NCT Number: NCT02999633

AMENDED CLINICAL TRIAL PROTOCOL NO. 01

COMPOUND: SAR650984 (isatuximab)

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

STUDY NUMBER: ACT14596

STUDY NAME: ISLAY

VERSION DATE / STATUS: Approval date (27-Feb-2017) / Approved

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NAMES AND ADDRESSES OF

COORDINATING INVESTIGATOR	Name: Address: Tel: Fax: E-mail:	[redacted]
MONITORING TEAM'S REPRESENTATIVE	Name: Address: Tel: Fax: E-mail:	
SPONSOR	Company: Address:	
OTHER EMERGENCY TELEPHONE NUMBERS		

CLINICAL TRIAL SUMMARY

COMPOUND: isatuximab (SAR650984)	**STUDY No.: ACT14596**
TITLE	Phase 2, safety and efficacy study of isatuximab, an anti-CD38 monoclonal antibody, administered by intravenous (IV) infusion in patients with relapsed or refractory T-acute lymphoblastic leukemia (-ALL) or T-lymphoblastic lymphoma (-LBL).
INVESTIGATOR/TRIAL LOCATION	International.
PHASE OF DEVELOPMENT	Phase 2.
STUDY OBJECTIVES	**Primary objectives:** 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). **Secondary objectives:** • To evaluate the safety profile of isatuximab. • To evaluate the duration of response (DOR). • To evaluate progression free survival (PFS) and overall survival (OS). • To evaluate the pharmacokinetics (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. **Exploratory objectives:** • To explore the relationship between CD38 expression and clinical response. • To explore the relationship between CD38 receptor occupancy and CD38 receptor density 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/pharmacodynamic (PDy) relationships.
STUDY DESIGN	This is a Phase 2, single arm, multicenter, 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: • Stage 1: an interim analysis of efficacy, safety and PK will be performed on the first 19 treated patients. • 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.

	Treatment scheme and duration of treatment The dose of isatuximab is 20 mg/kg. The cycle duration is 28 days. Induction period: Isatuximab will be administered by IV infusion, once every week (QW) for 4 weeks (1 induction cycle = 4 QW doses). If at Day (D)15-22 of the first induction cycle, bone marrow blast cells remain >5%, a second induction cycle will be administered. If bone marrow blast cells are $\leq$5%, the administration of a second induction cycle will be performed at the discretion of the Investigator. After a maximum of 2 cycles of induction therapy, patients will be withdrawn from the study treatment if they do not achieve an objective response, or, in case of disease progression, an unacceptable adverse event (AE), consent withdrawal or Investigator's decision (eg, patient is candidate for transplantation). Maintenance: In patients achieving an objective response following the induction period, isatuximab will be given once every 2 weeks (Q2W). Patients will be allowed to continue maintenance therapy until disease progression, an unacceptable AE, consent withdrawal or Investigator's decision (eg, patient is candidate for transplantation).
STUDY POPULATION **Selection criteria**	**Inclusion criteria:** I 01. Patients must have a known diagnosis of ALL of T cell origin, including T-LBL and T-ALL with isolated extramedullary involvement at relapse confirmed by biopsy. I 02. Patients must be previously treated for T-ALL or T-LBL and have relapsed or are refractory to most recent treatment. Patients in first relapse will be eligible regardless of the first remission duration. I 03. Patients must have been previously exposed to nelarabine in countries where this drug is available (unless due to a contraindication to its use or administrative issue). I 04. No more than 3 prior salvage therapies. I 05. Signed written informed consent. **Exclusion criteria:** **Exclusion criteria related to study methodology** E 01. Age <16 years. E 02. Patients must have been off prior treatment with immunotherapy/investigational agents for >3 weeks and chemotherapy for >2 weeks and must have recovered from acute toxicity (ie, to Grade 1 or less except alopecia or peripheral neuropathy Grade ≤2 without pain) before the first study treatment administration. Treatment may start earlier if necessitated by the patient's medical condition (eg, rapidly progressive disease) following discussion with the Sponsor. E 03. Prior stem cell transplant within 4 months and/or evidence of active systemic Graft versus Host Disease and/or immunosuppressive therapy for Graft versus Host Disease within 1 week before the first study treatment administration. E 04. Clinical evidence of active central nervous system (CNS) leukemia. Lumbar puncture should be negative before Cycle (C)1D1. In case of positivity for blast cells before or during the screening period, local treatment is allowed. Confirmed negativity of the lumbar puncture is mandatory within 3 days before the first administration of isatuximab (C1D1). Otherwise, the patient will be considered as non-eligible for the study.

	E 05. T-ALL with testicular involvement alone. E 06. Evidence of ongoing infection. E 07. Second malignancy other than basal cell or squamous cell carcinoma of the skin or in situ carcinoma of the cervix or the breast, unless they are successfully treated with curative intent for more than 3 years before entering the study. E 08. Poor condition/organ functions as defined by 1 of the following: • Eastern Cooperative Oncology Group (ECOG) performance status >2. • Total bilirubin >1.5 x upper limit of normal (ULN) unless Gilbert's syndrome. • Alanine aminotransferase, aspartate aminotransferase or alkaline phosphatase >2.5 x ULN, unless considered due to the disease. • Serum creatinine >2 x ULN and/or creatinine clearance <30 mL/min (Modification of Diet in Renal Disease formula; see Appendix A). E 09. Radiation therapy within 14 days prior to study treatment administration (this delay could be reduced if necessitated by patient's medical condition following discussion with Sponsor). E 10. Any serious active disease or co-morbid condition which, in the opinion of the Investigator, may interfere with the safety of the study treatment or the compliance with the study protocol. E 11. Any other severe underlying medical or administrative conditions, which could impair the ability to participate in the study or the interpretation of its results. E 12. Patient is the Investigator, Subinvestigator, research assistant, Pharmacist, study coordinator, other staff or relative thereof directly involved in the conduct of the protocol. E 13. Any technical/administrative reason (eg, patient homeless) that makes study participation impossible. E 14. Patient who has previously participated/Patient who has previously been treated in any clinical study with isatuximab or with a same class compound. E 15. Conditions/situations such as: Patient not suitable for participation, whatever the reason, as judged by the Investigator, or patients potentially at risk of noncompliance to study procedures. **Exclusion criteria related to the current knowledge of Sanofi compound** [redacted] E 17. Known human immunodeficiency virus positivity. E 18. Active hepatitis B virus (hepatitis B surface antigen, hepatitis B envelope antigen and viral DNA positive, with absence of antihepatitis B envelope antibody) or hepatitis C virus infection (presence of circulating antihepatitis C virus antibodies); nonactive disease that may flare up following the treatment (carriers for hepatitis B surface antigen with presence of hepatitis B core antibodies). E 19. Pregnant and breast-feeding women, female patients of childbearing potential and male patients with female partners of childbearing potential who are not willing to avoid pregnancy by using an adequate method of contraception (2 barrier method or 1 barrier method with a spermicide, intrauterine device, or hormonal contraception with

	inhibition of ovulation, for 2 weeks prior to the first dose of isatuximab, during treatment and 12 weeks after the last dose of study treatment). A woman is considered of childbearing potential, ie, fertile, following menarche and until becoming postmenopausal unless permanently sterile. E 20. Any country-related specific regulation that would prevent the subject from entering the study.
Total expected number of patients: **Expected number of sites:**	Approximately 39. Approximately 15-20.
STUDY TREATMENT **Investigational medicinal product** [redacted] **Route of administration:** **Dose regimen:**	**Isatuximab (SAR650984)** The drug product (isatuximab) is presented as a concentrate for solution for infusion in vials containing 20 mg/mL (500 mg/25 mL) isatuximab [redacted]. Isatuximab will be administered by the IV route. Within a cycle, the first day of isatuximab administration is D1. Isatuximab will be administered QW for 4 doses at the dose of 20 mg/kg (1 induction cycle). If at D15-22 of the first induction cycle, bone marrow blast cells remain >5%, a second induction cycle will be administered. If bone marrow blast cells are ≤5%, the administration of a second induction cycle will be performed at the discretion of the Investigator. Following the induction period, isatuximab will be administered Q2W at the dose of 20 mg/kg.
Non investigational medicinal products	**Isatuximab premedication to prevent infusion associated reactions** **Prior to the first isatuximab infusion** Dexamethasone 20 mg (IV or orally [PO]) administration at first infusion: as the risk of infusion associated reactions (IARs) to isatuximab is typically higher at the first infusion, dexamethasone will be administered 3 times before (once per day on D-2, D-1 and D1), and twice after (once per day on D2 and D3) the first study treatment administration. **Prior to each isatuximab infusion** All patients will receive the following premedication for prevention of IARs at least 15 to 30 minutes (but no longer than 60 minutes) prior to each isatuximab infusion: • Acetaminophen 650-1000 mg PO. • Ranitidine 50 mg IV (or equivalent). • Diphenhydramine 25-50 mg IV (or equivalent). • Dexamethasone 20 mg (IV or PO). Whatever the route of administration (IV or PO), dexamethasone will be administered only once per use of premedication. When dexamethasone is administered PO, the following order is recommended: dexamethasone, acetaminophen, ranitidine and diphenhydramine. When dexamethasone is administered IV, the following order is recommended: acetaminophen, ranitidine, diphenhydramine and

	dexamethasone. **Other medications:** In order to have rapid control of the tumor burden, the administration of cyclophosphamide 200 mg/m² before the first study treatment administration (up to 4 times, on D-3, D-2, D-1 and D1) is permitted for patients with hyperleucocytosis >50 000/mm³. Before C1D1, as per the institution's clinical practice, all patients will receive CNS relapse prophylaxis (eg, intrathecal methotrexate 15 mg and/or cytarabine 40 mg and/or dexamethasone 4 mg). Prophylaxis for tumor lysis syndrome and CNS relapse may be administered at the discretion of the treating physician during the treatment period.
ENDPOINTS	**Primary endpoints:** The primary efficacy endpoint is the ORR. Overall response rate is based on NCCN guidelines and is 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. **Secondary endpoints:** Secondary efficacy endpoints: • DOR 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. • PFS 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. • OS defined as the time interval from the date of first study treatment administration to death from any cause. **Other secondary endpoints:** • Safety assessment, in terms of AEs/serious adverse events (SAEs), laboratory parameters, vital signs, and physical examination. • PK parameters of isatuximab calculated using a non-compartmental and population PK approach. • Immunogenicity of isatuximab assessed throughout the study by detecting the presence of antidrug antibodies. • MRD by sequencing and/or flow cytometry in patients achieving CR and Cri. **Exploratory endpoints** Exploratory biomarkers: • Bone marrow and blood samples analyzed for CD38 receptor density and receptor occupancy on blast cells. • Bone marrow and blood samples analyzed for CD38 expression on blast cells (proportion of CD38 positive cells). • Bone marrow samples analyzed for tumor molecular alterations. • Blood samples analyzed to investigate the relationship between soluble CD38 and parameters of PK. • Blood samples analyzed for immune genetic determinants (including FcγR polymorphism genotyping and T cell receptor repertoire). Other genetic determinants, related to the drug action and/or effect of isatuximab, may be conducted on these samples during the study pending evolving literature.

	• Bone marrow and blood samples analyzed for immunophenotypes (such as B cell, T cell, and natural killer cell subsets). • Additional biomarker analysis, not specified in the protocol but related to the drug action and/or effect of isatuximab, may be conducted on remaining samples pending evolving literature. *Exploratory PK/PDy evaluation* • PK/PDy parameter estimates will be investigated as prognostic factors for clinical outcome including safety and efficacy endpoints, if possible.
ASSESSMENT SCHEDULE	**Efficacy data** Bone marrow aspirate and/or biopsy will be done at screening, between D15 and D22 during the first cycle (after the third isatuximab infusion), or to confirm response at the end of induction period (after 4, or 8 isatuximab infusions for patients receiving 2 induction cycles) and then every 2 cycles and when clinically indicated. No bone marrow is necessary if nonresponse or progressive disease can be diagnosed from peripheral blood evaluation, or, in patients with a white blood cell count <300/mm^3, if the bone marrow test is considered noncontributory by the Investigator. In case of T-LBL or for any extramedullary location, computed tomography (CT)/positron emission tomography-CT scan has to be performed at screening, then repeated every 2 cycles or when clinically indicated. **Safety data** Safety evaluation will be performed continuously throughout the study period. The following assessments will be obtained and reviewed by the Investigator prior to study treatment administration and at designated intervals throughout the study: • Vital signs, 12-lead electrocardiogram, physical examinations, respiratory assessment. • AEs. • Laboratory tests (complete blood counts, serum chemistry, coagulation tests). • ECOG performance status. • Immunogenicity. • Blood cytokines (tumor necrosis factor α, interleukin [IL]-1β, IL-4, IL-6, interferon γ), serum tryptase, markers of activated complement (C3a, C4, CH50) and tumor lysis syndrome markers. Adverse events will be collected from the signing of the study informed consent up to at least 30 days after the last dose of study treatment, or a new anticancer therapy is started, whichever is first. Adverse events will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), version 4.03 and coded according to the Medical Dictionary for Regulatory Activities. During the follow-up period, ongoing SAEs regardless of relationship to study treatment and ongoing or new study treatment-related AEs/SAEs will be followed until resolution or stabilization. **Pharmacokinetic data** Full PK profile sampling will be collected from patients in Stage 1 during the first induction cycle, to assess the PK profile of isatuximab using a non-compartmental analysis (including concentration at the end of infusion [C_{eoi}], maximum plasma concentration [C_{max}] and area under the plasma concentration versus time curve at Week 1 [AUC_{week1}] after the first administration [C1 Week 1] and trough plasma concentration [C_{trough}]

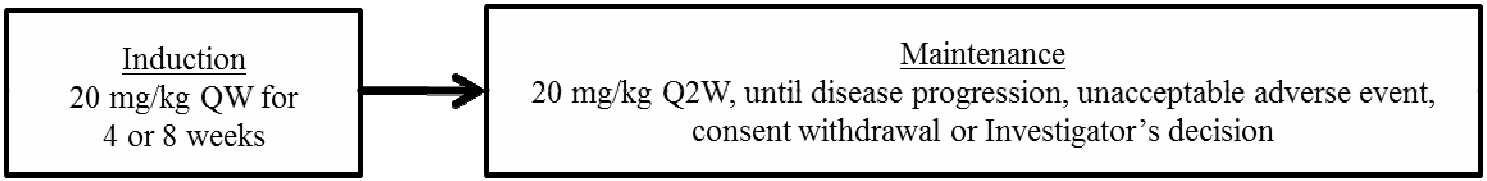
	throughout C1). Blood samples will be collected using a sparse sampling strategy in patients from Stage 1 from C2 onwards and in the remaining patients in Stage 2. All blood samples will be used to assess the PK profile of isatuximab using a population PK approach. This analysis will involve an estimation of the interpatient PK variability, the interoccasion PK variability, and the population PK parameters estimates of pathophysiologic covariate effects on the main PK parameters. Empirical Bayesian estimation of individual parameters and of individual exposure will also be performed. **Other data** • Immunophenotyping on bone marrow and blood cells at screening, between D15 and D22 during the first cycle (after the third isatuximab infusion), and end of treatment (EOT). • Molecular alteration data on blast cells in bone marrow at screening and immune genetic determinants in leukocytes in peripheral blood at C1D1 and before the start of first maintenance cycle, or at the end of the induction period (after 1 or 2 cycles) for patients who discontinue the study before the first maintenance cycle. • CD38 receptor occupancy (Stage 1 only), CD38 expression and CD38 receptor density on blast cells in bone marrow and blood samples at screening. Receptor occupancy will also be analyzed between D15 and D22 during the first cycle (after the third isatuximab infusion). • Soluble CD38 at C1D1. • MRD at screening and at CR.
STATISTICAL CONSIDERATIONS	**Sample size determination** A 2-stage Simon's Optimum design was used for sample size calculation. A maximum of 39 evaluable patients will be enrolled in the study. This sample size will provide 80% power to reject the null hypothesis that the true ORR is ≤15% if the true ORR rate is ≥30%, based on a 1-sided exact binomial test at a significance level of 0.1. • Stage 1: 19 patients. Proceed to Stage 2 if >3 responses are observed. • Stage 2: 39 patients (20 additional patients). If >8 responses are observed among the 39 patients analyzed, the null hypothesis will be rejected. **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. **Analysis population** The all-treated/safety population will include all 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. The PK population will include all patients from the all-treated/safety population with at least 1 PK parameter available. The PDy population will include patients from the all-treated/safety population

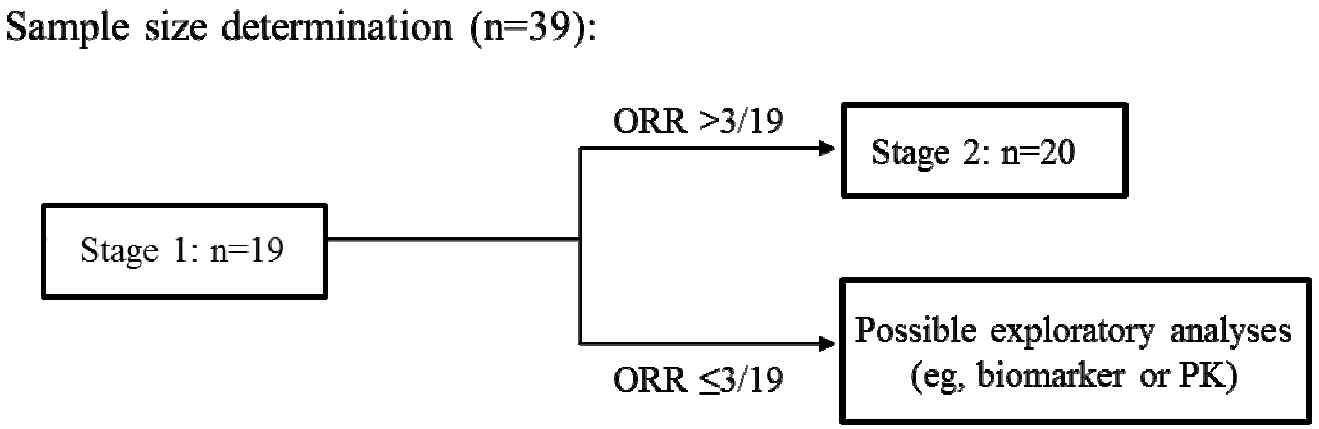
	who had data for at least 1 PDy parameter available. **General statistical approach** **Analysis of primary endpoint** The ORR will be summarized with descriptive statistics. Confidence intervals will be computed using the Clopper-Pearson method. **Analysis of secondary endpoints** The DOR, PFS and OS will be analyzed using the Kaplan-Meier method. Among patients who achieved a CR, the number of patients without MRD will be provided. Pharmacokinetics: individual plasma concentrations and PK parameters of isatuximab will be summarized by descriptive statistics. **Analysis of safety endpoints** Number (%) of patients experiencing treatment-emergent AEs (TEAEs) by primary system organ class and preferred term will be summarized by NCI-CTCAE grade (all grades and Grade ≥3) for the all-treated/safety population. Similar tables will be prepared for treatment related TEAEs, IARs, TEAEs leading to isatuximab discontinuation, TEAEs leading to dose modification, serious TEAEs, and AEs/SAEs occurring during the posttreatment dosing period. For patients with multiple occurrences of the same preferred term, the maximum grade within the analyzed observation period will be used. Complete blood counts and serum chemistry results will be graded according to the NCI-CTCAE version 4.03, when applicable. Number (%) of patients with laboratory abnormalities (ie, all grades and Grade ≥3) using the worst grade during the on-treatment period will be provided for the all-treated/safety population. **Analysis of exploratory endpoints** 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. **Cutoff dates/Planned database lock date** The cutoff date for interim analysis (Stage 1) will be approximately 2 months after last patient is treated in Stage 1. The cutoff date for primary analysis of ORR and other secondary endpoints will be 6 months after the last patient has had their 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 their first study treatment administration.
DURATION OF STUDY PERIOD (per patient)	The duration of the study for an individual patient will include: • The screening period of up to 3 weeks prior to the first study treatment administration. • The treatment period (in each period, the cycle duration is 28 days): - Induction period = QW dosing for 4 or 8 weeks, - Maintenance = dose Q2W. • An EOT visit 30 days after the last study treatment administration. • Follow-up period. Patients with documented disease progression at the EOT visit will be followed every 2 months until death or final analysis cutoff date, whichever comes first.

