NCT Number: NCT02999633

STATISTICAL ANALYSIS PLAN

A phase 2, safety and efficacy study of isatuximab (SAR650984), an anti-CD38 monoclonal antibody, administered by intravenous infusion in patients with relapsed or refractory T-acute lymphoblastic leukemia or T-lymphoblastic lymphoma

SAR650984-ACT14596

[redacted]

[redacted]

DATE OF ISSUE: 13-Dec-2017

Total number of pages: 42

TABLE OF CONTENTS

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ADA:	anti-drug antibody
ADI:	actual dose intensity
AESI:	adverse event of special interest
ALT:	alanine aminotransferase
ANC:	absolute neutrophils count
AST:	activated partial thromboplastin time, aspartate aminotransferase
ATC:	anatomic category
AUC:	area under the curve
BOR:	best overall response
CR:	complete response
CTCAE:	common terminology criteria for adverse events
DOR:	duration of response
ECOG:	Eastern Cooperative Oncology Group
eCRF:	electronic case report form
HLGT:	high level group term
HLT:	high level term
IAR:	infusion associated reaction
IMP:	Investigational medicinal product
INR:	International normalized ratio
MedDRA:	Medical Dictionary of Regulatory Activities
MRD:	minimal residual disease
NCI:	National Cancer Institute
ORR:	overall response rate
OS:	overall survival
PCSA:	potentially clinically significant abnormality
PD:	progressive disease
PDy:	pharmacodynamic
PFS:	progression free survival
PK:	Pharmacokinetic
PR:	partial response
PS:	performance status
PT:	preferred term
RBC:	red blood cell
SAE:	serious adverse event
SOC:	system organ class
TEAE:	treatment-emergent adverse event
WBC:	white blood cell
WHO-DD:	World Health Organization-Drug Dictionary

1 OVERVIEW AND INVESTIGATIONAL PLAN

1.1 STUDY DESIGN

This is a Phase 2, single arm, multicenter, multinational, open-label study evaluating the efficacy and safety of isatuximab in patients with relapsed or refractory T-ALL/T-LBL.

The study will be conducted in 2 stages. Approximately 39 patients previously treated for T-ALL/T-LBL will be enrolled in the study across approximately 15 to 20 sites globally. A Simon's 2-stage optimum design will be used.

- Stage 1: an interim analysis of efficacy, safety and PK will be performed on the first 19 treated patients. The study will proceed to Stage 2 if >3/19 responses are observed in Stage 1.
- Stage 2: 20 additional patients will be treated if the number of responses required to proceed to Stage 2 is reached at the interim analysis of Stage 1.

The duration of the study for a patient will include a period for screening of up to 3 weeks. The cycle duration is 28 days. The treatment period will include an induction period (QW dosing) for 4 or 8 weeks, followed by a maintenance period (Q2W). Patients will continue maintenance therapy until disease progression, unacceptable AE, consent withdrawal or Investigator's decision (eg, patient is a candidate for transplantation).

1.2 OBJECTIVES

1.2.1 Primary objectives

The primary objective of this study is to evaluate the efficacy of isatuximab in patients with relapsed or refractory T-ALL or T-LBL as measured by overall response rate (ORR) (as per National Comprehensive Cancer Network [NCCN] guidelines; Appendix D).

1.2.2 Secondary objectives

The secondary objectives are:

- To evaluate the safety profile of isatuximab.
- To compare the duration of response (DOR).
- To evaluate progression free survival (PFS) and overall survival (OS).
- To evaluate the PK of isatuximab in patients with T-ALL or T-LBL.
- To evaluate immunogenicity of isatuximab in patients with T-ALL or T-LBL.
- To assess minimal residual disease (MRD) and correlate it with clinical outcome.

1.2.3 Exploratory objectives

The exploratory objectives are:

- To explore the relationship between CD38 expression and clinical response.
- To explore the relationship between CD38 receptor occupancy (RO) and CD38 receptor density (RD) on blast cells (peripheral blood and bone marrow) and clinical response.
- To explore the relationship between acute leukemia tumor molecular alterations and clinical response.
- To explore the relationship of soluble CD38, the PK of isatuximab and clinical response.
- To explore the relationship between immune genetic determinants, immune phenotypes and clinical response.
- To explore PK/PDy relationships.

1.3 DETERMINATION OF SAMPLE SIZE

The sample size calculation is based on the primary efficacy endpoint (ie, ORR). The following assumptions were used:

- Null hypothesis: ORR ≤15%.
- Alternative hypothesis: ORR ≥30%.
- A two-stage Simon's Optimum design at a one-sided 10% significance level.

Based on the above assumptions, approximately 39 patients are needed to achieve an 80% power for the study.

- Stage 1: 19 patients will be enrolled. The study will proceed to stage 2 if >3 responses are observed.
- Stage 2: a total of 39 patients (20 additional treated patients). If >8 responses are observed among the 39 patients analyzed, the null hypothesis will be rejected.

1.4 STUDY PLAN

The complete study plan is presented in section 1.1 of the protocol.

1.5 MODIFICATIONS TO THE STATISTICAL SECTION OF THE PROTOCOL

To avoid inconsistencies between parts of the protocol, a clarification is required regarding the population used for analyses. All analyses will be done on the primary population which is the all-treated population.

1.6 STATISTICAL MODIFICATIONS MADE IN THE STATISTICAL ANALYSIS PLAN

Not applicable. This is not an amended SAP.

