period (on-treatment, post-treatment) and reasons for death (disease progression, AE, other).
- TEAEs with fatal outcome (on the AE eCRF page as reported by the Investigator), and TEAEs with fatal outcome during the post-treatment period summarized by SOC and PT
  - In context of disease progression (death within 30 days from last study intervention administration and the cause of death is disease progression),
  - In context other than disease progression (death within 30 days from last study intervention administration and for whom cause of death is not disease progression or the death occurred more than 30 days from last study intervention administration and the cause of death is AE).

4.7.5 Analysis of adverse events of special interest (AESIs)

Adverse events of special interest may be added, modified, or removed during a study by a protocol amendment. The following are specified as AESI for the study:

- Pregnancy: a female participant entered in a study as well as pregnancy occurring in a female partner of a male participant entered in a study with IMP/NIMP.
- Symptomatic overdose (serious or nonserious) with the IMP/NIMP reported.
- Infusion reaction of Grade 1 lasting more than 24 hours.
- Infusion reaction of Grade 2 or higher, regardless of duration.
- Seizures graded ≥3

Number (%) of participants experiencing at least one AESI will be provided for each category event of interest.

A listing of patients with at least one AESI will be provided.

4.7.6 Analysis of laboratory variables

4.7.6.1 Laboratory variables

Clinical laboratory data consists of blood and urine analysis including hematology, biochemistry and urinalysis. Clinical laboratory values will be converted into standard international units that will be used in all listings and tables.

Parameters measured before the first isatuximab administration will be considered as part of the baseline measurements.

For laboratory safety variables, the treatment period is defined as the time from the first dose of study treatment (irrespective of treatment) administration to the end of treatment (EOT) visit.

Blood and urine samples for clinical laboratories parameters will be taken as defined in the study flow charts and as clinically indicated.

The safety laboratory assessments required by protocol are listed in the table below.

Table 7 - Protocol required safety laboratory assessment

Laboratory assessments	Parameters			
Hematology	Platelet count		White blood cell count with differential:	
	Red blood cell count		Neutrophils	
	Hemoglobin		Lymphocytes	
	Hematocrit		Monocytes	
			Eosinophils	
			Basophils	
			Blasts	
Clinical chemistry[a]	Blood urea nitrogen	Potassium	Aspartate aminotransferase(AST)/Serum glutamic-oxaloacetic transaminase	Total and direct bilirubin
	Creatinine	Sodium	Alanine aminotransferase (ALT)/Serum glutamic-pyruvic transaminase	Total protein
	Glucose (fasting)	Total Calcium	Amylase	Albumin
	Uric acid	Phosphorus	Lactic acid dehydrogenase	Alkaline phosphatase
	Free T4	Free T3	Thyroid-stimulating hormone	
	Ferritin	CRP		
Coagulation[a]	D-dimers AT-III	Fibrinogen	Prothrombin time and international normalized ratio	Partial thromboplastin time
Routine urinalysis	pH, glucose, protein, blood, ketones, by dipstick			

a All events of ALT ≥3 × ULN and bilirubin ≥2 × ULN (>35% direct bilirubin) or ALT ≥3 × ULN and INR >1.5, if INR measured which may indicate severe liver injury (possible Hy's Law) must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis). INR = $(PT_{test} / PT_{normal})^{(ISI\ value)}$

4.7.6.2 Analyses of laboratory variables

Each laboratory test result will be graded by CTCAE criteria, when applicable. For hematological parameters and for some biochemistry parameters, Sanofi sponsor generic normal ranges will be used for the grading of laboratory abnormalities (see the parameters in Table 7). For other biochemistry parameters (eg, for hepatic parameters), grading will be derived using the local laboratory normal ranges.

The number (%) of patients with abnormal laboratory tests at baseline and during the on-treatment period will be presented by all grades and each grade. For patients with multiple occurrences of the same laboratory variable during the on-treatment period, the maximum grade (worst) per patient will be used.

The denominator used for percentage calculation is the number of patients with at least 1 evaluation of the laboratory test during the considered observation period.

Change from baseline to each post-baseline visit will be summarized for each parameter.

Baseline for laboratory analysis is defined as the last assessment prior to the first administration of isatuximab.

4.7.7 Analysis of vital signs

4.7.7.1 Vital signs variables

Vital signs include temperature, pulse rate, respiratory rate, and blood pressure will be summarized.

