AMENDED CLINICAL TRIAL PROTOCOL 05

Protocol title:	**Open-label, Single-arm Trial to Evaluate Antitumor Activity, Safety, and Pharmacokinetics of Isatuximab Used in Combination With Chemotherapy in Pediatric Patients From 28 Days to Less Than 18 Years of Age With Relapsed/Refractory B or T Acute Lymphoblastic Leukemia or Acute Myeloid Leukemia In First or Second Relapse**
Protocol number:	**ACT15378**
Amendment number:	**05**
Compound number (INN/Trademark):	**SAR650984 (isatuximab)**
Short title:	**Isatuximab in Combination with Chemotherapy in Pediatric Patients with Relapsed/Refractory Acute Lymphoblastic Leukemia or Acute Myeloid Leukemia (ISAKIDS)**
Sponsor name: **Legal registered address:**	**Sanofi aventis recherche & développement** **1 avenue Pierre Brossolette,** **91380 Chilly-Mazarin** **FRANCE**
Monitoring Team's Representative Name and Contact Information	

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PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY

Document	Country/countries impacted by amendment	Date, version
Amended Clinical Trial Protocol 05	All	14 October 2021, version 1 (electronic 5.0)
Amended Clinical Trial Protocol 04	All	24 November 2020, version 1 (electronic 4.0)
Amended Clinical Trial Protocol 03	All	30 July 2020, version 1 (electronic 3.0)
Amended Clinical Trial Protocol 02	All	04 December 2019, version 1 (electronic 2.0)
Amended Clinical Trial Protocol 01	All	11 March 2019, version 1 (electronic 1.0)
Original Protocol		21 September 2018, version 1 (electronic 1.0)

Amended protocol 05 (14 October 2021)

This amended protocol (amended protocol 05) is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

OVERALL RATIONALE FOR THE AMENDMENT

The primary driver for this amendment is to allow the enrollment of children <2 years old as after PK assessment, the dose of 20 mg/kg is confirmed in this young subpopulation.

The main changes are:

- Justification of the dose (20 mg/kg) for children <2 years old.
- Definition of evaluable patient update.
- Clarification on coagulation test frequency.
- Adding possibility to perform a PET-MRI instead of PET-CT when needed.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Section 1.1 Synopsis, Section 3 Objectives and Endpoints, and Section 10.6.1.1 Response criteria	Secondary endpoint regarding overall response rate is updated to “The overall response rate is defined as the proportion of participants with CR or CRi or PR for blood and bone marrow disease”.	Clarification.

Section # and Name	Description of Change	Brief Rationale
Section 1.1 Synopsis and Section 9.4 Statistical Consideration	"the last participant is treated "was updated to "the last participant is treated (last participant last dose)".	Clarification.
Section 1.1 Synopsis	The following statement was removed "Participant under 2 years of age can only be enrolled after the dose reassessment is completed on the first 20 participants who are 2 to less than 18 years of age".	To allow the enrollment of participants <2 years old as after PK assessment the recommendation is to keep same dose (20 mg/kg).
Section 1.1 Synopsis and Section 1.3 Schedule of Activities (SoA)	For AML, to be performed with BM aspiration samples at the time of hematological recovery or between Days 22 and 29, and/or at the time of each BM aspiration for disease assessment if CR or CRi is achieved.	To clarify that MRD assessment is mandatory, only the day is flexible.
Section 1.1 Synopsis and Section 9.3 Populations for Analyses: Table 12	The description of evaluable population was updated to: The evaluable population will include participants from the AT population who received at least 1 full dose of isatuximab in Cycle 1 and who had at least one valid response value that is evaluable.	Patients should benefit even out of 1 full dose of the drug.
Section 1.1 Synopsis and Section 9.4.1 Efficacy analyses	"Response to treatment that will be analyzed is the response after 1 full dose of isatuximab in Cycle 1 (induction)" is added.	Clarification.
Section 1.1 Synopsis and Section 9.4 Statistical Consideration	"In case of stop of one of the cohorts after IA the actual date of the cut-off IA will be considered for the primary analysis of CR and other secondary endpoints" is added.	To clarify the data to be collected if a cohort does not move to Stage 2.
Section 1.2 Schema: Figure 1	Hyperlink "a" for "Dexamethasone" is removed.	Correction of a typo.
Section 1.3 Schedule of Activities (SoA); Section 10.2 Appendix 2: clinical laboratory tests	Thyroid-stimulating hormone, free/total T3 and free T4 may be used to determine thyroid status at screening.	Clarification.
Section 1.3 Schedule of Activities (SoA)	Coagulation test will be done once a week until recovery and if clinically indicated, and country-German specific coagulation test related requirement is mentioned in Section 10.8.	To update according to current standards of treatment.
Section 1.3 Schedule of Activities (SoA) and Section 8.1 Efficacy Assessments, Section 10.9 Appendix 9: Contingency Measures for a regional or national emergency that is declared by a governmental agenecy	For ALL and AMLcohorts, CT, PET-CT or PET-MRI scans are suggested to be performed.	To allow PET-MRI and not only PET-CT imaging according to real practice in some countries.
Section 1.3 Schedule of Activities (SoA)	For ALL: Consolidation and Follow-up, 12-lead ECG and cardiac assessment should be performed during EOT visit.	Correction of a typo.

Section # and Name	Description of Change	Brief Rationale
Section 1.3 Schedule of Activities (SoA)	Footnote h) the text "AT-III substituted if necessary" was intended to read as "AT-III may be substituted if necessary".	Clarification.
Section 1.3 Schedule of Activities (SoA)	Footnote i) the text "in case of CRS occurrence…" was intended to read as "in case of CRS/TLS occurrence…".	Clarification.
Section 1.3 Schedule of Activities (SoA)	Vital signs monitoring in 2 hour after every isatuximab infusion and as clinically indicated mentioned already in section 8.2.2 was added in the footnote 'k' in SoA.	Consistency.
Section 1.3 Schedule of Activities (SoA) Table 1 and 2	12:00 AM was a typo, corrected to 12:00 PM.	Correction of a typo.
Section 1.3 Schedule of Activities (SoA): Table 1 and 2	PK and ADA predose samples must be collected just before administration of isatuximab and not in the 3 days before start of infusion, new footnote 'e' is inserted in Table 1 and 2.	Clarification.
Section 2.1 Study Rationale	"Among the patients who achieved a complete remission, 77% were MRD negative, the median relapse free survival (RFS) was 8.3 months, and the median OS was 5.7 months. Among patients reaching a complete remission, 42% were MRD negative, the median RFS was 5.6 months, and the median OS was 4.3 months" is removed.	Correction of a typo.
Section 4.3 Justification for Dose	Addition of the dose rationale for the youngest patients. Justification of the dose (20 mg/kg) for the cohort of children <2 years old, and figure 9 is inserted with reference to this change.	To allow the enrollment of participants <2 years old as after PK assessment the recommendation is to keep same dose (20 mg/kg).
Section 5.1 Inclusion criteria	Inclusion criteria I 01 is updated, participants who are under 2 years old are included.	To allow the enrollment of participants who are under 2 years old.
Section 5.4 Screen Failures	Rescreened participants should be assigned a new participant number.	Correction according to company procedures.
Section 6.1 Study intervention(s) administered	The following statement was updated: "A mandatory monitoring of patients after every isatuximab infusion for 2 hours after the infusion should be set up."	Clarification.
Section 6.1 Study intervention(s) administered	"Patients should be monitored on site for at least 2 hours after the first two infusions of isatuximab. Monitoring after subsequent infusions is recommended, but it is at the discretion of the investigator" is removed.	Correction for consistency.
Section 6.6.1 Guidelines for the management of potential infusion reactions	The following statement in Section 6.6.1 was updated: "Participants with a Grade 3 or 4 IR must follow rules described in the Table 6 and appropriate supportive therapy should be administered."	Consistency.

Section # and Name	Description of Change	Brief Rationale
Section 6.6.1 Guidelines for the management of potential infusion reactions: Table 6	The following statement in Section 6.6.1-table 6 was updated: "If the same Grade 3 infusion-related AE occurs for a third time, treatment with isatuximab will be permanently discontinued for that patient.".	Clarification.
Section 8.1 Efficacy assessments	The following statement was updated: "If not done, PET-CT or PET-MRI scan is suggested to be performed at screening if lymphomatous involvement is present".	Consistency.
Section 8.3 Adverse events and serious adverse events	The following statement was added "AE will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative".	Clarification.
Section 8.11 Data collection after premature stop of the study in case of sponsor decision to stage 2 criteria are not met for one of the cohorts	New section was added.	To clarify data collection after premature stop of the study in case of sponsor decision due to Stage 2 criteria are not met for one of the cohorts.
Section 9.3 Populations for Analyses:Table 12	The description of enrolled population was added: All participants who signed the ICF, regardless of whether the study intervention was received or not. The description of all-treated population was updated to: The AT population will include all participants who received at least 1 dose (even incomplete) of study intervention.	Correction based on updated SAP dated on 16 Dec 2020.
Section 10.3 Adverse events: definitions and procedures for recording, evaluating, follow-up, and reporting	Bullet point "Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition" was added in Events NOT meeting the AE definition subsection.	Clarification.
Section 10.8 Appendix 8: Country-specific requirements	The section was updated: "For German sites coagulation test will be done twice a week and if clinically indicated. For the rest of the world, it will remain once a week and if clinically indicated".	To update according to current standards of treatment.
Section 10.11 Appendix 11: Protocol amendment history	Summary of changes to last version of protocol has been added.	To provide summary of changes introduced in the last amended protocol 04.

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1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Protocol title: Open-label, Single-arm Trial to Evaluate Antitumor Activity, Safety, and Pharmacokinetics of Isatuximab Used in Combination With Chemotherapy in Pediatric Patients From 28 Days to Less Than 18 Years of Age With Relapsed/Refractory B or T Acute Lymphoblastic Leukemia or Acute Myeloid Leukemia In First or Second Relapse

Short title:

Isatuximab in Combination with Chemotherapy in Pediatric Patients with Relapsed/Refractory Acute Lymphoblastic Leukemia or Acute Myeloid Leukemia (ISAKIDS)

Rationale:

More than 80% of children affected by acute leukemia are successfully treated; however, relapse remains a remarkable clinical concern, with 50% to 60% of relapsing patients facing a fatal outcome. Management of relapsed patients includes standardized intensive risk-adapted regimens based on conventional drugs, and hematopoietic stem cells transplantation for patients with unfavorable features. Biological targeted drugs, in particular the monoclonal antibodies (mAbs), could be novel potential agents to be integrated in salvage acute leukemia therapy to further improve patients' outcomes.

Objectives and endpoints

Objectives	Endpoints
Primary	
To evaluate the antileukemic activity of isatuximab in combination with chemotherapies in pediatric participants of 28 days to less than 18 years of age with R/R ALL or AML.	CR rate is defined in this study as the proportion of participants with CR or CRi, in AML, B-ALL, and T-ALL cohorts. **For AML:** • CR: bone marrow blasts lower than 5%; No blasts with Auer rods or persistence of extramedullary disease; ANC higher than 1000/mm^3, platelets higher than 100 000/mm^3; red blood cells transfusion independence. If the physician documents transfusion dependency related to study treatment and not to the patient's underlying disease, CRi can be reported. • CRi: same criteria as for CR, except neutrophils and/or platelets recovery **For B-ALL and T-ALL:** • CR: bone marrow blasts lower than 5%, no circulating blasts or lymphoblasts in CSF or extramedullary disease; ANC higher than 1000/mm^3, platelets higher than 100 000/mm^3; red blood cells transfusion independence. If the physician documents transfusion

Objectives	Endpoints
	dependency related to study treatment and not to the patient's underlying disease, CRi can be reported. • CRi: same criteria as for CR, except neutrophils and/or platelets recovery. • Extramedullary disease: complete resolution of lymphomatous enlargement by CT. For participants with a previous positive PET scan, a post-treatment residual mass of any size is considered a CR as long as it is PET negative.
Secondary	
• Safety and tolerability assessments	• Safety assessment, in terms of AEs/SAEs. In addition, laboratory data, vital signs, and physical examination will be assessed throughout the study.
• Assessment of IRs	• Incidence and severity of IRs.
• PK of isatuximab	• PK parameters of isatuximab calculated using a population PK approach including at least C_{max}, C_{trough}, and AUC.
• Minimal residual disease	• Estimation of minimal residual disease in participants achieving CR or CRi.
• Overall response rate	• The overall response rate is defined as the proportion of participants with CR or CRi or PR for blood and bone marrow disease.
• Overall survival	• Overall survival is defined as the time interval from the date of first study intervention administration to death from any cause.
• Event free survival	• Event free survival is defined as the time interval from the date of first study intervention administration to the date of the first of: completion or going off protocol induction/consolidation therapy without CR, relapse from CR, or death due to any cause.
• Duration of response	• Duration of response is defined as the time from the date of the first response to the date of first disease progression or death from any cause, whichever happens first.
• Relationship between clinical effects and CD38 receptor density and occupancy	• CD38 receptor density will be assessed at baseline and CD38 receptor occupancy at Day 15 and correlated with clinical endpoints.

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

Overall design:

This is a Phase 2, single-arm, multicenter, open-label study evaluating the antitumor activity, safety, and pharmacokinetics (PK) of isatuximab in combination with standard salvage chemotherapies in pediatric participants with relapsed or refractory (R/R) acute lymphoblastic leukemia (ALL; including both T-cell [T]-ALL and B-cell [B]-ALL) and acute myeloid leukemia (AML) conducted in 3 separate cohorts. Male and female children from 28 days to less than 18 years of age with R/R B-ALL or T-ALL or AML in first or second relapse will be eligible.

Treatment periods

Study treatment period:

In all 3 disease cohorts, participants will receive 1 administration of single-agent isatuximab on Day 1. Starting on Day 8, combination chemotherapy will be added. Only if the clinical condition of the participant worsens **after Day 1** of the first isatuximab infusion and the participant's condition requires intensive therapy, chemotherapy can be started earlier, based on investigator's decision. Isatuximab schedule of administration will not be changed for later infusions.