2 STATISTICAL AND ANALYTICAL PROCEDURES

2.1 ANALYSIS ENDPOINTS

2.1.1 Demographic and baseline characteristics

The baseline value is defined as the last value or measurement taken up to the date and time of the first study treatment administration. This definition applies for all variables unless otherwise specified.

All baseline safety and efficacy parameters (apart from those listed below) are presented along with summary statistics in the safety and efficacy sections (Section 2.4.5 and Section 2.4.4).

Demographic characteristics

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

Medical or surgical history

Medical or surgical history includes relevant history of previous or associated pathologies other than the tumor, history of asthma, chronic obstructive pulmonary disorder, dyspnea and tobacco consumption.

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. Respiratory function history will be analyzed using two groupings (see details in Section 2.1.4.1)

Disease characteristics at baseline

The following leukemia/lymphoma characteristics at initial diagnosis will be described:

- Time from initial diagnosis of leukemia/lymphoma to first study treatment administration (in months).
- Leukemia/lymphoma type (T-ALL/T-LBL, cell type) (as collected in eCRF).
- Cytogenetic abnormality (as collected in eCRF).
- Disease involvement location (as collected in eCRF).

Disease characteristics at study entry

The following leukemia/lymphoma characteristics at study entry will be described:

- Refractory status.
  - Relapsed: patients who achieve CR of any duration with the last treatment and progressed before entering the study,
  - Refractory: failure to achieve CR with the last treatment received.

Prior anticancer therapies

- Prior anti-CD38 treatments

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

- Number of prior regimens,
- Number of prior salvage therapies,
- Intent of prior anti-leukemia/lymphoma therapies,
- Reason for discontinuation,
- Best overall response (BOR),
- Transplant Type: number (%) of patients with allogeneic transplant, number (%) of patients with autologus transplant,
- Nelarabine: number (%) of patients who have been previously exposed to nelarabine.

- Prior surgery: number (%) of patients with any prior surgery related to leukemia/lymphoma, type of procedure and time from last surgery to first study treatment administration (months).
- Prior radiotherapy: number (%) of patients with any prior radiotherapy related to leukemia/lymphoma, intent and time from last radiotherapy to first study treatment administration (months).

2.1.2 Prior or concomitant medications (other than anticancer therapies)

All treatments being taken by the patient for up to 7 days prior to the first dose of IMP, and at any time during the treatment period and for up to 30 days after the last dose are regarded as prior and concomitant treatments, respectively, and will be reported on the appropriate pages of the electronic Case Report Form (eCRF).

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

Post treatment medications are those the patient took in the period running from 30 days after the last dose up to the end of the study. After the end of treatment, only further anticancer therapy will be reported.

IAR medications

As defined in Section 8.2 of the study protocol, patients will routinely receive premedications prior to infusion to reduce the risk and severity of infusion associated reactions (IARs) commonly observed with monoclonal antibodies. Premedications are defined in the protocol as non-investigational medicinal product(s) and should be reported in a specific form of the eCRF. Analysis of premedications will focus on those given (drug class, start and stop dates) on the days of isatuximab administrations for prophylaxis reason.

Medication given in curative intent of IAR will be also analyzed (drug class, start and stop dates).

Any technical details related to computation, dates, imputation for missing dates are described in Section 2.5.

2.1.3 Efficacy endpoints

2.1.3.1 Primary efficacy endpoint(s)

The primary endpoint is the Overall Response Rate (ORR) defined as the proportion of patients with complete response (CR) or CR with incomplete peripheral recovery (CRi) for blood and bone marrow disease; partial response will be considered in case of mediastinal or any extramedullary disease. CR, CRi and PR are defined in Appendix D.

An assessment will be performed during induction cycles, then every 2 months and as clinically indicated until disease progression or further therapy.

Best Overall Response (BOR)

BOR is the best tumor response observed from the first study drug intake until disease progression, death, study cutoff date, initiation of post-treatment anti-cancer therapy, whichever occurs first.

The BOR can be either Progressive Disease (PD), Partial Response (PR), Complete Response (CR), Complete response with incomplete peripheral recovery (CRi) or unevaluable.

- If there is 1 involvement in bone marrow (BM), or extramedullary involvement, the BOR will be the only response from the given involvement. In case of refractory disease, relapsed disease or no response, the BOR will be set as PD.
- If there are 2 involvements: BM and extramedullary
  - BOR = PD when:
    - BM response is either PD, refractory disease or relapsed disease whatever the response for extramedullary involvement
    - Extramedullary response is either PD, no response or relapsed disease whatever the response for BM
  - BOR = PR when: BM response is CR or CRi and extramedullary response is PR
  - BOR = CR when: BM response is CR and extramedullary response is CR
  - BOR = CRi when: BM response is CRi and extramedullary response is CR
  - BOR = unevaluable when:
    - BM response is unevaluable and extramedullary response is either CR, PR or unevaluable
    - BM response is CR or CRi and extramedullary response is unevaluable

Per inclusion criteria, all patients should be CNS negative at screening. If a patient is CNS positive during the course of the study, the BOR will be PD.

We may combine assessments (involvement in BM or extramedullary involvement) if they are performed at different visits within the same assessment period:

- Between screening and first infusion of the study drug
- Between Cycle 1 and Cycle 2
- After Cycle 2 and before maintenance period

2.1.3.2 Secondary efficacy endpoint(s)

Three secondary efficacy endpoints are considered:

- Duration of Response (DOR).
- Progression Free Survival (PFS).
- Overall Survival (OS).