	Patients 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 month until initiation of another anticancer therapy, disease progression, death or final analysis cutoff date, whichever comes first. Then, after disease progression, or after initiation of further anticancer therapy for patients without disease progression, patients will be followed every 2 months until death or final analysis cutoff date, whichever comes first.

1 FLOW CHARTS

1.1 GRAPHICAL STUDY DESIGN





ORR: overall response rate; PK: pharmacokinetics; Q2W: once every 2 weeks; QW: once every week.

1.1.1 Graphical representation of study treatment

Induction Cycle 1

	D-2	D-1	D1	D2	D3	D8	D15	D22	D28	D29
Isatuximab			●			●	●	●		=D1 of the next cycle
Dexamethasone 20 mg	●	●	●	●	●	●	●	●		
Premedication*			●			●	●	●		

Induction Cycle 2 (if applicable)

D1	D8	D15	D22	D28
●	●	●	●	
●	●	●	●	
●	●	●	●	

Maintenance

	D1	D8	D15	D22	D28	D29
Isatuximab	●		●			=D1 of the next cycle
Dexamethasone 20 mg	●		●			
Premedication*	●		●			

C: Cycle; CNS: central nervous system; D: Day; IV: intravenously; PO: orally.

* All patients will receive premedication for prevention of infusion-associated reactions at least 15 to 30 minutes (but no longer than 60 minutes) prior to infusion. Premedication includes: dexamethasone 20 mg PO or IV (noted in separate line), acetaminophen 650 to 1000 mg PO, ranitidine 50 mg IV (or equivalent), and diphenhydramine 25 to 50 mg IV (or equivalent). Whatever the route of administration (IV or PO), dexamethasone will be administered only once per use of premedication.
Patients with hyperleucocytosis >50 000/mm^3: prior to the first isatuximab administration, administration of cyclophosphamide 200 mg/m^2 on D-3, D-2, D-1 and D1 is permitted.
Before C1D1, all patients will receive CNS relapse prophylaxis per the institution's clinical practice (eg, intrathecal methotrexate 15 mg and/or cytarabine 40 mg and/or dexamethasone 4 mg).

1.2 STUDY FLOW CHART

Assessment	Screening period (up to 3 weeks)		Treatment period						End of Treatment (30 days after the last treatment dose ±5 days)	Follow-up period[a]
			Induction period (QW administration) 1 or 2 28-day cycles				Maintenance period (Q2W administration) 28-day cycles			
	Within ≤21days of Day 1	Within 1 week of Day 1	Day 1	Day 8	Day 15	Day 22	Day 1	Day 15		
Informed consent/Inclusion and exclusion criteria	X		X (C1D1)							
Demography, study patient card, medical/surgical and disease history[b]	X									
Blood type phenotyping/genotyping, screen[c]	X									
Physical exam including respiratory function and ECOG PS[d]	X		X	X	X	X	X	X	X	X
Lumbar puncture (to exclude CNS involvement)	X		X (when clinically indicated)							
Weight/height (height at screening only)	X		X	X	X	X	X	X	X	
Vital signs[e]	X		X	X	X	X	X	X	X	
12-lead ECG[f]	X		When clinically indicated						X	
Chest X-ray	X									
CT/PET-CT scan[g]	X		At CR confirmation then every 2 cycles if extramedullary involvement or when clinically indicated[g]						X	
Blood cell counts[h]	X	X	X (C2 if applicable)	X	X	X	X	X	X	X
Serum chemistry tests[i]	X	X	X (C2 if applicable)	X	X	X	X	X	X	

Assessment	Screening period (up to 3 weeks)		Treatment period						End of Treatment (30 days after the last treatment dose ±5 days)	Follow-up period[a]
			Induction period (QW administration) 1 or 2 28-day cycles				Maintenance period (Q2W administration) 28-day cycles			
	Within ≤21days of Day 1	Within 1 week of Day 1	Day 1	Day 8	Day 15	Day 22	Day 1	Day 15		
Coagulation tests[j]		X	X (C2 if applicable)							
Pregnancy test for WOCBP[k]		X	X (C2 if applicable)				X		X	X
Hepatitis B and C virus serology	X									
Exploratory laboratory assessments (central laboratory)										
Soluble CD38 (blood)[l]			X (predose C1D1)							
Immunophenotyping (bone marrow and blood)[m]	X				X (C1D15-D22)				X	
CD38 receptor positivity and density (RD, bone marrow and blood)[n]	X									
CD38 receptor occupancy (RO, bone marrow and blood)[o]	X				X (C1D15-D22)					
Tumor molecular alterations (bone marrow)[p]	X									
Immune genetic determinants (blood)[q]			X (predose C1D1)				X			
Optional pharmacogenetic sample (blood)[r]			X (predose C1D1)							
Safety laboratory assessment										
TLS markers (blood; local laboratory) [s]			X (predose C1D1)	When IAR ≥ Grade 2 occurs						

Assessment	Screening period (up to 3 weeks)		Treatment period						End of Treatment (30 days after the last treatment dose ±5 days)	Follow-up period[a]
			Induction period (QW administration) 1 or 2 28-day cycles				Maintenance period (Q2W administration) 28-day cycles			
	Within ≤21days of Day 1	Within 1 week of Day 1	Day 1	Day 8	Day 15	Day 22	Day 1	Day 15		
Cytokines (TNFα, IL-1β, IL-4, IL-6, IFNγ) (blood; central laboratory)	See PK/PDy flowchart									
Markers of activated complement (C3a, C4, CH50), and serum tryptase (blood; central laboratory)	See PK/PDy flowchart									
Immunogenicity (ADAs)(blood; central laboratory)	See PK/PDy flowchart									
Disease assessment										
Bone marrow aspirate / biopsy[t]	X				X		X (before start of maintenance, then every 2 cycles or if clinically indicated)			X
MRD assessment (bone marrow or blood)[u]	X		X (at CR)							
Administration of isatuximab										
Isatuximab intravenous infusion			X	X	X	X	X	X		
Premedication		X (D-2, D-1, D1, D2, D3)		X	X	X	X	X		
CNS relapse prophylaxis	X		X (as per the institution's clinical practice)							
PK assessment	See PK/PDy flowchart									
AE/SAE assessment[v]	Continuously									
Prior/concomitant medications[w]	Continuously									
Post-IMP anticancer therapies	Not applicable								X	X
Survival	Not applicable									X

Assessment	Screening period (up to 3 weeks)		Treatment period						End of Treatment (30 days after the last treatment dose ±5 days)	Follow-up period[a]
			Induction period (QW administration) 1 or 2 28-day cycles				Maintenance period (Q2W administration) 28-day cycles			
	Within ≤21days of Day 1	Within 1 week of Day 1	Day 1	Day 8	Day 15	Day 22	Day 1	Day 15		

ADA: antidrug antibody; AE: adverse event; ALL: acute lymphoblastic leukemia; C: cycle; CNS: central nervous system; CR: complete response; CT: computed tomography; D: day; ECG: electrocardiogram; ECOG PS: Eastern Cooperative Oncology Group performance status; eCRF: electronic case report form; EOT: End of Treatment; IAR: infusion associated reaction; IFNγ: interferon gamma; IL: interleukin; IMP: investigative medicinal product; LBL: lymphoblastic lymphoma; LDH: lactate dehydrogenase; MRD: minimal residual disease; PDy: pharmacodynamics; PET: positron emission tomography; PK: pharmacokinetics; Q2W: once every 2 weeks; QW: once every week; SAE: serious adverse event; RD: receptor density; RO: receptor occupancy; TLS: tumor lysis syndrome; TNFα: tumor necrosis factor alpha; WOCBP: women of childbearing potential.

a **Follow-up:** First follow-up visit will be 60 days after last treatment dose (±5 days). Patients with documented disease progression at the EOT visit will be followed every 2 months until death or final analysis cutoff date, whichever comes first. Patients 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 month until initiation of another anticancer therapy, disease progression, death or final analysis cutoff date, whichever comes first. Then, after disease progression, or after initiation of further anticancer therapy for patients without disease progression, patients will be followed every 2 months until death or final analysis cutoff date, whichever comes first.

b **Demography, medical/surgical and disease history:** Includes age, gender, race, relevant medical/surgical history, disease history including date of initial diagnosis, type of disease (T-ALL/T-LBL, immunophenotypic and cytogenetic), previous anti-leukemia treatment (reason for discontinuation, date of relapse and best overall response to prior treatments). History of asthma, chronic obstructive bronchopneumonia,dyspnea and tobacco consumption will be collected and reported in the eCRF.

c **Blood type phenotyping/genotyping, screen:** If not previously performed, blood type phenotyping (or genotyping) and screen to be done after enrolment in the study and prior to first study treatment administration. The transfusion service should be made aware that the patient is receiving an anti-CD38 treatment (SAR650984). During the study treatment the transfusion service should follow the recommendations issued in the AABB bulletin in case a blood red cells transfusion is needed. The web link to the AABB bulletin will be indicated on the study patient card (see Appendix F). Patients should keep together their study patient card with their blood type card throughout the duration of the study treatment.

d **Physical examination:** Examination of major body systems including neurological examination, digestive, skin/mucosae, mediastinal, testicular localizations, respiratory, hepatomegaly, splenomegaly, and lymphadenopathy. Respiratory function will be monitored at C1D1 and before each study treatment administration, and at EOT visit including respiratory frequency, pulmonary auscultation, signs and symptoms such as cough, dyspnea, and expectoration. Patients with respiratory signs/symptoms Grade ≥2 that could be attributed to the study treatment, will have the respiratory evaluation repeated QW until improvement to Grade 1. Physical examination to be performed every 4 weeks during follow-up for patients who discontinue treatment for other reason than disease progression until initiation of another anticancer therapy, disease progression, death or final analysis cutoff date, whichever comes first. ECOG PS will be evaluated at screening, before each study treatment and at EOT visit.

e **Vital signs:** Blood pressure, heart rate, temperature, and respiration rate performed at screening and at preinfusion, 1 hour after starting the infusion, and at the end of infusion on D1, D8, D15 and D22 of induction cycle(s), then preinfusion and as clinically indicated for subsequent cycles. The final measurements will be performed at the EOT visit.

f **12-lead ECG**: To be performed at screening, at EOT visit and when clinically indicated.

g **CT/PET-CT scan:** A CT of chest with IV contrast and/or PET-CT scan (CT/PET-CT scan) should be performed at screening and at the EOT visit. In case of extramedullary involvement or T-LBL, both CT and PET-CT should be performed at baseline and at CR confirmation, whenever possible. Then CT and/or PET-CT scan every 2 cycles thereafter.

h **Blood cell counts**: Complete blood count with differential, hemoglobin and platelets to be performed at screening. To be repeated within 3 days before the first study treatment administration if performed >7 days before the first study treatment administration. To be performed at the time points specified in the table and when clinically indicated. To be performed every 4 weeks during follow-up for patients who discontinue treatment for other reason than disease progression until initiation of another anticancer therapy, disease progression, death or final analysis cutoff date, whichever comes first.

i **Serum chemistry:** To be repeated within 3 days before the first study treatment administration if performed >7 days before the first study treatment administration. From C1D8 onwards, to be performed and reviewed by the Investigator within 24 hours before the day of dosing. To be performed at the time points specified in the table and when clinically indicated. Chemistry includes: glucose (fasting), albumin, total protein, aspartate aminotransferase, alanine aminotransferase, bilirubin (total and direct), alkaline phosphatase, LDH, sodium, potassium, chloride, bicarbonate/carbon dioxide, total calcium, magnesium, phosphate, uric acid, blood urea nitrogen, serum creatinine and estimated creatinine clearance (Modification of Diet in Renal Disease formula; see Appendix A). In case of Grade 3 or 4 abnormalities, additional tests will be repeated every 2 to 3 days until recovery to baseline value or Grade≤1.

j **Coagulation tests:** To be performed within 7 days before the first study treatment administration and as clinically indicated. Coagulation includes: prothrombin time or international normalized ratio, and activated partial thromboplastin time.

k **Serum or urine pregnancy test:** Performed for WOCBP. To be repeated within 3 days before the first study treatment administration if performed >7 days before the first study treatment administration. To be performed every 4 weeks (before D1 of each cycle of study treatment administration). To be performed up to 3 months after the last administration of study treatment, or before starting further anticancer therapy.

l **Blood sample for soluble CD38:** To be performed on C1D1 prior to first study treatment administration. Analysis will be performed by central laboratory.

m **Immunophenotyping:** From bone marrow aspirate at screening only and from peripheral blood at screening, between D15 and D22 during the first cycle (after the third isatuximab infusion), and at the EOT visit. Sample collection from blood must be done before dexamethasone premedication. Analysis will be performed by central laboratory.

n **CD38 receptor positivity and density:** From bone marrow aspirate and peripheral blood collected at screening within 21 days before first study treatment administration. Sample collection from blood must be done before dexamethasone premedication. Analysis will be performed by central laboratory. This sample collection will be applicable in selected countries only.

o **CD38 receptor occupancy:** Stage 1 only. From bone marrow aspirate and peripheral blood collected at screening within 21 days before first study treatment administration, and between D15 and D22 during the first cycle (after the third isatuximab infusion). Sample collection from blood must be done before dexamethasone premedication. Analysis will be performed by central laboratory. This sample collection will be applicable in selected countries only.

p **Bone marrow aspirate for tumor molecular alteration assessment:** To be performed at screening. Analysis will be performed by central laboratory. In parallel, the local data will also be collected through report or access to data established at diagnosis or at the most recent relapse available.

q **Blood sample for immune genetic determinants:** To be performed on C1D1, prior to first study treatment administration and during the treatment period (before start of first maintenance cycle, or at the end of the induction period [after 1 or 2 cycles] for patients who discontinue the study before the first maintenance cycle) for some specific markers. Analysis will be performed by central laboratory.

r **Pharmacogenetics (optional):** To be performed on C1D1, prior to study treatment administration.

s **TLS markers and isatuximab safety labs:** Baseline sample to be drawn prior to first study treatment administration at C1D1. Should a isatuximab IAR of Grade ≥2 occur (as per National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03), additional blood sampling during the AE is required for analysis of markers of potential TLS (uric acid, LDH, blood urea nitrogen/creatinine, potassium, phosphate, and ionized and corrected calcium). Analysis of TLS markers will be performed by a local laboratory.

t **Bone marrow aspirate/biopsy for disease assessment:** To be performed at screening, between D15 and D22 (after the third isatuximab infusion), to confirm response at the end of induction period (after 4 isatuximab infusions, or 8 for patients receiving 2 induction cycles) and then before D1 of every other cycle (every 2 cycles) or when clinically indicated. Patients who discontinue for other reasons than disease progression will be followed every 4 weeks, but bone marrow aspirate will only be performed when clinically indicated. No bone marrow is necessary if nonresponse or progressive disease can be diagnosed from peripheral blood evaluation, or, in patients with a white blood cell count <300/mm3, if the bone marrow test is considered noncontributory by the Investigator. Analysis of bone marrow aspirate/biopsy for disease assessment will be performed by a local laboratory.

u **MRD assessment:** To be performed on bone marrow aspirate at screening and on blood at CR (in case of MRD positivity at first CR observation, assessment will be repeated after 2 to 3 cycles). Analysis will be performed by central laboratory.

v **Adverse Event/Serious Adverse Event:** The period of safety observation extends from the date informed consent is signed, until the end of treatment (at least 30 days after the last dose of study treatment, or a new anticancer therapy is started, whichever is first). Related AEs and any SAE ongoing at the end of treatment must be followed until resolution or stabilization. Any AE or SAE assessed as related to IMP that are new during the follow-up period will be reported and followed until recovery or stabilization.

w **Concomitant medication:** 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. After the end of treatment, only further anticancer therapy will be reported.

1.3 PHARMACOKINETICS/PHARMACODYNAMICS FLOWCHART: STAGE 1

Study Period	**Induction Cycle 1 +/- Cycle 2**													**Maintenance Period**								**EOT**	**Follow-up**	
Cycle	**Cycle 1**									**Cycle 2 (optional)**				**1st Cycle**			**2nd Cycle**				**Subsequent cycles**		**30 days after last IMP admin**	**60 days after last IMP admin**	**Monthly/ Bi-monthly[g]**
Day	**1**	**1**	**1**	**2**	**3**	**4**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**1**	**15**	**1**	**1**	**1**	**15**	**1**	**15**			
Time (decimal hours)	0h[b]	EOI[c]	EOI + 4h[d]	24h	48h	72h	0h[b]	0h[b]	0h[b]	0h[b]	0h[b]	0h[b]	0h[b]	0h[b]	EOI[c]	0h[b]	0h[b]	EOI[c]	EOI + 1h[e]	0h[b]	0h[b]	0h[b]			
Time window[k]		±10min	±30min	±4h	±8h	±12h									±10min			±10min	±10min				±5 days	±5 days	±5 days
Indicative clock time	8 am	12 pm	4 pm	8 am	8 am	8 am	8 am	8 am	8 am	8 am	8 am	8 am	8 am	8 am	12 pm	8 am	8 am	12 pm	1 pm	8 am	8 am	8 am	8 am	8 am	8 am
Isatuximab IV infusion	X---	---X					X	X	X	X	X	X	X	X---	---X	X	X---	---X		X	X	X			
Pharmacokinetics[a]																									
Isatuximab	P00	P01	P02	P03	P04	P05	P06	P07	P08	P00	P01	P02	P03	P00	P01	P02	P00	P01	P02	P03	P00	P01	PF00	PF01	
Pharmacodynamics[a]																									
Immunogenicity (ADA)	AB00							AB01		AB00		AB01		AB00			AB00				AB00		ABF00	ABF01[f]	ABF0x[f]
C3a, C4, CH50 & serum tryptase[h,i]	S00																								
Cytokines (TNFα, IL-1β, IL-4 IL-6 & IFNγ)[i,j]	P00																								

AB: antibody; ADA: antidrug antibody; EOI: end of infusion; EOT: end of treatment; h: hour; IMP: investigational medicinal product; IFNγ: interferon gamma; IL: interleukin; IV: intravenous; min: minutes; P: plasma; S: serum; TNFα: tumor necrosis factor alpha.

For the comfort of patients, some PK, PDy and/or ADA samplings may be deleted during the course of the study if they are no longer deemed necessary by the sponsor.

a Refer to Laboratory Manual for sample collection, processing and shipment.

b Start of infusion: sample collected just and strictly prior to study treatment administration.

c Sample collected immediately prior to actual EOI. A time window of ±10 minutes around the actual EOI is permitted.

d Sample collected 4 hours after the actual EOI.

e Sample collected 1 hour after the actual EOI.

f At 60 days. If patient is positive or inconclusive for ADAs, additional ADA sampling is required every 30 days (±5 days) until sample is negative (sample ID: ABF02, ABF03, etc).

g First follow-up visit will be 60 days after last treatment dose (±5 days). Patients with documented disease progression at the EOT visit will be followed every 2 months until death or final analysis cutoff date, whichever comes first. Patients 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 month until initiation of another anticancer therapy, disease progression, death or final analysis cutoff date, whichever comes first. Then, after disease progression, or after initiation of further anticancer therapy for patients without disease progression, patients will be followed every 2 months until death or final analysis cutoff date, whichever comes first.

h In case of infusion associated reaction ≥Grade 2, an additional sample will be collected as SF00.

i Samples will be drawn before first study treatment administration. The sample ID should be reported for each C3a, C4, CH50, serum tryptase, TNFα, IL-1β, IL-4, IL-6 and IFNγ.

j In case of infusion associated reaction ≥Grade 2, an additional sample will be collected as PF00.

k Time window permitted for PK/PDy sampling.