A bone marrow (BM) aspiration will be performed as follows:

- Acute myeloid leukemia:
  - Once at screening
  - Once from Days 8 and 15 (optional, between the second and third isatuximab infusions, during Cycle 1 only)
  - Once from Days 22 to 29 (MRD [minimal residual disease])
  - Once during hematological recovery (including MRD; at least 48 hours after the last injection of granulocyte colony-stimulating factor [G-CSF], when neutrophils reach 1 G/L and platelet count 100 G/L; this last sample is recommended but not mandatory if peripheral blood blasts are present)
- Acute lymphoid leukemia:
  - Once at screening (including MRD baseline sample)
  - Once from Days 8 and 15 (optional, between the second and third isatuximab infusions)
  - Once from Days 36 to 43
  - Once during hematological recovery (at least 48 hours after the last injection of G-CSF, when neutrophils reach 1 G/L and platelet count 100 G/L; this last sample is recommended but not mandatory if peripheral blood blasts are present).

In case hematological recovery cannot be reached for any reason, in both AML and ALL participants, BM aspiration could be done at any time if investigator does not expect any more hematological change and/or urgent need for therapeutic strategy decision. Any additional BM aspirations will be performed at the Investigator's discretion and should be reported in the electronic case report form (eCRF).

The mandatory cytoreductive chemotherapy drugs to be administered before isatuximab infusion in patient with high tumor burden (WBC counts higher than 20 x 10^9/L and below 50 x 10^9/L with or without pulmonary leukostasis or significant organ involvement as per Investigator's judgement) at screening are cyclophosphamide (ALL), hydroxyurea (AML), or cytarabine (AML) and dexamethasone. Refer to Section 6.5.1 for details.

In order to have rapid control of the tumor burden, the administration of cyclophosphamide 200 mg/m² is allowed (optional for both AML and ALL cohorts). Dexamethasone 10 mg/m²/day (or equivalent) before the first study intervention administration (at least 3 times, on Days -3, -2, and -1) is mandatory for ALL cohorts as a part of study treatment and optional for AML cohort. Administration of dexamethasone on Day 1 is mandatory in both cohorts as part of isatuximab premedication.

Intrathecal prophylaxis is mandatory for all cohorts; the drugs that will be used (methotrexate/aracytine/steroids) are per investigator discretion (only one drug, or two or all three).

When dexamethasone is administered at 10 mg/m^2 per os, it can be divided in two daily doses. This does not apply to dexamethasone administration as part of isatuximab premedication.

AML combination therapies:

In the AML cohort, up to 2 cycles will be given as defined below. Refer to Figure 1 and Section 1.3 for days of investigational medicinal product (IMP) administration.

Cycle 1 (first induction):

- Isatuximab 20 mg/kg IV
- Dexamethasone or equivalent IV or oral administration (PO) 10 mg/m^2
- Fludarabine 30 mg/m² IV
- Cytarabine 2 g/m² IV
- Intrathecal prophylaxis as per site practice
- G-CSF (filgrastim or equivalent) 200 µg/m²/day SC or IV (optional)
- Anthracyclines (mandatory in Cycle 1 Day 8, optional in Cycle 1 Days 10 and 12 and in Cycle 2), after administration of fludarabine - either liposomal daunorubicin 60 mg/m^2 IV, nonliposomal daunorubicin 60 mg/m^2, or idarubicin 10 mg/m^2. The choice of anthracyclines is at the Investigator's discretion (either liposomal daunorubicin, nonliposomal daunorubicin, or idarubicin) and the same anthracycline should be used throughout the study.

Cycle 2 (second induction):

If the BM aspiration performed 1 week after the end of induction treatment shows less than 20% blasts, a second cycle of combination therapy can be administered if neutrophils of $\geq 500/mm^3$ and platelets of $\geq 50\ 000/mm^3$, while keeping the same schedule and doses. Anthracyclines are optional in Cycle 2 and will be administered at the Investigator's discretion.

T-ALL and B-ALL combination therapies:

In the ALL cohorts, the treatment period will include 1 induction and 1 consolidation cycle.

Induction cycle:

- Isatuximab 20 mg/kg IV
- Intrathecal chemotherapy (as per site's practice)
- Dexamethasone or equivalent IV or PO 10 mg/m^2
- Vincristine 1.5 mg/m^2 IV (should not exceed 2 mg per infusion in any patient)
- pegaspargase 1000 IU/m^2 (or L-asparaginase [Erwinase] 25 000 IU/m^2 only in case of confirmed hypersensitivity reaction to pegaspargase prior or during the study or loss of asparaginase activity and/or country availability and regulations, IM or IV
- Anthracyclines - either: doxorubicin 25 mg/m^2 IV or mitoxantrone 10 mg/m^2 IV

Consolidation cycle:

- Isatuximab 20 mg/kg
- Intrathecal chemotherapy (as per site's practice)
- Dexamethasone or equivalent IV or PO 10 mg/m^2
- Vincristine 1.5 mg/m^2 IV (should not exceed 2 mg per infusion in any patient)
- Methotrexate 1000 mg/m^2 IV
- pegaspargase 1000 IU/m^2 (or L-asparaginase [Erwinase] 25000 IU/m^2 only in case of confirmed hypersensitivity reaction to pegaspargase prior or during the study or loss of asparaginase activity and/or country availability and regulations), IM or IV
- Cyclophosphamide 440 mg/m^2 IV
- Etoposide 100 mg/m^2 IV

Before starting consolidation cycle, the patient must have neutrophils of $\geq 500/mm^3$ and platelets of $\geq 50\ 000/mm^3$.

Poststudy treatment period:

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

Number of participants:

Three cohorts of participants will be treated: T-ALL, B-ALL, and AML. Approximately 128 participants will be screened (32, 48, and 48, respectively) to achieve 104 assigned to study intervention (approximately 26, 39, and 39, respectively) and 96 evaluable participants for an estimated total of 24, 36, and 36 evaluable participants per cohort, respectively. In addition, for each cohort, at least 5 participants should be recruited for each of the following age groups: 28 days to 4 years, 5 to 11 years, and 12 to 18 years.

Intervention groups and duration:

Intervention groups and duration are described in the following section.

Investigational medicinal products

AML Cohort			
Investigational medicinal products	**Formulation**	**Route of administration**	**Dose regimen**
Isatuximab	Isatuximab drug product will be presented as a concentrate for solution for infusion in vials containing 20 mg/mL (500 mg/25 mL and 100 mg/5 mL) of isatuximab in 20 mM histidine, 10% (w/v) sucrose, and 0.02% (w/v) polysorbate 80 at pH 6.0. It is packed in 30 and 6 mL glass vials fitted with elastomeric closure. Each vial will contain a nominal content of 500 or 100 mg isatuximab. The fill volume has been established to ensure removal of 25 or 5 mL.	IV	20 mg/kg weekly on Days 1, 8, and 15 (mandatory for Cycles 1 and 2).
Dexamethasone or equivalent	Please refer to the product approved leaflet for further information.	IV or PO	Dexamethasone, is part of isatuximab premedication in the AML cohort, and will be given as premedication for prevention of infusion associated reactions before each administration of isatuximab, at least 15 to 30 minutes (but no longer than 60 minutes) prior to infusion Dexamethasone 10 mg/m^2 (maximum 20 mg) IV or PO on Days 1, 8, and 15 during the induction period (mandatory for Cycle 1 and before first isatuximab infusion Cycle 2). It could be optionally used for rapid control of tumor burden on Days -3, -2 and -1. When dexamethasone is administered at 10 mg/m^2 per os, it can be divided in two daily doses. This does not apply to dexamethasone administration as part of isatuximab premedication.

AML Cohort			
Investigational medicinal products	**Formulation**	**Route of administration**	**Dose regimen**
Fludarabine	Please refer to the product approved leaflet for further information.	IV	30 mg/m² on Days 8 to 12, inclusive (mandatory for Cycles 1 and 2).
Cytarabine	Please refer to the product approved leaflet for further information.	IV	2 g/m² on Days 8 to 12, inclusive (mandatory for Cycles 1 and 2).
Liposomal daunorubicin	Please refer to the package insert for further information.	IV	60 mg/m², mandatory for Cycle 1 Day 8, optional for Cycle 1 Days 10 and 12, and optional for Cycle 2.
Nonliposomal daunorubicin	Please refer to the product approved leaflet for further information.	IV	60 mg/m², mandatory for Cycle 1 Day 8, optional for Cycle 1 Days 10 and 12, and optional for Cycle 2.
Idarubicin	Please refer to the product approved leaflet for further information.	IV	10 mg/m², mandatory for Cycle 1 Day 8, optional for Cycle 1 Days 10 and 12, and optional for Cycle 2.
Granulocyte colony-stimulating factor (Filgrastim or equivalent)	Please refer to the product approved leaflet for further information.	SC or IV	200 µg/m²/day on Days 7 to 12, inclusive; can be continued until neutrophil recovery (optional for Cycles 1 and 2).

AML = acute myeloid leukemia; EU = Europe; IV = intravenous(ly); PO = oral; SC = subcutaneous; w/v = weight per volume.

ALL cohorts			
Investigational medicinal products	**Formulation**	**Route of administration**	**Dose regimen**
Isatuximab	Isatuximab drug product will be presented as a concentrate for solution for infusion in vials containing 20 mg/mL (500 mg/25 mL and 100 mg/5 mL) of isatuximab in 20 mM histidine, 10% (w/v) sucrose, and 0.02% (w/v) polysorbate 80 at pH 6.0. It is packed in 30 and 6 mL glass vials fitted with elastomeric closure. Each vial will contain a nominal content of 500 or 100 mg isatuximab. The fill volume has been established to ensure removal of 25 or 5 mL.	IV	20 mg/kg weekly Days 1, 8, 15, 22, 29, 43, and 57.
Dexamethasone or equivalent	Please refer to the product approved leaflet for further information.	IV or PO	Dexamethasone, being part of both backbone treatment regimen and isatuximab premedication, before each administration of isatuximab, at least 15 to 30 minutes (but no longer than 60 minutes) prior to infusion, will be given as premedication for prevention of infusion associated reactions consisting of

ALL cohorts			
Investigational medicinal products	**Formulation**	**Route of administration**	**Dose regimen**
			dexamethasone 10 mg/m² (maximum 20 mg) IV or PO on Days -3, -2, and -1 before isatuximab administration, Days 1, 8, 15 to 19, 22, and 29 to 33 during the induction period, and on Days 43 to 47 and 57 during the consolidation period.
Mitoxantrone	Please refer to the product approved leaflet for further information.	IV	10 mg/m² on Days 8 and 9 of the induction period.
Doxorubicin	Please refer to the product approved leaflet for further information.	IV	25 mg/m² on Days 10, 17, 24, and 31 of the induction period.
Vincristine	Please refer to the product approved leaflet for further information.	IV	1.5 mg/m² on Days 10, 17, 24, and 31 during the induction period (should not exceed 2 mg per infusion in any patient); on Day 38 during the consolidation period.
Pegaspargase	Please refer to the product approved leaflet for further information.	IM or IV	1000 IU/m² on Days 10 and 24 during the induction period; Day 44 during the consolidation period.
L-asparaginase (Erwinase)	Please refer to the product approved leaflet for further information.	IM or IV	25000 IU/m² on Days 8, 10, 12, 15, 17, 19, 22, 24, 26, 29, 31, 33 during induction and days 43, 45, 47, 50, 52, 54 during consolidation, only in case of confirmed hypersensitivity reaction to pegaspargase prior or during the study or loss of asparaginase activity and/or country availability and regulations.
Cyclophosphamide	Please refer to the product approved leaflet for further information.	IV	440 mg/m² on Days 50 to 54 inclusive, during the consolidation period.
Etoposide	Please refer to the product approved leaflet for further information.	IV	100 mg/m² on Days 50 to 54, inclusive, during the consolidation period.
Methotrexate	Please refer to the product approved leaflet for further information.	IV	1000 mg/m² on Day 43 during the consolidation period.

ALL = acute lymphoblastic leukemia; IM = intramuscular(ly); IV = intravenous(ly); PO = oral; w/v = weight per volume.

Noninvestigational Medicinal Products

The recommended isatuximab premedication agents are: montelukast, diphenhydramine (or equivalent), methylprednisolone, and acetaminophen (paracetamol) PO. Taking into consideration the disease context and the frequent use of steroids in acute leukemia, methylprednisolone will be replaced by dexamethasone.

The mandatory cytoreductive chemotherapy drugs to be administered before isatuximab infusion in patient with high tumor burden at screening are cyclophosphamide (ALL), hydroxyurea (AML), or cytarabine (AML) and dexamethasone. Refer to Section 6.5.1 for details.

Noninvestigational medicinal products	Formulation[a]	Route of administration	Dose regimen
Paracetamol (acetaminophen)		PO	Paracetamol (acetaminophen) will be given 15 to 30 minutes (but no longer than 60 minutes) before isatuximab infusion and at dose per weight as follows: ≤10 kg: 7.5 mg/kg, >10 to 50 kg: 15 mg/kg, and >50 kg: 1 g.
Diphenhydramine or equivalent		IV	Diphenhydramine or equivalent will be given at a dose of 1 mg/kg, 15 to 30 minutes (but no longer than to 60 minutes) before isatuximab infusion.
Montelukast		PO	Montelukast should be given to a child under adult supervision, before isatuximab infusion. The recommended dosage for pediatric participants: • Montelukast is not recommended for participants less than 2 years of age • 4 mg for participants 2 to 5 years of age • 5 mg for participants of 6 to 14 years of age • 10 mg for participants ≥15 years of age
Folinic acid (Leucovorin®)		PO, IM, or IV	Folinic acid should be administered 48 hours after the start of methotrexate infusion at a dose of 30 mg/m^2 PO, IM, or IV and 15 mg/m^2 at 54 hours. Folinate rescue can be modified at the Investigator's discretion.
Dexamethasone		PO or IV	Dexamethasone is part of isatuximab premedication in the AML cohort only, and will be given as premedication for prevention of infusion associated reactions before each administration of isatuximab, at least 15 to 30 minutes (but no longer than 60 minutes) prior to infusion. Dexamethasone 10 mg/m^2 (maximum 20 mg) IV or PO on Days 1, 8, and 15 during the induction period (mandatory for Cycle 1 and before first isatuximab infusion at Cycle 2).

IM = intramuscularl(ly); IV = intravenous(ly); PO = oral.

a Noninvestigational medicinal products will be locally sourced and the formulation may vary.

Statistical considerations:

Sample size determination:

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

T-ALL: a maximum of 24 evaluable participants will be enrolled in this cohort. This sample size will provide 80% power to reject the null hypothesis that the complete response (CR + CRi) rate

is ≤60% if the CR rate is ≥80%, based on a 1-sided exact binomial test at a significance level of 0.1:

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

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

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

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

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

Close safety monitoring of each participant is planned, and an independent Data Monitoring Committee (DMC) will regularly monitor participant safety. A first safety review by the DMC is planned after the first 10 participants will have completed at least 1 induction cycle.