Date of disease progression determination

The date of the disease progression is the earliest date that indicates disease progression.

Duration of response (DOR)

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 the absence of the confirmation of subsequent disease progression or death before the analysis cut-off date the DOR will be censored at the date of the last valid disease assessment not showing disease progression performed prior to initiation of a further anti-leukemia or anti-lymphoma treatment or the analysis cut-off date, whichever is earlier.

Duration of response is determined only for patients who have achieved a response of PR or better (subsequently confirmed).

Progression free survival (PFS)

PFS is the defined as the time from the date of first study treatment administration to the date of first disease progression or the date of death from any cause, whichever happens first. If progression and death are not observed before the analysis cutoff date, PFS will be censored at the earlier of the date of the last valid disease assessment not showing disease progression performed prior to initiation of a new anti-cancer treatment (if any) and the analysis cutoff date, whichever comes first.

Overall survival (OS)

OS is as the time interval from the date of first study treatment administration to death from any cause. If death is not observed before the analysis data cut-off date, OS will be censored at the last date that the patient is known to be alive or at the cut-off date, whichever comes first.

Minimal Residual Disease (MRD)

MRD will be measured by sequencing and/or flow cytometry in patients achieving CR and CRi, to determine the depth of response at a molecular level.

2.1.4 Safety endpoints

The safety analysis will be based on the reported adverse events (AEs) and other safety information, such as clinical laboratory data, vital signs, weight and Eastern Cooperative Oncology Group (ECOG) performance status (PS).

Observation period

The observation period starts from the time when the patient gives informed consent and is divided into 3 periods:

- **The pre-treatment** period is defined as the time from the signed informed consent date up to the first dose of study treatment.
- The **treatment** period is defined as the time from the first dose of study treatments administration to the last dose of study treatment + 30 days.
- The **post treatment** period is defined as the period of time starting the day after the end of the treatment period up to the end of the study (as defined in the protocol).

2.1.4.1 Adverse events variables

AEs (including serious adverse events [SAEs] and AEs of special interest [AESI]) will be collected from the time of signed informed consent until the end of study.

Adverse event observation period

- Pre-treatment adverse events are defined as any adverse event reported during the pre-treatment period.
- Treatment-emergent adverse events (TEAEs) are adverse events that developed or worsened or became serious during the treatment period.
- Post-treatment adverse events are adverse events that developed or worsened or became serious during the post-treatment period.

All AEs (including SAEs and AESI) will be graded according to National cancer institute common terminology for adverse events (NCI-CTCAE) v4.03 and coded to a lower-level term (LLT), preferred term (PT), high-level term (HLT), high-level group term (HLGT) and associated primary system organ class (SOC) using the version of Medical Dictionary for Regulatory Activities (MedDRA) currently in effect at Sanofi at the time of database lock.

Adverse events of special interest

AESI include the following terms:

- Acute infusion associated reactions (IARs) of Grade ≥3
- Pregnancy of female patient entered in a study as well as pregnancy occurring in a female partner of a male entered in a study with IMP
- Symptomatic overdose (serious or non-serious) of study treatment.

Infusion associated reactions

IARs are commonly observed with monoclonal antibodies, and generally include AEs with onset typically within 24 hours from the start of the isatuximab infusion.

The main IAR analysis will be based on the Investigator's reporting of IARs. For each IAR, the sites are instructed to report as an AE a generic term (infusion associated reaction). Symptoms of

the IAR will be reported in a separate form providing symptoms severity, start and end date and will be analyzed in specific analyses describing IARs.

An additional analysis will include TEAEs occurring within 24 hours from the start of each isatuximab infusion (selecting any TEAEs starting the day of the isatuximab infusion or the day after).

Respiratory TEAEs

Analysis of selected respiratory TEAEs will focus particularly on the following groupings:

- Lower Respiratory events, selected using HLGT 'Bronchial disorders (excluding neoplasms)', HLGT 'Lower respiratory tract disorders (excluding obstruction and infection)' excluding HLT 'Lower respiratory tract radiation disorders' and HLGT 'Respiratory disorders NEC' (excluding 'Upper respiratory tract signs and symptoms' HLT),
- Respiratory infections, selected using HLGT 'Respiratory tract infections' from "Respiratory, thoracic and mediastinal disorders" SOC, HLT 'Lower respiratory tract and lung infections' and HLT 'Upper respiratory tract infection' from infection and infestation SOC

Late respiratory events (ie, occurring, worsening or becoming serious more than 30 days after last dose) will be analyzed as part of the post-TEAEs analysis.

Specific hematological analysis

Neutropenia (from laboratory abnormalities) will be displayed along with neutropenic complications (eg, neutropenic infections, febrile neutropenia).

2.1.4.2 Deaths

The deaths observation period are per the observation periods defined above.

- Death on-treatment: deaths occurring during the TEAE period.
- Death post-treatment: deaths occurring during the post-treatment period.

2.1.4.3 Laboratory safety variables

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

Blood samples for clinical laboratories will be taken as defined in the study flowchart and as clinically indicated. The laboratory parameters (excluding those used for disease assessment) will be classified as follows:

- Hematology
  - **Red blood cells (RBC) and coagulation**: hemoglobin, blasts, RBC, prothrombin time (PT) or international normalized ratio (INR), activated partial thromboplastin time (aPTT),

- **Platelet count,**
- **White blood cells (WBC)**: WBC with differential, absolute neutrophil count (ANC), lymphocyte count.