1.4 PHARMACOKINETICS/PHARMACODYNAMICS FLOWCHART: STAGE 2

Study Period	Induction Cycle 1 +/- Cycle 2							Maintenance Period									EOT	Follow-up	
Cycle	Cycle 1 +/- Cycle 2							1st Cycle			2nd Cycle				Subsequent cycles		30 days after last IMP admin	60 days after last IMP admin	Monthly/ Bi-monthly[f]
Day	1	1	1	8	15	15	22	1	1	15	1	1	1	15	1	15			
Time (decimal hours)	0h[b]	EOI[c]	EOI + 1h[d]	0h[b]	0h[b]	EOI[c]	0h[b]	0h[b]	EOI[c]	0h[b]	0h[b]	EOI[c]	EOI + 1h[d]	0h[b]	0h[b]	0h[b]			
Time window[j]		±10min	±10min			±10min			±10min			±10min	±10min				±5 days	±5 days	±5 days
Indicative clock time	8 am	12 pm	1 pm	8 am	8 am	12 pm	8 am	8 am	12 pm	8 am	8 am	12 pm	1 pm	8 am	8 am	8 am	8 am	8 am	8 am
Isatuximab IV infusion	X---	---X		X	X---	---X	X	X---	---X	X	X---	---X		X	X	X			
Pharmacokinetics[a]																			
Isatuximab	P00	P01	P02	P03	P04	P05	P06	P00	P01	P02	P00	P01	P02	P03	P00	P01	PF00	PF01	
Pharmacodynamics[a]																			
Immunogenicity (ADA)	AB00				AB01			AB00			AB00				AB00		ABF00	ABF01[e]	ABF0x[e]
C3a, C4, CH50 & serum tryptase[g,h]	S00																		
Cytokines (TNFα, IL-1β, IL-4, IL-6 & IFNγ)[h,i]	P00																		

AB: antibody; ADA: antidrug antibody; EOI: end of infusion; EOT: end of treatment; h: hour; IMP: investigational medicinal product; IFNγ: interferon gamma; IL: interleukin; IV: intravenous; P: plasma; S: serum; TNFα: tumor necrosis factor alpha.

For the comfort of patients, some PK, PDy and/or ADA samplings may be deleted during the course of the study if they are no longer deemed necessary by the sponsor.

a Refer to Laboratory Manual for sample collection, processing and shipment.

b Start of infusion: sample collected immediately just and strictly prior to study treatment administration.

c Sample collected immediately prior to actual EOI. A time window of ±10 minutes around the actual EOI is permitted.

d Sample collected 1 hour after the actual EOI.

e At 60 days. If patient is positive or inconclusive for ADAs, additional ADA sampling is required every 30 days (±5 days) until sample is negative (sample ID: ABF02, ABF03, etc).

f First follow-up visit will be 60 days after last treatment dose (±5 days). Patients with documented disease progression at the EOT visit will be followed every 2 months until death or final analysis cutoff date, whichever comes first. Patients 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 month until initiation of another anticancer therapy, disease progression, death or final analysis cutoff date, whichever comes first. Then, after disease progression, or after initiation of further anticancer therapy for patients without disease progression, patients will be followed every 2 months until death or final analysis cutoff date, whichever comes first.

g In case of infusion associated reaction ≥Grade 2, an additional sample will be collected as SF00.

h Samples will be drawn before first study treatment administration. The sample ID should be reported for each C3a, C4, CH50, serum tryptase, TNFα, IL-1β, IL-4, IL-6 and IFNγ.

i In case of infusion associated reaction ≥Grade 2, an additional sample will be collected as PF00.

j Time window permitted for PK/PDy sampling.

2 TABLE OF CONTENTS

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3 LIST OF ABBREVIATIONS

ADA: antidrug antibody
ADCC: antibody-dependent cellular cytotoxicity
ADCP: antibody-dependent cellular phagocytosis
AE: adverse event
AESI: adverse event of special interest
ALL: acute lymphoblastic leukemia
ALT: alanine aminotransferase
AST: aspartate aminotransferase
AUC: area under the plasma concentration versus time curve
AUC_{last}: area under the plasma concentration versus time curve calculated using the trapezoidal method from time 0 to the time of last concentration observed above the lower limit of quantification
AUC_{Week1}: area under the plasma concentration versus time curve calculated using the trapezoidal method over the first week of treatment
C: cycle
CDC: complement-dependent cytotoxicity
C_{eoi}: concentration at the end of an intravenous infusion
C_{last}: last concentration observed above the lower limit of quantification
C_{max}: maximum plasma concentration observed
CNS: central nervous system
CR: complete response
CRi: incomplete peripheral recovery
C_{trough}: plasma trough concentration
D: day
DOR: duration of response
ECG: electrocardiogram
ECOG: Eastern Cooperative Oncology Group
eCRF: electronic Case Report Form
ELISA: enzyme-linked immunosorbent assay
EOT: end of treatment
GCP: good clinical practice
IAR: infusion associated reaction
ICH: International Council for Harmonisation
IEC: independent ethics committee
IFNγ: interferon gamma
IL: interleukin
IMP: investigational medicinal product
IRB: institutional review board
IV: intravenous
LBL: lymphoblastic lymphoma
mAb: monoclonal antibody
MedDRA: Medical Dictionary for Regulatory Activities

MRD:	minimal residual disease
NCCN:	National Comprehensive Cancer Network
NCI-CTCAE:	National Cancer Institute Common Terminology Criteria for Adverse Events
NIMP:	noninvestigational medicinal products
NK:	natural killer
ORR:	overall response rate
OS:	overall survival
[redacted]	[redacted]
PCSA:	potentially clinically significant abnormality
PDy:	pharmacodynamics
PFS:	progression free survival
PK:	pharmacokinetic
PO:	orally
PS:	performance status
PT:	preferred term
Q2W:	once every 2 weeks
QW:	once every week
RD:	receptor density
RO:	receptor occupancy
SAE:	serious adverse event
SOC:	system organ class
TEAE:	treatment-emergent adverse event
TLS:	tumor lysis syndrome
t_{max}:	time to reach Cmax
TNFα:	tumor necrosis factor alpha
ULN:	upper limit of normal
WOCBP:	woman of childbearing potential

4 INTRODUCTION AND RATIONALE

CD38 is a type II glycosylated 45 kilodalton membrane protein that was identified as a lymphocyte marker (1). CD38 has a role in leukocyte homeostasis through modulation of hematopoietic cell survival and differentiation (2). CD38 functions as a receptor binding to CD31 and is involved in cell adhesion and signal transduction. The function of CD38 in signal transduction appears to be versatile depending on the cell lineage, the differentiation stage, and, possibly, the association with different coreceptors (2). CD38 is also an ectoenzyme catalyzing the synthesis and hydrolysis of cyclic adenosine-diphosphate-ribose from nicotinamide adenine dinucleotide to adenosine diphosphate-ribose (3). These reaction products are implicated in calcium mobilization and intracellular signaling.

The expression of CD38 in healthy humans can be detected on natural killer (NK) cells, monocytes, dendritic cells, macrophages, granulocytes, activated T and B cells, and plasma cells. In contrast, expression has not been detected in hematopoietic stem cells, resting T and B cells, or tissue macrophages. Several hematological malignancies express CD38 including those of B cell, T cell and myeloid origin. Moreover, CD38 was identified as a negative prognostic marker in some hematological malignancies, such as chronic lymphocytic leukemia.

In acute lymphoblastic leukemia (ALL), limited and conflicting data are available. One study showed that an increased CD38 expression was associated with favorable prognosis in newly diagnosed adult ALL (4). In adult patients with ALL (N=134), CD38 expression was associated with higher complete response (CR) duration (p=0.0220) but the difference in overall survival (OS) was not statistically different (p=0.12). The difference may have been accounted for by the significant association of low CD38 expression and the Philadelphia chromosome-positive subtype of ALL. Another study (5), concluded that CD38 expression was not related to any clinical or biological feature and that event-free survival did not differ significantly between CD38+ and CD38- cases of childhood ALL (N=325).

4.1 ACUTE LYMPHOBLASTIC LEUKEMIA

Acute lymphoblastic leukemia is a heterogeneous hematological disease characterized by the proliferation of immature lymphoid cells in the bone marrow, peripheral blood and other organs. The incidence rate of ALL in the United States is 1.77 per 100 000 individuals per year, with approximately 6250 new cases and 1450 deaths estimated in 2015 (6).

The risk for developing ALL is highest in children younger than 5 years of age. The risk then declines slowly until the mid-20s, and begins to rise again slowly after age 40, with a peak of incidence around 50 years. The median age at diagnosis is 14 years with 58.8% of patients diagnosed at younger than 20 years of age. In contrast, 25.5% of cases are diagnosed at 45 years or older and only approximately 11% of patients are diagnosed at 65 years or older. Acute lymphoblastic leukemia represents 75% to 80% of acute leukemias among children, but only approximately 20% of all leukemias among adults.

There are 2 main ALL subtypes, B-cell ALL and T-cell ALL (T-ALL): T-ALL accounts for 15% of pediatric cases and 20% of adults cases.

Lymphoblastic lymphoma (LBL) is in the same disease entity as ALL. The term LBL has been used to describe predominantly lymph node–based disease; however, clinical distinction between LBL and ALL has been arbitrary and has varied among different studies and institutions. Lymphoblastic lymphoma is relatively rare, comprising only 2% of all non-Hodgkin lymphomas.

The diagnosis of ALL generally requires demonstration of 20% or greater bone marrow lymphoblasts on bone marrow aspirates and biopsy materials. The 2008 World Health Organization classification lists ALL and LBL as the same entity, distinguished only by the primary location of the disease (7, 8). When the disease is restricted to a mass lesion primarily involving nodal or extranodal sites with no or minimal involvement in blood or bone marrow (generally defined as <20% lymphoblasts in the marrow), the case would be consistent with a diagnosis of LBL.

The cure rates and survival outcomes for patients with ALL have improved over the past decades, primarily among children. Adults have the poorest 5-year OS rate of 24.1% for patients between the ages of 40 and 59 years and an even lower rate of 17.7% for patients between the ages of 60 and 69 years.

Adult patients with ALL who relapse after initial therapy have extremely poor long-term outcomes. The median OS after relapse is only 4.5 to 6 months; the 5-year OS rate is 7% to 10% (8, 9). Approximately 20% to 30% of patients experience a second CR with second-line therapies (10). Treatment of adult patients with relapsed and/or refractory ALL remains a challenge.

Clofarabine, a nucleoside analog, has shown to be active in combination with other chemotherapy regimens in adults with relapsed/refractory disease, with a CR rate ranging from 44% to 73%, median OS of 6.5 to 7.7 months (11, 12). The most common Grade 3 and 4 toxicities included infection (58%) and liver toxicities (24%).

Nelarabine is a nucleoside analog that is currently approved in many European countries and the United States for the treatment of patients with T ALL who have not experienced either a disease response or who have relapsed disease after at least 2 chemotherapy regimens (13). In a Phase 2 study in 39 adult patients, the CR rate was 31%. Median disease-free survival and OS were both 20 weeks and the 1-year OS rate was 28% (14). Grade 3 and 4 myelosuppression was common. Since Nelarabine approval (more than 10 years ago), no other drug has been approved in relapsed or refractory T-ALL, making this indication a real unmet medical need.

4.2 DESCRIPTION OF ISATUXIMAB

Isatuximab (SAR650984) is a chimeric IgG1 monoclonal antibody (mAb) directed against CD38 that was derived from mu38SB19, a murine anti-CD38 antibody, raised by immunizing mice with a murine pre-B cell over-expressing cell surface human CD38. The humanized version displays the same affinity for CD38 as the murine version with isatuximab selectively binding to human CD38 with an affinity of 2×10^{-10} M.

4.3 PHARMACOLOGY

Isatuximab targets CD38, an antigen expressed in hematological malignancies and represents a new treatment entity displaying 3 key biological properties of tumor cell lysis in vitro: antibody-dependent cellular cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC) and induction of apoptosis. Isatuximab also demonstrated in vivo antitumor activity as a single agent and in combination with reference treatments in several CD38+ tumor models. In addition, isatuximab demonstrated antitumor activity against primary patient-derived tumor cells ex vivo without significant cytokine release, cellular activation, or depletion in vitro assays with normal human peripheral blood mononuclear cells supporting its clinical evaluation in CD38+ hematological malignancies.

4.3.1 Toxicology

Isatuximab is specific for human CD38 protein. In the absence of a relevant animal species for toxicity testing with isatuximab, no single or repeated dose toxicity studies were performed. No studies have been performed to evaluate genotoxicity, as this drug is a mAb with no potential to interact with cellular DNA. No carcinogenicity studies will be conducted, as this drug is a therapeutic mAb being developed for oncology indications. There is no evidence or scientific rationale indicating a potential risk for tumorigenicity. Reproductive toxicology studies have not yet been performed.

For more information please refer to the product Investigator's Brochure.

4.3.2 Metabolism and pharmacokinetic profile in animals

Not applicable.

4.4 BACKGROUND INFORMATION ON CD38 IN ACUTE LYMPHOBLASTIC LEUKEMIA

4.4.1 Preclinical data

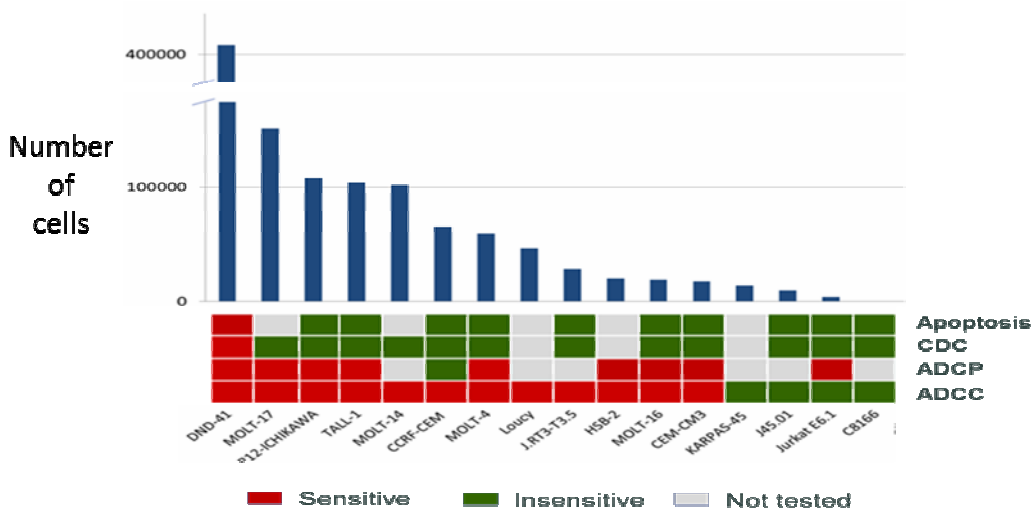
4.4.1.1 Isatuximab activity in ALL cell lines and patient-derived ALL cells

The different mechanisms by which isatuximab can trigger destruction of a CD38 expressing tumor cell were evaluated on a panel of T-ALL cell lines (N=16).

The pro-apoptotic activity of isatuximab was tested in 11 cell lines and the CDC activity of isatuximab was tested in 13 cell lines. Only the cell line with the highest receptor density (RD; DND-1) was sensitive to these 2 mechanisms.

A total of 10 and 16 cell lines were tested for antibody-dependent cellular phagocytosis (ADCP) and ADCC, respectively. Most cell lines are killed by isatuximab in the presence of effector NK cells and macrophages; 9 of 10 T-ALL cell lines were sensitive to ADCP. Twelve of 16 T-ALL cell lines were ADCC-sensitive (Figure 1).

Figure 1 - Isatuximab activity in T-ALL cell lines

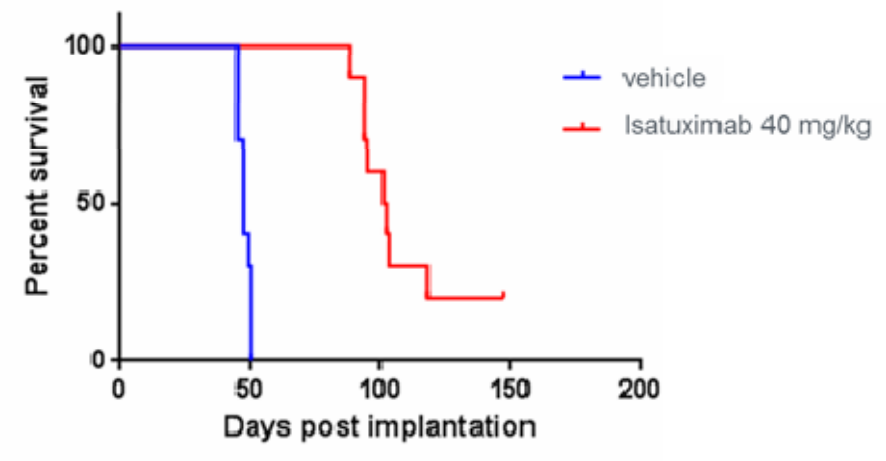


ADCC: antibody-dependent cellular cytotoxicity; ADCP: antibody-dependent cellular phagocytosis; CDC: complement-dependent cytotoxicity.

4.4.1.2 Isatuximab in vivo activity in xenograft mouse models

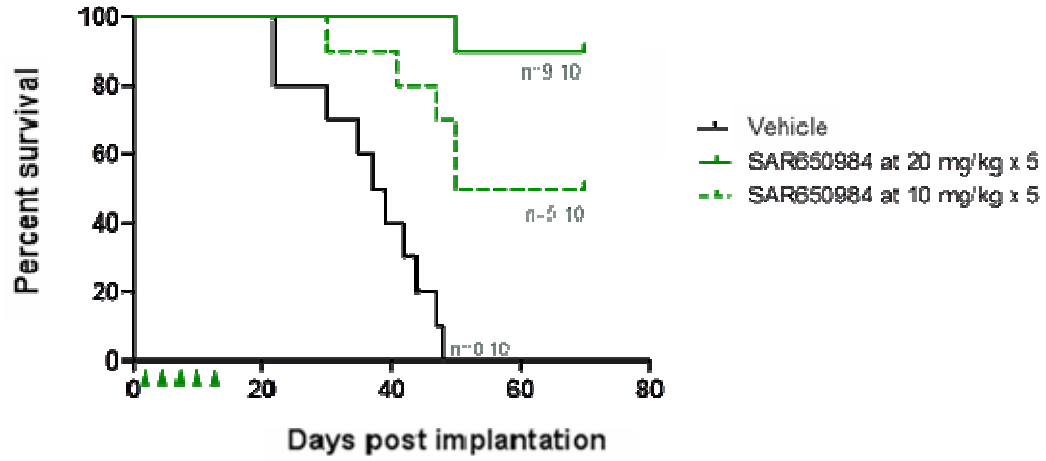
Isatuximab was evaluated in a disseminated T-ALL xenograft model, where 2 million CCRF-CEM cells were implanted via intravenous (IV) injection into severe combined immunodeficiency mice and isatuximab was dosed at 40 mg/kg every 3 days for 3 weeks. The median survival increased from 47 days in the control group to 98 days in the treatment group. Two animals survived until the end of the study, 147 days postimplantation (Figure 2).

Figure 2 - Disseminated T-ALL xenograft model of survival (isatuximab versus control vehicle)



Isatuximab was also evaluated in a disseminated syngeneic model, where 0.5 million of EL4 murine T cell lymphoma cells engineered to express approximately 100 000 human CD38 molecules/cell were implanted via IV injection into immunocompetent C57Bl/6 mice and isatuximab was dosed at 10 mg/kg and 20 mg/kg every 3 days for 2 weeks. Median survival in the control group was 39 days. In the low dose group, 5 of 10 animals survived until the end of the study (Day [D] 70), and in the 20 mg/kg group, 9 of 10 animals were alive at D70 (Figure 3).

Figure 3 - Disseminated syngeneic model of survival (isatuximab versus control vehicle)



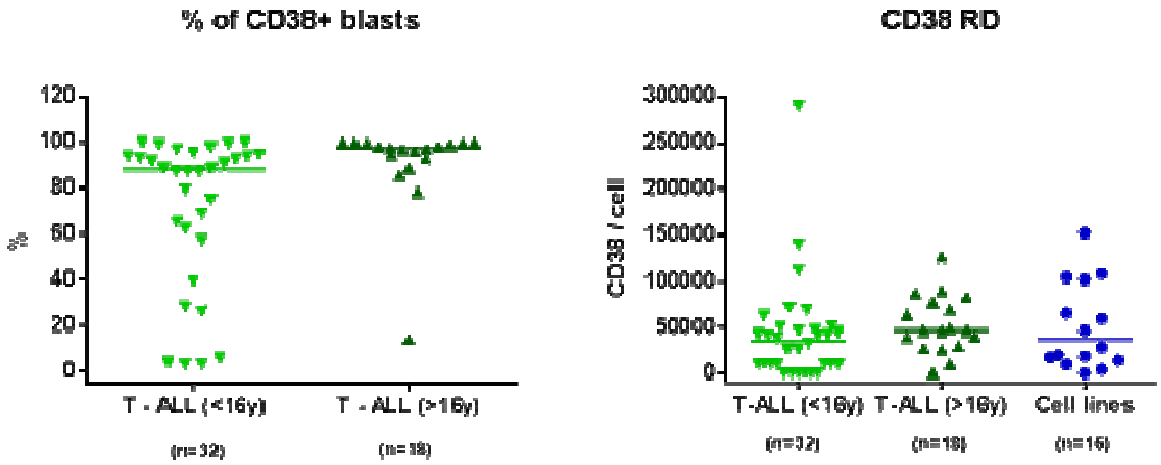
4.4.2 Clinical data

4.4.2.1 CD38 expression in T-ALL

A total of 50 samples from the bone marrow (n=44) or peripheral blood (n=6) of patients with T-ALL with a median age of 12.5 years (1.5 to 53 years) were tested for CD38 expression by flow cytometry (internal data). The percentage of T cell lymphoblasts in the white blood cells from these patients varied from 1.1% to 91% (median value of 13.1%).