Main analysis population: the all-treated (AT) population will include all participants who receive at least 1 dose (even incomplete) of study intervention. This population is the primary population for safety parameters. The evaluable population will include participants from the AT population who received at least 1 full dose of isatuximab in Cycle 1 and who had at least one valid response value that is evaluable (5 infusions for ALL cohorts and 3 infusions for AML cohort). The evaluable population will be the primary population for the analyses of efficacy parameters. The PK population will include all participants from the AT population with at least one available concentration post-baseline (whatever the cycle and even if dosing is incomplete) with adequate documentation of dosing and sampling dates and times. The antidrug antibody (ADA) evaluable population will include all participants from the AT population with at least 1 nonmissing ADA result during the on-study observation period.

Response to treatment that will be analyzed is the response after 1 full dose of isatuximab in Cycle 1 (induction).

General statistical approach

Unless otherwise specified, analyses will be descriptive and performed on the AT population except for the analyses of efficacy endpoints that will utilize the evaluable population. Tables and listings will be presented for each cohort separately.

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

Analysis of primary endpoint:

The CR rate, defined as the proportion of participants with CR or CR with incomplete peripheral recovery (CRi), will be summarized with descriptive statistics on the evaluable population. Confidence intervals will be computed using the Clopper-Pearson method.

Analysis of secondary endpoints:

The duration of response (DOR), event free survival (EFS), and overall survival (OS) will be analyzed using the Kaplan-Meier method. Among participants who achieved CR or CRi, the number and percentage of participants by MRD status will be provided in the evaluable population.

The overall response rate (ORR) will be summarized with descriptive statistics. Confidence intervals will be computed using the Clopper-Pearson method.

Individual PK parameters for isatuximab will be summarized.

Receptor density and occupancy data: The descriptive statistics of receptor density and receptor occupancy will be summarized by cohort and overall as well as for best overall response (responders versus non-responders) will be calculated.

Analysis of safety endpoints:

Number (%) of participants experiencing treatment-emergent adverse events (TEAEs) by primary system organ class and preferred term will be summarized by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 5.0 grade (all grades and Grade ≥3) for the AT population. Similar tables will be prepared for treatment-related TEAEs, AEs of special interest, TEAEs leading to treatment discontinuation, TEAEs leading to dose modification, serious TEAEs, TEAEs with fatal outcome, and adverse events (AEs)/serious AEs (SAEs) occurring during the post-treatment dosing period. For participants with multiple occurrences of the same preferred term, the most severe grade within the observation period analyzed will be used.

Number (%) of participants experiencing infusion reactions by primary system organ class and preferred term will be summarized by NCI-CTCAE Version 5.0 grade.

All the laboratory abnormalities will be graded according to the NCI-CTCAE Version 5.0, when applicable. Number (%) of participants with laboratory abnormalities (ie, all grades and by grades) using the worst grade during the on-treatment period will be provided for the AT population.

Analysis of tertiary/exploratory endpoints:

The number and the percentage of participants with positive/negative ADA will be provided.

Cut-off dates/Planned database lock date

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

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

Data Monitoring Committee: Yes

1.2 SCHEMA

Figure 1 - Graphical study design: AML cohort

Agent	Dosage	Application	Screening	Week 1	Week 2	Week 3	Week 4	Week 5	Hematological recovery
Dexamethasone	10 mg/m^2 (max: 20 mg)	IV or PO							
Isatuximab	20 mg/kg	IV							
Fludarabine[a]	30 mg/m^2	IV							
Cytarabine[b]	2 g/m^2	IV							
Anthracycline[c,d]	Investigator discretion[c]	IV							
G-CSF[e] (optional)	200 µg/m^2	SC or IV							
IT chemotherapy	As per site practice	IT							
		Day	-21 -3 -2 -1	1 2 3 4 5 6 7	8 9 10 11 12 13 14	15 16 17 18 19 20 21	22 23 24 25 26 27 28	29	

Screening: BMA

Days 8 to 15: optional BMA only in Cycle 1

Days 22 to 29: BMA + optional MRD

BMA + MRD

AML = Acute Myeloid Leukemia; BMA = bone marrow aspiration; G-CSF = granulocyte colony-stimulating factor; IT = intrathecal; IV = intravenous; max = maximum; MRD = minimal residual disease; PO = oral; SC = subcutaneous.

a Fludarabine is given as a 30-minute infusion after G-CSF administration, if any.

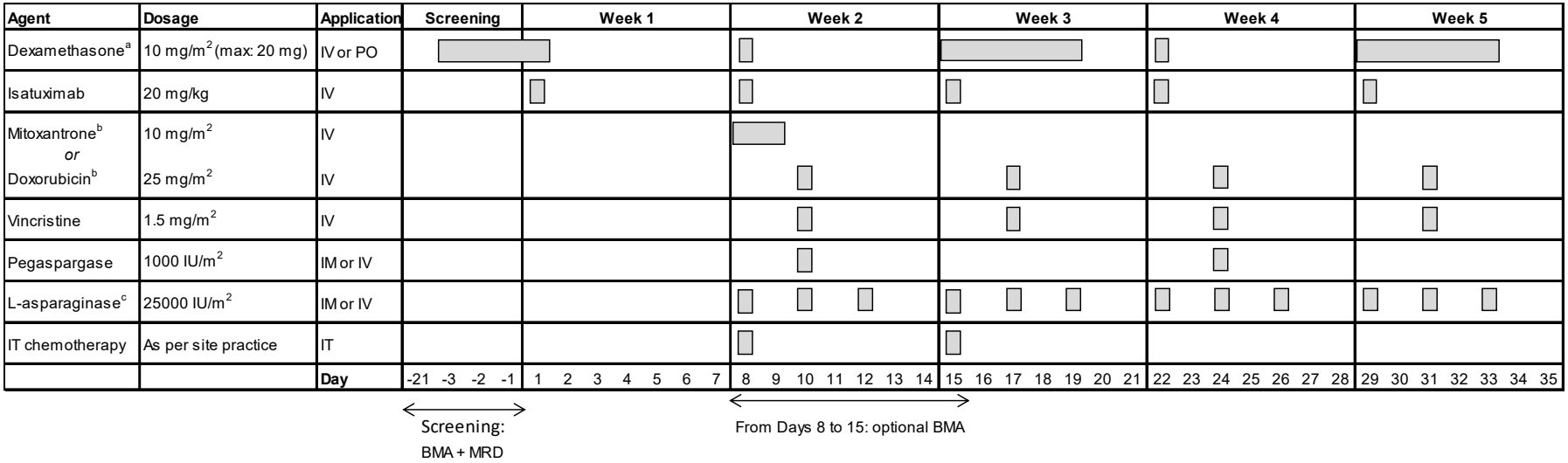
b Cytarabine is given as a 4-hour infusion, beginning 4 hours after start of fludarabine.

c Anthracycline (a choice of liposomal daunorubicin 60 mg/m^2, nonliposomal daunorubicin 60 mg/m^2, or idarubicin 10 mg/m^2) is given after administration of fludarabine.

d Anthracycline administration on Day 8 in Cycle 1 is mandatory. Administrations on Cycle 1 Days 10 and 12 and on Cycle 2 are at the Investigator's discretion.

e G-CSF is optional and can be continued until neutrophil recovery.

Figure 2 - Graphical study design: ALL cohorts - induction



ALL = Acute Lymphoblastic Leukemia; BMA = bone marrow aspiration; IM = intramuscular; IT = intrathecal; IV = intravenous(ly); max = maximum; MRD = minimal residual disease; PO = oral.

a Dexamethasone is a part of both backbone treatment regimen and isatuximab premedication.

b Mitoxantrone and Doxorubicin are given IV over 15 minutes.

c Only in case of intolerance to pegaspargase prior or during the study or loss of asparaginase activity if known and/or country availability and regulations. If patient will present intolerance to Pegaspargase at Day 10, L-asparaginase (Erwinase) should be started at Week 4, in order to avoid cumulative toxicities, unless Investigator's judgement is that dose infused at Day 10 was not significant. In this case Erwinase can be started earlier.

Figure 3 - Graphical study design - ALL cohorts - consolidation

Agent	Dosage	Application	Week 6	Week 7	Week 8	Week 9	Hematological recovery
Dexamethasone[a]	10 mg/m^2 (max: 20 mg)	IV or PO					
Isatuximab	20 mg/kg	IV					
Methotrexate[b]	1000 mg/m^2	IV					
Cyclophosphamide[c]	440 mg/m^2	IV					
Etoposide[d]	100 mg/m^2	IV					
Vincristine	1.5 mg/m^2	IV					
Pegaspargase	1000 IU/m^2	IM or IV					
L-asparaginase[e]	25000 IU/m^2	IM or IV					
IT chemotherapy	As per site practice	IT					
		Day	36 37 38 39 40 41 42	43 44 45 46 47 48 49	50 51 52 53 54 55 56	57	

From Days 36 to 43: BMA + MRD

BMA + MRD

ALL = Acute Lymphoblastic Leukemia; BMA = bone marrow aspiration; IM = intramuscular; IT = intrathecal; IV = intravenous; max = maximum; MRD = minimal residual disease; PO = oral.

a Dexamethasone is a part of both backbone treatment regimen and isatuximab premedication.

b Methotrexate is infused over 36 hours and calcium folinate rescue started 48 hours from start of infusion.

c Cyclophosphamide is given as a 1-hour infusion.

d Etoposide is given as a 2-hour infusion.

e Only in case of intolerance to pegaspargase prior or during the study or loss of asparaginase (Erwinase) activity if known and/or country availability and regulations. If patient will present intolerance to Pegaspargase at Day 10, L-asparaginase (Erwinase) should be started at Week 4, in order to avoid cumulative toxicities, unless Investigator's judgement is that dose infused at Day 10 was not significant. In this case Erwinase can be started earlier.

1.3 SCHEDULE OF ACTIVITIES (SOA)

AML cohort

Procedures	Screening				Induction period												FU
	-D21 to -D1	-D3	-D2	-D1	D1	D2	D3	D7	D8	D9	D10	D11	D12	D15	D22-29	Hematological recovery	EOT	
Informed consent	X																	
Inclusion/exclusion criteria	X																	
Demography[a]	X																	
Physical examination[b]	X				Physical examination every day during hospitalization or at each visit until hematological recovery												X	
Medical history	X																	
Past and current medical conditions[c]	X																	
CNS leukemia assessment	X																	
Blood type phenotyping/genotyping, screen[d]	X	IAT to be tested once after Cycle 1 Day 1[d]																
Pregnancy test (WOCBP only)[e]	X				X	Monthly during the treatment period											X	X
HIV, hepatitis B and C[f]	X				As clinically indicated													
Hematology[g]	X				Every 2 days until recovery												X	
Coagulation[h]	X				Once weekly until recovery and if clinically indicated												X	
Biochemistry[i]	X				Twice weekly until recovery												X	
TSH, free/total T3 and free T4	X																	
Ferritin, CRP	X				To be repeated in case of CRS occurrence of any grade, at 3 days and 1 week after CRS occurrence													

Procedures	Screening				Induction period													FU
	-D21 to -D1	-D3	-D2	-D1	D1	D2	D3	D7	D8	D9	D10	D11	D12	D15	D22-29	Hematological recovery	EOT	
Cytokines[t]	X				To be repeated in case of CRS occurrence of any grade, at 3 days and 1 week after CRS occurrence													
Urinalysis[j]	X				Once weekly until recovery												X	
12-lead ECG	X				If clinically indicated											X	X	
Vital signs[k]	X				X				X					X				
Chest X-ray[u]	X				X	If clinically indicated												
Cardiac assessment[l]	X				If clinically indicated											X	X	
Bone marrow for disease assessment[m]	X								Optional, during Cycle 1 only						X	X		
MRD assessment[n]															X	X		
Extramedullary disease assessment[o]	X (Optional)															X (Optional)	X (Optional)	
Lumbar puncture with IT chemotherapy	X							X										
Isatuximab administration					X				X					X				
Dexamethasone or equivalent administration		X	X	X	X				X					X				
Anthracycline administration[p]									X		X (Optional)		X (Optional)					
Fludarabine administration									X	X	X	X	X					
Cytarabine administration									X	X	X	X	X					
G-CSF administration (Optional)								X	X	X	X	X	X					

Procedures	Screening				Induction period													FU
	-D21 to -D1	-D3	-D2	-D1	D1	D2	D3	D7	D8	D9	D10	D11	D12	D15	D22-29	Hematological recovery	EOT	
AE/SAE review[q]	X	X	X	X	Continuously													X
Concomitant medication[s]	X	X	X	X	Continuously													
PK					See flowchart (Table 1)													
ADA					See flowchart (Table 1)													
CD38 biomarker					See flowchart (Table 1)													
Disease status																		X

ALL cohorts: Screening and Induction

Procedures	Screening				Induction																			
	-D21 to -D1	-D3	-D2	-D1	D1	D3	D8	D9	D10	D12	D15	D16	D17	D18	D19	D22	D24	D25	D26	D29	D30	D31	D32	D33
Informed consent	X																							
Inclusion/exclusion criteria	X																							
Demography[a]	X																							
Physical examination[b]	X				Physical examination every day during hospitalization or at each visit until hematological recovery																			
Medical history	X																							
Past and current medical conditions[c]	X																							
CNS leukemia assessment	X																							
Blood type phenotyping/genotyping, screen[d]	X	IAT to be tested once after Day 1[d]																						
Pregnancy test (WOCBP only)[e]	X				X	Monthly during the treatment period																		
HIV, hepatitis B and C[f]	X				As clinically indicated																			
Hematology[g]	X				Every 2 days until recovery																			
Coagulation[h]	X				Once per week until recovery and if clinically indicated																			
Biochemistry[i]	X				Twice weekly until recovery																			
TSH, free/total T3, and free T4	X																							
Ferritin, CRP	X	To be repeated in case of CRS occurrence of any grade, at 3 days and 1 week after CRS occurrence																						
Cytokines[t]	X	To be repeated in case of CRS occurrence of any grade, at 3 days and 1 week after CRS occurrence																						
Urinalysis[j]	X				Once per week until recovery																			
12-lead ECG	X				If clinically indicated																			
Vital signs[k]	X				X		X				X					X				X				
Chest X-ray[u]	X				X	If clinically indicated																		