- Biochemistry
  - **Metabolism**: fasting glucose, total protein, albumin,
  - **Electrolytes**: sodium, potassium, chloride, calcium, corrected serum calcium, bicarbonate/carbon dioxide, magnesium, phosphate,
  - **Renal function**: serum creatinine, estimated creatinine clearance by MDRD formula, blood urea nitrogen (BUN), uric acid,
  - **Liver parameters**: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, lactate dehydrogenase (LDH), total and direct bilirubin,
  - **Pregnancy test**: female patients of childbearing potential.

Technical formulas are described in Section 2.5.1.

2.1.4.4 Vital signs variables

Vital signs include: heart rate, systolic and diastolic blood pressure, weight and ECOG PS (0, 1, 2, 3, 4).

2.1.4.5 Electrocardiogram variables

Electrocardiogram assessments will be described as normal or abnormal.

2.1.4.6 Other safety endpoints

Other safety endpoints include:

- IAR laboratory tests :
  - Cytokines (TNF-α, IL-1-β, IL-4, IL-6, IFN-γ)
  - Markers of complement (C3a, C4, CH50)
  - Serum tryptase

2.1.5 Pharmacokinetic variables

The population PK parameters of isatuximab, their inter-patients PK variability and inter-occasion PK variability will be estimated. The effect of pathophysiological and demographic covariates on main PK parameters will be assessed.

Empirical Bayesian estimation of individual parameters and of individual exposure (Area Under the Curve [AUC]) will also be performed.

2.1.6 Pharmacodynamic variables

Bone marrow aspirates and blood samples will be collected for assessment of receptor density (RD) and CD38 expression (proportion of CD38 positive cells) at screening, and, if relevant, correlated with clinical response endpoints.

Bone marrow aspirates and blood samples from patients in Stage 1 only will be taken to assess receptor occupancy (RO) at screening and between Day 15 and Day 22 during the first cycle (after the third isatuximab infusion), for correlation with PK parameters and, if relevant, correlation with clinical response endpoints.

CD38 receptor occupancy and receptor density will be summarized by study visit. Moreover, the set of PDy parameters will be described and, if relevant, correlated with the clinical response.

These analyses will be applicable in selected countries only.

2.1.7 Immunogenicity endpoints

Human anti-drug antibodies (ADAs) to isatuximab will be assessed during the study as described in the protocol and will be analyzed using patients evaluable for ADAs.

Periods of observation:

- ADA pre-treatment period: The ADA pre-treatment period is defined as the time from signed informed consent to the first isatuximab administration.
- ADA on-study observation period: the ADA on-study observation period is defined as the time from first isatuximab administration until the end of the study.

ADA attributes:

- **Pre-existing ADAs** are defined as ADAs that were present in samples drawn during the pre-treatment period.
- **Treatment boosted ADAs** are defined as pre-existing ADA with a significant increase in titer during the study compared to the baseline titer.
- **Treatment induced ADAs** are defined as ADAs that developed at any time during the ADA on-study observation period in patients without pre-existing ADA, including patients without pre-treatment samples.
- **Transient ADA response** is defined by:
  - Treatment-induced ADA detected only at one sampling time point during the ADA on-study observation period (excluding the last sampling time point) OR,
  - Treatment-induced ADA detected at two or more sampling time points during the on-study observation period, where the first and last ADA-positive samples (irrespective of any negative samples in between) are separated by a period less than 16 weeks and the subject's last sampling time point is ADA-negative.
- **Persistent ADA response** is defined by:
  - Treatment-induced ADA detected at two or more sampling time points during the ADA on-study observation period, where the first and last ADA-positive on-study

samples are separated by a period of 16 weeks or longer (irrespective of any negative samples in between), OR,

- Treatment-induced ADA detected in the last two sampling time points (both positive), irrespective of the time period in between.

- **Indeterminate ADA** is defined by treatment induced ADA detected only the last sampling time point with all previous samples being negative or the last two samples are ADA-positive and separated by a period of less than 16 weeks.

ADA response endpoints:

- **ADA negative patients** are patients without any treatment induced or treatment boosted ADA during the on –study observation period.
- **ADA positive patients**, defined as patients with at least one treatment-induced or treatment-boosted ADA positive sample at any time following the first study treatment administration.
- **ADA incidence** is defined of the number of ADA positive patients divided by the number of evaluable patients.
- **ADA prevalence** is defined as proportion of all patients tested positive for ADAs (including preexisting ADAs, treatment boosted ADAs and treatment induced ADAs) at any time point.

2.1.8 Further therapy after discontinuation of investigational medicinal product administration during the study

Further therapies after discontinuation of IMP include further anti-leukemia/lymphoma treatments.

Time to Next Treatment

TNT is defined as the time from first study treatment administration to the start of further anti-leukemia/lymphoma treatment. Patients who do not receive any further anti-leukemia/lymphoma treatment will be censored at the date of their last FU visit or the cut-off date, whichever comes first. Patients with no FU visit will be censored at their last study treatment administration or the cut-off date whichever comes first.

2.2 DISPOSITION OF PATIENTS

This section describes patient disposition for both patient study status and the patient analysis populations.

Screened patients are defined as any patients who signed the study informed consent.