The percentage of CD38 expressing cells within the abnormal T cell populations ranged from 2.9% to 100% (median value of 92.9%). The estimated CD38 RD for the 50 samples varied between 0 and 290 000 molecules/cell, with a median value of 41 000 molecules/cell, similar to that in a panel of T-ALL cell lines (N=16), with a median CD38 RD of 46 000 CD38 molecules/cell (0 to 212 000 molecules/cell). The percentage of CD38 positivity and RD was not significantly different in patients above or below 16 years of age (Figure 4).

Figure 4 - CD38 positivity and receptor density in T-ALL patients above or below 16 years of age



ALL: acute lymphoblastic leukemia; RD: receptor density; y: years.

4.4.2.2 Isatuximab clinical data

Please refer to the current Investigator's Brochure of isatuximab for details on the clinical experience to date.

As of 05 January 2016, 263 patients have been treated with isatuximab in 5 clinical studies. No patients with T-ALL have been treated with isatuximab in ongoing studies at the data lock point.

In the 186 patients who received isatuximab as single agent in the TED10893 study, isatuximab appeared to be well tolerated at all dose levels tested. At doses ≥10 mg/kg, preliminary data show no difference in terms of type, incidence and severity of treatment-emergent adverse events (TEAEs). The most common TEAEs (in ≥20% of patients) consisted of infusion related reaction (49.4%), fatigue (37.1%), nausea (32.6%), anemia (28.1%), cough (22.5%), upper respiratory tract infection (22.5%), back pain (20.2%), and diarrhea (20.2%). Infusion associated reactions (IARs) occurred in approximately half of all patients. Symptoms of IARs were of Grade ≥3 severity in 13 (7.0%) patients and 4 (2.2%) patients discontinued treatment due to Grade 3 or 4 IARs. Ninety percent of the IARs occurred upon the first administration of isatuximab. Eight (4.3%) patients had an IAR during their second or subsequent infusions. All IARs resolved with or without treatment.

Of the 97 patients enrolled in the Phase 2 part, at the highest dose levels of 10 and 20 mg/kg, the most common non-hematological TEAEs were nausea (36.5%), cough and fatigue (33.8% each), diarrhea (27%), and dyspnea (25.7%).

Preliminary efficacy data of the Phase 2 part of TED10893 showed a dose response effect between the 3 mg/kg once every 2 weeks (Q2W) dose (overall response rate [ORR] <10%) and the doses ≥10 mg/kg (ORR ≥20% in all arms: 10 mg/kg Q2W, 10 mg/kg Q2W then every 4 weeks and 20 mg/kg once every week [QW] followed by Q2W). At doses of 10 mg/kg and 20 mg/kg, the response rate ranged from 20% to 29%, without a clear dose response between the 10 mg/kg and 20 mg/kg arms. For the patients enrolled in the 10 mg/kg arms, the median duration of response (DOR) was 9.2 to 12.9 months (6/12 responder patients had progressive disease). For patients in the

20 mg/kg group, DOR data is still maturing and at time of the analysis, median duration of response was >8 months (4/6 responders patients had progressive disease) (15).

4.5 RATIONALE

4.5.1 Study design rationale

4.5.1.1 Dose selection rationale in multiple myeloma

Clinical data from the TED10893 trial did not show an obvious difference between 10 and 20 mg/kg isatuximab. A preliminary PK/PDy analysis to evaluate the relationship between ORR and PK parameters was performed using a generalized additive model with pooled Phase 1 and Phase 2 data from the TED10893 study. This analysis showed that plasma trough concentration (C_{trough}) at Week 4 was a significant predictor of ORR. The probability of response to treatment increases as C_{trough} at Week 4 increases up to a plateau. This plateau was reached for C_{trough} at Week 4 following a weekly administration at 20 mg/kg, indicating that frequent administration

together with a high dose in the first cycle is needed to optimize the response (4 once weekly administrations at 20 mg/kg).

In addition, modeling and simulations of exposure-response to isatuximab, based on the M-protein concentration-time profile, showed a higher response to treatment in terms of reduction in myeloma-protein at 8 or 12 weeks following 20 mg/kg QW for 4 weeks followed by 20 mg/kg Q2W compared to lower doses (ie, 10 mg/kg QW for 4 weeks followed by 10 mg/kg Q2W).

Therefore, based on safety, efficacy and PK/PDy modeling and simulation, the selected dose and schedule of administrations of isatuximab as a single agent for multiple myeloma patients is 20 mg/kg QW for 1 cycle, followed by 20 mg/kg Q2W for subsequent cycles [redacted]

4.5.1.2 Acute Lymphoblastic Leukemia

Despite improvements in the achievement of CR and progress in the supportive care of adults with ALL during the last decade, the majority of patients will relapse. The recent approach of adapting therapy according to biological features appears to be resulting in significant progress. Thus, studies of targeted therapy like isatuximab in T-ALL would be highly attractive, because of the potential efficacy and with an acceptable safety profile and a population with an unmet medical need. This Phase 2, single arm study of isatuximab will explore the efficacy and safety of single agent isatuximab in patients with relapsed/refractory T-ALL or T-LBL.

The treatment period will consist of an induction period followed by a maintenance period. The induction treatment will consist of 4 QW administrations of isatuximab. A second induction cycle will be permitted under certain conditions (see Section 6.1). The maintenance period will consist of administration of isatuximab at the same dose as for the induction period, with a Q2W schedule. Patients will be allowed to continue maintenance therapy until disease progression, an unacceptable adverse event (AE), consent withdrawal or Investigator's decision.

The dose of isatuximab in this study will be 20 mg/kg, following results in Phase 1 and 2 studies in multiple myeloma (see Section 4.5.1.1). An interim analysis will be performed when all patients in Stage 1 (19 treated patients) have completed either 2 induction cycles plus D1 of the first maintenance cycle or 1 induction cycle plus 1 maintenance cycle.

Although 80% to 95% of adult patients with ALL achieve complete clinical remission with current treatment protocols, a significant proportion of them ultimately relapse. Relapses are caused by residual malignant cells that are undetectable by standard diagnostic techniques. With the development of sensitive molecular and flow cytometric techniques for the quantitative detection of residual leukemic cells, the presence of minimal residual disease (MRD) in patients in complete clinical remission has clearly been demonstrated. Several studies have shown that detection of MRD in adult ALL is an independent risk parameter of high clinical relevance, both in de novo and relapsed ALL.

The risk-benefit balance inherent to the therapy with isatuximab has been carefully considered in the planning of this study. The design of the study and the dosage regimen of the study treatment are considered justified on the basis of the nonclinical and clinical isatuximab experience available to date.

5 STUDY OBJECTIVES

5.1 PRIMARY

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 ORR (as per National Comprehensive Cancer Network [NCCN] guidelines; Appendix C).

5.2 SECONDARY

- To evaluate the safety profile of isatuximab.
- To evaluate the duration of response (DOR).
- To evaluate progression free survival (PFS) and 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 MRD and correlate it with clinical outcome.

5.3 EXPLORATORY

- To explore the relationship between CD38 expression and clinical response.
- To explore the relationship between CD38 receptor occupancy (RO) and CD38 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.

6 STUDY DESIGN

6.1 DESCRIPTION OF THE STUDY

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 evaluable 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 dose of isatuximab is 20 mg/kg. The cycle duration is 28 days.

During the induction period, isatuximab will be administered by IV infusion, QW for 4 weeks (1 induction cycle = 4 QW doses). If at D15-22 of the first induction cycle, bone marrow blast cells remain >5%, a second induction cycle will be administered. If bone marrow blast cells are ≤5%, the administration of a second induction cycle will be performed at the discretion of the Investigator.

After a maximum of 2 cycles of induction therapy, patients will be withdrawn from the study treatment if they do not achieve an objective response, or, in case of disease progression, an unacceptable AE, consent withdrawal or Investigator's decision (eg, patient is candidate for transplantation).

During maintenance, in patients achieving an objective response following the induction period, isatuximab will be given Q2W. Patients will be allowed to continue maintenance therapy until disease progression, an unacceptable AE, consent withdrawal or Investigator's decision (eg, patient is a candidate for transplantation).

6.2 DURATION OF STUDY PARTICIPATION

6.2.1 Duration of study participation for each patient

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

- The screening period of up to 3 weeks prior to the first study treatment administration.
- The treatment period (in each period, the cycle duration is 28 days):
  - Induction period = QW dosing for 4 or 8 weeks,
  - Maintenance period = Q2W dosing.
- An end of treatment (EOT) visit 30 days after the last study treatment administration.
- Follow-up period.

Patients with documented disease progression at the EOT visit will be followed every 2 months until death or final analysis cutoff date, whichever comes first.

Patients without documented disease progression at the EOT visit and who have not yet started treatment with another anticancer therapy will perform follow-up visits every month until initiation of another anticancer therapy, disease progression, death or final analysis cutoff date, whichever comes first. Then, after disease progression, or after initiation of further anticancer therapy for patients without disease progression, patients will be followed every 2 months until death or final analysis cutoff date, whichever comes first.

6.2.2 Determination of end of clinical trial (all patients)

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 study treatment administration. Patients still on treatment at 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.

6.3 RETREATMENT OF PATIENTS

In case of AEs, the patient must have improved to Grade ≤1 or to his/her baseline status before being considered for the next administration of isatuximab. Patients can continue the study treatment until disease progression, an unacceptable AE, consent withdrawal or Investigator's decision (eg, patient is a candidate for transplantation).

6.4 DOSE DELAYS/DOSE MODIFICATIONS

No dose reduction is authorized for isatuximab in an individual patient.

Cycle delay up to 14 days is allowed. If administration within 14 days following the planned date is not possible, the patient will discontinue the study treatment unless in case of clinical benefit and in agreement with the Sponsor.

Within a cycle (induction or maintenance), an isatuximab administration can be delayed for up to 3 days. If the dose cannot be administered within 3 days, the isatuximab dose will be omitted.

Only 1 omission per cycle is permitted. Further omissions must be discussed on a case by case basis with the Sponsor.

If a patient experiences several AEs and there are conflicting recommendations, the most conservative dose adjustment recommended (dose delay/omission appropriate to the most severe AE) should be followed.

6.5 INTERIM ANALYSIS

Interim analysis is described in Section 11.5.

6.6 STUDY COMMITTEE

The Study Committee will be comprised of the Coordinating Investigator, at least 2 additional study investigators and Sponsor representatives. Regular meetings will be organized as appropriate throughout the study. They will be responsible for:

- Reviewing the conduct of the study.
- Reviewing the efficacy and safety results from the Stage 1 analysis.
- Reviewing the overall efficacy and safety data at the end of the study.

7 SELECTION OF PATIENTS

7.1 INCLUSION CRITERIA

I 01. Patients must have a known diagnosis of ALL of T cell origin, including T-LBL and T-ALL with isolated extramedullary involvement at relapse confirmed by biopsy.

I 02. Patients must be previously treated for T-ALL or T-LBL and have relapsed or are refractory to most recent treatment (see Appendix C). Patients in first relapse will be eligible regardless of the first remission duration.

I 03. Patients must have been previously exposed to nelarabine in countries where this drug is available (unless due to a contraindication to its use or administrative issue).

I 04. No more than 3 prior salvage therapies.

I 05. Signed written informed consent.

7.2 EXCLUSION CRITERIA

Patients who have met all the above inclusion criteria listed in Section 7.1 will be screened for the following exclusion criteria which are sorted and numbered in the following 2 subsections:

7.2.1 Exclusion criteria related to study methodology

E 01. Age <16 years.

E 02. Patients must have been off prior treatment with immunotherapy/investigational agents for >3 weeks and chemotherapy for >2 weeks and must have recovered from acute toxicity (ie, to Grade 1 or less except alopecia or peripheral neuropathy Grade ≤2 without pain) before the first study treatment administration. Treatment may start earlier if necessitated by the patient's medical condition (eg, rapidly progressive disease) following discussion with the Sponsor.

E 03. Prior stem cell transplant within 4 months and/or evidence of active systemic Graft versus Host Disease and/or immunosuppressive therapy for Graft versus Host Disease within 1 week before the first study treatment administration.

E 04. Clinical evidence of active central nervous system (CNS) leukemia. Lumbar puncture should be negative before C1D1. In case of positivity for blast cells before or during the screening period, local treatment is allowed. Confirmed negativity of the lumbar puncture is mandatory within 3 days before the first administration of isatuximab (C1D1). Otherwise, the patient will be considered as non-eligible for the study.

E 05. T-ALL with testicular involvement alone.

E 06. Evidence of ongoing infection.

E 07. Second malignancy other than basal cell or squamous cell carcinoma of the skin or in situ carcinoma of the cervix or the breast, unless they are successfully treated with curative intent for more than 3 years before entering the study.

E 08. Poor condition/organ functions as defined by 1 of the following:
- Eastern Cooperative Oncology Group (ECOG) performance status (PS) >2 (Appendix B).
- Total bilirubin >1.5 x upper limit of normal (ULN) unless Gilbert's syndrome.
- Alanine aminotransferase (ALT), aspartate aminotransferase (AST) or alkaline phosphatase >2.5 x ULN, unless considered due to the disease.
- Serum creatinine >2 x ULN and/or creatinine clearance <30 mL/min (Modification of Diet in Renal Disease formula; Appendix A).

E 09. Radiation therapy within 14 days prior to study treatment administration (this delay could be reduced if necessitated by patient's medical condition following discussion with Sponsor).

E 10. Any serious active disease or comorbid condition which, in the opinion of the Investigator, may interfere with the safety of the study treatment or the compliance with the study protocol.

E 11. Any other severe underlying medical or administrative conditions, which could impair the ability to participate in the study or the interpretation of its results.

E 12. Patient is the Investigator, Subinvestigator, research assistant, Pharmacist, study coordinator, other staff or relative thereof directly involved in the conduct of the protocol.

E 13. Any technical/administrative reason (eg, patient homeless) that makes study participation impossible.

E 14. Patient who has previously participated/Patient who has previously been treated in any clinical study with isatuximab or with a same class compound.

E 15. Conditions/situations such as: Patient not suitable for participation, whatever the reason, as judged by the Investigator, or patients potentially at risk of noncompliance to study procedures.

7.2.2 Exclusion criteria related to the current knowledge of Sanofi compound

[redacted]

E 17. Known human immunodeficiency virus positivity.

E 18. Active hepatitis B virus (hepatitis B surface antigen, hepatitis B envelope antigen and viral DNA positive, with absence of antihepatitis B envelope antibody) or hepatitis C virus infection (presence of circulating antihepatitis C virus antibodies); nonactive disease that may flare up following the treatment (carriers for hepatitis B surface antigen with presence of hepatitis B core antibodies).

E 19. Pregnant and breastfeeding women, female patients of childbearing potential (WOCBP) and male patients with female partners of childbearing potential who are not willing to avoid pregnancy by using an adequate method of contraception (2 barrier method or 1 barrier method with a spermicide, intrauterine device, or hormonal contraception with inhibition of ovulation for 2 weeks prior to the first dose of isatuximab, during treatment and 12 weeks after the last dose of study treatment). See Section 8.8.3. A woman is considered of childbearing potential, ie, fertile, following menarche and until becoming postmenopausal unless permanently sterile.

E 20. Any country-related specific regulation that would prevent the subject from entering the study.

8 STUDY TREATMENTS

8.1 INVESTIGATIONAL MEDICINAL PRODUCT(S)

Isatuximab (SAR650984) is the only investigational medicinal product (IMP) in this study.

8.1.1 Pharmaceutical form

The drug product (isatuximab, SAR650984) is presented as a concentrate for solution for infusion in vials containing 20 mg/mL (500 mg/25 mL) isatuximab [redacted].

It is supplied for parenteral administration as a sterile, nonpyrogenic, injectable, colorless, 20 mg/mL concentrate for solution for infusion that may contain white to off-white particulates and is packaged in 30 mL glass vials fitted with elastomeric closure. Each vial contains a nominal content of 500 mg of isatuximab [redacted]. The fill volume has been established to ensure removal of 25 mL.

[redacted]

For administration to patients, the appropriate volume of isatuximab will be diluted in an infusion bag of 0.9% sodium chloride solution. The final infusion volume corresponding to the dose of isatuximab will be administered for a period of time that will depend on dose administered and will be based on protein amount given per hour.

8.1.2 Dose of drug per administration

The dose of isatuximab is 20 mg/kg.

The patient's weight should be measured prior to each treatment administration to allow calculation of the dose.

Induction period: isatuximab will be administered by IV infusion QW for 4 weeks (1 induction cycle = 4 QW doses). If at D15-22 of the first induction cycle, bone marrow blast cells remain >5%, a second induction cycle will be administered. If bone marrow blast cells are ≤5%, the administration of a second induction cycle will be performed at the discretion of the Investigator.

Maintenance period: In patients achieving an objective response following the induction period, isatuximab will be given Q2W, see Section 6.1.

The rate of infusion should be initiated at 175 mg/hour.

In the absence of IARs after 1 hour of the first infusion, the infusion rate should be increased by 50 mg/hour increments every 30 minutes, to a maximum of 400 mg/hour.

For subsequent infusions: the infusion should be initiated at 175 mg/hour. In the absence of IARs after 1 hour of infusion, the infusion rate should be increased by 100 mg/hour increments every 30 minutes, to a maximum of 400 mg/hour.

In case of infusion interruption due to IAR, the infusion can be restarted after the IAR improves to Grade ≤1. The infusion rate should be one half of the original infusion rate. If symptoms do not recur after 30 minutes, the infusion rate may be increased by 50 mg/hour increments every 30 minutes, to a maximum of 400 mg/hour.

Examples of IARs and typically associated symptoms are presented in Appendix E. Instructions for the management of IARs are presented in Section 10.6.1.

8.1.3 Dilution method

The isatuximab concentrate for solution for infusion will be diluted in an infusion bag with 0.9% sodium chloride solution to achieve the appropriate drug concentration for infusion.

Infusion via a central line is preferred if available. Patients with local intolerance after peripheral IV infusion should receive next dose(s) using a central line. The final infusion volume corresponding to the dose of isatuximab will be administered by IV infusion for the period of time that will depend on dose administered and on the protein amount administered per hour (Section 8.1.2).

Prior to dosing, each patient's dose will be individually prepared by the study Pharmacist and labeled with protocol number, patient number, and treatment description.

A 0.2 µm in-line filter is required for administration.

Therefore, for IV infusion, an IV tubing administration set with a 0.20-micron in-line filter will be used; if an in-line filter is unavailable, a 0.2 µm filter unit may be attached to the administration set before administration.

Detailed instruction for dilution of the isatuximab concentrate for solution for infusion is provided in the Pharmacy Manual.

8.2 NONINVESTIGATIONAL MEDICINAL PRODUCTS

Premedication (noninvestigational medicinal products [NIMP]) must be given to patients to prevent IARs. A graphical representation of study treatment is provided in Section 1.1.1.

Prior to the first isatuximab infusion:

Dexamethasone 20 mg (IV or orally [PO]) administration at first infusion: as the risk of IARs to isatuximab is typically higher at the first infusion, dexamethasone will be administered 3 times before (once per day on D-2, D-1 and D1), and twice after (once per day on D2 and D3) the first study treatment administration.

Prior to each isatuximab infusion:

All patients will receive the following premedication for prevention of IARs at least 15 to 30 minutes (but no longer than 60 minutes) prior to each isatuximab infusion:

- Acetaminophen 650-1000 mg PO.
- Ranitidine 50 mg IV (or equivalent).
- Diphenhydramine 25-50 mg IV (or equivalent).
- Dexamethasone 20 mg (IV or PO).

On the day of isatuximab administration, dexamethasone will be administered only once per use of premedication/backbone therapy, whatever the route of administration (IV or PO).