Procedures	Screening				Induction																			
	-D21 to -D1	-D3	-D2	-D1	D1	D3	D8	D9	D10	D12	D15	D16	D17	D18	D19	D22	D24	D25	D26	D29	D30	D31	D32	D33
Cardiac assessment[l]	X				If clinically indicated																			
Bone marrow for disease assessment[m]	X						Optional																	
MRD assessment[n]	X																							
Extramedullary disease assessment[o]	X (Optional)																							
Lumbar puncture with IT chemotherapy	X						X				X													
Isatuximab administration					X		X				X					X				X				
Dexamethasone or equivalent administration		X	X	X	X		X				X	X	X	X	X	X				X	X	X	X	X
Mitoxantrone administration (if doxorubicin is not used)							X	X																
Doxorubicin administration (if mitoxantrone is not used)									X				X				X					X		
Vincristine administration									X				X				X					X		
Pegaspargase administration[q]									X								X							
L-asparaginase (Erwinase) administration[q]							X		X	X	X		X		X	X	X		X	X		X		X
AE/SAE review[r]	X	X	X	X	Continuously																			
Concomitant medication[s]	X	X	X	X	Continuously																			
PK					See flowchart (Table 2)																			
ADA					See flowchart (Table 2)																			

ALL cohorts: Consolidation and Follow-up

Procedures	Consolidation															FU
	D36	D38	D43	D44	D45	D46	D47	D50	D51	D52	D53	D54	D57	Hematological recovery	EOT	
Physical examination[b]	Physical examination every day during hospitalization or at each visit until hematological recovery														X	
Hematology[g]	Every 2 days until recovery														X	
Coagulation[h]	Once per week until recovery and if clinically indicated														X	
Biochemistry[i]	Twice weekly until recovery														X	
Ferritin, CRP	To be repeated in case of CRS occurrence of any grade, at 3 days and 1 week after CRS occurrence															
Cytokines[t]	To be repeated in case of CRS occurrence of any grade, at 3 days and 1 week after CRS occurrence															
Urinalysis[j]	Once per week until recovery														X	
12-lead ECG	If clinically indicated													X	X	
Vital signs[k]			X										X			
Blood type phenotyping/genotyping, screen[d]	IAT to be tested once after Day 1[d]															
Pregnancy test (WOCBP only)[e]	Monthly during the treatment period														X	X
HIV, hepatitis B and C[f]	As clinically indicated															
Chest X-ray[u]	If clinically indicated															
Cardiac assessment[l]	If clinically indicated													X	X	
Bone marrow for disease assessment[m]	X (from Days 36 to 43)													X		
MRD assessment[n]	X (from Days 36 to 43)													X		
Extramedullary disease assessment[o]														X (Optional)	X (Optional)	

Procedures	Consolidation															FU
	D36	D38	D43	D44	D45	D46	D47	D50	D51	D52	D53	D54	D57	Hematological recovery	EOT	
Lumbar puncture with IT chemotherapy			X													
Isatuximab administration			X										X			
Dexamethasone or equivalent administration			X	X	X	X	X						X			
Vincristine administration		X														
Methotrexate administration			X													
Pegaspargase administration[q]				X												
L-asparaginase (Erwinase) administration[q]			X		X		X	X		X		X				
Cyclophosphamide administration								X	X	X	X	X				
Etoposide administration								X	X	X	X	X				
AE/SAE review[r]	Continuously															X
Concomitant medication[s]	Continuously															
PK	See flowchart (Table 2)															
ADA	See flowchart (Table 2)															
CD38 biomarker	See flowchart (Table 2)															
Disease status																X

AABB = American Association of Blood Banks; ADA = antidrug antibody; AE = adverse event; ALL = acute lymphoblastic leukemia; AML = acute myeloid leukemia; aPTT = activated partial thromboplastin time; B = B-cell; BM = bone marrow; CNS = central nervous system; CR = complete response; CRi = complete response with incomplete peripheral recovery; CT = computed tomography; D = Day; DNA = deoxyribonucleic acid; DTT = dithiothreitol; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic case report form; EOT = end of treatment; FU = follow-up; G-CSF = granulocyte colony-stimulating factor; HIV = human immunodeficiency virus; HLA = human leukocyte antigen; IAT = indirect antiglobulin test; IMP = investigational medicinal product; INR = international normalized ratio; IT = intrathecal; IV = intravenous(ly); LBL = lymphoblastic lymphoma; LDH = lactic acid dehydrogenase; MRD = minimal residual disease; MUGA = multigated acquisition scan; PET = positron emission tomography; PK = pharmacokinetics; PT = prothrombin time; RNA = ribonucleic acid; SAE = serious adverse event; T = T-cell; WOCBP = women of childbearing potential.

a **Demography**: date of birth (age derived), gender, and race (if local regulation allows).

b **Physical examination**: Examination of major body systems including weight, neurological examination, digestive, skin/mucosae, mediastinal, testicular involvements, respiratory, hepatomegaly, splenomegaly, lymphadenopathy, and ECOG or Lansky score (this assessment will be collected during treatment if clinically relevant). Height will be measured only at screening.

c **Past and current medical condition**: date of initial diagnosis, type of disease (T-ALL/T-LBL, B-ALL, B-LBL, AML, immunophenotyping and cytogenetic, molecular profile), previous antileukemia treatment (reason for discontinuation, date of relapse, and best overall response to prior treatments), risk group as per site institutional practice (including clinical factors but also cytogenetic and molecular ones; as an example, but not limited to: MLL rearrangement/KMT2A rearrangement; Ph+ [BCR/ABL translocation]; Hypodiploidy; IKZF1 del; TCF3-HLF [t(17,19)], Abnormalities chromosome 3, 5, 7; FLT3 mutated; 11q23 [KMT2A] rearrangement; T(6,9); TP53 mut).

d **Blood type phenotyping/genotyping**: Blood typing and complete blood phenotyping (C,c; E,e; Kell. Kidd; Duffy; S,s is recommended, if not available, the site's standard will be followed) if not already done, and antibody screening (IAT) to be obtained prior to the start of the study treatment. After the start of the study treatment, a new IAT assessment will be performed once. If the second test is positive, a DTT test should be performed (in accordance with Section 10.6.6). Results of IAT (and DTT test, if applicable) will be recorded in the eCRF, including those performed prior to any transfusion during study intervention. Transfusions are to be recorded in the eCRF. The transfusion service should be made aware that the participant is receiving an antiCD38 treatment (isatuximab). During the study intervention, 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 participant card. Participants should keep their study participant card with their blood type card together throughout the duration of the study intervention.

e **Pregnancy testing** should be carried out in WOCBP as follows: for ALL induction: within 2 weeks prior to first dose, Day 1 (predose), and Day 30 (predose). For ALL consolidation: on Day 57 (predose), end of treatment (30 days after last dose), and monthly during the follow-up period for 180 days (6 months) after the last dose of isatuximab, or 12 months after the last dose of cyclophosphamide. For AML: within 2 weeks prior to first dose, Cycle 1 Day 1 (predose), Cycle 2 Day 1 (predose), end of treatment (30 days after last dose), and monthly during the follow-up period for 180 days (6 months) after the last dose of isatuximab, or 12 months after the last dose of cyclophosphamide.

f **Viral serologies**: HIV serology will be collected in countries where required by local regulations. Screening with serological tests for hepatitis B and C should be done prior to randomization/enrollment (HBsAg, anti-HBs, anti-HBc (total and IgM), anti-HCV, HCV RNA level) or at any time if not performed within 1 year. Patient not having been tested for HBV/HCV at screening that are still on treatment at the time of the amended protocol 4 will need to be tested additionally for HBsAg, anti HBs, anti-HBc (total and IgM), anti-HCV, HCV RNA level. Patients with anti-HBc positive (HBsAg positive patients being not eligible), HBV DNA testing by PCR will also be done at baseline. In case HBV vaccination will be started before first study treatment administration, anti-HBs should be monitored at 1, 2 and 3 months after end of vaccination.

g **Hematology**: Hemoglobin, hematocrit, white blood cell count with differential, percentage of blasts, platelet count (please see Table 15 for a complete list). Hematology sample collection is recommended every 2 days, but mandatory at least weekly. Hematology test including WBC with differential is mandatory for all patients prior to the first isatuximab infusion on Day 1. Hematology test should be assessed prior to the first isatuximab infusion. In case of high tumor burden at screening requiring cytoreductive chemotherapy or occurrence of CRS event, WBC with differential count must be repeated every day.

h **Coagulation**: D-dimer, fibrinogen, PT (and INR), and aPTT. In ALL patients on treatment with pegaspargase or L-asparaginase (Erwinia) weekly (Section 10.8) monitoring of INR, PTT, fibrinogen and AT-III must be performed and fibrinogen; AT-III may be substituted if necessary.

i **Biochemistry**: glucose (fasting; if the participant has not fasted overnight, glucose should not be measured), albumin, total protein, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, bilirubin (total and direct), LDH, sodium, potassium, total calcium, corrected and ionized calcium (corrected calcium = total calcium level in milligrams per deciliter + 0.8 × [4 albumin in grams per deciliter]; ionized calcium level in milligrams per deciliter = total calcium level in milligrams per deciliter + 0.02*[40 - albumin in grams per deciliter]), phosphorus, uric acid, blood urea nitrogen, serum creatinine, amylase (please see Table 15 for a complete list). Prior to the first infusion on Day 1, potassium, phosphorus, uric acid, corrected calcium are to be assessed to rule out tumor lysis syndrome. If it is not possible to organize this test (potassium, phosphorus, uric acid, corrected calcium) to be done and assessed prior to infusion on Day 1, it can be done on Day -1 or Day -2, and only in case this is not possible – on Day -3. In case of CRS/TLS occurrence, potassium, phosphorus, uric acid, corrected calcium, blood urea nitrogen, creatinine are to be repeated every day until resolution of the event.

j **Urinalysis**: Dipstick only. If other analytes are collected based on clinical context, they must be reported in the eCRF

k **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 isatuximab infusion, 2 hour after every isatuximab infusion and as clinically indicated. In case of high tumor burden at screening requiring cytoreductive chemotherapy or occurrence of CRS event, continuous monitoring of vital signs is required as per site clinical practice.

l **Cardiac assessment**: Left ventricular ejection fraction measured by echocardiogram, cardiac scintigraphy, or MUGA.

m **Bone marrow for disease assessment**: To be performed once at screening, once between Days 8 and 15 (optional), once at the end of induction for ALL (first week of consolidation), once between Days 22 and 29 for AML, and once at the time of complete hematological recovery (at least 48 hours after the last injection of G-CSF, when neutrophils reach 1 G/L and platelet count 100 G/L). In case hematological recovery cannot be reached for any reason, in both AML and ALL participants, BM aspiration could be done at any time if investigator does not expect any more hematological change and/or urgent need for therapeutic strategy decision. No BM assessment is necessary if nonresponse or progressive disease can be diagnosed with peripheral blood evaluation, or if the BM assessment is considered noncontributory by the Investigator. Any additional BM aspirations will be performed at the Investigator's discretion and should be reported in the eCRF. If BM aspirate fails, BM biopsy could be an option.

n **MRD assessment:** For ALL, to be performed with BM aspiration at screening and with peripheral blood samples at the end of induction (between Days 36 and 43), at the time of hematological recovery, and/or at the time of each BM aspiration for disease assessment if CR or CRi is achieved. For AML, to be performed with BM aspiration samples at the time of hematological recovery or between Days 22 and 29, and/or at the time of each BM aspiration for disease assessment if CR or CRi is achieved.

o **Extramedullary disease assessment**: For ALL, CT, PET-CT or PET-MRI scans are suggested to be performed at screening and at hematological recovery or at EOT (if no hematological recovery) if lymphomatous involvement is suspected. If not done, PET-CT or PET-MRI scan is suggested to be performed at screening if lymphomatous involvement is present. If positive at screening, PET-CT or PET-MRI will be repeated at the time of CR in BM. For AML, physical examination may be used for specific locations when imaging is not appropriate (ex cutaneous location). CT, PET-CT or PET-MRI can be performed if clinically indicated.

p **Anthracycline**: The choice of anthracycline (liposomal daunorubicin, nonliposomal daunorubicin, or idarubicin) is at the Investigator's discretion and the same anthracycline should be used throughout the study. The administration of Day 8 in Cycle 1 is mandatory. Other administrations of anthracycline, including Day 8 in Cycle 2, are at the Investigator's discretion.

q Only in case of confirmed hypersensitivity to pegaspargase prior or during the study or loss of asparaginase and/or country availability and regulations L-asparaginase (Erwinase) may be used. Hypersensitivity to pegaspargase and/or loss of asparaginase activity should be documented in the eCRF.

r **AE/SAE**: The period of safety observation extends from the date informed consent is signed, until the time of hematological recovery 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 study intervention that are new during the follow-up period will be reported and followed until recovery or stabilization.

s **Concomitant treatments**: All treatments being taken by the participant for up to 7 days prior to the first dose of study intervention and at any time during the treatment period and for up to hematological recovery are regarded as prior and concomitant treatments. Then, only further anticancer therapy will be reported.

t Following **cytokines** will be collected at baseline – proinflammatory cytokine panel (including interleukin IL2, IL6, IL8, IL10, interferon (IFN) γ, tumor necrosis factor (TNF) alpha). In case of CRS occurrence, cytokines are to be repeated 3 days and 1 week after CRS occurrence.

u **Chest X-ray**: Prior to the first infusion on Day 1, should be done and assessed. If it is not possible to organize on Day 1 prior it can be done on Day -1 or Day -2. In case of high tumor burden at screening or occurrence of CRS event, chest X-ray must be repeated every day. CT-scan can also be used based on site's clinical practice.

PK and PD flowcharts

Table 1 - PK and PD flowchart - AML cohort

		Study period									
Procedure		Induction									FUP
Day within cycle		D1			D4	D8	D15			30 days after last isatuximab admininistration (±5 days)	90 days after last isatuximab administration (±5 days)
Time (decimal hours)		SOI	EOI	EOI +4 h	72 h	SOI	SOI	EOI	EOI +1 h		
Indicative clock time		8:00 AM	12:00 PM	4:00 PM	8:00 AM	8:00 AM	8:00 AM	12:00 PM	1:00 PM		
Time window		-120 min, SOI	±10 min	±30 min	±5 h	-10 min, SOI	-10 min, SOI	±10 min	±10 min		
Treatment											
Isatuximab (IV infusion)		X----------X				X	X----------X				
Pharmacokinetics[a]											
Isatuximab		P00[e]	P01[c]	P02	P03	P04[e]	P05[e]	P06[c]	P07	PF0	
Immunogenicity											
Antidrug antibody[d]		AB00[e]					AB01[e]			ABF0	ABF1
Pharmacodynamics											
CD38 Receptor density and occupancy in blood		X[b]					X[b]				

AB = antibody; ABF = antibody at end of treatment or follow-up; ADA = antidrug antibody; D = Day; EOI = end of infusion; FUP = follow-up period (post-treatment safety); h = hour; ID = identification; IV = intravenous; min = minute; P = plasma; PF = plasma at end of treatment or follow-up; PK = pharmacokinetic; SOI = start of infusion.