For patient study status, patients in each of the following categories will be presented in the clinical study report using a flowchart diagram or summary table:

- Screened patients

- Screen failure patients and reasons for screen failure (if any)
- Patients who discontinued study treatment
- Patients still on treatment
- Status at last study contact
- Patients with date of last contact obtained before the cutoff date and duration from last contact to cut-off date (0-2 weeks, 2-4 weeks, 4-8 weeks, >8 weeks)

A summary of the reasons for definitive treatment discontinuation will be provided. Definitive treatment discontinuation is defined as the discontinuation of the study drug. For all categories of patients (except for the screened) percentages will be calculated using the number of patients in the all-treated/safety population as the denominator.

All critical or major deviations potentially impacting efficacy analyses, and other major or critical deviations will be summarized in tables giving numbers and percentages of deviations.

Additionally, the following analysis populations will be summarized in a table by number of patients on the all-treated/safety population:

- All-treated/safety population: primary population for efficacy and safety analyses.
- Pharmacokinetics population.
- Pharmacodynamic population.
- ADA population.

Definition of study populations are provided in Section 2.3.

2.3 ANALYSIS POPULATIONS

2.3.1 All-treated/Safety population

The all-treated/safety population will include patients who received at least 1 dose (even incomplete) of isatuximab. This population is the primary population for the analyses of efficacy and safety parameters.

2.3.2 Pharmacokinetics population

The PK population will include all patients from the all-treated/safety population, with at least 1 PK parameter available.

2.3.3 Pharmacodynamic population

The PDy population will include patients from the all-treated/safety population who had data for at least 1 PDy parameter available.

2.3.4 ADA population

The ADA population will include safety population patients with at least one ADA assessment during the ADA on-study observation period with a reportable result.

2.4 STATISTICAL METHODS

Unless otherwise specified, analyses will be descriptive and performed based on the all-treated/safety population.

Continuous data will be summarized using the number of available data, mean, standard deviation (SD), median, minimum and maximum. Categorical and ordinal data will be summarized using the number and percentage of patients.

2.4.1 Demographics and baseline characteristics

Parameters described in Section 2.1.1 will be summarized on the all-treated population using descriptive statistics.

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

2.4.2 Prior or concomitant medications (other than anticancer therapies)

The prior and concomitant medications will be presented for the all-treated population

Medications will be summarized according to the WHO-DD dictionary, considering the first digit of the anatomic category (ATC) class (anatomic category) and the first 3 digits of the ATC class (therapeutic category). All ATC codes corresponding to a medication will be summarized, and patients will be counted once in each ATC category (anatomic or therapeutic) linked to the medication. Therefore patients may be counted several times for the same medication.

IAR medications

Number (%) of patients with IAR medications (prophylaxis and curative intent) including diphenhydramine (or equivalent) and steroids as defined in Section 2.1.2 will be provided. Number of infusions with prophylactic IAR medications and number of infusions with curative IAR medications will also be summarized. Further analyses on cumulative steroids exposure may be performed as needed.

2.4.3 Extent of investigational medicinal product exposure and compliance

The following variables will be calculated and summarized with descriptive statistics to describe exposure of isatuximab:

- Number of cycles started.

- Duration of exposure (in weeks), defined as follow:
  - [First day of last cycle - first day of first cycle + 28 days]/7
- Cumulative dose (mg/kg): the cumulative dose is the sum of all doses administered from first to last dose.
- Actual dose intensity (ADI) in mg/kg/week: defined as the cumulative dose (in mg/kg) divided by the number of weeks on study.
- Planned dose intensity in mg/kg/week corresponds to the planned dose (mg/kg) at C1D1, regardless of dose changes, multiplied by the theoretical total number of doses during the started cycles (4 for weekly dose, 2 for Q2W dose), and divided by the theoretical cycle duration expressed in weeks (ie, 4 weeks per cycle started)
- Relative dose intensity (RDI) in % is an indicator of the feasibility of the chosen schedule of administration and is defined as follow

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

Total number of cycles started, number of cycles started by patient as a quantitative variable and by category (ie, number (%) of patients receiving at least 1 cycle, at least 2 cycles, etc), duration of exposure, cumulative dose, ADI and RDI will be summarized by descriptive statistics.

The following variables will be computed to describe isatuximab dose modifications (delay/omission/interruption):

- Infusion delays: within a QW or Q2W cycle, a dose is deemed to have been delayed if the study treatment is >3 days beyond the theoretical day of treatment.
- Cycle delay: the start of a cycle can be delayed for up to 14 days.
- Infusion interruption: an infusion is considered to be interrupted if the administration is stopped during an infusion regardless if the infusion is re-started or not.
- Dose omission: a dose is considered omitted if the dose is not administered for the scheduled visit and there are positive dose(s) afterwards.

Dose modification will be analyzed at the patient and total number of isatuximab infusions levels as follows:

- Patient level:
  - Number of patients treated (used for % calculation for this level).
  - Number (%) of patients with at least one infusion delay
  - Number (%) of patients with at least one isatuximab dose omission
  - Number (%) patients with a least 1 infusion interruption
- Total number of isatuximab infusions level:
  - Total number of isatuximab infusions (used for % calculation for this level).
  - Number of isatuximab infusions interrupted
  - Number (%, calculated using the total number of infusion interrupted) of isatuximab administrations interrupted at
    - 1st infusion

- 2nd infusion
- Subsequent infusions

- Time from infusion start to first interruption in minutes (quantitative and qualitative: 5 - 10, 11 - 30, 31 - 40, 41 - 50, 51 - 60, 61 - 90, 91 - 120, >120)
- Duration of infusion: defined as the time from the start (date/time) of infusion to the end (date/time) of infusion. It will be summarized for first and subsequent infusions.