When dexamethasone is administered PO, the following order is recommended: dexamethasone, acetaminophen, ranitidine and diphenhydramine.

When dexamethasone is administered IV, the following order is recommended: acetaminophen, ranitidine, diphenhydramine and dexamethasone.

8.3 BLINDING PROCEDURES

Not applicable as this is an open label and single arm study of isatuximab monotherapy.

8.4 METHOD OF ASSIGNING PATIENTS TO TREATMENT GROUP

This is an open label, single arm, non-randomized study.

Patients who meet all the inclusion criteria, and none of the exclusion criteria, will be enrolled in the study. Each patient will be enrolled and receive an incremental identification number per site corresponding to the chronological order of inclusion.

Only screen failure patients will be replaced.

8.5 PACKAGING AND LABELING

The IMP is packaged in 30 mL glass vials fitted with elastomeric closure. See Section 8.1.1 for further details.

The content of the labeling is in accordance with the local regulatory specifications and requirements.

8.6 STORAGE CONDITIONS AND SHELF LIFE

Investigators or other authorized persons (eg, Pharmacists) are responsible for storing the IMP in a secure and safe place with restricted access in accordance with local regulations, labeling specifications, policies, and procedures.

Control of IMP storage conditions, especially control of temperature (eg, refrigerated storage) and information on in-use stability and instructions for handling the sanofi compound should be managed according to the rules provided by the Sponsor.

The IMP is to be stored at +2°C to +8°C (36°F to 46°F). All vials must be kept in their box until use.

No protection from light is required for storage in the infusion bags.

Details of the storage conditions for the diluted solution are provided in the Pharmacy Manual.

8.7 RESPONSIBILITIES

The Investigator, the hospital Pharmacist, or other personnel allowed to store and dispense the IMP will be responsible for ensuring that the IMP used in the clinical study is securely maintained as specified by the Sponsor and in accordance with applicable regulatory requirements.

All IMP will be dispensed in accordance with the Investigator's prescription and it is the Investigator's responsibility to ensure that an accurate record of IMP issued and returned is maintained.

Any quality issue noticed with the receipt or use of an IMP (deficiency in condition, appearance, pertaining documentation, labeling, expiration date, etc) should be promptly notified to the Sponsor. Some deficiencies may be recorded through a complaint procedure.

A potential defect in the quality of IMP may be subject to initiation of a recall procedure by the Sponsor. In this case, the Investigator will be responsible for promptly addressing any request made by the Sponsor, in order to recall the IMP and eliminate potential hazards.

Under no circumstances the Investigator will supply IMP to a third party, allow the IMP to be used other than as directed by this clinical study protocol, or dispose of IMP in any other manner.

8.7.1 Treatment accountability and compliance

Administration of the IMP will be supervised by the Investigator or Subinvestigator.

The person responsible for drug dispensing is required to maintain adequate records of the IMP. These records (eg, drug movement form) include the date the IMP is received from the Sponsor, dispensed for patient and destroyed or returned to the Sponsor. The packaging batch number on the vial must be recorded on the drug accountability form.

The person responsible for study treatment administration to the patient will record precisely the date and the time of the study treatment administration to the patient.

8.7.2 Return and/or destruction of treatments

Partially used and used vials of isatuximab will be destroyed at the study site according to the standard practices of the site after an accurate accountability has been performed and signed by the Investigator (or the Pharmacist). A detailed treatment log form of the destroyed IMP will be established with the Investigator (or the Pharmacist) and countersigned by the Investigator and the Monitoring Team.

The Investigator will not destroy the unused IMP unless the Sponsor provides written authorization.

8.8 CONCOMITANT MEDICATION

8.8.1 Permitted concomitant therapy

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).

The type, dose and route of administration must be documented on the appropriate pages of the eCRF.

Concomitant medications should be kept to a minimum during the study. However, if these are considered necessary for the patient's welfare and are unlikely to interfere with the study treatment, they may be given at the discretion of the Investigator and recorded in the eCRF.

Supportive treatment as medically indicated for the patient's well-being may be prescribed at the Investigator's discretion. Every medication or treatment taken by the patient during the study and the reason for its administration must be recorded on the eCRF.

In order to have rapid control of the tumor burden, the administration of cyclophosphamide 200 mg/m² before the first study treatment administration (up to 4 times, on D-3, D-2, D-1 and D1) is permitted for patients with hyperleucocytosis >50 000/mm^3.

Before C1D1, as per the institution's clinical practice, all patients will receive CNS relapse prophylaxis (eg, intrathecal methotrexate 15 mg and/or cytarabine 40 mg and/or dexamethasone 4 mg).

Prophylaxis for tumor lysis syndrome (TLS) and CNS relapse may be administered at the discretion of the treating physician during the treatment period, following local standard practice.

8.8.2 Prohibited concomitant therapy

The following concomitant therapies are not permitted during this study:

- Concurrent treatment with other investigational drugs.
- Concurrent treatment with any other anticancer therapy not specified in Section 8.8.1, including immunotherapy, hormonal therapy, targeted therapy, steroid therapy or biological therapies.

8.8.3 Contraceptive measures

Female patients of childbearing potential and male patients with female partners of childbearing potential shall be required to use effective contraceptive methods (2 barrier method or 1 barrier method with a spermicide, intrauterine device, or hormonal contraception with inhibition of ovulation) starting 2 weeks prior to the first dose of isatuximab, while on treatment and for 12 weeks following the last dose of study treatment. A WOCBP, ie, fertile, following menarche and until becoming postmenopausal unless permanently sterile. The following highly effective methods of contraception are accepted:

- Established use of oral, intravaginal, or transdermal combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation.
- Established use of oral, injectable, or implantable progestogen-only hormonal contraception associated with inhibition of ovulation.
- Placement of an intrauterine device or intrauterine hormone-releasing system.
- Barrier methods of contraception: male condom with either cap, diaphragm or sponge with spermicide (double barrier methods). The use of double barrier methods should always be supplemented with the use of a spermicide. Female condom and male condom should not be used together.
- Male sterilization (provided that the partner is the sole sexual partner of the patient and that the sterilized partner has received medical assessment of the surgical success).
- Sexual abstinence.

9 ASSESSMENT OF INVESTIGATIONAL MEDICINAL PRODUCT

9.1 ENDPOINTS

9.1.1 Primary endpoints

The primary efficacy endpoint is ORR. ORR is based on NCCN guidelines and is defined as the proportion of patients with CR or incomplete peripheral recovery (CRi) for blood and bone marrow disease; partial response will be considered in case of mediastinal or any extramedullary disease (Appendix C).

9.1.2 Secondary endpoints

The secondary efficacy endpoints are:

- DOR 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. The same censoring rules as PFS will be used (see below).
- PFS, 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.
- OS defined as the time interval from the date of first study treatment administration to death from any cause. Patients without death prior to the analysis cutoff date will be censored at the earlier of the last date the patient was known to be alive and the analysis cutoff date, whichever comes first.

Other secondary endpoints:

- Safety assessment, in terms of AEs/SAEs, laboratory parameters, vital signs, and physical examination.
- PK parameters of isatuximab calculated using a non-compartmental and population PK approach.
- Immunogenicity of isatuximab assessed throughout the study by detecting the presence of antidrug antibodies (ADAs).
- MRD, measured by sequencing and/or flow cytometry in patients achieving CR and CRi.

9.1.3 Exploratory endpoints

The exploratory biomarkers endpoints are:

- Bone marrow and blood samples analyzed for CD38 receptor density and receptor occupancy on blast cells.
- Bone marrow and blood samples analyzed for CD38 expression on blast cells (proportion of CD38 positive cells).
- Bone marrow samples analyzed for tumor molecular alterations.
- Blood samples analyzed to investigate the relationship between soluble CD38 and parameters of PK.
- Blood samples analyzed for immune genetic determinants (including FcγR polymorphism genotyping and T cell receptor repertoire). Other genetic determinants, related to the drug action and/or effect of isatuximab, may be conducted on these samples during the study pending evolving literature.
- Bone marrow and blood samples analyzed for immunophenotypes (such as B cell, T cell, and NK cell subsets).
- Additional biomarker analysis, not specified in the protocol but related to the drug action and/or effect of isatuximab, may be conducted on remaining samples pending evolving literature.

Exploratory PK/PDy endpoint:

- PK/PDy parameter estimates will be investigated as prognostic factors for clinical outcome including safety and efficacy endpoints, if possible.

9.2 SAFETY

Safety evaluation will be performed continuously throughout the study period. The following assessments will be obtained and reviewed by the Investigator prior to study treatment administration and at designated intervals throughout the study: vital signs, 12-lead electrocardiogram (ECG), physical examinations, respiratory assessment, AEs, laboratory tests (complete blood counts, serum chemistry, and coagulation tests), ECOG PS, immunogenicity, blood cytokines (tumor necrosis factor alpha [TNFα], interleukin [IL]-1β, IL-4, IL-6, interferon gamma [IFNγ]), serum tryptase, markers of activated complement (C3a, C4, CH50), and TLS markers.

9.2.1 Adverse events

Adverse events will be collected from the date informed consent is signed until at least 30 days after the last administration of isatuximab, or a new anticancer therapy is started, whichever is first. Adverse events will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03 (Appendix D) and coded according to the Medical Dictionary for Regulatory Activities (MedDRA). During the follow-up period, ongoing SAEs regardless of relationship to study treatment and ongoing or new study treatment-related AEs/SAEs will be followed until resolution or stabilization.

Refer to Section 10.4 to Section 10.7 for further details.

9.2.2 Laboratory safety variables

The clinical laboratory data consist of blood analysis (complete blood counts, serum chemistry, and coagulation tests). These tests will be performed by the local laboratory.

Further details are provided in the flowchart and footnotes in Section 1.2.

The complete blood counts and serum chemistry analyses are to be performed at screening, at the time points specified in the flowchart (Section 1.2), and when clinically indicated. Tests performed at screening must be repeated within 3 days before the first study treatment administration if performed >7 days before the first study treatment administration (ie, C1D1).

From C1D8 onwards, serum chemistry analyses will be performed and reviewed by the Investigator within 24 hours before the day of dosing. In case of Grade 3 or 4 abnormalities, additional tests will be repeated every 2 to 3 days until recovery to baseline value or Grade ≤1 (see Section 6.3).

Coagulation tests are to be performed within 7 days before initiation of C1D1 and as clinically indicated.

A serum or urine pregnancy test must be performed for WOCBP. Tests must be repeated within 3 days before the first study treatment administration if performed >7 days before the first study treatment administration (ie, C1D1). Pregnancy tests must be repeated every 4 weeks (before D1 of each cycle of study treatment administration) and for up to 3 months after the last administration of the study treatment (or before start of another anticancer therapy).

Blood samples for cytokines, markers of activated complement, serum tryptase, and markers of TLS are to be drawn at C1D1 before first study treatment administration, and when clinically indicated (ie, in cases of IAR of Grade ≥2 as described below). Analysis of cytokines, serum tryptase and markers of complement activation will be performed by central laboratory. Analysis of TLS markers will be performed by a local laboratory.

Should an isatuximab IAR of Grade ≥2 occur (as per NCI-CTCAE, version 4.03), additional blood sampling during the AE is required for analysis of cytokine release, markers of activated complement, serum tryptase, and markers of potential TLS.

A Patient Card will be issued to the patient indicating that the patient is enrolled in a clinical trial evaluating isatuximab, an antiCD38 compound, and specifying the study medications they are receiving. Due to the potential interference of antiCD38 compounds such as isatuximab with blood bank serological testing, Investigators should ensure that the recommendations proposed by the American Association of Blood Banks are followed (see Appendix F). Investigators should instruct patients to carry their Blood Type Card and Patient Card with them at all times and present them if they need to receive medical treatment from someone other than the Investigator or his/her staff.

Further details of central laboratory testing are provided in the Laboratory Manual.

9.2.3 Physical examination

Physical examination of major body systems will include neurological examination, digestive, skin/mucosae, mediastinal, testicular localizations, respiratory, hepatomegaly, splenomegaly, and lymphadenopathy. Physical examination should preferably be performed by the same physician.

Respiratory function will be monitored at C1D1 and before each study treatment administration, and at the end of study treatment including respiratory frequency, pulmonary auscultation, signs and symptoms such as cough, dyspnea, and expectoration. Additional tests such as chest X-ray will be performed when clinically indicated at the discretion of the Investigator. Patients with respiratory signs/symptoms Grade ≥2 that could be attributed to the study treatment, will have the respiratory evaluation repeated QW until improvement to Grade 1.

The ECOG PS will be evaluated at screening, before each study treatment and at the end of treatment (Appendix B).

Only clinically relevant findings will be reported in the eCRF as AEs.

9.2.4 Vital signs

Vital signs, including blood pressure, heart rate, temperature, and respiration rate, will be performed at screening and at preinfusion, 1 hour after starting the infusion, and at the end of infusion on D1, D8, D15 and D22 of the induction cycle(s), then preinfusion and as clinically indicated for subsequent cycles. The final measurements will be performed at the EOT visit (see flowchart in Section 1.2).

9.2.5 12-lead electrocardiogram

A 12-lead ECG will be performed at screening, at EOT and when clinically indicated (see flowchart in Section 1.2).

Electrocardiogram data will be assessed by the Investigator based on the automatic device reading.

9.2.6 Immunogenicity

Antidrug antibody (ADA) against isatuximab will be assessed throughout the study. The sampling times for blood collection are provided in the flowcharts in Section 1.3 and Section 1.4.

It is of utmost importance to collect all blood samples at the specified times.

Samples not collected, missed, or lost, for any reason should be documented. Actual dates and times of blood collection should be recorded in the eCRF. The dates and the times of study treatment administration should also be precisely recorded.

For the comfort of patients, some ADA samplings may be deleted during the course of the study if they are no longer deemed necessary by the sponsor.

Special procedures for collection, storage, and shipment should be provided in a separate Laboratory Manual.

Bioanalytical method used for immunogenicity assessment is summarized in Table 1.

Table 1 - Bioanalytical method for isatuximab immune response assessment

Analyte	ANTIDRUG ANTIBODY
Matrix	Plasma
Analytical technique	PandA method
Lower Limit of Quantification	Not applicable
Assay volume	100 µL
Site of bioanalysis	Refer to laboratory manual

In case of a positive or inconclusive sample for ADA at 60 days after the last study treatment administration, additional assessment of ADA will be performed every 30 days (±5 days) until sample is negative.

The ADA results will be communicated to investigational sites on an ongoing basis.

9.3 EFFICACY

To assess response (NCCN guideline), bone marrow aspiration, or biopsy if clinically indicated (bone marrow aspirate/biopsy), as well as CT of chest with IV contrast and/or PET-CT scan (CT/PET-CT scan) will be performed for disease assessment at the time points indicated in the flowchart (Section 1.2) and as summarized hereafter.

Bone marrow aspirate and/or biopsy will be done at screening, between D15 and D22 during the first cycle (after the third isatuximab infusion), or to confirm response at the end of induction period (after 4, or 8 isatuximab infusions for patients receiving 2 induction cycles) and then every 2 cycles and when clinically indicated. No bone marrow is necessary if nonresponse or progressive disease can be diagnosed from peripheral blood evaluation, or, in patients with a white blood cell count <300/mm^3, if the bone marrow test is considered noncontributory by the Investigator. Patients who discontinue for other reasons than disease progression will be followed every 4 weeks, but bone marrow aspirate will be performed only when clinically indicated.

Analysis of bone marrow aspirate/biopsy for disease assessment will be performed by a local laboratory.

CT/PET-CT scan should be performed at screening and at the EOT visit. In case of extramedullary involvement or T-LBL, both CT and PET-CT should be performed at baseline and at CR confirmation, whenever possible. Then CT and/or PET-CT scan every 2 cycles or thereafter.

Lumbar puncture to exclude CNS involvement will be performed at screening and when clinically indicated (see exclusion criterion E04, Section 7.2.1).

An assessment of MRD will be performed on bone marrow aspirate at screening and on blood at CR (in case of MRD positivity at first CR observation, assessment will be repeated after 2 to 3 cycles). The assessment of MRD will be performed by a central laboratory.

Detailed instructions for blood and bone marrow samples preparation and shipment will be provided to the study sites in a separate Laboratory Manual.

9.4 PHARMACOKINETIC EVALUATION

9.4.1 Sampling time and sample blood volume

Additional details of PK sampling are provided in the PK/PDy flowcharts in Section 1.3 and Section 1.4.

It is of utmost importance to collect all blood samples at the specified times.

Samples not collected, missed or lost, for any reason should be documented. Actual dates and times of blood collection should be recorded in the eCRF. The dates and the times of study treatment administration should also be precisely recorded.

9.4.2 Pharmacokinetics handling procedure

Special procedures for collection, storage, and shipment will be provided in a separate Laboratory Manual.

9.4.3 Isatuximab bioanalytical method

Bioanalytical method is summarized in Table 2.

Table 2 - Bioanalytical method for isatuximab pharmacokinetic analysis

Analyte	Isatuximab
Matrix	plasma
Analytical technique	ELISA
Lower limit of quantification	0.500 ng/mL
Assay volume	100 µL
Site of bioanalysis	Refer to laboratory manual

ELISA: enzyme-linked immunosorbent assay

9.4.4 Pharmacokinetics parameters

9.4.4.1 Non-compartmental pharmacokinetic analysis

Full PK profile sampling will be collected from patients in Stage 1 during the first induction cycle, to assess the PK profile of isatuximab using a non-compartmental analysis. Blood samples will be collected using a sparse sampling strategy in patients from Stage 1 from C2 onwards and in the remaining patients in Stage 2. For the comfort of patients, some PK samplings may be deleted during the course of the study if they are no longer deemed necessary by the sponsor.

Plasma concentrations of isatuximab and actual time values will be used to calculate the following PK parameters using non-compartmental analysis with validated software. The parameters will include, but may not be limited to C_{eoi}, C_{max}, C_{trough}, t_{max}, AUC_{Week1}, AUC_{last} and C_{last} (defined in Table 3).

Table 3 - List of isatuximab pharmacokinetic parameters and definitions calculated by non-compartmental analysis after the first cycle of treatment

Parameters	Definition/calculation
C_{eoi}	Concentration at the end of an intravenous infusion
C_{max}	Maximum plasma concentration observed
C_{trough}	Plasma concentration observed just before treatment administration during repeated dosing
t_{max}	Time to reach C_{max}
AUC_{Week1}	Area under the plasma concentration versus time curve calculated using the trapezoidal method over the first week of treatment
AUC_{last}	Area under the plasma concentration versus time curve calculated using the trapezoidal method from time 0 to the time of last concentration observed above the lower limit of quantification (t_{last})
C_{last}	Last concentration observed above the lower limit of quantification

Also, C_{trough} will be reported at subsequent cycles.

9.4.4.2 Pharmacokinetic population analysis

Blood concentrations of isatuximab will be used for population PK analysis by non-linear mixed effects modeling. Additional details of the analysis plan and the results will be provided in a separate document. This analysis will involve an estimation of interpatient PK variability, the population PK parameters estimates and the assessments of pathophysiologic covariate effects on clearance and possibly on volume if warranted. Empirical Bayesian estimation of individual parameters and of individual exposure (area under the plasma concentration versus time curves; AUCs) will also be performed. The PK parameter estimates will then be investigated as prognostic factors for clinical outcome including safety and efficacy endpoints, if possible.

9.5 SPECIFIC ASSESSMENTS

9.5.1 Sample times, handling procedures, and bioanalytical methods

Additional details of sampling are provided in the PK/PDy flowcharts in Section 1.3 and Section 1.4.

It is of utmost importance to collect all blood samples at the specified times.

Samples not collected, missed or lost, for any reason should be documented. Actual dates and times of blood collection should be recorded in the eCRF. The dates and the times of study treatment administration should also be precisely recorded.

Special procedures for collection, storage, and shipment will be provided in a separate Laboratory Manual.

9.5.2 Cytokines

Bioanalytical methods for assessment of cytokines are summarized in Table 4.

Table 4 - Bioanalytical methods for cytokine analysis

Analyte	IL-1β, IL-4, IL-6, TNFα, IFNγ
Matrix	Serum
Analytical technique	Immunoassay
Site of bioanalysis	Refer to laboratory manual

IFNγ : interferon gamma ; IL : interleukin ; TNFα : tumor necrosis factor alpha

9.5.3 Markers of activated complement and serum tryptase

Bioanalytical methods for assessment of activated complement and serum tryptase are summarized in Table 5.