Note: In case a Cycle 2 (second induction) is administered, PK samples must be taken only at predose on Days 1 and 15.

a Refer to the Laboratory Manual for sample collection, processing, and shipping procedures.

b Sample should be collected just before isatuximab administration or up to 3 days prior to it.

c Sample collected just before actual end of infusion.

d If the ABF1 ADA result is positive or inconclusive, no additional ADA are required.

e PK and ADA predose samples must be collected just before administration of isatuximab.

Table 2 - PK and PD flowchart ALL cohorts

		Study period													
Procedure		**Induction**										**Consolidation**			**FUP**
Day within cycle		**D1**			**D4**	**D8**	**D15**	**D22**	**D29**			**D43**	**D57**	**30 days after last isatuximab administration (±5 days)**	**90 days after last isatuximab administration (±5 days)**
Time (decimal hours)		SOI	EOI	EOI +4 h	72 h	SOI	SOI	SOI	SOI	EOI	EOI +1 h	SOI	SOI		
Indicative clock time		8:00 AM	12:00 PM	4:00 PM	8:00 AM	8:00 AM	8:00 AM	8:00 AM	8:00 AM	12:00 PM	1:00 PM	8:00 AM	8:00 AM		
Time window		-120 min, SOI	±10 min	±30 min	± 5 h	-10 min, SOI	-10 min, SOI	-10 min, SOI	-10 min, SOI	±10 min	±10 min	-10 min, SOI	-10 min, SOI		
Treatment															
Isatuximab (IV infusion)		X----------	X			X	X	X	X			X	X		
Pharmacokinetics[a]															
Isatuximab		P00[e]	P01[c]	P02	P03	P04[e]	P05[e]	P06[e]	P07[e]	P08[c]	P09	P10[e]	P11[e]	PF0	
Immunogenicity															
Antidrug antibody[d]		AB00[e]					AB02[e]		AB03[e]			AB04[e]	AB05[e]	ABF0	ABF1
Pharmacodynamics															
CD38 Receptor density and occupancy in blood		X[b]					X[b]								

AB = antibody; ABF = antibody at end of treatment or follow-up; ADA = antidrug antibody; D = Day; EOI = end of infusion; FUP = follow-up period (post-treatment safety); h = hour; ID = identification; IV = intravenous; min = minute; P = plasma; PF = plasma at end of treatment or follow-up; PK = pharmacokinetic; SOI = start of infusion.

a Refer to the Laboratory Manual for sample collection, processing, and shipping procedures.

b Sample should be collected just before isatuximab administration or up to 3 days prior to it.

c Sample collected just before actual end of infusion.

d If the ABF1 ADA result is positive or inconclusive, no additional ADA are required.

e PK and ADA predose samples must be collected just before administration of isatuximab.

2 INTRODUCTION

Cancer in children and adolescents is rare, although the overall incidence of childhood cancer, including acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML), has been slowly increasing since 1975 (1).

Acute lymphoblastic leukemia is the most common cancer diagnosed in children and represents approximately 25% of cancer diagnoses among children younger than 15 years of age (2, 3). A sharp peak in ALL incidence is observed among children 2 to 3 years of age (>90 cases per 1 million per year), with rates decreasing to fewer than 30 cases per 1 million by 8 years of age (2, 3). The incidence of ALL among children 2 to 3 years of age is approximately 4-fold greater than that for infants and is likewise 4- to 5-fold greater than that for children 10 years of age and older (2, 3).

Approximately 20% of childhood leukemias are of myeloid origin, and they represent a spectrum of hematopoietic malignancies (4). The majority of myeloid leukemias are acute.

Dramatic improvements in survival have been achieved in children and adolescents with cancer (1). Between 1975 and 2010, childhood cancer mortality decreased by more than 50% (1, 2, 3). For ALL, the 5-year survival rate has increased over the same time from 60% to approximately 90% for children younger than 15 years of age and from 28% to more than 75% for adolescents aged 15 to 19 years (5). For AML, the 5-year survival rate increased over the same time from less than 20% to 68% for children younger than 15 years of age and from less than 20% to 57% for adolescents aged 15 to 19 years (1).

2.1 STUDY RATIONALE

Acute Lymphoblastic Leukemia

In case of relapsed or refractory (R/R) acute leukemia, the outcome after first salvage therapy including transplantation is poor, whatever the treatment prescribed, and a number of new agents are currently being studied in this setting. Leukemia relapse represents the outgrowth of a clonal cell population not completely eliminated by treatment.

For patients with R/R disease after an initial complete response (CR), the approach to second-line treatment may depend on duration of the initial response. For late relapses (ie, ≥36 months from initial diagnosis), re-treatment with the same induction regimen may be a reasonable option. Participation in a clinical study is preferred, but in absence of a clinical study, the patient may be considered for second-line therapy with induction regimens not previously used.

Standard salvage regimens for relapsed ALL are still mostly based on different combinations of the same agents used in frontline therapy in various doses and schedules (6, 7). Many groups adopt treatment strategies consisting of risk-adapted, alternating short-course multiagent systemic and intrathecal (IT) chemotherapy, in some cases together with cranial/craniospinal irradiation, and conventional maintenance therapy.

Overall, remission can be achieved in >70% of early relapses and in up to 96% of late bone marrow (BM) relapses. Response rates cluster approximately 40% in second and subsequent relapse, although only 19 of 235 survivors (8%) have been reported among patients achieving a third remission after a second BM relapse (6, 7).

A United Kingdom-based randomized study of ALL patients in first relapse compared reinduction with a 4-drug combination using idarubicin versus mitoxantrone (8). There was no difference in second CR rates or end-reinduction minimal residual disease (MRD) levels between the 2 study arms. A significant improvement in overall survival (OS) in the mitoxantrone arm (69% versus 45%, p=.004) due to decreased relapse after transplantation was reported.

Of the children and adolescents diagnosed with precursor B-cell (B)-ALL each year (based on 2009 Surveillance, Epidemiology, and End Results Program data), approximately 25% will experience relapse or fail to achieve remission. The majority (85%) of those in first relapse will achieve a second remission (9). Response to chemotherapy decreases with each successive relapse. Approximately 44% of pediatric patients with a second marrow relapse of ALL and 27% of those with a third marrow relapse achieve a subsequent complete remission. Five-year disease-free survival (DFS) rates in patients with a second and third remission are reported to be 27% and 15%, respectively (9).

Two percent of children with ALL who do not achieve a remission are classified as having refractory disease (10) and suffer a worse prognosis compared with patients with relapsed ALL.

Patients with relapsed T-cell (T)-ALL have much lower rates of achieving a second CR with standard reinduction regimens than patients with precursor B-cell phenotype (7).

Reinduction failure is a poor prognostic factor, but subsequent attempts to obtain remission can be successful and lead to survival after hematopoietic stem cell transplantation (HSCT). Approaches have traditionally included the use of drug combinations distinct from the first attempt at treatment; these regimens often contain newer agents under investigation in clinical studies. Although survival is progressively less likely after each attempt, 2 to 4 additional attempts are often pursued, with diminishing levels of success measured after each attempt (9).

For patients with T-cell ALL (T-ALL) who achieved remission after BM relapse, outcomes with postreinduction chemotherapy alone have generally been poor (11), and these patients are usually treated with allogeneic HSCT in a second CR, regardless of time to relapse. At 3 years after allogeneic transplant, OS for T-ALL in a second remission was reported to be 48% and DFS was 46% (12).

Treatment Options for Second and Subsequent Bone Marrow ALL Relapse

Although there are no studies directly comparing chemotherapy with HSCT for patients in a third or subsequent CR, because cure with chemotherapy alone is rare, transplant is generally considered a reasonable approach for those achieving remission. Long-term survival for all patients after a second relapse is particularly poor, in the range of less than 10% to 20% (13). One of the main reasons for this is failure to obtain a third remission. Numerous attempts at novel combination approaches have resulted in only about 40% of children in a second relapse

achieving remission (14). However, 2 studies that added bortezomib to standard reinduction agents in multiple relapsed refractory patients have resulted in 70% to 80% complete remission rates (15, 16). If these patients achieve CR, HSCT has been shown to cure 20% to 35%, with failures occurring due to high rates of relapse and transplant-related mortality (17, 18, 19, 20, 21).

Central Nervous System-Directed Therapy for Childhood ALL

Because the central nervous system (CNS) is a sanctuary site (ie, an anatomic space that is poorly penetrated by many of the systemically administered chemotherapy agents typically used to treat ALL), specific CNS-directed therapies must be instituted early in treatment to eliminate clinically evident CNS disease at diagnosis and to prevent CNS relapse in all patients. Historically, survival rates for children with ALL improved dramatically after CNS-directed therapies were added to treatment regimens.

Acute Myeloid Leukemia

Despite second remission induction in over half of children with AML treated with drugs similar to drugs used in initial induction therapy, the prognosis for a child with recurrent or progressive AML is generally poor (22, 23).

Approximately 50% to 60% of relapses occur within the first year after diagnosis, with most relapses occurring by 4 years from diagnosis (22). The vast majority of relapses occur in the bone marrow, and CNS relapse is very uncommon (22).

Treatment options for children with recurrent AML may include chemotherapy and HSCT.

Regimens that have been successfully used to induce remission in children with recurrent AML have commonly included high-dose cytarabine given in combination with the following agents:

- Mitoxantrone (23)
- Fludarabine and idarubicin (24, 25, 26)
- L-asparaginase (Erwinase) (27)
- Etoposide
- Liposomal daunorubicin. A study by the International Berlin Frankfurt Munster Group compared fludarabine, cytarabine, and granulocyte colony-stimulating factor (G-CSF) with fludarabine, aracytine, G-CSF (FLAG) plus liposomal daunorubicin. Four-year OS was 38%, with no difference in survival for the total group; however, the addition of liposomal daunorubicin increased the likelihood of obtaining a remission and led to significant improvement in OS in patients with core-binding factor mutations (82%, FLAG plus liposomal daunorubicin versus 58%, FLAG; p=.04) (28). Regimens built upon clofarabine have also been used as have regimens of 2-chloroadenosine (29). The COG AAML0523 (NCT00372619) study evaluated the combination of clofarabine plus high-dose cytarabine in patients with relapsed AML; the response rate was 48% and the OS rate, with 21 of 23 responders undergoing HSCT, was 46%. Minimal residual disease before HSCT was a strong predictor of survival (30)

Central Nervous System Prophylaxis for AML

Therapy with either radiation or IT chemotherapy has been used to treat CNS leukemia present at diagnosis and to prevent later development of CNS leukemia. The use of radiation has essentially been abandoned as a means of prophylaxis because of the lack of documented benefit and long-term sequelae. The Children's Oncology Group has used single-agent cytarabine for both CNS prophylaxis and therapy (31). Other groups have attempted to prevent CNS relapse by using additional IT agents (32).

Unmet Medical Need

The population targeted by this pediatric study includes R/R ALL in a first and second bone marrow relapse, including relapse after allogeneic HSCT. This population has a poor prognosis and few effective standard treatment options. Existing treatment regimens for this disease rely heavily on high-intensity chemotherapy that consists of combinations of a few classes of drugs, eg, antimetabolites, anthracyclines, and alkylating agents. For patients who are refractory after such treatment, or who relapse, there is a higher probability of cross-resistance to available chemotherapeutic agents. Patients who undergo an allogeneic HSCT usually have received very intensive multidrug treatment regimens for induction/reinduction, consolidation, and additional conditioning followed by allogeneic HSCT, a procedure that is also associated with severe adverse reactions.

Acute leukemia is a heterogeneous disease, and there is a clear need for increased efficacy within several poorer-prognosis subgroups, particularly patients with treatment-refractory or relapsed disease, including infants and adolescents. Novel agents are needed that provide a higher response rate or better quality of response than conventional drugs in order to contribute substantially to cure, without adding toxicities.

Currently, acute leukemia therapy relies essentially on agents displaying only cytotoxic properties. Although cytotoxic drugs have proved their efficacy, the use of many of these compounds is limited due to:

- A lack of selectivity, which can result in severe damage to healthy tissues, especially to hematopoietic cells and gastrointestinal mucosa (tissues with high cell proliferation rates).
- Drug resistance, which can be either intrinsic or readily developed (acquired), mainly because the genetic mutations and the heterogeneity of the tumor cells allow the tumor to have a great adaptability to stress.

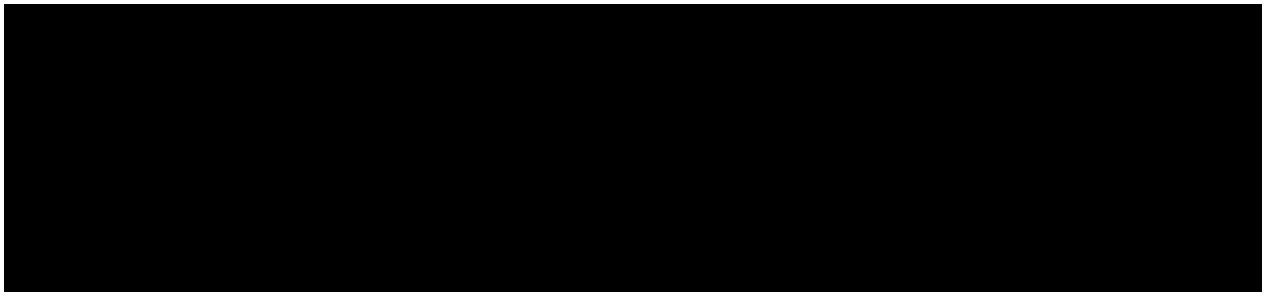
Therefore, there is a need to find new systemic treatment for cancer and new approaches are now being tested: compounds targeting specific protein/components of the tumor cells, which do not exist on normal cells or are over-expressed in cancer cells. An effective biologic agent could represent a valuable treatment option for these patients.