Parameters measured before the first isatuximab administration will be considered as part of the baseline measurements.

4.7.7.2 Analysis of vital signs

Descriptive statistics at each visit and change from baseline to each post-baseline visit will be provided for all vital signs.

The incidence of a potentially clinically significant abnormality (PCSA) at any time during the on-treatment period will be summarized regardless of the baseline level and according to the following baseline status categories:

- Normal/missing
- Abnormal according to PCSA criterion or criteria

The PCSA criteria will determine which participants had at least 1 PCSA during the on-treatment period, taking into account all evaluations performed during the on-treatment period, including nonscheduled or repeated evaluations.

A listing of participants with at least 1 PSCA will be provided.

4.7.8 Analysis of electrocardiograms (ECGs)

4.7.8.1 Electrocardiogram variables

12-lead ECG assessments will be described as normal or abnormal.

4.7.8.2 Analyses of electrocardiogram variables

For ECG, the incidence of participants with at least one abnormal ECG during the treatment-emergent period will be summarized regardless of the baseline level and according to the following baseline status categories:

- Normal/missing
- Abnormal

A listing of patients with ECG results will be provided

4.8 OTHER ANALYSES

4.8.1 Analyses of pharmacokinetic variables

4.8.1.1 Over treatment concentrations: C_{trough} and C_{eoi}

C_{trough} defined as a sample collected before dosing, in a time window of 6 to 8 days after the previous infusion for the QW administration, in a time window of 12 to 16 days after the previous infusion for the Q2W administration, will be included in the descriptive analysis irrespectively of interruption of infusion. However, C_{trough} drawn outside time collection window described in the protocol PK flowcharts or collected after a dose deviation higher than ±50% from intended dose will be excluded from the analyses.

C_{eoi} collected after significant infusion interruption, drawn outside collection of time window described in the PK flowcharts of the protocol or collected after a dose deviation higher than ± 50% from intended dose will be excluded from the analyses.

Individual C_{trough} and C_{eoi} will be listed and summarized by descriptive statistics (such as the number of observations, arithmetic and geometric mean, median, standard deviation (SD), standard error (SE), coefficient of variation (CV)%, minimum, and maximum).

Mean (±SE) of C_{trough} will be plotted over treatment phase.

For ALL cohort, individual C_{trough} ratio (D29 vs D8, D43 vs D8, and D57 vs D8) and C_{eoi} ratio (D29 vs D1) will be listed and summarized by descriptive statistics as described above.

For AML cohort, individual C_{trough} ratio (D15 vs D8) and C_{eoi} ratio (D15 vs D1) will be listed and summarized by descriptive statistics as described above.

4.8.1.2 Population PK analysis

The population PK analyses will be described in the population PK analysis plan provided by Modeling and Simulation unit, Pharmacokinetics and Drug Metabolism (PKDM), Translational Medicine and Early Development (TMED) department.

4.8.1.3 Immunogenicity impact on PK

4.8.2 Immunogenicity analyses

Participant's ADA status, response variable (see definitions below) will be summarized on the ADA population. A summary table with the number of evaluable participants, number (%) of pre-existing ADA and negative participants at baseline, number (%) of boosted and induced participants (either transient, persistent or indeterminate) will be reported, along with descriptive

statistics of titer. Prevalence and incidence will also be presented. Kinetics of ADA responses will be described for participants with treatment-induced ADA and for participants with treatment-boosted ADA, separately.

In addition, for positive ADA participants, time to onset, duration of ADA response, and the characterization of the immune response (transient, persistent, indeterminate) will be provided.

An individual data listing with ADA samples status (positive, negative or inconclusive), the titer if applicabledate of first/last dose, duration of exposure, study period, cycle/day, time point and date/time of sampling along with C_{trough} value of the drug will be provided for positive and inconclusive ADA participants.

The impact of positive immune response on efficacy, PK and safety variables may be further explored, depending on ADA incidence.