Table 5 - Bioanalytical methods for markers of activated complement and serum tryptase

Analyte	C3a	C4	CH50	Serum tryptase
Matrix	Plasma EDTA	Serum	Serum	Serum
Analytical technique	Enzyme Immunoassay	Immunonephelometry	Hemolytic assay	Enzyme Immunoassay
Site of bioanalysis	Refer to laboratory manual	Refer to laboratory manual	Refer to laboratory manual	Refer to laboratory manual

9.6 EXPLORATORY BIOMARKERS ANALYSES

9.6.1 Receptor density, receptor occupancy, and CD38 expression

Further details of the RD, RO, and CD38 expression sampling is provided in the flowchart in Section 1.2, Section 1.3, and Section 1.4.

Bone marrow aspirates and blood samples will be collected for assessment of 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 RO at screening and between D15 and D22 during the first cycle (after the third isatuximab infusion), for correlation with PK parameters and, if relevant, correlation with clinical response endpoints.

These analyses will be applicable in selected countries only.

9.6.2 Other biomarkers

Bone marrow aspirates and/or blood samples for exploratory analysis will be collected as detailed in the flowcharts in Section 1.2, Section 1.3, and Section 1.4.

The bone marrow and blood samples will be analyzed for the following purposes:

- Multiple leukemia tumor molecular alterations will be tested and, if relevant, will be correlated with clinical response endpoints. Genetic analysis will be performed, [redacted] Bone marrow samples will be collected at screening.
  For genetic/genomics studies, DNA/RNA may be isolated from tumor cells and sequenced to identify somatic mutations present only in the tumor cells (not in the patient's heritable genome). Sequencing studies may include whole exome or whole genome sequencing (for DNA), or whole transcriptome sequencing (for RNA) to quantify gene expression or identify expressed gene fusions, mutations or other tumor-specific transcripts.
- Immune genetic determinants (such as FcγR gene polymorphisms and T cell receptor repertoire) will be tested and, if relevant, will be correlated with clinical response endpoints. Blood samples collected on C1D1, prior to first study treatment administration, and during the treatment period (before the start of first maintenance cycle, or at the end of the induction period [after 1 or 2 cycles] for patients who discontinue the study before the first maintenance cycle) for some specific markers, will be used for this analysis. This germline genetic analysis is a mandatory part of the protocol and will not be performed under separate pharmacogenetic consent. The germline DNA sequence will not be used in this case to determine risk or prognosis to any malignancies. Other genetic determinants, related to the drug action and/or effect of isatuximab, may be conducted on these samples during the study pending evolving literature.
- Immune phenotypes in bone marrow and/or peripheral blood will be tested and, if relevant, will be correlated with clinical response endpoints. Immune cell populations including B cell, T cell and NK cell subsets will be characterized by multiparametric flow cytometry based on the expression of cell surface markers. The proportion of cells positive for a given marker or set of markers (eg, regulatory T cells) may be correlated with clinical response endpoints. Bone marrow aspirate collected at screening and peripheral blood samples collected at screening, between D15 and D22 during the first cycle (after the third isatuximab infusion), and EOT will be used for this analysis.
- Soluble CD38 levels in blood samples taken at C1D1, prior to first study treatment administration, will be correlated with PK parameters and, if relevant, correlated with clinical response endpoints.
- Additional biomarker analysis, not specified in the protocol but related to the drug action and/or effect of isatuximab, may be conducted on remaining samples pending evolving literature.

9.6.3 Pharmacogenetic assessment

9.6.3.1 Mandatory or optional drug metabolizing enzymes DNA sample

Not applicable.

9.6.3.2 Optional stored DNA sample

For those patients who sign the specific pharmacogenetic informed consent form, a blood sample (10 mL) will be collected at C1D1 prior to first study treatment administration as specified in the study flow chart and this sample will be stored.

This sample may be used to determine how the body processes isatuximab, possible relationship between genes and response to treatment with isatuximab, and possible side effects to isatuximab. Genes that could be studied include those of the immune system.

This blood sample will be transferred to a site that will, on behalf of sanofi, extract DNA from the sample. This contractor can be located outside of the participating country, within or outside of the European Union.

This blood sample, and the DNA that is extracted from it, will be assigned a second number, a Genetic ID (deidentification code) that is different from the Patient ID. This “double coding” is performed to separate a patient’s medical information and DNA data.

The clinical study data (coded by Patient ID) will be stored in the clinical data management system, which is a distinct database in a separate environment from the database containing the pharmacogenetic data (coded by Genetic ID). The key linking Patient ID and Genetic ID will be maintained by a third party, under appropriate access control. The matching of clinical data and pharmacogenetic data, for the purpose of data analysis, will be possible only by using this key, which will be under strict access control. All data will be reported only in coded form in order to maintain confidentiality.

The DNA will be stored at a secure site under the responsibility of the Sponsor for up to 15 years from the completion of the clinical study report.

Special procedures for storage and shipment of pharmacogenetic samples are described in Table 6 and more details will be included in a separate Laboratory Manual.

Table 6 - Summary of handling procedures for pharmacogenetic samples

Sample type	Pharmacogenetic
Blood sample volume	10 mL for genotyping analysis
Anticoagulant	K2 EDTA
Blood handling procedures	Keep blood on ice and frozen within 30 minutes of sampling time. DO NOT CENTRIFUGE BLOOD (for details refer to Laboratory Manual)
Storage conditions	-70°C or colder

EDTA: ethylenediaminetetraacetic acid

9.7 FUTURE USE OF SAMPLES

Not all of the samples collected during this study may be used for the tests planned in this clinical study. For patients who have consented to it, the samples that are unused or left over after testing may be used for research purposes (excluding genetic analysis providing information on the likelihood of developing a disease) related to isatuximab efficacy, safety, metabolism or related to T-ALL or T-LBL other than those defined in the present protocol.

These other research analyses will help to understand either disease subtypes or drug response, or to develop and/or validate a bioassay method, or to identify new drug targets or biomarkers.

These samples will remain labelled with the same identifiers used during the study (ie, Patient ID). They will be transferred to a sanofi site (or a subcontractor site) which can be located outside of the country where the study is conducted. The Sponsor has included safeguards for protecting patient confidentiality and personal data (see Section 14.3 and Section 14.5).

9.8 APPROPRIATENESS OF MEASUREMENTS

Each of the efficacy and safety assessments chosen for use in this study are considered well-established and relevant in a hemato-oncology setting. Although this is the first clinical study of isatuximab in T-ALL/T-LBL, suitable steps have been built into each of these assessments to ensure their reliability and accuracy.

10 STUDY PROCEDURES

10.1 VISIT SCHEDULE

During the course of the study, all patients entering the study must be evaluated according to the schedule outlined in the flowcharts (see Section 1.2, Section 1.3, and Section 1.4) and described below. The results of the evaluation will be recorded in the eCRF pages until the patients are no longer followed.

10.1.1 Screening

The screening assessments are to be performed within 3 weeks prior to the first study treatment administration (C1D1), unless indicated otherwise. All of the inclusion criteria (and none of the exclusion criteria) must be met, and informed consent must be signed by the patient before any study-specific procedure is performed.

The following procedures are to be performed/assessed:

- Demography (including age, gender, race).
- A study patient card will be provided to the patient indicating that he/she is receiving an anti-CD38 treatment (Appendix F).
- The site will notify its blood bank that the patient is receiving an anti-CD38 treatment (see Appendix F).
- Blood type, phenotyping (or genotyping) and screen, if not previously performed (see Appendix F).
- Relevant medical/surgical history (including relevant history of previous/associated pathologies, other than the tumor, history of asthma, chronic obstructive pulmonary disorder, dyspnea and tobacco consumption).
- Disease history including date of initial diagnosis, type of disease (T-ALL/T-LBL, immunophenotypic and cytogenetic), previous anti-leukemia treatment (reason for discontinuation, date of relapse and best overall response to prior treatments).
- Body weight and height.
- Physical examination and ECOG PS.
- Lumbar puncture to exclude CNS involvement and to confirm patient eligibility.
- Prior medications.
- AEs.
- Vital signs (including blood pressure, heart rate, temperature, and respiration rate).
- 12-lead ECG.
- Chest X-ray.
- CT of chest with IV contrast and/or PET-CT scan. In case of extramedullary involvement or T-LBL, both CT and PET-CT should be performed.
- Complete blood counts, serum chemistry and coagulation tests.

- Serum/urine pregnancy test for WOCBP.
- Hepatitis B and C virus serology.
- Bone marrow aspirate/biopsy for disease assessment.
- Bone marrow aspirate for MRD assessment.
- Bone marrow aspirates and blood samples for RO (Stage 1 only), RD and CD38 expression (in selected countries only). Blood sample collection must be performed before dexamethasone premedication as dexamethasone has been shown to kill blast cells in blood tubes.
- Bone marrow aspirates and blood samples for exploratory biomarkers analysis (tumor molecular alterations and immunophenotyping). Blood sample collection must be performed before dexamethasone premedication as dexamethasone has been shown to kill blast cells in blood tubes.
- CNS relapse prophylaxis will be administered during screening, and during the treatment period, as per the institution's clinical practice.

10.1.2 Induction period

During the induction period, patients will receive 1 or 2 induction cycles of therapy (1 induction cycle = 4 QW doses of isatuximab). If at D15-22 of the first induction cycle, bone marrow blast cells remain >5%, a second induction cycle will be administered. If bone marrow blast cells are ≤5%, the administration of a second induction cycle will be performed at the discretion of the Investigator. Patients who do not achieve an objective response after a maximum of 2 cycles of induction therapy will be withdrawn from the study treatment.

10.1.2.1 Cycle 1 (and Cycle 2, if applicable): Day 1

At C1D1, the inclusion/exclusion criteria and informed consent must be rechecked before any study-specific procedure is performed.

The following procedures/information are to be performed/collected prior to study treatment administration:

- Body weight.
- Physical examination, respiratory function and ECOG PS.
- Prior medications.
- Complete blood counts and serum chemistry (to be done within 3 days if performed >7 days prior to first study treatment administration at screening), and coagulation tests (to be done within 7 days if performed >7 days prior to first study treatment administration at screening). To be repeated at C2D1, if applicable.
- Serum/urine pregnancy test for WOCBP (to be done within 3 days if performed >7 days prior to first study treatment administration at screening). To be repeated at C2D1, if applicable.
- ADA sampling (see Section 1.3 and Section 1.4).
- Blood sample for soluble CD38 (C1D1 only).
- Blood sample for immune genetic determinants (C1D1 only).

- Optional blood sample for pharmacogenetic testing (C1D1 only).
- Preinfusion vital signs (including blood pressure, heart rate, temperature, and respiration rate).
- Blood sample for TLS markers, cytokines, markers of activated complement and serum tryptase (C1D1 only).
- Preinfusion PK sampling (see Section 1.3 and Section 1.4).
- Premedication (NIMP) administration (D-2, D-1 and D1 for dexamethasone, and cyclophosphamide on D-3, D-2, D-1 and D1 for Cycle 1 only; see Section 8.2 and Section 8.8.1). For premedication at C2D1, see Section 8.2.
- 12-lead ECG or lumbar puncture should be performed when clinically indicated.

After completion of the above procedures, isatuximab will be administered.

The following procedures/information are to be performed/collected during and/or after study treatment administration:

- Vital signs (including blood pressure, heart rate, temperature, and respiration rate) at 1 hour after starting the infusion, and at the end of infusion.
- PK sampling (end of infusion, 4, 24, 48 and 72 hours post end of infusion for patients in Stage 1, and end of infusion and 1 hour post end of infusion for patients in Stage 2) (see Section 1.3 and Section 1.4).
- Cytokines, TLS markers, markers of activated complement, and serum tryptase if an IAR ≥Grade 2 occurs.
- Premedication (NIMP) administration (D2 to D3 for Cycle 1 only; see Section 8.2).
- Concomitant medications (to be assessed continuously throughout the on-treatment period).
- AEs (to be assessed continuously throughout the on-treatment period).

10.1.2.2 Cycle 1 (and 2, if applicable): Days 8, 15, and 22

The following procedures/information are to be performed/collected prior to study treatment administration:

- Body weight.
- Physical examination, respiratory function and ECOG PS.
- Preinfusion vital signs (including blood pressure, heart rate, temperature, and respiration rate).
- Complete blood counts and serum chemistry (to be performed and reviewed by the Investigator within 24 hours before the day of dosing).
- ADA sampling on D15 only.
- Preinfusion PK sampling (see Section 1.3 and Section 1.4).
- Premedication (NIMP) administration (see Section 8.2).
- 12-lead ECG or lumbar puncture should be performed when clinically indicated.

After completion of the above procedures, isatuximab will be administered.

The following procedures/information are to be performed/collected during and/or after study treatment administration:

- Vital signs (including blood pressure, heart rate, temperature, and respiration rate) at 1 hour after starting the infusion, and at the end of infusion.
- PK sampling at end of infusion on D15 for patients in Stage 2 (see Section 1.4).
- Bone marrow aspirate/biopsy for disease assessment (between D15 and D22, after third isatuximab infusion and again at the end of the induction period to confirm response).
- Bone marrow aspirate and blood sample for RO (Stage 1 patients; between D15 and D22 during the first cycle after the third isatuximab infusion) before dexamethasone premedication (in selected countries only).
- Blood sample for immunophenotyping (between D15 and D22 during the first cycle after the third isatuximab infusion) before dexamethasone premedication.
- CT of chest with IV contrast and PET-CT scan if extramedullary involvement or T-LBL, at the end of induction for CR confirmation.
- Cytokines, TLS markers, markers of activated complement, and serum tryptase if an IAR ≥Grade 2 occurs.
- Concomitant medications (to be assessed continuously throughout the on-treatment period).
- AEs (to be assessed continuously throughout the on-treatment period).

Assessment of MRD will be performed at CR (in case of MRD positivity at first CR observation, assessment will be repeated after 2 to 3 cycles).

10.1.3 Maintenance

Patients who achieve an objective response during the induction period can continue on to the maintenance period. During maintenance, patients will receive Q2W administration of isatuximab (28-day cycles). Patients will be allowed to continue maintenance therapy until disease progression, an unacceptable AE, consent withdrawal or Investigator's decision (eg, patient is a candidate for transplantation).

10.1.3.1 Maintenance cycles: Days 1 and 15

The following procedures/information are to be performed/collected prior to study treatment administration:

- Body weight.
- Physical examination, respiratory function and ECOG PS.
- Vital signs (including blood pressure, heart rate, temperature, and respiration rate) at preinfusion, and if clinically indicated.
- Complete blood counts and serum chemistry.
- Serum/urine pregnancy test for WOCBP (D1 only).
- Blood sample for immune genetic determinants (before start of first maintenance cycle, or at the end of the induction period [after 1 or 2 cycles] for patients who discontinue the study before the first maintenance cycle).

- ADA sampling at D1 only.
- Bone marrow aspirate/biopsy for disease assessment (prior to the start of maintenance and every 2 cycles thereafter, or if clinically indicated).
- Preinfusion PK sampling (see Section 1.3 and Section 1.4).
- Premedication (NIMP) administration (see Section 8.2).
- 12-lead ECG or lumbar puncture should be performed when clinically indicated.

After completion of the above procedures, isatuximab will be administered.

The following procedures/information are to be performed/collected during and/or after study treatment administration:

- PK sampling at end of infusion on D1 of the first and second maintenance cycles, and 1 hour post end of infusion on D1 of the second maintenance cycle (see Section 1.3 and Section 1.4).
- Cytokines, TLS markers, markers of activated complement, and serum tryptase in cases of IAR ≥Grade 2.
- Concomitant medications (to be assessed continuously throughout the on-treatment period).
- AEs (to be assessed continuously throughout the on-treatment period).

In case of extramedullary disease or T-LBL, a CT and/or PET-CT scan should be performed every 2 cycles.

In case of MRD positivity at first CR observation, assessment will be repeated after 2 to 3 cycles.

10.1.4 Post-treatment period

10.1.4.1 End of treatment

The EOT visit will be performed 30 days (±5 days) after last isatuximab administration, or prior to initiation of a new anticancer therapy, whichever is first.

The following procedures/information are to be performed/collected:

- Body weight.
- Physical examination, respiratory function and ECOG PS.
- Concomitant medications.
- AEs.
- Vital signs (including blood pressure, heart rate, temperature, and respiration rate).
- 12-lead ECG.
- CT and/or PET-CT scan.
- Complete blood counts and serum chemistry.
- Serum/urine pregnancy test for WOCBP.
- Blood sample for immunophenotyping.
- Posttreatment anticancer therapy.
- PK sampling (see Section 1.3 and Section 1.4).
- ADA sampling.

10.1.4.2 Follow-up

The first follow-up visit for all patients will be performed 60 days (±5 days) after last isatuximab administration.

Patients with documented disease progression at the EOT visit will be followed every 2 months until death or final analysis cutoff date, whichever comes first.

Patients 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 month until initiation of another anticancer therapy, disease progression, death or final analysis cutoff date, whichever comes first. Then, after disease progression, or after initiation of further anticancer therapy for patients without disease progression, patients will be followed every 2 months until death or final analysis cutoff date, whichever comes first.

The following procedures are to be performed/assessed:

- Physical examination (for patients who discontinue treatment for other reason than disease progression).
- Related AEs and any SAE ongoing at the EOT visit must be followed until resolution or stabilization. Any related AE or related SAE that is new during the follow-up period must be reported and followed until recovery or stabilization.
- Complete blood counts (for patients who discontinue treatment for other reason than disease progression).
- Serum/urine pregnancy test for WOCBP (to be performed up to 3 months after the last administration of study treatment, or before initiation of anticancer therapy, whichever is first).
- Bone marrow aspirate/biopsy for disease assessment, if clinically indicated.
- Posttreatment anticancer therapy.
- Survival status to be collected (eg, alive with date of last contact, death with date of death). Efforts should be made by the study staff to contact the patient in order to avoid a patient becoming lost to follow-up.
- PK sampling (at 60 days after last isatuximab administration only).
- ADA sampling. If patient is positive or inconclusive for ADAs at 60 days after last isatuximab administration, additional ADA sampling is required every 30 days (±5 days) until sample is negative.

10.2 DEFINITION OF SOURCE DATA

Not applicable, no results of certain examinations or evaluations will be recorded directly in the eCRF.

10.3 HANDLING OF PATIENT TEMPORARY OR PERMANENT TREATMENT DISCONTINUATION AND OF PATIENT STUDY DISCONTINUATION

Patients are free to withdraw their participation at any time during this study. The Investigator has the right to remove any patient from study treatment or participation in the study. However, sanofi requests that the Investigator consult with the sanofi Clinical Study Director before prematurely removing a patient.

Patients who decide to withdraw from the study, or meet the withdrawal criteria, should undergo an EOT visit (see Section 1.2 and Section 10.1.4.1).

Any study treatment discontinuation should be fully documented in the eCRF.

Pregnancy will lead to definitive treatment discontinuation in all cases.

10.3.1 Temporary treatment discontinuation with investigational medicinal product

Not applicable, from a hemato-oncology perspective, treatment delays and permitted dose omissions are not considered discontinuations (see Section 6.4).

10.3.2 Permanent treatment discontinuation with investigational medicinal product

Permanent treatment discontinuation is any treatment discontinuation associated with the definitive decision from the Investigator or the patient not to re-expose the patient to the study treatment at any time.

10.3.3 List of criteria for permanent treatment discontinuation

The patients may withdraw from study treatment if they decide to do so, at any time and irrespective of the reason, or this may be the Investigator's decision.

All efforts should be made to document the reason(s) for treatment discontinuation and this should be documented in the eCRF.

At the patient's request, at any time and irrespective of the reason (consent withdrawal), or at the request of their legally authorized representative. "Legally authorized representative" is considered to be an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective patient to the patient's participation in the procedure(s) involved in the research. It is critical to distinguish withdrawal of consent for treatment and withdrawal of consent for follow-up visits (see Section 10.3.5).

- Disease progression.
- If, in the Investigator's opinion, continuation of the study treatment would be detrimental to the patient's well-being, such as:
  - An unacceptable AE,
  - Poor compliance to the study protocol,
  - Any other reason such as intercurrent illness that prevents further administration of study treatment (will be specified).
- Investigator's decision (eg, patient is candidate for transplantation).
- Patient is lost to follow-up.