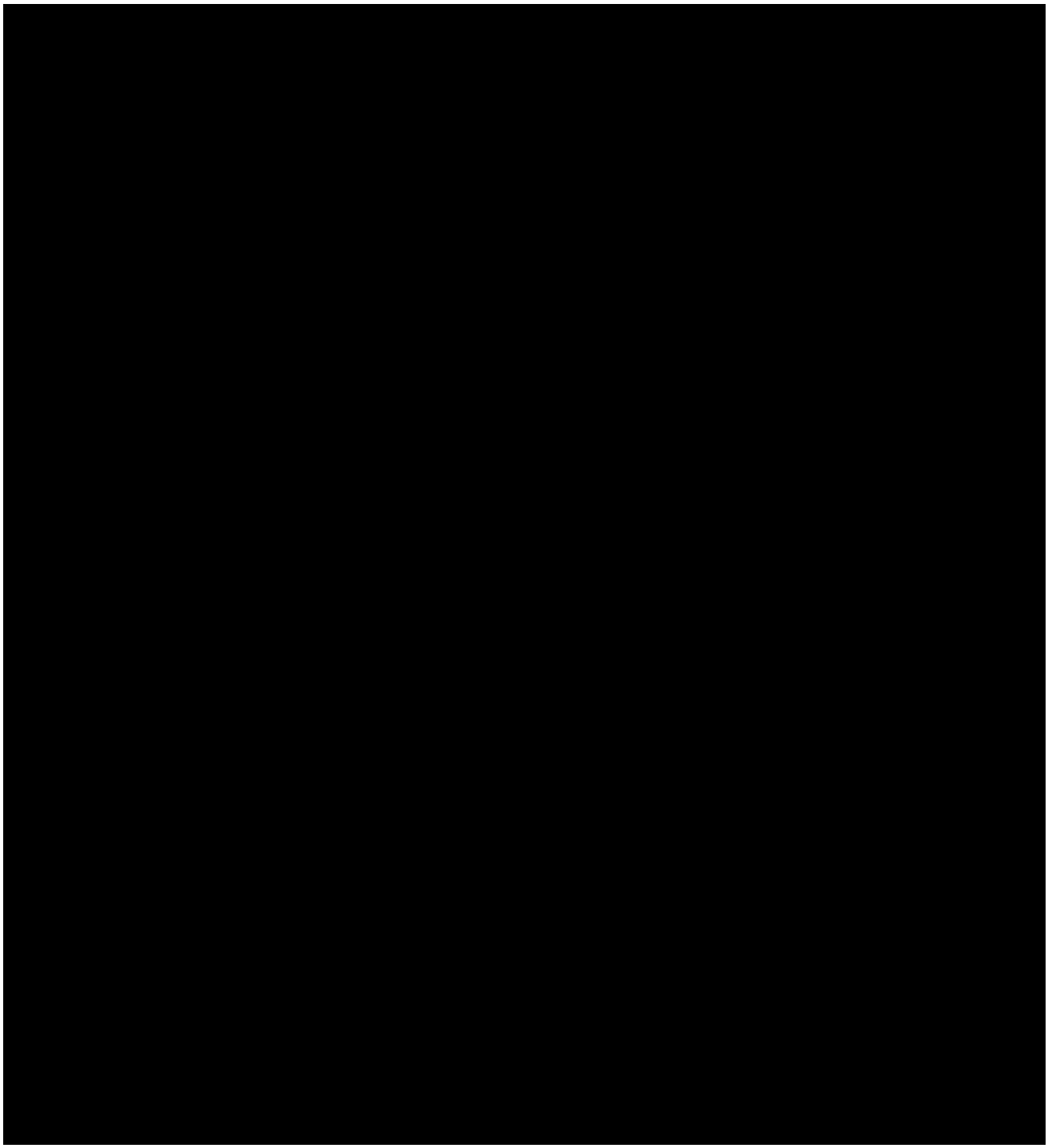
This approach was provided by blinatumomab, a genetically modified antibody that contains fragments that recognize both CD19 and CD3 (which is present on all T-cells) and therefore brings T-cells into direct contact with B-cell ALL (B-ALL) cells, allowing the cytotoxic T-cells to kill them (33). The Food and Drug Administration (FDA) has granted an accelerated approval to

blinatumomab (Blincyto) for the treatment of pediatric and adolescent patients with Philadelphia chromosome (Ph)-negative R/R B-cell precursor acute ALL. The approval of the anti-CD19 immunotherapy in this setting was based on data from a single-arm Phase 1/2 study, known as Study 205, which met its primary Phase 2 endpoint of complete remission within the first 2 cycles of blinatumomab. In previously published data from Phase 1 of Study 205, the complete remission rate was approximately 32% among 41 patients with R/R ALL (34).

Pharmacological rationale

Preclinical rationale





2.2 BACKGROUND

Isatuximab (SAR650984) is an immunoglobulin G1 class naked monoclonal antibody (mAb) binding selectively the human CD38 membrane protein, which is expressed in a number of hematological malignancies from B-lymphocyte, T-lymphocyte, and myeloid origin.

Isatuximab has the capacity to kill CD38 positive tumor cells by a combination of 4 distinct biological mechanisms:

- Antibody-dependent cell mediated cytotoxicity
- Antibody-dependent cellular phagocytosis
- Complement-dependent cytotoxicity
- Pro-apoptotic activity

Isatuximab demonstrated in vivo antitumor activity as a single agent and in combination with reference treatments on several CD38-positive tumor models. In addition, isatuximab demonstrated antitumor activity against primary patient cells ex vivo supporting its clinical evaluation in CD38+ multiple myeloma (MM), non-Hodgkin's lymphoma, and leukemia patients including ALL of both B- and T-cell origin and AML.

Isatuximab is being developed for the treatment of a number of hematological malignancies expressing the CD38 antigen, particularly MM in adults.

For more details on clinical studies, please refer to the IB.

In general, isatuximab is well tolerated clinically with a manageable safety profile. The most common adverse reactions are infusion reactions (IRs) which are clinically manageable. The IRs are not dose dependent and tend to occur most frequently during the first infusion. Participants who experience Grade 2 IRs may subsequently resume isatuximab treatment after receiving supportive care as needed. Both the mandatory prophylaxis against IRs and the additional medication in participants in whom the infusion of isatuximab was temporarily interrupted because of such reactions limit the risk of recurrence and have allowed participants to continue their therapy without sequelae.

Overall, the most current findings from the clinical experience acquired from multiple clinical studies with isatuximab have not identified any potential safety risks or concerns in addition to those described in the IB of isatuximab.

When given in combination with other anticancer agents, the overall safety profile of the combinations appears consistent with the safety profile of each drug individually.

Together with efficacy and pharmacokinetic (PK)/pharmacodynamic (PD) analyses, 20 mg/kg given every week for the first 28-day cycle, and every other week after Cycle 1 is the selected dose for the single-agent study in the MM indication.

For information regarding clinical studies in MM, please refer to the IB.

Preliminary clinical PK data in adult participants with MM

A preliminary analysis of the PK characteristics of isatuximab in participants with MM shows a nonlinear PK behavior with dose increase.

Isatuximab PK was best described by a 2-compartment model with parallel linear and nonlinear elimination from the central compartment, reflecting Michaelis-Menten approximation of target-mediated drug disposition. To account for the time-dependent phenomenon (ie, change of isatuximab PK over time influenced by the reduction of the CD38 target on tumor cells and by the change of pathophysiological status of the participant during the course of treatment), the time dependency of isatuximab linear clearance was further evaluated: the linear clearance was modeled as the sum of time-dependent clearance with associated decay coefficient, and time-independent clearance (CL_{inf}).

In the once every 2 weeks (Q2W) dosing schedule, the exposure, area under the curve from time 0 to the last measurable concentration (AUC_{last}) after first administration appeared to increase more than proportionally with the dose from 0.03 to 20 mg/kg, suggesting the presence of target-mediated clearance. However, based on AUC_{1week}, no major deviation to the dose proportionality was observed between the 2 highest doses tested (10 and 20 mg/kg once a week (QW) × 4, Studies TCD11863 and TCD14079).

Additionally, 4 doses of 20 mg/kg each week showed that total clearance (sum of nonlinear and linear clearances) approached linear clearance (CL) (indicating target saturation) after which the 20 mg Q2W schedule appeared to maintain the total clearance close to the CL. Repeated dosing resulted in an accumulation of 2.2 and 3.3 at Cycle 2, respectively, for maximum serum concentration reached by the drug after a dose (C_{max}) and lowest serum concentration reached by a drug before the next dose is administered (C_{trough}) for the 20 mg/kg QW/Q2W schedule of administration. Accumulation ratios were similar at Cycle 6, showing that the steady state was reached from Cycle 2 for this administration schedule.

Using both time-independent and time-dependent clearance models, the population estimated for CL (0.0071 to 0.0077 L/h, monotherapy) or for CL_{inf} (0.00723 L/h, pooled analysis [monotherapy-combination lenalidomide]) were very close to the clearance of nonspecific endogenous IgG and the volume of distribution of central compartment approached the blood volume (4.83 to 4.96 L). The half-life associated to the linear elimination was 28 days.

Because isatuximab is an antibody, it is expected to be eliminated by proteolytic catabolism.

Preliminary population PK analyses indicated that the central volume of distribution and isatuximab CL increase with increasing body weight (allometric exponents of 0.692 and 0.946, respectively), supporting the body weight-based dosing regimen. In addition, participants with higher CL values were also associated with higher M-protein.

Since isatuximab appeared to be well tolerated, the exposure-response analyses focused on the efficacy endpoint. The preliminary PK/PD analyses to evaluate the relationship between overall response rate (ORR) and PK parameters were performed using an Emax model with pooled monotherapy TED10893 Phase 1 and Phase 2 (Stage 1) data.

Briefly, the exposure-response analyses showed that C_{trough} at 4 weeks is a significant predictor of ORR and the probability of response to treatment increases as C_{trough} at 4 weeks increases up to a plateau. The dose of 20 mg/kg would maximize the number of patients close to the plateau (high interpatient variability) with the highest probability of success to reach a response rate ≥30%. Additional PK/PD modeling and simulations using M-protein concentration-time profiles to assess the benefit of changing dosing regimens over time showed a deeper response in terms of

decreases in M-protein levels at Weeks 8 and 12 using 20 mg/kg QW for 4 weeks followed by 20 mg/kg Q2W. Thus, based on clinical efficacy, safety, PK simulations, and PK/PD analyses, 20 mg/kg QW for 4 weeks followed by 20 mg/kg Q2W was chosen for dose and schedule for further monotherapy studies.

Trial simulations of ORR and serum M-protein simulations using isatuximab/lenalidomide combination data showed a clear dose response with higher predicted ORR, and a deeper reduction in serum M-protein at 8 and 12 weeks from baseline at doses ≥10 mg/kg for lenalidomide combination was observed. Furthermore, the models predict minimal increased efficacy when increasing the isatuximab dose from 10 to 20 mg/kg QW × 4, Q2W. Therefore, based on clinical efficacy, safety, PK simulations, and PK/PD analyses, 10 mg/kg QW for 4 weeks followed by 10 mg/kg Q2W was chosen for dose and schedule for further combination studies in MM.

Matching PK exposure between pediatric and adult patients can be performed in case of same indication, similar disease pathophysiology and same outcome of therapy (eg, efficacy end-point) in children and adults.

Therefore, preliminary PK in adults with ALL was developed using a population PK model and data from 14 patients with ALL treated with isatuximab at 20 mg/kg QW/Q2W. The PK in adult patients with ALL were comparable with those obtained in adults with MM with a typical CL value of 0.00882 L/h.

2.3 BENEFIT/RISK ASSESSMENT

At the cut-off date of 05 January 2019, the clinical development program with isatuximab consisted of Phase 1/2/3 studies of isatuximab as a single agent or in various therapeutic combinations with other agents. A total of 1301 patients have been exposed to isatuximab thus far in the completed studies. During the dose-escalation phase (Phase 1) of the TED10893 study (monotherapy in R/R MM and other hematological malignancies), dose-limiting toxicities (DLTs) consistent with IRs (which were initially included in the definition of DLTs), occurred at Cycle 1 in 2 participants with MM. After the occurrence of these 2 adverse events (AEs), the definition of DLTs has been corrected to not include IRs because these reactions are not dose dependent.

The IRs associated with isatuximab in participants who are administered appropriate primary prophylaxis are most common with the first administration of the drug, are not dose dependent, are most frequently Grade 1 to Grade 2 in severity, are manageable with standardized precautions detailed in each study protocol, are resolved either spontaneously or with standard medication by the next day following the infusion in most cases, and the participants do not appear to sustain sequelae. The IRs generally do not cause treatment discontinuation and do not tend to recur at subsequent administrations of isatuximab.

Infusion reactions may involve immunogenicity mechanisms (human antihuman antigen) and hypersensitivity reactions and are well known to occur in association with other therapeutic mAb proteins. These adverse reactions, whether acute or delayed, may be serious and systemic (eg, anaphylactic reaction).

Overall, the safety profiles of backbone chemotherapies used in this study for ALL and AML are reported as well characterized and manageable. The adverse reactions possibly associated with isatuximab in combination with these backbone chemotherapies, however, cannot be predicted.

Close safety monitoring of each participant is planned, and an independent DMC will regularly monitor participant safety. A first safety review by the DMC is planned after the first 10 participants have completed at least 1 induction cycle.

Study ACT14596 (isatuximab as a single agent in R/R adults T-ALL) was terminated prematurely, after no clinical response was reported in the first 14 participants treated with isatuximab as a single-agent. On that basis, sanofi has decided not to continue with the development of isatuximab as a single agent in adult participants with R/R T-ALL or T-cell lymphoblastic lymphoma (T-LBL).

Based on the efficacy results from a pooled analysis of completed monotherapy studies TED10893 (Phase 1 and Phase 2 Stage 1) and TED14154 (monotherapy in R/R MM, Part A) (N = 212), overall response rate was 19.8%. Clinical benefit response (≥ minimal response) was 28.3% and best response was stable disease in 39.2% of the treated participants.

Administration of isatuximab in combination with lenalidomide and dexamethasone was evaluated for participants with R/R MM in the TCD11863 study. The first part of the trial evaluated 3 doses of isatuximab 3, 5, and 10 mg/kg using the Q2W schedule of administration; among the participants treated at 10 mg/kg (n = 24), the ORR was 62.5% with a PR rate of 20.8%, very good PR rate of 33.3%, and stringent CR rate of 8.3%. Administration of isatuximab in combination with standard therapy shows greater efficacy for participants with R/R MM.

In addition to isatuximab, all participants treated in all cohorts in this ACT15378 study will receive combination chemotherapies that are part of established standard treatment options for participants with ALL or AML.

Despite the result of isatuximab monotherapy for adult participants with T-ALL in the ACT14596 study, administration of isatuximab with combination chemotherapies could provide additional benefit to the pediatric participants with R/R ALL or AML.