Participant's ADA status

- Participants with **pre-existing ADA**s correspond to participants with ADAs present in samples drawn before first administration of intervention. Participants with missing ADA sample at baseline will be considered as without pre-existing ADA.
- Participants with **treatment-emergent ADA** correspond to participants with at least one treatment-induced/boosted ADA.
    - Participants with **treatment-induced ADA**s correspond to participants with ADAs that developed during the treatment-emergent (TE) period and without pre-existing ADA (including participants without pre-treatment samples).
    - Participants with **treatment-boosted ADA**s correspond to participants with pre-existing ADAs that are boosted during the TE period to a significant higher titer than the baseline. A low serial dilution schema (2-fold or 3-fold) should be applied during titration. A difference in titer values of two titer steps between treatment or follow-up sample and its baseline sample is considered significant. For examples, at least a 4-fold increase in titers for 2- fold serial dilution schema (or 9-fold increase in titers for 3- fold serial dilution schema). If no titer could be determined for a positive sample, the titer will be reported as the minimal required dilution of the assay.
- Participants **without treatment-emergent ADA** correspond to participants without treatment-induced/boosted ADA and without any inconclusive sample during the TE period.
- Participants **with inconclusive ADA** are defined as participants which cannot irrefutably be classified as with or without treatment-emergent ADA.
- Participants with cross-reactivity with endogenous protein(s) and/or cross-neutralization of endogenous protein(s)

ADA response variable:

ADA incidence is defined as the proportion of participants found to have seroconverted (treatment-induced ADAs) or boosted their pre-existing ADA response (treatment-boosted ADAs) at any time point during the TE period.

ADA prevalence defines the proportion of all subjects tested positive for ADAs (including preexisting antibodies, treatment boosted ADAs and treatment induced ADAs) at any point in time.

4.8.3 Analyses of biomarker variables

CD38 receptor density (RD) and occupancy (RO) data will be presented in summary statistics by cohort, including changes from baseline to post-baseline visits.

The data by groups of responders versus non-responders in best overall response will also be summarized.

4.8.4 Analyses of quality of life/health economics variables

Not planned for this study.

4.9 INTERIM ANALYSES (IA)

For each cohort, an interim analysis of efficacy, safety, and other data will be performed after the completion of enrollment in Stage 1 (Section 2). Enrollment may be interrupted at the end of Stage 1 until the interim analysis is performed, unless the required number of responses is reached before completion of enrollment.

A subgroup PK analysis will be performed after the first 20 participants of 2 years of age or more (at least 5 participants in the age group of 2 to 10 years, including approximately 3 patients between 2 and 5 years old) are exposed to isatuximab. The dosage for participants aged less than 2 years will be reassessed based on the results.

The analysis will include the following parameters/analyses (defined in Section 4 and Section 5.3): demographics and baseline characteristics, prior or concomitant medication, AEs (TEAE, death, SAE, TEAE leading to discontinuation, IR, AESI), efficacy (primary and selected secondary), and PK.

4.9.1 Data Monitoring Committee

Close safety monitoring of each participant is planned, and an independent DMC will regularly monitor participant safety. The first meeting will be set up to review early safety results (eg, after approximately 10 participants have completed at least one induction period), and then periodically.

Ad hoc DMC meetings may also be held if a significant safety issue or issue deemed important for discussion arises on this or any other isatuximab studies. After each meeting, the DMC will advise the Sponsor's representatives on recommendations regarding the continued safety of treating ongoing and future study participants, as well as the course of action regarding the conduct of the trial.

4.9.2 Cut-off date

For each cohort, the cut-off date for interim analysis (Stage 1) will be approximately 2 months after the last participant is treated in Stage 1. In case of stop of one of the cohorts after IA the actual date of the cut-off IA will be considered for the primary analysis of CR and other secondary endpoints.

For each cohort, the cut-off date for the primary analysis of CR and other secondary endpoints will be approximately 6 months after the last participant has had their first study intervention administration. The final analysis cut-off date for the analysis of OS and other secondary endpoints will be approximately 12 months after the last participant has had their first study intervention administration.

5 SUPPORTING DOCUMENTATION

5.1 APPENDIX 1 LIST OF ABBREVIATIONS

ADA:	anti-drug antibody
AE:	adverse event
AESI:	adverse event of special interest
ALT:	alanine aminotransferase
AST:	aspartate aminotransferase
AUC:	area under the curve
CD38:	cluster of differentiation 38
CR:	complete response
CRS:	cytokine-release syndrome
CTCAE:	Common Terminology Criteria for Adverse Events
DOR:	duration of response
ECG:	electrocardiogram
ECOG:	Eastern Cooperative Oncology Group
eCRF:	electronic case report form
EOT:	end of treatment
IRs:	infusion reactions
IMP:	investigational medicinal product
INR:	international normalized ratio
IV:	intravenous
MedDRA:	Medical Dictionary for Regulatory Activities
ORR:	objective response rate
OS:	overall survival
PCSA:	potentially clinically significant abnormality
PD:	progressive disease
PK:	pharmacokinetics
PK/PD:	pharmacokinetics/pharmacodynamics
PR:	partial response
PT:	preferred term
SAE:	serious adverse event
SAP:	Statistical Analysis Plan
SD:	stable disease
SOC:	system organ class
TEAE:	treatment-emergent adverse event
WBC:	whole blood cell
WHO-DD:	World Health Organization-Drug Dictionary