If patients are clinically stable (ie, achieve an objective response [CR or CRi for blood and bone marrow disease; partial response will be considered in case of mediastinal or any extramedullary disease] after 1 or 2 induction cycles), and possibly deriving clinical benefit from therapy with minimal toxicity, the patient will be maintained on treatment for the maximum period of time defined in Section 6.2.

Patients who have been withdrawn from the study treatment cannot be re-included in the study. Their inclusion and treatment number must not be re-used.

10.3.4 Handling of patients after permanent treatment discontinuation

For details see Section 10.1.4.2. All cases of permanent treatment discontinuation should be recorded by the Investigator in the appropriate pages of the eCRF when considered as confirmed.

10.3.5 Procedure and consequence for patient withdrawal from study

The patients may withdraw from the study before study completion if they decide to do so, at any time and irrespective of the reason. Withdrawal of consent for treatment should be distinguished from withdrawal of consent for follow-up visits and from withdrawal of consent for nonpatient contact follow-up, eg, medical records check. The discussion with the patient detailing the level of consent withdrawal should be documented in the patient's medical records. Patients requesting withdrawal should be informed that withdrawal of consent for follow-up may jeopardize the public health value of the study.

If possible, the patients are assessed using the procedure normally planned for the EOT visit (see Section 1.2, Section 1.3, and Section 1.4).

Patients who withdraw should be explicitly asked about the contribution of possible AEs to their decision to withdraw consent, and any AE information elicited should be documented. Preferably the patient should withdraw consent in writing and, if the patient or the patient's representative refuses or is physically unavailable, the site should document and sign the reason for the patient's failure to withdraw consent in writing.

All study withdrawals should be recorded by the Investigator in the appropriate screens of the eCRF and in the patient's medical records when considered as confirmed. In the medical record, at least the date of the withdrawal and the reason should be documented.

For patients who fail to return to the site, unless the patient withdraws consent for follow-up, the Investigator should make the best effort to recontact the patient (eg, contact patient's family or private physician, review available registries or health care databases), and to determine his/her health status, including at least his/her vital status. Attempts to contact such patients must be documented in the patient's records (eg, times and dates of attempted telephone contact, receipt for sending a registered letter).

The statistical analysis plan will specify how these patients lost to follow-up for their efficacy endpoints will be considered.

Patients who have withdrawn from the study cannot be reallocated (treated) in the study. Their inclusion and treatment numbers must not be reused.

10.4 OBLIGATION OF THE INVESTIGATOR REGARDING SAFETY REPORTING

10.4.1 Definitions of adverse events

10.4.1.1 Adverse event

An **adverse event** is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

10.4.1.2 Serious adverse event

A **serious adverse event** is any untoward medical occurrence that at any dose:

- Results in death, or,
- Is life-threatening, or,
  Note: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization, or,
- Results in persistent or significant disability/incapacity, or,
- Is a congenital anomaly/birth defect.
- Is a medically important AE.
  Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical AEs that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require medical or surgical intervention (ie, specific measures or corrective treatment) to prevent one of the other outcomes listed in the definition above.

Note: The following list of medically important AEs is intended to serve as a guideline for determining which condition has to be considered a medically important event. The list is not intended to be exhaustive:

- Intensive treatment in an emergency room or at home for:
  - Allergic bronchospasm,
  - Blood dyscrasias (ie, agranulocytosis, aplastic anemia, bone marrow aplasia, myelodysplasia, pancytopenia, etc),
  - Convulsions (seizures, epilepsy, epileptic fit, absence, etc).
- Development of drug dependence or drug abuse.
- ALT >3 x ULN + total bilirubin >2 x ULN or asymptomatic ALT increase >10 x ULN.
- Suicide attempt or any event suggestive of suicidality.
- Syncope, loss of consciousness (except if documented as a consequence of blood sampling).
- Bullous cutaneous eruptions.

10.4.1.3 Adverse event of special interest

An AESI is an AE (serious or nonserious) of scientific and medical concern specific to isatuximab, for which ongoing monitoring and immediate notification by the Investigator to the Sponsor is required. Such AEs may require further investigation in order to characterize and understand them. Adverse events of special interest may be added, modified or removed during a study by protocol amendment.

The following AEs are considered AESIs:

- IARs of Grade ≥3 (see Appendix E for diagnosis and symptoms typical of an IAR). An IAR is an AE related to isatuximab with onset typically within 24 hours from the start of the infusion.
- Pregnancy occurring in a female patient entered in the clinical study or in a female partner of a male patient entered in the clinical study will be recorded as an AE in all cases and will be qualified as an SAE only if it fulfills one of the seriousness criteria (see Section 10.4.1.2). In the event of pregnancy in a female participant, treatment with the study treatment should be discontinued and the Monitoring Team should be informed immediately (within 24 hours), even if the event does not fulfill a seriousness criterion, using the AE form together with the SAE complementary form to be sent to the representative of the Monitoring Team whose name, address and fax number appear on page 2 of the clinical trial protocol.

  Follow-up of the pregnancy in a female patient or in a female partner of a male participant is mandatory until the outcome has been determined (see Section 10.4.4).
- Symptomatic overdose (serious or non-serious) of study treatment. An overdose (accidental or intentional) with the study treatment is an event suspected by the Investigator or spontaneously notified by the patient and defined as an increase of at least 30% of the dose to be administered in the specified duration. Of note, asymptomatic overdose has to be reported as a standard AE. In case of accidental or intentional overdose with the study treatment, even not fulfilling a seriousness criterion, is to be reported to the Sponsor immediately (within 24 hours) using the AE form together with the SAE complementary form to be entered in the eCRF.

10.4.2 General guidelines for reporting adverse events

All AEs, regardless of seriousness or relationship to IMP, spanning from the signature of the informed consent form until the end of the study (at least 30 days after the last dose of study treatment, or a new anticancer therapy is started, whichever is first), are to be recorded on the corresponding page(s) or screen(s) of the eCRF for included patients. For screen failed patients, recording in the eCRF is only performed in case of SAE occurring during the screening period or in case of AE when some screening procedures expose the patient to safety risks (eg, any substance administered as premedication, invasive tests performed or chronic treatment interrupted).

Whenever possible, diagnosis or single syndrome should be reported instead of symptoms. The Investigator should specify the date of onset, grade, action taken with respect to IMP, corrective

treatment/therapy given, additional investigations performed, outcome and his/her opinion as to whether there is a reasonable possibility that the AE was caused by the IMP.

All study treatment-related AEs and all SAEs (regardless of their causal relationship to study treatment) ongoing at the time of study treatment discontinuation need to be followed until resolution or stabilization. Any AE or SAE assessed as study treatment-related that are new during the follow-up period are to be reported and followed until resolution or stabilization.

When treatment is discontinued, observations will continue for that patient as defined by the protocol.

Vital signs or ECG abnormalities are to be recorded as AEs only if they are symptomatic and/or requiring corrective treatment and/or leading to treatment discontinuation and/or modification of dosing and/or fulfilling a serious criterion and/or is defined as an AESI.

Laboratory abnormalities are to be recorded as AEs only if they lead to treatment discontinuation and/or modification of dosing and/or fulfill a serious criterion and/or are defined as an AESI. Laboratory values will be reported in the appropriate pages of eCRF.

10.4.3 Instructions for reporting serious adverse events

In the case of a SAE or an AESI, the Investigator must immediately:

- ENTER (within 24 hours) the information related to the SAE in the appropriate screens of the eCRF; the system will automatically send the notification to the Monitoring Team after approval of the Investigator within the eCRF or after a standard delay.
- SEND (preferably by e-mail) the photocopy of all examinations carried out and the dates on which these examinations were performed, to the representative of the Monitoring Team whose name, fax number and email address appear on the Clinical Trial Protocol;. Care should be taken to ensure that the patient's identity is protected and the patient's identifiers in the Clinical Trial are properly mentioned on any copy of a source document provided to sanofi. For laboratory results, include the laboratory normal ranges.
- All further data updates should be recorded in the eCRF as appropriate, and further documentation as well as additional information (for laboratory data, concomitant medication, patient status) should be sent (by e-mail) to the Monitoring Team within 24 hours of knowledge. In addition, every effort should be made to further document each SAE that is fatal or life threatening within the week (7 days) following initial notification.
- A back-up plan is used (using paper flow) when the eCRF system does not work.

10.4.4 Instructions for follow-up of adverse events

The Investigator should take all appropriate measures to ensure the safety of the patients, notably he/she should follow up the outcome of any AEs (clinical signs, laboratory values, etc) until the return to normal or consolidation of the patient's condition.

In case of any SAE, the patient must be followed up until clinical recovery is complete and laboratory results have returned to normal, or until outcome has been stabilized. This may imply that follow-up may continue after the patient has left the study and that additional investigations may be requested by the Monitoring Team.

In case of any AE or SAE brought to the attention of the Investigator at any time after cessation of IMP and considered by him/her to be caused by the IMP with a reasonable possibility, this should be reported to the Monitoring Team.

10.4.5 Treatment discontinuation due to nonserious adverse event

In the case of a treatment discontinuation due to a nonserious AE:

- ENTER (within 24 hours) the information related to treatment discontinuation due to a nonserious AE in the appropriate screens of the eCRF (AE with the box "action taken with IMP" ticked "permanently discontinued", together with the end of treatment form with reason that should be ticked "Adverse Event"); the system will automatically send the notification to the Monitoring Team after approval of the Investigator within the eCRF or after a standard delay.

10.5 OBLIGATIONS OF SANOFI

During the course of the study, the Sponsor will report in an expedited manner:

- All SAEs that are both unexpected and at least reasonably related to the IMP (suspected unexpected serious adverse reaction), to the regulatory authorities, independent ethics committees (IECs)/institutional review boards (IRBs) as appropriate and to the Investigators, according to local regulations.
- AEs that are considered expected as specified by the reference safety information (see the current version of the Investigator's Brochure).

Sanofi will report all safety observations made during the conduct of the study in the clinical study report.

10.6 SAFETY INSTRUCTIONS

10.6.1 Guidelines for the management of potential infusion associated reactions

Patients should routinely receive premedications (NIMP) prior to isatuximab infusion as detailed in Section 8.2 to reduce the risk and severity of IARs commonly observed with mAb. Infusion associated reactions (NCI-CTCAE, version 4.03 term 'allergic/hypersensitivity reactions' or 'cytokine release syndrome/acute infusion reaction') are defined as AEs related to isatuximab with onset typically within 24 hours from the start of the infusion.

Patients who experience Grade 2 IAR(s) may subsequently resume isatuximab infusion under close monitoring and supportive care as needed. Patients may receive additional premedication per the judgment of the Investigator. Additional recommended premedications are diphenhydramine 25 mg IV (or equivalent) and methylprednisolone 100 mg IV (or equivalent). These patients must be informed of the potential risk of recurrent allergic reactions.

Once a Grade 2 IAR has improved to Grade ≤1, the infusion may be restarted at one half the original infusion rates. If symptoms do not recur after 30 minutes, the infusion rate may be increased by 50 mg/hour increments every 30 minutes, to a maximum of 400 mg/hour.

Patients with a Grade 3 or 4 isatuximab IAR must have isatuximab permanently discontinued and appropriate supportive therapy should be administered.

Should an isatuximab IAR of Grade ≥2 occur, additional blood sampling during the AE is required for analysis of cytokine levels (TNFα, IL-1β, IL-4, IL-6 and IFNγ), markers of activated complement (C3a, C4, CH50), serum tryptase, and markers of potential TLS (uric acid, lactate dehydrogenase, blood urea nitrogen/creatinine, potassium, phosphate, and ionized and corrected calcium). The IAR and the therapy administered must be documented in the eCRF.

All IARs of Grade ≥3 must be reported as AESIs (see Section 10.4.1.3). Study personnel should consult the Medical Monitor for further guidance regarding retreatment of patients with IARs and regarding issues of premedication management (eg, alternative medications for patients allergic or intolerant to premedication agents) or to determine if locally used equivalent medications are acceptable.

General guidelines for the management of IARs are provided in Table 7.

Table 7 - Management of infusion associated reaction

NCI-CTCAE version 4.03 criteria definition	Intervention recommendation
Mild (Grade 1) Infusion interruption or intervention not indicated	Continuation of isatuximab infusion per the judgment of the Investigator following close direct monitoring of the patient's clinical status. Isatuximab infusion may be stopped at any time if deemed necessary. If stopped, IAR will be classified as a Grade 2 as per NCI-CTCAE.
Moderate (Grade 2) Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hours)	Stop isatuximab infusion. Give additional premedication with IV diphenhydramine 25 mg IV (or equivalent) and/ or IV methylprednisolone 100 mg (or equivalent) as needed. Isatuximab may be resumed only after patient recovery, with slower infusion rate and with close monitoring. Blood samples for additional safety labs will be collected. Important: additional blood sampling during the AE is required for analysis of cytokine levels (TNFα, IL-4, IL-6, IL-1β, and IFNγ), markers of activated complement (C3a, C4, CH50), serum tryptase, and markers of potential TLS.
Severe or life-threatening (Grade 3 or 4) Grade 3: prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae Grade 4: life-threatening consequences; urgent intervention indicated	Stop isatuximab infusion. Give additional premedication with diphenhydramine 25 mg IV (or equivalent) and/ or IV methylprednisolone 100 mg (or equivalent) and/or epinephrine as needed. Blood samples for additional safety labs will be collected. Definitive treatment discontinuation. Important: additional blood sampling during the AE is required for analysis of cytokine levels (TNFα, IL-4, IL-6, IL-1β, and IFNγ), markers of activated complement (C3a, C4, CH50), serum tryptase, and markers of potential TLS.

Note: The infusion should be completed within 7.5 hours from the end of infusion preparation or a new infusion should be prepared with the remaining dose to be administered the same day.
AE: adverse event; IAR: infusion associated reaction; IFNγ: interferon gamma; IL: interleukin; IV: intravenous; NCI-CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events; NSAIDs: nonsteroidal anti-inflammatory drugs; TLS: tumor lysis syndrome; TNFα: tumor necrosis factor alpha.

10.6.2 Guidelines for the management of tumor lysis syndrome

General guidelines for the management of TLS are provided in Table 8.

Table 8 - Management of tumor lysis syndrome

Symptom	Recommended action
Laboratory TLS: ≥2 simultaneous abnormalities within 3 days prior to and up to 7 days after treatment start • Uric acid >8 mg/dL (>475.8 µmol/L). • Potassium >6.0 mmol/L. • Phosphorus >4.5 mg/dL (>1.5 mmol/L). • Corrected calcium <7.0 mg/dL (<1.75 mmol/L), ionized calcium <1.12 mg/dL (<0.3mmol/L)[a]	Omit study treatment until all serum chemistries have resolved. Ensure normal hydration, correct laboratory abnormalities, fluid overload, electrolyte or acid-base deviation. Monitor TLS complications including renal functions. Reinstitute study treatment at full dose after resolution.
Clinical TLS: laboratory TLS in addition to 1 of the following complications • Acute kidney injury: increase in the serum creatinine level of 0.3 mg/dL (26.5 µmol/L) or the presence of oliguria, defined as an average urine output of <0.5 mL/kg/hour for 6 hours. • Seizures, cardiac dysrhythmia, neuromuscular irritability (tetany, paresthesias, muscle twitching, carpopedal spasm, Trousseau's sign, Chvostek's sign, laryngospasm, bronchospasm), hypotension, or heart failure probably or definitely caused by hypocalcemia. • Dysrhythmias probably or definitely caused by hyperkalemia.	Same as above

TLS: tumor lysis syndrome

a The corrected calcium level in milligrams per deciliter = measured calcium level in milligrams per deciliter + 0.8 x (4-albumin in grams per deciliter)

10.7 ADVERSE EVENTS MONITORING

All events will be managed and reported in compliance with all applicable regulations, and included in the final clinical study report.

11 STATISTICAL CONSIDERATIONS

11.1 DETERMINATION OF SAMPLE SIZE

A 2-stage Simon's Optimum design was used for sample size calculation and a maximum of 39 evaluable patients will be enrolled in the study. This sample size will provide 80% power to reject the null hypothesis that the true ORR is ≤15% if the true ORR rate is ≥30%, based on a 1-sided exact binomial test at a significance level of 0.1.

- 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.

11.2 DISPOSITION OF PATIENTS

The number of registered patients (patients who signed the informed consent) as well as the number and percentage of patients included in the analysis populations defined in Section 11.3 will be provided.

Reasons for treatment discontinuation will be summarized using the all-treated/safety population.

11.3 ANALYSIS POPULATIONS

11.3.1 All-treated/safety population

The all-treated/safety population will include all 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.

11.3.2 Pharmacokinetic population

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

Patients with at least one evaluable ADA results during the ADA pretreatment period will be considered as evaluable at baseline. Patients with at least one evaluable ADA result during the ADA on-study observation period will be considered evaluable during the on-study observation period.

11.3.3 Pharmacodynamic population

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

11.4 STATISTICAL METHODS

A list of study endpoints and their definitions are provided in Section 9.1.

Unless otherwise specified, analyses will be descriptive and performed based on the all-treated/safety population. The baseline for a given parameter is defined as the last assessment for this parameter before the first study treatment administration.

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

The cutoff date for interim analysis (Stage 1) will be approximately 2 months after last patient is treated in Stage 1.

The cutoff date for primary analysis of ORR and other secondary endpoints will be 6 months after the last patient has had their first study treatment administration. The final cutoff date for OS analysis and updated analysis of ORR and other secondary endpoints will be approximately 12 months after the last patient has had their first study treatment administration.

11.4.1 Extent of study treatment exposure and compliance

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

- Number of cycles started.
- Duration of exposure in weeks: ([First day of last cycle – first day of first cycle + 28 days]/7).
- Cumulative dose (in mg/kg). The cumulative dose is the sum of all doses administered from first to last dose.
- Actual dose intensity, defined as the cumulative dose divided by the number of weeks on study.
- Relative dose intensity (in %), defined as the ratio of the actual dose intensity to the planned dose intensity. The relative dose intensity is an indicator of the feasibility of the chosen schedule of administration.
- Dose delays. The start of a cycle can be delayed for up to 14 days. 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.
- Dose interruption.
- Dose omission.

11.4.2 Analyses of efficacy endpoints

11.4.2.1 Analysis of primary efficacy endpoint

The primary efficacy endpoint is the ORR. The ORR will be summarized with descriptive statistics. Confidence intervals will be computed using the Clopper-Pearson method.

11.4.2.2 Analyses of secondary efficacy endpoints

The DOR, PFS and OS will be analyzed using Kaplan-Meier methods. Among patients who achieved a CR, the number of patients without MRD will be provided.

11.4.2.3 Multiplicity considerations

Not applicable.

11.4.3 Analyses of safety data

11.4.3.1 Adverse events

Adverse Events will be collected from the date informed consent is signed, until the end of treatment (at least 30 days after the last dose of study treatment, or a new anticancer therapy is started, whichever is first).

Adverse Events will be graded according to the NCI-CTCAE version 4.03 (Appendix D) and classified by system organ class (SOC)/preferred term (PT) according to the latest available version of the MedDRA dictionary.

The observation period will be divided into 3 segments: screening, TEAE and posttreatment:

- The screening period is defined as the time informed consent is signed until the first study treatment administration.
- The TEAE observation period is defined as the time from the first study treatment administration up to at least 30 days after the last study treatment administration, or a new anticancer therapy is started, whichever is first.
- The posttreatment period is defined as the time starting 31 days after the last study treatment administration or a new anticancer therapy is started (whichever is first) to study closure.

Pretreatment AEs are defined as any AE reported during the screening period.

Treatment-emergent AEs are defined as AEs that developed, worsened (according to the Investigator opinion), or became serious during the TEAE period.

Posttreatment AEs are defined as AEs that are reported during the posttreatment period.

The grade will be taken into account in the summary. For patients with multiple occurrences of the same PT, the maximum grade within the analyzed observation period will be used.

The primary focus of AE reporting will be on TEAEs. Pretreatment and posttreatment AEs will be described separately.

11.4.3.2 Treatment-emergent adverse events

An overall summary of TEAEs will be provided. The number and percentage of patients who experienced any of the following will be provided:

- TEAEs.
- TEAEs of Grade ≥3.
- Treatment-related TEAEs.
- Treatment-related TEAEs of Grade ≥3.
- Serious TEAEs.
- Serious treatment-related TEAEs.
- TEAE with a fatal outcome.
- TEAE leading to permanent treatment discontinuation.
- AESIs.
- AESIs of Grade ≥3.
- IARs.
- IARs of Grade ≥3.