A risk of hepatitis reactivation has been identified in the IB edition 11 (30-Apr-2020). Therefore, screening with serological tests for hepatitis B and hepatitis C must be done prior to enrollment. In case of viral reactivation during study treatment, the treatment will be held, and specialist consulted for initiation of anti-viral treatment and monitoring of the participant.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of isatuximab may be found in Section 2.1 and in the IB of isatuximab.

In conclusion, the overall anticipated benefit/risk ratio appears favorable and supports the evaluation of the combination of isatuximab with chemotherapy in pediatric participants with R/R AML and ALL.

Benefit/risk assessment added in amended protocol 04

The study DMC has evaluated on 01 Oct 2020 the adverse events recorded in the first 9 treated pediatric patients including the first fatal case (primarily pulmonary in nature which may have been secondary to CRS). DMC recommended the continuation of study with amendment to the protocol to include their recommendations with immediate need to restrict the treated population to those with a WBC <20 x 10^9/L.

- Benefit Assessment: The 2-year survival rate for patients with relapsed post-transplant AML, who are eligible for the current study, is reported at less than 20%. Isatuximab is therefore being used as additive therapy where participants treated in all cohorts in the ACT15378 study receive combination chemotherapies that are part of established standard treatment options for participants with ALL or AML. It is known that patients with ALL/AML have elevated expression of CD-38 on leukemic blasts. Given its mechanism of action and established clinical efficacy in other hematologic malignancies, isatuximab when combined with chemotherapy may have the potential to improve the remission rate for children with relapsed/refractory AML. Only 9 patients have been enrolled to date, including 6 patients with AML; of the 4 evaluable patients for efficacy in AML cohort, two have achieved CRi. It is still too early to know whether isatuximab has efficacy in this population.
- Risk assessment: There is an acceptable benefit risk profile within the isatuximab labelled indication for multiple myeloma. In the pediatric leukemic population there could be a change in the risk profile especially in the pediatric patients with WBC >100 000/mm^3 who are at higher risk for disease related treatment complications; thus restricting the treated population to those with a WBC <20 x 10^9/L should allow an appropriate benefit-risk in this population with limited therapeutic choices.

3 OBJECTIVES AND ENDPOINTS

Table 3 - Objectives and endpoints

Objectives	Endpoints
Primary	
• To evaluate the antileukemic activity of isatuximab in combination with chemotherapies in pediatric participants of 28 days to less than 18 years of age with R/R ALL or AML.	CR rate is defined in this study as the proportion of participants with CR or CRi, in AML, B-ALL, and T-ALL cohorts. **For AML:** • CR: bone marrow blasts lower than 5%; No blasts with Auer rods or persistence of extramedullary disease; ANC higher than 1000/mm^3, platelets higher than 100 000/mm^3; red blood cells transfusion independence. If the physician documents transfusion dependency related to study treatment and not to the patient's underlying disease, CRi can be reported. • CRi: same criteria as for CR, except neutrophils and/or platelets recovery **For B-ALL and T-ALL:** • CR: bone marrow blasts lower than 5%, no circulating blasts or lymphoblasts in CSF or extramedullary disease; ANC higher than 1000/mm^3, platelets higher than 100 000/mm^3; red blood cells transfusion independence. If the physician documents transfusion dependency related to study treatment and not to the patient's underlying disease, CRi can be reported. • CRi: same criteria as for CR, except neutrophils and/or platelets recovery. • Extramedullary disease: complete resolution of lymphomatous enlargement by CT. For participants with a previous positive PET scan, a post-treatment residual mass of any size is considered a CR as long as it is PET negative.
Secondary	
• Safety and tolerability assessments	• Safety assessment, in terms of AEs/SAEs. In addition, laboratory data, vital signs, and physical examination will be assessed throughout the study.
• Assessment of IRs	• Incidence and severity of IRs.
• PK of isatuximab	• PK parameters of isatuximab calculated using a population PK approach including at least C_{max}, C_{trough}, and AUC.
• Minimal residual disease	• Estimation of minimal residual disease in participants achieving CR or CRi.

Objectives	Endpoints
• Overall response rate	• The overall response rate is defined as the proportion of participants with CR or CRi or PR for blood and bone marrow disease.
• Overall survival	• Overall survival is defined as the time interval from the date of first study intervention administration to death from any cause.
• Event free survival	• Event free survival is defined as the time interval from the date of first study intervention administration to the date of the first of: completion or going off protocol induction/consolidation therapy without CR, relapse from CR, or death due to any cause.
• Duration of response	• Duration of response is defined as the time from the date of the first response to the date of first disease progression or death from any cause, whichever happens first.
• Relationship between clinical effects and CD38 receptor density and occupancy	• CD38 receptor density will be assessed at baseline and CD38 receptor occupancy at Day 15 and correlated with clinical endpoints.
Tertiary/exploratory	
• Immunogenicity of isatuximab	• Immunogenicity of isatuximab assessed throughout the study by detecting the presence of antidrug antibodies.
• PK/PD relationships with regards to safety and efficacy endpoints.	• PK/PD parameters estimated as prognostic factors for clinical outcomes including safety and efficacy endpoints, if possible

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

3.1 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, and suitable steps have been built into each of these assessments to ensure their reliability and accuracy.

4 STUDY DESIGN

4.1 OVERALL DESIGN

This is a Phase 2, single-arm, multicenter, open-label study evaluating the antitumor activity, safety, and PK of isatuximab in combination with standard salvage chemotherapies in pediatric participants with R/R ALL (including both T-ALL and B-ALL) and AML conducted in 3 separate cohorts. Male and female children from 28 days to less than 18 years of age with R/R T-ALL, B-ALL, or AML in first or second relapse will be eligible. Participants under 2 years of age can only be enrolled after the dose reassessment is completed on the first 20 participants who are 2 to less than 18 years of age (Section 4.3 and Section 9.5).

4.1.1 Study participants and cohorts

Three cohorts of study participants will be treated:

- B-ALL
- T-ALL
- AML

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

For an assessment of the dose for children younger than 2 years of age, 20 participants of 2 years of age or more (at least 5 participants in the age group of 2 to 10 years, including approximately 3 patients between 2 and 5 year-old) will be enrolled first to check the isatuximab exposure (see Section 4.3).

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

4.1.2 Screening

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

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

Screening procedures are to be performed/assessed in accordance with the Schedule of Activities (SOA) in Section 1.3.

In patients with high tumor burden (WBC count higher than 20 x 10^9/L (and <50 x 10^9/L) at screening with or without pulmonary leukostasis, or significant organ involvement as per Investigator's judgement), a rescue cytoreductive chemotherapy should be started as recommended in order to decrease their WBC count <20 x 10^9/L by Day 1. For patients with WBC count <20 x 10^9/L at screening, but higher than 20 x 10^9/L on Day 1, a cytoreductive chemotherapy should be started as recommended in order to decrease their WBC count and the screening period will be extended without a deviation. Please refer to Section 6.5.1 for more details. Patients with >20 x 10^9/L on Day 1 cannot receive isatuximab on Day 1 and should be registered as screen failed.

During this period of cytoreductive therapy, all patients should have a close monitoring (at least three times a day) of clinical and biological parameters and a rapid fast institution of life sustaining therapy, if required, as per site clinical practice. WBC count, biochemistry (potassium, phosphorus, uric acid, corrected calcium, blood urea nitrogen, creatinine) as well as chest X-ray should be performed daily, to monitor potential tumor lysis syndrome (TLS) and pulmonary leukostasis.

For management of CRS and TLS syndromes please see Section 6.6.3 and Section 6.6.4.

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

Intrathecal prophylaxis is mandatory for all cohorts; the drugs that will be used (methotrexate/aracytine/steroids) are per investigator discretion (only one drug, or two or all three).

When dexamethasone is administered at 10 mg/m^2 per os, it can be divided in two daily doses. This does not apply to dexamethasone administration as part of isatuximab premedication.

4.1.3 Study treatment period

In all 3 disease cohorts, participants will receive 1 administration of single-agent isatuximab on Day 1.

On Day 1, before initiation of the first infusion of isatuximab, a chest X-ray, a hematology test including WBC with differential to rule out leukocyte elevation, and a biochemistry panel (including potassium, phosphorus, uric acid, corrected and ionized calcium (corrected calcium = total calcium level in milligrams per deciliter + 0.8 × [4 albumin in grams per deciliter]; ionized calcium level in milligrams per deciliter = total calcium level in milligrams per deciliter + 0.02*[40 – albumin in grams per deciliter]) should be performed and results assessed by an investigator. If it is not possible to organize chest X-ray on Day 1 prior it can be done on Day -1 or Day -2. If it is not possible to assess potassium, phosphorus, uric acid, corrected and ionized

calcium prior to the infusion on Day 1, it can be done on Day -1 or Day -2, and only in case this is not possible – on Day -3. Additional evaluations such as blood cultures would be performed if infection is suspected. Please see Section 1.3 for more details.

Starting on Day 8, combination chemotherapy will be added. Only if the clinical condition of the participant worsens after Day 1 of the first isatuximab infusion and the participant's condition requires intensive therapy, chemotherapy can be started earlier, based on investigator's decision. Isatuximab schedule of administration will not be changed for later infusions. The details of the combination chemotherapies are in Section 6.1.

Bone marrow aspirations will be performed in accordance with the SOA (Section 1.3). Any additional BM aspirations will be performed at the Investigator's discretion and should be reported in the electronic case report form (eCRF). Minimal residual disease assessments will be done at screening and at the end of induction for ALL only, at the time of hematological recovery and/or at the time of each BM aspiration for disease assessment if CR or CR with incomplete peripheral recovery (CRi) is achieved for both ALL and AML.

In case hematological recovery cannot be reached for any reason, in both AML and ALL participants, BM aspiration could be done at any time if investigator does not expect any more hematological change and/or urgent need for therapeutic strategy decision.

Patient not having been tested for HBV/HCV at screening that are still on treatment at the time of the amended protocol 4 will need to be tested additionally for HBsAg, anti HBs, anti-HBc (total and IgM), anti-HCV, HCV RNA level.

4.1.4 Post-study treatment period

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

4.1.5 Study duration

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

- the screening period of up to 3 weeks prior to the first study intervention administration;
- the treatment period as described above (see Section 4.1.3);
- the period of aplasia followed by recovery period;
- an EOT visit within 30 days after hematological recovery;
- follow-up period.

In case hematological recovery cannot be reached for any reason, in both AML and ALL participants, BM aspiration could be done at any time if investigator does not expect any more hematological change and/or urgent need for therapeutic strategy decision.

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

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

Also, during the follow-up period, women of childbearing potential will perform pregnancy assessments every month, until 6 months after the last dose of isatuximab, or 12 months after the last dose of cyclophosphamide.

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

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

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

More than 80% of children affected by acute leukemia are successfully treated; however, relapse remains a remarkable clinical concern, with 50% to 60% of relapsing patients facing a fatal outcome. Management of relapsed patients includes standardized intensive risk-adapted regimens based on conventional drugs and hematopoietic stem cells transplantation for patients with unfavorable features. Biological targeted drugs, in particular the mAbs, could be novel potential agents to be integrated in salvage acute leukemia therapy to further improve patients' outcomes.

Isatuximab is being developed for the treatment of a number of hematological malignancies expressing the CD38 antigen. In general, isatuximab is well tolerated clinically with a manageable safety profile. This study will further evaluate the safety, efficacy, and PK parameters in children with ALL or AML.

Please refer to Section 2.1 for further details on the study design rationale.

4.3 JUSTIFICATION FOR DOSE

Taking into account the higher tumor burden in acute leukemia compared with MM, and based on PK data indicating a saturation of the target at 20 mg/kg in MM (see Section 2.2), the dose selected for acute leukemia indication is 20 mg/kg, even for combination studies.

Weekly infusions will be administered during the induction period of administration of backbone chemotherapy and every 2 weeks during the consolidation period for ALL. Compared with MM studies, after the end of the chemotherapy administration, isatuximab will not be administered because of the potential risk of treatment-related BM depression. At present, however, there is no evidence to suggest the risk of increased hematological abnormalities with isatuximab infusions. If future data from the first randomized, controlled study in MM confirms the lack of

hematological effects, the isatuximab administration after the end of backbone chemotherapy could be reconsidered.

The dose in pediatric participants was selected by matching the exposure between pediatric participants and adults with ALL, assuming that same exposure (area under the curve [AUC]) in pediatric participants as the exposure in adults will lead to the same efficacy in pediatric participants. The target exposure for this study is the one estimated in adults with ALL of 15 000 µg•h/mL that was observed following a dose of 20 mg/kg.

At first, the CL in pediatric participants was extrapolated from the adult exposure using allometric scaling on weight. As there is no consensus on the use of allometric methods for mAbs, 2 allometric exponents were used:

- 0.75: a commonly used allometric exponent for pediatric extrapolation.
- 0.85: a classical allometric exponent used for translation from animal to human for mAbs.

As depicted in Figure 7 and Figure 8, the body weight normalized CL increase in participants younger than 2 years of age, leading to a higher predicted dose for these participants. A dose of 20 mg/kg could lead to an under-exposure of up to 0.50-fold for participants <2 years of age.

Therefore, 20 participants of 2 years of age or more (at least 5 participants in the age groups of 2 to 10 years, including approximately 3 patients between 2 and 5 year-old) will be enrolled first to check the exposure. Based on these results, a reassessment of the dose will be done with the possibility to increase the dose to 25 or 30 mg/kg in children younger than 2 years of age.