5.2 APPENDIX 2 CHANGES TO PROTOCOL-PLANNED ANALYSES

There are no changes from the protocol-planned analyses.

5.3 APPENDIX 3 DEMOGRAPHICS AND BASELINE CHARACTERISTICS, PRIOR OR CONCOMITANT MEDICATIONS

Demographics and baseline characteristics will be summarized on the all-treated population.

The medical and surgical history will be summarized according to the SOC and PT (SOC will be sorted according to the internationally agreed order and PT by overall decreasing frequency).

Disease characteristics at diagnosis and at study entry will be summarized.

5.3.1 Demographic and baseline characteristics

The baseline value is defined as the last assessment for this parameter before first administration of study treatment (ie, isatuximab).

Demographics characteristics

Demographic variables include age in years and/or months, sex, ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not reported, Unknown), race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Not reported, Unknown), weight (kg), height (cm) and eastern cooperative oncology group (ECOG) performance status at baseline.

Medical or surgical history

Medical or surgical history includes relevant history of previous or associated pathologies other than the tumor.

This information will be coded using the version of Medical Dictionary for Regulatory Activities (MedDRA) currently in effect at Sanofi at the time of database lock.

Disease characteristics at diagnosis

The following disease characteristics at initial diagnosis will be described:

- French-American-British (FAB) classification of Diagnosis
- Disease Involvement Location (Bone Marrow, Central Nervous System, Mediastinal Lymph Node, Lymph Node, Testis, Other, If Other, Specify)
- Leukemia / Lymphoma Diagnosis, Cytogenetic abnormality by category as collected
  - AML (inv(16), t(16;16), t(8;21), t(15;17), t(9;11), 11q23, t(9;22) Other)
  - B-ALL (Hyperdiploidy, Hypodiploidy, t(12;21), t(4;11), 14q23, t(9;22), Other)
  - T-ALL (Hyperdiploidy, Hypodiploidy, 1p32, t(11;14), t(10;11), Other

Disease characteristics at study entry/baseline

The following disease characteristics at study entry will be described:

- Type of disease (as collected in eCRF)
  - Acute Myeloid Leukaemia
  - B-cell Acute Lymphoblastic Leukemia/Lymphoma
  - T-cell Acute Lymphoblastic Leukemia/Lymphoma
- Disease status
  - Refractory
  - Relapsed
- Blasts
  - 0 - 20
  - 21 - 50
  - ≥ 50
- WBC counts (x109/L)
  - 0 to 5
  - 6 to 10
  - 11 to 20
  - 20 to 50
  - > 50
- Extramedullary disease
- CNS impairment
  - Normal
  - Abnormal
- Selected cytogenetics
  - 11q23,
  - t(12;21)
  - t(9;22)
  - 'Other': IAMP21, T(1;19)
- Selected Immunophenotyping
  - CD19, CD22 for B-ALL
  - CD33 for AML
- Time from initial diagnosis to first study treatment administration (in years),

Prior anti-leukemia/lymphoma therapies

Prior anti-leukemia/lymphoma treatments are collected by regimen in the eCRF. The following variables will be summarized:

- Time from last Relapse/Progression to first study treatment administration (in years)
- Best response at last regimen
- Number of prior regimens (quantitatively and by category: 1, 2, …7 and ≥8)
- Number of prior lines (quantitatively and by category: 1 or 2)
  - A prior line of therapy is defined as all treatment received by the participant up to the occurrence of relapse or progressive disease.
  - A line may be represented by one or multiple regiments.
- Prior radiation therapies
- Prior cell therapies
- Prior transplant received

Prior radiation therapy was collected and will also be summarized in number (%) of patients with any prior radiotherapy.