2.4.4 Analyses of efficacy endpoints

All efficacy analyses will be performed in the all-treated/safety population.

2.4.4.1 Analysis of primary efficacy endpoint(s)

Primary analysis will consist of ORR summarized on the all-treated/safety population with descriptive statistics. Confidence intervals will be computed using the Clopper-Pearson method.

The cutoff date for primary analysis of ORR and other secondary endpoints will be 6 months after the last patient has had his/her first study treatment administration. Then, the final analysis cutoff date for analysis of OS and updated analyses of ORR and other secondary endpoints will be 12 months after the last patient has had his/her first treatment administration. Patients still on treatment at the time of the final analysis cutoff date and who still continue to benefit from treatment with isatuximab will have the option to continue treatment under this protocol.

Best overall response will be summarized with descriptive statistics.

2.4.4.2 Analyses of secondary efficacy endpoints

PFS, DOR and OS

These time-to-event endpoints will be analyzed using Kaplan-Meier methods.

The following estimates will be provided for each time-to-event endpoint:

- Data will be analyzed using the Kaplan-Meier method in the all-treated/safety population:
  - Kaplan-Meier estimates of the 25th, 50th and 75th percentiles and their associated 95% CIs will be provided
  - Number of patients at risk as well as the probabilities of surviving at least 1 and 2 months with 95% CI will be estimated using the Kaplan-Meier method.
- Kaplan-Meier curves will be plotted

If progression and death are not observed before the analysis data cut-off date, PFS and DOR will be censored at the date of the last valid disease assessment not showing disease progression performed prior to initiation of further anti-leukemia or anti-lymphoma treatment (if any) or the data cut-off date, whichever comes first.

Analysis of the pre-specified secondary endpoints will be descriptive only. Any testing procedure carried out on these endpoints will be considered as exploratory.

Minimal residual disease (MRD)

Among patients who achieve a CR with MRD assessment, the MRD status (negative, positive) will be summarized using descriptive statistics. The timing (study day from first dose) of MRD negative status will also be described.

2.4.4.3 Multiplicity issues

Not applicable.

2.4.5 Analyses of safety data

General common rules

All safety analyses will be performed on the safety population as defined in Section 2.3.1, unless otherwise specified.

2.4.5.1 Analyses of adverse events

Generalities

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 adverse event date/time of onset (occurrence, worsening, or becoming serious) is incomplete, an imputation algorithm will be used to classify the adverse event as pretreatment, treatment-emergent, or posttreatment. The algorithm for imputing date/time of onset will be conservative and will classify an adverse event as treatment emergent unless there is definitive information to determine it is pretreatment or posttreatment. Details on classification of adverse events with missing or partial onset dates are provided in Section 2.5.3.

The severity grade will be taken into account in the summary. For patients with multiple occurrences of the same adverse event, the maximum (worst) grade by period of observation is used. Summaries will be provided for all grades and for Grade ≥3 (including Grade 5). Missing grades, if any, will be included in the "all grades" category.

Sorting within tables ensures the same presentation for the set of all adverse events within the observation period (pre-treatment, treatment-emergent and post-treatment). For that purpose, the table of all treatment-emergent adverse events presented by SOC and PT sorted by the internationally agreed SOC order (see Appendix B) and decreasing frequency of PTs within SOCs will define the presentation order for all other tables unless otherwise specified.

The AE incidence tables presented by primary SOC, HLGT, HLT and PT will present the number (n) and percentage (%) of patients experiencing an AE sorted by SOC internationally agreed order, then by alphabetic order of HLGT, HLT and PT.

Analysis of all treatment-emergent adverse events

The following TEAE summaries will be generated for the all-treated/safety population.

- Overview of TEAEs, summarizing number (%) of patients with any
  - TEAE,
  - TEAE of Grade ≥3,
  - TEAE of Grade 3-4,
  - TEAE with Grade 5 (any TEAE with fatal outcome during the treatment period),
  - Serious TEAE,
  - TEAE leading to permanent discontinuation,
  - Treatment-related TEAEs,
  - Treatment-related TEAEs of Grade ≥3,
  - Serious treatment-related TEAE,
  - AESIs: AESIs of Grade ≥3, IARs, IARs of Grade ≥3, pregnancy and overdose.

Analysis of adverse events will be performed according to following domains:

- TEAEs (regardless relationship to study treatment),
- Drug related TEAEs,
- Deaths, serious adverse events, adverse events leading to withdrawal, and other significant adverse events (IAR and associated symptoms, Selected respiratory TEAEs, Specific hematological analysis , Second primary malignancies, TEAE leading to dose modification, pre- and post-treatment AE)
- The following frequency distributions of TEAEs (incidence tables) will be provided for the all-treated/safety population, for all grades combined and Grade ≥3:
  - All TEAEs by primary SOC, HLGT, HLT and PT, showing number (%) of patients with at least 1 TEAE sorted by the SOC internationally agreed order. The other levels (HLGT, HLT, PT) will be presented in alphabetical order
  - All TEAEs by primary SOC and PT, showing the number (%) of patients with at least 1 TEAE, sorted by the internationally agreed SOC order and by decreasing incidence of PTs within each SOC. This sorting order will be applied to all other tables, unless otherwise specified.

Analysis of all treatment-related TEAEs

- All treatment-related TEAEs by primary SOC and PT, showing the number (%) of patients with at least 1 TEAE, sorted by the internationally agreed SOC order and decreasing frequency of PT.