Number and percentage of patients experiencing TEAEs by primary SOC and PT will be summarized by NCI-CTCAE grade (all grades and Grade ≥3). Similar tables will be prepared for treatment-related TEAEs, IARs, TEAEs leading to isatuximab discontinuation, TEAEs leading to dose modification, serious TEAEs, TEAEs with a fatal outcome and AEs/SAEs occurring during the posttreatment dosing period.

Sorting within tables should ensure the same presentation for the set of all AEs within the observation period (screening, TEAE and posttreatment). For that purpose, the table of all TEAEs will be presented by SOC and PT sorted by internationally agreed, order unless otherwise specified.

Infusion associated reactions will be analyzed using both investigator reporting and treatment-related TEAEs occurring within 24 hours after isatuximab administration.

The following listings will be provided if relevant:

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

11.4.3.3 Deaths

A summary of the number and proportion of patients who died by study period (screening, TEAE and posttreatment) and cause will be generated.

A listing of deaths will be provided.

11.4.3.4 Other safety variables

Incidence of TLS including the description of the TLS criteria will be summarized with descriptive statistics. Corresponding listings will be provided.

Cytokines at baseline will be described with descriptive statistics. For patients with post-baseline assessments, maximum change from baseline will be described including time to maximum change.

Potentially clinically significant abnormality (PCSA) values are defined as abnormal values considered medically important by the Sponsor according to predefined criteria/thresholds based on literature review.

The incidence of PCSA for vital signs and at any time during the TEAE period will be summarized irrespective of the baseline level (ie, last assessment before the first study treatment administration) and 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.

Clinical laboratory values will be analyzed after conversion into standard international units. International units will be used in all listings and tables. Complete blood count and serum chemistry results will be graded according to NCI-CTCAE version 4.03, when applicable. For patients with multiple occurrences of the same laboratory variable during the on-treatment period (ie, TEAE 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.

The number and proportion of patients with abnormal laboratory tests at baseline (ie, last assessment before the first study treatment administration) will be presented for all grades and Grades 3 and 4. Similar tables showing abnormalities during the on-treatment period will be provided.

When the NCI-CTCAE version 4.03 scale is not applicable, the number of patients with a treatment-emergent out-of-normal laboratory range value will be displayed.

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

11.4.3.5 Immunogenicity

The observation period for ADAs will be divided into 2 periods:

- The ADA pretreatment period will be defined as the time that informed consent is signed until the first study treatment administration.
- The ADA on-study observation period will be defined as the time from the first study treatment administration until the end of the study.

Patients with at least one evaluable ADA result during the ADA pretreatment period will be considered as evaluable at baseline. Patients with at least one evaluable ADA result during the ADA on-study observation period will be considered evaluable during the on-study observation period.

Definitions:

- Pre-existing ADA, defined as ADA that are present in samples drawn during the pretreatment period.
- Treatment-induced ADA, defined as ADA that developed at any time during the ADA on-study observation period in patients without pre-existing ADA (including patients without pretreatment samples).
- Treatment boosted ADA, defined as pre-existing ADA with a significant increase in the ADA titer during the study compared to the baseline titer.
- 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 prevalence, defined as the sum of the number of patients with pre-existing ADA and the number of patients with treatment induced ADAs, divided by the number of evaluable patients.
- ADA incidence, defined as the number of ADA positive patients divided by the number of evaluable patients.

The immunogenicity for isatuximab will be assessed by summarizing the number (%) of patients with pre-existing ADA and ADA negative at baseline, and by summarizing the number (%) of ADA positive patients (including treatment-induced ADA and treatment boosted ADA) during the on-study observation period.

ADA prevalence and ADA incidence will be also described.

11.4.4 Analyses of pharmacokinetic 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.

11.4.5 Analyses of pharmacodynamic variables

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

11.5 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 (see Section 6.1).

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.

12 ETHICAL AND REGULATORY CONSIDERATIONS

12.1 ETHICAL AND REGULATORY STANDARDS

This clinical study will be conducted by the Sponsor, the Investigator, and delegated Investigator staff and Subinvestigator, in accordance with consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki, and the International Council for Harmonisation (ICH) guidelines for good clinical practice (GCP), all applicable laws, rules and regulations.

This clinical study will be recorded in a free, publicly accessible, internet-based registry, no later than 21 days after the first patient enrollment, in compliance with applicable regulatory requirements and with sanofi public disclosure commitments.

12.2 INFORMED CONSENT

The Investigator (according to applicable regulatory requirements), or a person designated by the Investigator, and under the Investigator's responsibility, should fully inform the patient of all pertinent aspects of the clinical trial including the written information giving approval/favorable opinion by the ethics committee (IRB/IEC). All participants should be informed to the fullest extent possible about the study, in language and terms they are able to understand.

Prior to a patient’s participation in the clinical study, the written informed consent form should be signed, name filled in and personally dated by the patient or by the patient’s legally acceptable representative, and by the person who conducted the informed consent discussion. A copy of the signed and dated written informed consent form will be provided to the patient.

Prior to collection of blood for pharmacogenetics, the optional pharmacogenetic informed consent form (written) should be signed, name filled in, and personally dated by the patient or by the patient’s legally acceptable representative, and by the person who conducted the informed consent discussion. A copy of the signed and dated written optional informed consent form will be provided to the patient.

The informed consent form and the optional pharmacogenetic informed consent form used by the Investigator for obtaining the patient's informed consent must be reviewed and approved by the Sponsor prior to submission to the appropriate ethics committee (IRB/IEC) for approval/favorable opinion.

For pediatric patients, the Investigator (according to applicable regulatory requirements), or a person designated by the Investigator, should fully inform the patient (and the parent[s] or guardian[s]) of all pertinent aspects of the clinical trial including the written information given approval/favorable opinion by the ethics committee (IRB/IEC). All participants should be informed to the fullest extent possible about the study in language and terms they are able to understand. Local law must be observed in deciding whether 1 or both parents/guardians consent is required. If only 1 parent or guardian signs the consent form, the Investigator must document the reason for only 1 parent or guardian’s signature.

In addition, participants will assent as detailed below or will follow the ethics committee (IRB/IEC) approved standard practice for pediatric participants at each participating center (age of assent to be determined by the IRB's/IEC's or be consistent with the local requirements):

Participants who can read the assent form will do so before writing their name and dating or signing and dating the form.

Participants who can write but cannot read will have the assent form read to them before writing their name on the form.

Participants who can understand but who can neither write nor read will have the assent form read to them in presence of an impartial witness, who will sign and date the assent form to confirm that assent was given.

The informed consent form and the assent form used by the Investigator for obtaining the Patient's Informed Consent must be reviewed and approved by the Sponsor prior to submission to the appropriate ethics committee (IRB/IEC) for approval/favorable opinion.

In relation with the population of patients exposed in the trial ie, pediatric/minor patients, the IRB/IEC should ensure proper advice from specialist with pediatrics expertise (competent in the area of clinical, ethical and psychosocial problems in the field of pediatrics) according to national regulations. This should be documented.

12.3 HEALTH AUTHORITIES AND INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE (IRB/IEC)

As required by local regulation, the Investigator or the Sponsor must submit this clinical study protocol to the health authorities (competent regulatory authority) and the appropriate IRB/IEC, and is required to forward to the respective other party a copy of the written and dated approval/favorable opinion signed by the chairman with IRB/IEC composition.

The clinical study (study number, clinical study protocol title and version number), the documents reviewed (clinical trial protocol, informed consent form, Investigator's Brochure with any addenda or labeling documents (summary of product characteristics, package insert, Investigator's curriculum vitae, etc) and the date of the review should be clearly stated on the written (IRB/IEC) approval/favorable opinion.

The IMP will not be released at the study site and the Investigator will not start the study before the written and dated approval/favorable opinion is received by the Investigator and the Sponsor.

During the clinical study, any amendment or modification to the clinical trial protocol should be submitted to the health authorities (competent regulatory authority), as required by local regulation, in addition to the IRB/IEC before implementation, unless the change is necessary to eliminate an immediate hazard to the patients, in which case the health authorities (competent regulatory authority) and the IRB/IEC should be informed as soon as possible. They should also be informed of any event likely to affect the safety of patients or the continued conduct of the clinical trial, in particular any change in safety. All updates to the Investigator's Brochure or labeling information, will be sent to the IRB/IEC and to health authorities (competent regulatory authority), as required by local regulation.

A progress report is sent to the IRB/IEC at least annually and a summary of the clinical study's outcome at the end of the clinical study.

13 STUDY MONITORING

13.1 RESPONSIBILITIES OF THE INVESTIGATOR(S)

The Investigator is required to ensure compliance with all procedures required by the clinical trial protocol and with all study procedures provided by the Sponsor (including security rules). The Investigator agrees to provide reliable data and all information requested by the clinical trial protocol (with the help of the eCRF, Discrepancy Resolution Form or other appropriate instrument) in an accurate and legible manner according to the instructions provided and to ensure direct access to source documents by Sponsor representatives.

If any circuit includes transfer of data particular attention should be paid to the confidentiality of the patient's data to be transferred.

The Investigator may appoint such other individuals as he/she may deem appropriate as Subinvestigators to assist in the conduct of the clinical trial in accordance with the clinical trial protocol. All Subinvestigators shall be appointed and listed in a timely manner. The Subinvestigators will be supervised by and work under the responsibility of the Investigator. The Investigator will provide them with a copy of the clinical trial protocol and all necessary information.

13.2 RESPONSIBILITIES OF THE SPONSOR

The Sponsor of this clinical study is responsible to regulatory authorities for taking all reasonable steps to ensure the proper conduct of the clinical study as regards ethics, clinical trial protocol compliance, and integrity and validity of the data recorded on the eCRFs. Thus, the main duty of the Monitoring Team is to help the Investigator and the Sponsor maintain a high level of ethical, scientific, technical and regulatory quality in all aspects of the clinical study.

At regular intervals during the clinical study, the site will be contacted, through monitoring visits, letters or telephone calls, by a representative of the Monitoring Team to review study progress, Investigator and patient compliance with clinical trial protocol requirements and any emergent problems. These monitoring visits will include but not be limited to review of the following aspects: patient informed consent, patient recruitment and follow-up, SAE documentation and reporting, AESI documentation and reporting, AE documentation, IMP allocation, patient compliance with the IMP regimen, IMP accountability, concomitant therapy use and quality of data.

13.3 SOURCE DOCUMENT REQUIREMENTS

According to the ICH GCP, the Monitoring Team must check the eCRF entries against the source documents, except for the pre-identified source data directly recorded in the eCRF. The informed consent form will include a statement by which the patient allows the Sponsor’s duly authorized personnel, the ethics committee (IRB/IEC), and the regulatory authorities to have direct access to original medical records which support the data on the eCRFs (eg, patient's medical file, appointment books, original laboratory records, etc). These personnel, bound by professional secrecy, must maintain the confidentiality of all personal identity or personal medical information (according to confidentiality and personal data protection rules).

13.4 USE AND COMPLETION OF CASE REPORT FORMS AND ADDITIONAL REQUEST

It is the responsibility of the Investigator to maintain adequate and accurate eCRFs (according to the technology used) designed by the Sponsor to record (according to Sponsor instructions) all observations and other data pertinent to the clinical investigation in a timely manner. All eCRFs should be completed in their entirety in a neat, legible manner to ensure accurate interpretation of data.

Should a correction be made, the corrected information will be entered in the eCRF overwriting the initial information. An audit trail allows identifying the modification.

Data are available within the system to the Sponsor as soon as they are entered in the eCRF.

The computerized handling of the data by the Sponsor may generate additional requests (Discrepancy Resolution Form) to which the Investigator is obliged to respond by confirming or modifying the data questioned. The requests with their responses will be managed through the eCRF.

13.5 USE OF COMPUTERIZED SYSTEMS

The complete list of computerized systems used for the study is provided in a separate document which is maintained in the Sponsor and Investigator study files.

14 ADDITIONAL REQUIREMENTS

14.1 CURRICULUM VITAE

A current copy of the curriculum vitae describing the experience, qualification and training of each Investigator and Subinvestigator will be signed, dated and provided to the Sponsor prior to the beginning of the clinical study.

14.2 RECORD RETENTION IN STUDY SITES

The Investigator must maintain confidential all study documentation, and take measures to prevent accidental or premature destruction of these documents.

The Investigator should retain the study documents at least 15 years after the completion or discontinuation of the clinical study.

However, applicable regulatory requirements should be taken into account in the event that a longer period is required.

The Investigator must notify the Sponsor prior to destroying any study essential documents following the clinical study completion or discontinuation.

If the Investigator's personal situation is such that archiving can no longer be ensured by him/her, the Investigator shall inform the Sponsor and the relevant records shall be transferred to a mutually agreed upon designee.

14.3 CONFIDENTIALITY

All information disclosed or provided by the Sponsor (or any company/institution acting on their behalf), or produced during the clinical study, including, but not limited to, the clinical trial protocol, personal data in relation to the patients, the eCRFs, the Investigator's Brochure, and the results obtained during the course of the clinical study, is confidential, prior to the publication of results. The Investigator and any person under his/her authority agree to undertake to keep confidential and not to disclose the information to any third party without the prior written approval of the Sponsor.

However, the submission of this clinical trial protocol and other necessary documentation to the ethics committee (IRB/IEC) is expressly permitted, the IRB/IEC members having the same obligation of confidentiality.

The Subinvestigators shall be bound by the same obligation as the Investigator. The Investigator shall inform the Subinvestigators of the confidential nature of the clinical study.

The Investigator and the Subinvestigators shall use the information solely for the purposes of the clinical study, to the exclusion of any use for their own or for a third party's account.

14.4 PROPERTY RIGHTS

All information, documents and IMP provided by the Sponsor or its designee are and remain the sole property of the Sponsor.

The Investigator shall not and shall cause the delegated Investigator staff/Subinvestigator not to mention any information or the Product in any application for a patent or for any other intellectual property rights.

All the results, data, documents and inventions, which arise directly or indirectly from the clinical trial in any form, shall be the immediate and exclusive property of the Sponsor.

The Sponsor may use or exploit all the results at its own discretion, without any limitation to its property right (territory, field, continuance). The Sponsor shall be under no obligation to patent, develop, market or otherwise use the results of the clinical study.

As the case may be, the Investigator and/or the Subinvestigators shall provide all assistance required by the Sponsor, at the Sponsor's expense, for obtaining and defending any patent, including signature of legal documents.

14.5 DATA PROTECTION

- The patient's personal data, which are included in the Sponsor database shall be treated in compliance with all applicable laws and regulations.
- When archiving or processing personal data pertaining to the Investigator and/or to the patients, the Sponsor shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.
- The Sponsor also collects specific data regarding Investigator as well as personal data from any person involved in the study which may be included in the Sponsor’s databases, shall be treated by both the Sponsor and the Investigator in compliance with all applicable laws and regulations.

Patient race or ethnicity (including ‘Caucasian/white, Black, Asian/Oriental’) will be collected in this study because these data are required by several regulatory authorities (eg, on Afro-American population for the Food and Drug Administration, on the Japanese population for the Pharmaceuticals and Medical Devices Agency in Japan, or on the Chinese population for the China Food and Drug Administration in China).

The data collected in this study will only be used for the purpose(s) of the study and to document the evaluation of the benefit/risk ratio, efficacy, and safety of the product(s). They may be further processed if they have been anonymized.

14.6 INSURANCE COMPENSATION

The Sponsor certifies that it has taken out a liability insurance policy covering all clinical studies under its sponsorship. This insurance policy is in accordance with local laws and requirements. The insurance of the Sponsor does not relieve the Investigator and the collaborators from any obligation to maintain their own liability insurance policy. An insurance certificate will be provided to the IECs/IRBs or regulatory authorities in countries requiring this document.

14.7 SPONSOR AUDITS AND INSPECTIONS BY REGULATORY AGENCIES

For the purpose of ensuring compliance with the clinical trial protocol, GCP, and applicable regulatory requirements, the Investigator should permit auditing by or on the behalf of the Sponsor and inspection by regulatory authorities.

The Investigator agrees to allow the auditors/inspectors to have direct access to his/her study records for review, being understood that these personnel are bound by professional secrecy, and as such will not disclose any personal identity or personal medical information.

The Investigator will make every effort to help with the performance of the audits and inspections, giving access to all necessary facilities, data, and documents.

As soon as the Investigator is notified of a planned inspection by the authorities, he will inform the Sponsor and authorize the Sponsor to participate in this inspection.

The confidentiality of the data verified and the protection of the patients should be respected during these inspections.

Any result and information arising from the inspections by the regulatory authorities will be immediately communicated by the Investigator to the Sponsor.

The Investigator shall take appropriate measures required by the Sponsor to take corrective actions for all problems found during the audit or inspections.

14.8 PREMATURE DISCONTINUATION OF THE STUDY OR PREMATURE CLOSE-OUT OF A SITE

14.8.1 By the Sponsor

The Sponsor has the right to terminate the participation of either an individual site or the study at any time, for any reason, including but not limited to the following:

- The information on the product leads to doubt as to the benefit/risk ratio.
- Patient enrollment is unsatisfactory.
- The Investigator has received from the Sponsor all IMP, means, and information necessary to perform the clinical trial and has not included any patient after a reasonable period of time mutually agreed upon.
- Noncompliance of the Investigator or Subinvestigator, delegated staff with any provision of the clinical trial protocol, and breach of the applicable laws and regulations or breach of the ICH GCP.
- The total number of patients is included earlier than expected.

In any case the Sponsor will notify the Investigator of its decision by written notice.

14.8.2 By the Investigator

The Investigator may terminate his/her participation upon 30 days' prior written notice if the study site or the Investigator for any reason becomes unable to perform or complete the clinical study.

In the event of premature discontinuation of the study or premature close-out of a site, for any reason whatsoever, the appropriate IRB/IEC and regulatory authorities should be informed according to applicable regulatory requirements.

14.9 CLINICAL TRIAL RESULTS

The Sponsor will be responsible for preparing a clinical study report and to provide a summary of study results to the Investigator.

14.10 PUBLICATIONS AND COMMUNICATIONS

The Investigator undertakes not to make any publication or release pertaining to the study and/or results of the study prior to the Sponsor's written consent, being understood that the Sponsor will not unreasonably withhold its approval.

As the study is being conducted at multiple sites, the Sponsor agrees that, consistent with scientific standards, a primary presentation or publication of the study results based on global study outcomes shall be sought. However, if no multicenter publication is submitted, underway, or planned within 12 months of the completion of this study at all sites, the Investigator shall have the right to publish or present independently the results of this study in agreement with other Investigators and stakeholders. The Investigator shall provide the Sponsor with a copy of any such presentation or publication for review and comment at least 30 days in advance of any presentation or submission for publication. In addition, if requested by the Sponsor, any presentation or submission for publication shall be delayed for a limited time, not to exceed 90 days, to allow for filing of a patent application or such other justified measures as the Sponsor deems appropriate to establish and preserve its proprietary rights.

The Investigator shall not use the name(s) of the Sponsor and/or its employees in advertising or promotional material or publication without the prior written consent of the Sponsor. The Sponsor shall not use the name(s) of the Investigator and/or the collaborators in advertising or promotional material or publication without having received his/her and/or their prior written consent(s).

The Sponsor has the right at any time to publish the results of the study.

15 CLINICAL TRIAL PROTOCOL AMENDMENTS

All appendices attached hereto and referred to herein are made part of this clinical trial protocol.

The Investigator should not implement any deviation from, or changes to the clinical trial protocol without agreement by the Sponsor and prior review and documented approval/favorable opinion from the IRB/IEC and/or notification/approval of health authorities (competent regulatory authority) of an amendment, as required by local regulation, except where necessary to eliminate an immediate hazard(s) to clinical study patients, or when the change(s) involves only logistical or administrative aspects of the study. Any change agreed upon will be recorded in writing, the written amendment will be signed by the Investigator and by the Sponsor and the signed amendment will be filed with this clinical trial protocol.

Any amendment to the clinical trial protocol requires written approval/favorable opinion by the IRB/IEC prior to its implementation, unless there are overriding safety reasons.

In case of substantial amendment to the clinical trial protocol, approval from the health authorities (competent regulatory authority) will be sought before implementation.

In some instances, an amendment may require a change to the informed consent form. The Investigator must receive an IRB/IEC approval/favorable opinion concerning the revised informed consent form prior to implementation of the change and patient signature should be recollected if necessary.

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