5.3.2 Prior, concomitant or post medications (other than anticancer therapies)

All medications will be coded using the World Health Organization-Drug Dictionary (WHO-DD), using the version currently in effect at Sanofi at the time of database lock.

- Prior medications are those the patient used prior to first study treatment administration. Prior medications can be discontinued before first dosing or can be ongoing during treatment phase.
- Concomitant medications are any treatments received by the patient concomitantly to the study treatment from up to 7 days prior to the first treatment to the last administration + 30 days.
- Post-treatment medications are those the patient took in the period running from the day after the last study treatment administration +30 days up to the end of the study.

Infusion reaction (IR) medications

Participants should routinely receive premedication prior to isatuximab infusion as detailed in Section 6.1 of the study protocol to reduce the risk and severity of IRs commonly observed with mAbs. Infusion reactions (National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] version 5.0 term “allergic/hypersensitivity reactions” or “cytokine release syndrome/acute infusion reaction”) are defined as AEs related to isatuximab with onset within 24 hours from the start of the infusion.

Any technical details related to imputation for missing dates are described in Section 5.4.

5.3.3 Anticancer therapies

Prior anti-cancer treatments will be summarized for the all-treated population. Number (%) of patients with the anti-cancer treatments will be summarized as described in Section 5.3.

5.4 APPENDIX 4 DATA HANDLING CONVENTIONS

5.4.1 General conventions

The following formulas will be used for computation of the lab parameters.

Creatinine clearance (eGRF) using the equation of MDRD formula:

$$GFR = 175 \times (Scr)^{-1.154} \times (Age)^{-0.203} \times (0.742 \text{ if Female}) \times (1.212 \text{ if African American})$$

with serum creatinine in mg/dL and age in year.

Corrected calcium formula:

Corrected Calcium (mmol/L) = Serum Calcium (in mmol/L) + 0.8 (4 - serum albumin [in g/dL] x 0.1)) x 0.25

5.4.2 Missing data

The analyses and summaries of continuous and categorical variables will be based on observed data only. Percentages will be calculated using as denominator the number of patients with non-missing observation in the considered population. When relevant, the number of patients with missing data is presented.

When incomplete or missing dates were found in the eCRF, attempts were made to retrieve the complete date, especially for dates within the month prior to first dose. However, if some dates remain incomplete, the following rules will be applied:

Handling of disease characteristics missing/partial dates

- If the day is missing, it will be estimated by 1
- If the month is missing, it will be estimated by 1 (only for medical history variables).
- If the year is missing, no estimation will be performed.

Handling of medication missing/partial dates

No imputation of medication (other than anti-cancer therapies) start/end dates or times will be performed. If a medication date or time is missing or partially missing and it cannot be determined whether it was taken prior or concomitantly, it will be considered a prior, concomitant, and post-treatment medication.

For prior anti-cancer therapies, following rules will be applied:

Missing/partial start date will be imputed as follows:

- If year and month exist, day is missing, impute as the first day of the month;
- If only year exists, month and day are missing, impute as the first day of the year;
- If year, month, and day are all missing, no imputation will be applied.

Missing/partial end date will be imputed in a two-step approach as follows:

- Step 1: Use the following rule to impute end date:
  - If year and month exist, day is missing, impute as the first day of the month;
  - If only year exists, month and day are missing, impute as the first day of the year;
  - If year, month, and day are all missing, no imputation will be applied.
- Step 2: If imputed end date is earlier than start date, set the imputed end date the same as start date;

Imputation of incomplete date for post anti-cancer treatment start date

For post anti-cancer treatments, if the medication start date is missing, it will be imputed as follows:

- If the medication start day and month are missing and the medication start year is the same as treatment end year, the medication start date will be set equal to treatment end date +1.
- If the medication start day and month are missing and the medication start year is after the treatment end year, the medication start day and month will each be set to 01.
- If the medication start day is missing and medication start year and month is the same as the treatment end year and month, the medication start day will be set equal to the treatment end day +1.
- If the medication start day is missing and medication start month is before the treatment end month and the medication start year is the same as treatment end year, the medication start day will be set to 01.
- If the medication start day is missing and the medication start month is after the treatment end month and the medication start year is the same as treatment end year, the medication start day will be set to 01.
- If the medication start day is missing and the medication start month is not missing and the medication start year is after the treatment end year, the medication start day will be set to 01.
- If the medication start day, start month and start year is missing, the medication start date will be set equal to the treatment end date +1.