Analysis of infusion associated reactions

The following summaries of IARs (reported by investigator) will be presented:

- Number (%) of patients with at least one IAR and all the associated symptoms (all grades, Grades ≥3), sorted by decreasing incidence of PTs.
- A summary will be provided to further describe the characteristics of the IAR, showing:
  - Number (%) of patients by worst grade,
  - Number of episodes by patient,
  - Number (%) of patients with IAR at the first and subsequent infusions,
  - Number (%) of patients with at least two episodes of IARs at the same infusion
  - Infusion of occurrence of the first IAR
  - Day of onset from the isatuximab infusion

In addition, the following summaries will be presented:

- Number (%) of patients with at least one TEAE (all grades, Grades ≥3) occurring within 24 hours from the start of each isatuximab infusion (Day 1-2 from start of each isatuximab infusion), by primary SOC and PT.

Analysis of all treatment-emergent adverse event(s) leading to treatment discontinuation

- All TEAE leading to treatment discontinuation by primary SOC and PT, showing the number (%) of patients with at least 1 TEAE, sorted by the internationally agreed SOC order and decreasing frequency of PT.

Analysis of all treatment-emergent adverse event(s) leading to dose modification

The following summary tables are based on the investigator's intent reported in the AE page ("action taken"):

- All TEAEs leading to dose interruption, by primary SOC and PT, showing the number (%) of patients, sorted by the sorting order defined above.
- All TEAEs leading to any dose delay by primary SOC and PT, showing the number (%) of patients, sorted by the sorting order defined above.

Analysis of all treatment emergent serious adverse event(s)

- All serious TEAEs by primary SOC and PT, showing the number (%) of patients with at least 1 TEAE, sorted by the internationally agreed SOC order and by decreasing incidence of PTs within each SOC.
- All serious TEAEs related to treatment, by primary SOC and PT, showing the number (%) of patients with at least 1 serious TEAE, sorted by the internationally agreed SOC order.

Analysis of all TEAEs with a fatal outcome

- All TEAEs with a fatal outcome by primary SOC and PT, showing the number (%) of patients with a TEAE with a fatal outcome, sorted by the internationally agreed SOC order and decreasing frequency of PT.

Analysis of AEs/SAEs occurring during the pre-treatment and post-treatment dosing periods

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

Analysis of adverse events of special interest

Number (%) of patients with at least one AESI cited in Section 2.1.4.1 sorted by decreasing incidence of PT (presented separately for each category of AESI)

Respiratory TEAEs

Respiratory TEAEs will be analyzed using selections defined in Section 2.1.4.1 and will be presented by PT, sorted by decreasing incidence.

Specific hematological analysis

- Number (%) of patients with neutropenia (from laboratory abnormalities), neutropenic infections and febrile neutropenia by grade.

Second primary malignancies

A listing of patients who reported second primary malignancies during the study will be provided. This listing will include diagnosis, study day of diagnosis (from first dose), number of days from last study treatment to diagnosis, prior exposure to anti-leukemia/anti-lymphoma treatments, and whether or not patient received subsequent anti-cancer treatment.

Overdose

A listing of patients who reported overdose during the study will be provided. This listing will include drug with overdose, cycle of occurrence, associated TEAE, outcome.

The following listings will be provided if relevant:

- AESIs (non-IARs)
- IARs
- AEs leading to treatment discontinuation
- AEs leading to dose modification
- SAEs

2.4.5.2 Deaths

The following summaries of deaths will be generated for the all-treated/safety population.

- Number and proportion (%) of patients who died by study period (screening, TEAE observation period and post-treatment) and reasons for death (disease progression, AE, other).
- Listing of deaths

2.4.5.3 Analyses of laboratory variables

Hematological and clinical biochemistry toxicities will be assessed from laboratory test parameters. Each test result will be graded by NCI-CTCAE version 4.03, whenever applicable.

For hematological parameters and for some selected biochemistry parameters, sanofi sponsor generic ranges (LLN, ULN) are defined and will be used for grading (see list of parameters in Appendix C). For other biochemistry parameters (eg, for hepatic enzymes ALT, AST, Alkaline phosphatase, total bilirubin), grading will be derived using local laboratory normal ranges.

The number of patients with abnormal laboratory tests at baseline will be presented by grade and all grades together. The frequency of patients in each grade and all grades of laboratory abnormalities during treatment will be summarized. For patients with multiple occurrences of the same laboratory variable during the treatment, 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.

When appropriate, the summary table will present the frequency of patients with any grade of abnormal laboratory tests and with Grade 3-4 abnormal laboratory tests.

For laboratory tests for which NCI-CTCAE V4.03 scale is not applicable, potentially clinically significant abnormalities (PCSA) values are defined as abnormal values considered medically important by the Sponsor according to predefined criteria/thresholds based on literature review. PCSA criteria will determine which patients 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. The incidence of PCSA any time during the on-treatment period will be summarized irrespective of the baseline level.

For drug-induced liver injury, a listing of possible Hy's law cases identified (eg, patients with elevated AST or ALT of >3ULN and elevated total bilirubin >ULN), will be provided.

Anemia, thrombocytopenia and neutropenia

Shift tables showing the number of patients in each grade at baseline by worst grade during the on-treatment period and the bone marrow involvement at baseline by worst grade during the on-treatment period will be provided.

Further analyses including summary of cycle of onset (all grades and Grade ≥3), duration and concomitance with other hematological abnormalities will also be provided

2.4.5.4 Analyses of vital sign variables

A shift table of baseline ECOG PS versus best and worst ECOG PS on treatment will be provided.

For blood pressure/heart rate parameters, potentially clinically significant abnormality (PCSA), see Appendix A values are defined as abnormal values considered medically important by the Sponsor according to predefined criteria/thresholds based on literature review.

The incidence of PCSAs for vital signs and at any time during the TEAE period will be summarized whatever the baseline level (ie, the last assessment before the first study treatment administration) and/or according to the following baseline status (ie, status of last assessment before the first study treatment administration) categories:

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

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

2.4.5.5 Analyses of electrocardiogram variables

The incidence of patients with at least 1 abnormal ECG at any time during the TEAE period will be summarized irrespective of the baseline level and/or according to the following baseline status categories:

- Normal/missing
- Abnormal

2.4.5.6 Analyses of other safety endpoints

The summary statistics (including number, mean, median, standard deviation, minimum and maximum) of baseline values, peak values, change from baseline and relative change from baseline will be calculated for Cytokines (TNF-α, IL-1-β, IL-4, IL-6, IFN-γ), markers of complement (C3a, C4, CH50) and serum tryptase when available.

2.4.6 Analyses of pharmacokinetic and pharmacodynamic variables

Individual plasma concentrations and PK parameters of isatuximab will be summarized by descriptive statistics (such as mean, geometric mean, median, standard deviation, standard error of the mean, coefficient of variation, minimum, and maximum) under the responsibility of sanofi. Individual and mean profiles will be presented graphically.

The CD38 RO and RD will be summarized by study visits. Moreover, the set of PDy parameters will be described and, if relevant, correlated with the clinical response.

2.4.7 Analyses of immunogenicity variables

ADA attributes and response endpoints defined in Section 2.1.7 will be summarized in the ADA population. Titers will be also described using descriptive statistics. Further analyses may be performed, such as time to onset and duration of ADA.

The impact of positive immune response on efficacy, PK and safety endpoints may be further explored by graphical methods or descriptively, depending on ADA prevalence.

The following summaries of ADA will be generated:

- Number (%) of patients with pre-existing ADA and ADA negative at baseline, for patients evaluable at baseline
- Number (%) of ADA positive patients (including treatment-induced ADA and treatment boosted ADA) during the on-study observation period, for patients evaluable during the on-study observation period.

ADA prevalence and ADA incidence will be also described.

2.4.8 Further therapy after discontinuation of investigational medicinal product administration during the study

A summary table, including the number of different regimens, will be provided for further anti-leukemia or anti-lymphoma treatments based on WHO-DD coding.

Time to next treatment

TNT will be analyzed using Kaplan-Meier methods.

2.5 DATA HANDLING CONVENTIONS

2.5.1 General conventions

The following formulas will be used for computation of parameters.

Renal function formulas

Creatinine clearance will be estimated using the equation of MDRD:

GFR (mL/min/1.73 m²) = 175 x (Scr) – 1.154 x (Age) – 0.203 x (0.742 if Female) x (1.212 if African-American)

Corrected calcium formula

Corrected Calcium = Serum Calcium (in mmol/L) + 0.8 (4 - serum albumin [in G/dL])

2.5.2 Data handling conventions for secondary efficacy variables

Not applicable.

2.5.3 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.

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 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.

Imputation of incomplete date for post leukemia/lymphoma treatments start date

For post leukemia/lymphoma 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.

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.

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.

2.5.4 Windows for time points

Laboratory data

An episode occurred during a cycle if the date of sampling is after (>) the first day of the cycle, but prior or equal (≤) to the first day of the next cycle.

2.5.5 Unscheduled visits

Unscheduled visit measurements of laboratory data, vital signs, and ECG will be used for computation of baseline and worst values and/or grades.

2.5.6 Pooling of centers for statistical analyses

Not applicable.

2.5.7 Statistical technical issues

Not applicable.

3 INTERIM ANALYSIS

An interim analysis of efficacy, safety and other data (including PK) will be performed after the completion of enrollment in Stage 1; this interim analysis will be performed when all patients have completed either 2 induction cycles plus D1 of the first maintenance cycle or 1 induction cycle plus 1 maintenance cycle. Enrollment will 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.

At the end of each stage, additional statistical analyses could be performed in order to identify a subpopulation who would respond better to the treatment. If a relevant biomarker is actually identified, then a relevant threshold could be explored to define a subgroup of better responders.

4 DATABASE LOCK

Estimated cut-off date for primary analysis of ORR and other secondary endpoints will be 6 months after the last patient has had its first study treatment administration. The estimated final analysis cut-off date for OS analysis and updated analyses of ORR and other secondary endpoints will be 12 months after the last patient has had its first study treatment administration.

5 SOFTWARE DOCUMENTATION

All summaries and statistical analyses will be generated using SAS version 9.4 or higher. Biomarkers analyses will be generated using R version 3.3.2.

6 REFERENCES

1. National Comprehensive Cancer Network Guidelines for Acute Lymphoblastic Leukemia, Version 2.2016.

2. NEJM (N Engl J Med 2004;351:1548-63.): “Laboratory Reference Values”, Alexander Kratz, M.D., Ph.D., M.P.H., Maryjane Ferraro, Ph.D., M.P.H., Patrick M. Sluss, Ph.D., and Kent B. Lewandrowski, M.D.