No imputation will be done for the missing/partial end date.

Handling of adverse events with missing or partial date of onset

Missing or partial adverse event onset dates (occurrence or becoming serious) will be imputed so that if the partial adverse event onset date information or visit number does not indicate that the adverse event started prior to treatment or after the treatment-emergent adverse event period, the adverse event will be classified as treatment-emergent. In case of AEs worsening during the study, the emergence will also be based on the cycle of worsening. No imputation of adverse event end dates will be performed. These data imputations are for categorization purpose only and will not be used in listings. No imputation is planned for date of adverse event resolution.

Handling of death with missing or partial date of death

The imputation for missing or partial death date will proceed as follows:

- If the death day is missing and the death month and year are the same as the last month and year the patient was last known to be alive, the death day will be set equal to the last day the patient was known to be alive +1.
- If the death day is missing and the death month is after the month the patient was last known to be alive and the death year is the same as the year the patient was last known to be alive, the death day will be set to 01.
- If the death day and month are missing and the death year is the same as the year the patient was last known to be alive, the death date will be set equal to the date the patient was last known to be alive +1.
- If the death day and month are missing and the death year is after the year the patient was last known to be alive, the death day and month will both be set to 01.

If the date the patient was last known to be alive is partial or missing, no imputation for missing or partial death date will be performed. The last date the patient was known to be alive is the last of: date of last dose, date of last visit performed (when the patient is known to be alive according to subject vital status), date of last laboratory assessment, and date of last vital signs.

Handling of AEs with missing grade

If the grade is missing for one of the treatment emergent occurrences of an AE, the maximal severity on the remaining occurrences will be considered. If the severity is missing for all the occurrences, no imputation will be done, and missing grades will be summarized in the “all grades” category.

Handling of missing assessment of relationship of adverse events to investigational medicinal product

If the assessment of the relationship to the regimen is missing, then the relationship to the regimen has to be assumed and the adverse event considered as such in the frequency tables of possibly related adverse events, but no imputation should be done at the data level. No imputation will be done for relationship to NMIP.

Handling of parameters expressed as inequality or approximation

For some parameters (such as laboratory parameters), if the value is expressed as "< xx", "≤xx, half of the numeric portion of the entry or limit of quantification will be used in calculations.

Handling of other missing dates

Incomplete date of cancer diagnosis:

- If the day of the cancer diagnosis is missing, the date will be imputed to the first day of the month.
- If day and month of the cancer diagnosis are missing, no imputation will be done.

Incomplete date of progression for the last prior regimen:

- If the day of the progression for the last prior regimen is missing, the date will be imputed to the end day of the month.
- If day and month of the progression for the last prior regimen are missing, no imputation will be done.

Incomplete date of prior surgery:

- If the day of the last prior surgery is missing, the date will be imputed to the end day of the month.
- If day and month of the last prior surgery are missing, no imputation will be done.

Incomplete date of prior radiotherapy:

- If the day of the last prior radiotherapy is missing, the date will be imputed to the end day of the month.

If day and month of the last prior radiotherapy are missing, no imputation will be done.

5.4.3 Windows for time points

Laboratory data

A protocol planned laboratory test is considered to have occurred during a cycle if the date of sampling is after (>) the first day of the cycle, but prior to or equal (≤) to the first day of the next cycle. For unscheduled tests, a test is considered to have occurred during a cycle if the date of sampling is equal to or after (≥) the first day of the cycle, but prior (<) to the first day of the next cycle.

5.4.4 Unscheduled visits

Unscheduled visit measurements of laboratory data, vital signs and ECG will be used for computation of worst values and/or grades on treatment. Unscheduled visits prior to first

administration will be also used for computation of baseline except if they are not collected on the day of first administration.

5.4.5 Pooling of centers for statistical analyses

Data from all sites will be pooled together for analyses.

5.4.6 Statistical technical issues

There are no expected statistical technical issues.

6 REFERENCES

Not applicable.

Signature Page for VV-CLIN-0629547 v1.0
act15378-16-1-9-amended-sap01

Approve & eSign	[redacted] Clinical 02-May-2022 15:09:23 GMT+0000
Approve & eSign	[redacted] Clinical 02-May-2022 19:30:50 GMT+0000
Approve & eSign	[redacted] Clinical 02-May-2022 20:24:21 GMT+0000