Figure 7 - Body weight normalized clearance versus age

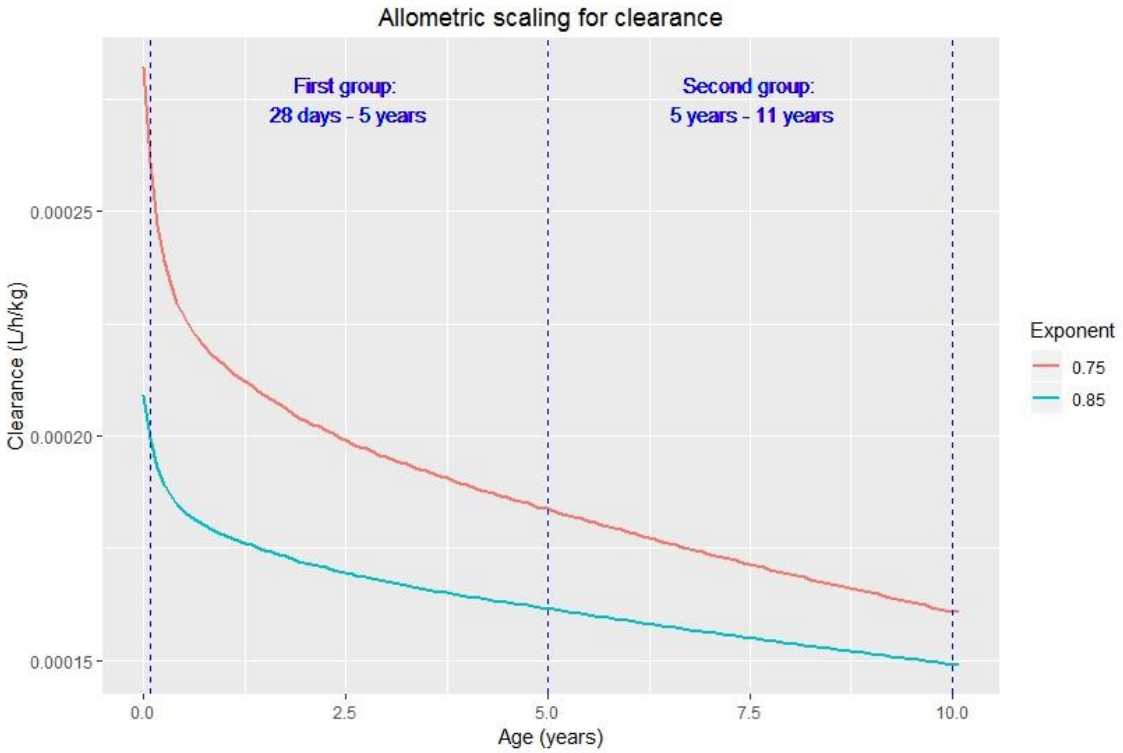
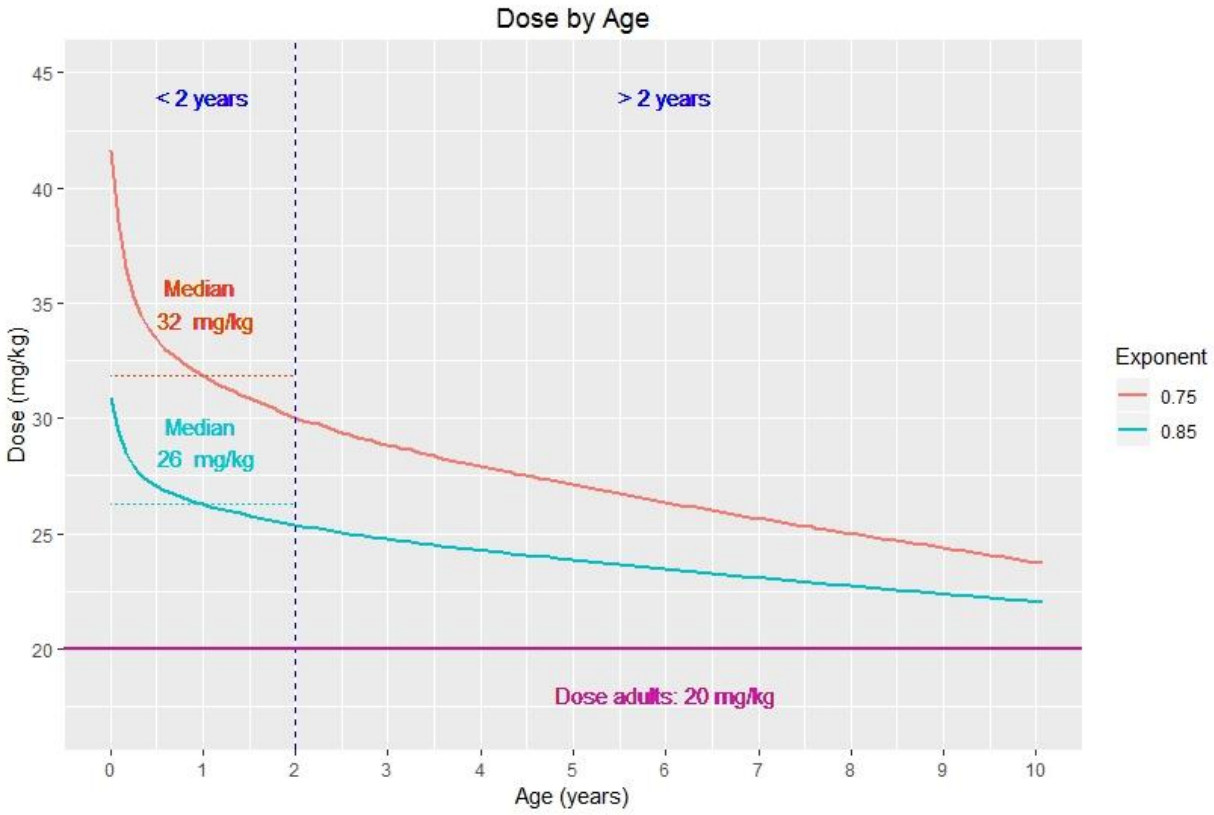


Figure 8 - Body weight-based doses versus age



A reassessment of the dose was done at the time of the interim analysis (ie among 20 participants treated and 18 evaluable for PK assessment, among them 6 participant 2 to 5 years old) and confirm the dose of 20 mg/kg in children younger than 2 years of age.

A population PK model was developed with pooled data from 14 adults with T-ALL, aged 16 to 74 years and weighing 46 to 93 kg coming from ACT14596 study and from the 18 pediatric patients with ALL or AML aged from 2 to 17 and weighting from 11to 65 kg to estimate the PK and derived exposure in pediatrics (≥2 years) and to predict the exposure in patient <2 years old. The pharmacokinetics of isatuximab were described by a two-compartment structural kinetic model with linear elimination from the central compartment, a proportional error model and interindividual variability on all parameters. Body weight allometric coefficients fixed to 0.85 for clearances (CL and Q) and 1 for volumes of distribution enable to well describe the observed data. No additional age effect was observed when body weight is included into the model.

Since the steady-state may not be achieved given the short period of treatment, different cumulated AUCs matching with different treatment durations were simulated:

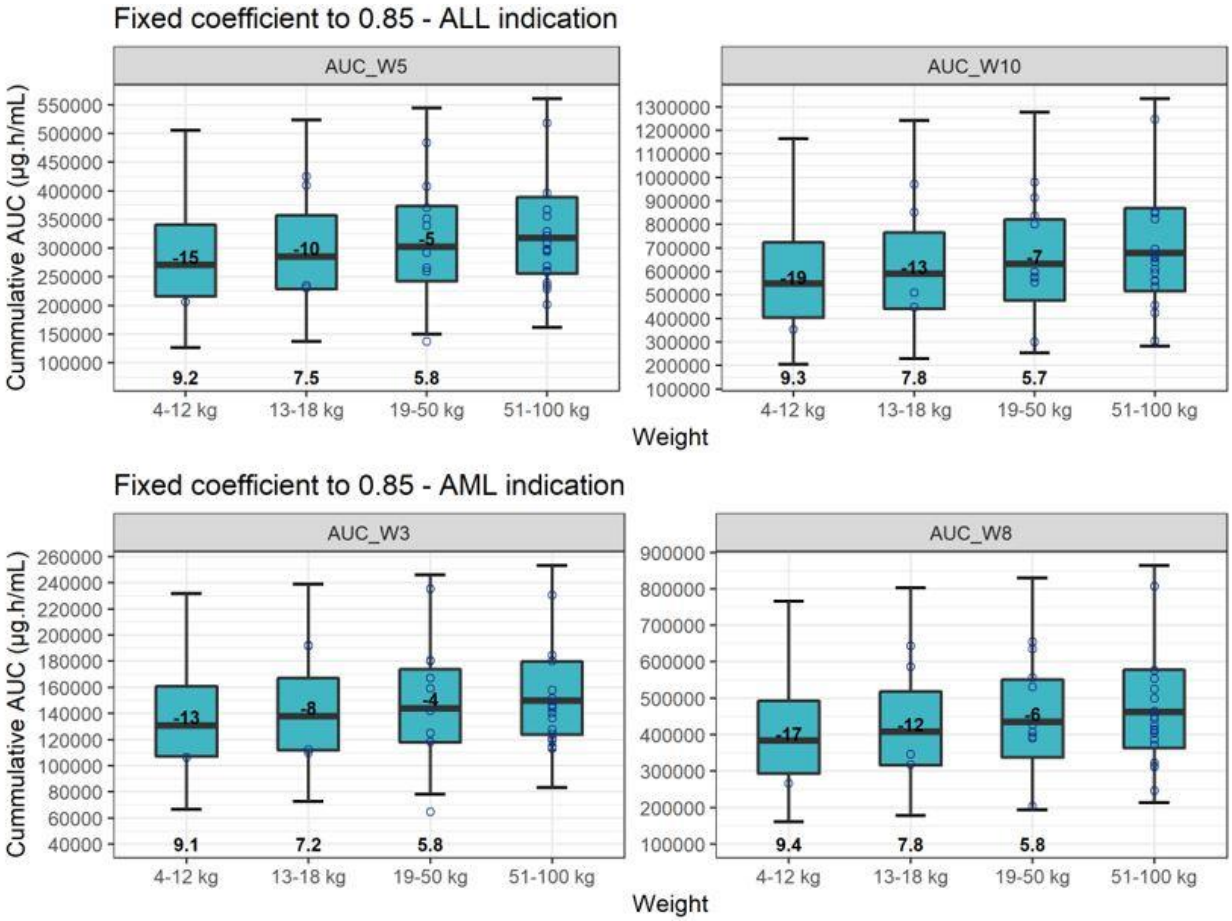
- Cumulated AUC at week 5 (AUC_W5) and cumulated at week 10 (AUC_W10) for ALL design
- Cumulated AUC at week 3 (AUC_W3) and cumulated at week 8 (AUC_W8) for AML design.

As shown in Figure 9, less than 20% median decrease is predicted in the youngest patients (4-12 kg, corresponding to 1 to 24 months) versus the reference group patients (51-100 kg).

In addition, there is no evidence of a trend between PK exposure and efficacy (ORR).

Therefore, taking all together, there is no need to change the dose (20 mg/kg) in patients younger than 2 years.

Figure 9 - Boxplots of predicted and simulated AUCs for a 20 mg/kg isatuximab dose administered under ALL and AML design, by weight groups



Figures within boxplots are median percent change compared with 51-100 kg considered as the reference adult. Figures outside boxplots are the percent of patients outside the 95% Prediction Interval of the reference. Circles are the individual predicted values.

4.4 END OF STUDY DEFINITION

A participant is considered to have completed the study if he/she has completed all periods of the study including the last scheduled procedure shown in the SOA (Section 1.3).

The end of the study is defined as the date of the last visit of the last participant in the study or last scheduled procedure shown in the SOA for the last participant in the study globally.

5 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 INCLUSION CRITERIA

Participants are eligible to be included in the study only if all of the following criteria apply:

I 01. Age

Participant must be 28 days to less than 18 years of age at the time of the signing of the informed consent (including participants who are under 2 years old). (see Section 4.3 and Section 9.5).

I 02. Type of participant and disease characteristics

Participants must have a confirmed diagnosis of relapsed ALL of T- or B-cell origin including lymphoblastic lymphoma (LBL, or relapsed AML (excluding M3 type: acute promyelocytic leukemia) including participants with history of myelodysplasia (MDS).

Participants must be previously treated for their disease and have relapsed or are refractory to most recent treatment. Participants in first or second relapse will be eligible regardless of the remission duration.

Participants with no more than 1 prior salvage therapy.

I 03. Sex

Male or Female

A) Male participants: A male participant with a female partner of childbearing potential must agree to use contraception as detailed in Appendix 4 (Section 10.4) of this protocol during the treatment period and for at least 6 months after the last dose of isatuximab, 12 months after the last dose of cyclophosphamide, and at least 6 months after other IMPs discontinuation (vincristine, pegaspargase, L-asparaginase (Erwinase), methotrexate, etoposide, doxorubicin, mitoxantrone, fludarabine, cytarabine), whatever occurs last and with the longest recommended period of contraception, and refrain from donating sperm during this period.

B) Female participants: A female participant is eligible to participate if she is not pregnant (see Appendix 4 [Section 10.4]), not breastfeeding, and at least one of the following conditions applies:

- Not a woman of childbearing potential (WOCBP) as defined in Appendix 4 (Section 10.4)

  OR

- A WOCBP who agrees to follow the contraceptive guidance in Appendix 4 (Section 10.4) during the treatment period and for at least 6 months after the last dose of isatuximab, 12 months after the last dose of cyclophosphamide, and at least 6 months after other IMPs discontinuation (vincristine, pegaspargase, L-asparaginase (Erwinase), methotrexate, etoposide, doxorubicin, mitoxantrone, fludarabine, cytarabine), whatever occurs last and with the longest recommended period of contraception.

I 04. Informed Consent

The participant who has reached legal age of majority as defined by local regulation or the parent(s)/legal guardian(s) must provide signed informed consent prior to any study-related procedures being performed. If the participant is legally a minor per local regulations, assent shall be obtained from the participant, if applicable.

I 05. Criterion added in amended protocol 04

WBC counts below 20 x 10^9/L on Day 1 before isatuximab administration.

5.2 EXCLUSION CRITERIA

Participants are excluded from the study if any of the following criteria apply:

Medical conditions

E 01. Evidence of ongoing infection or seropositivity for human immunodeficiency virus (**HIV**), or uncontrolled or active **HBV** infection (defined as either positive hepatitis B surface [HBs] antigen or positive HBV deoxyribonucleic acid [DNA] test above the lower limit of detection of the assay), or **HCV** infection (defined as positive HCV ribonucleic acid (RNA) and negative anti-HCV.

Note: Patient can be eligible if anti-HBc immunoglobulin G (IgG) positive (with or without positive anti-HBs) but HBsAg and HBV DNA are negative. If anti-HBV therapy in relation with prior infection was started before initiation of IMP, the anti-HBV therapy and monitoring should continue throughout the study treatment period (see Section 1.3). Patients with negative HBsAg and positive HBV DNA observed during screening period will be evaluated by a specialist for start of anti-viral treatment: study treatment could be proposed if HBV DNA becomes negative and all the other study criteria are still met. Patients with antiviral therapy for HCV started before initiation of IMP and positive HCV antibodies are eligible. The antiviral therapy for HCV should continue throughout the treatment period until seroconversion. Patients with positive anti-HCV and undetectable HCV RNA without antiviral therapy for HCV are eligible.

E 02. Second malignancy other than basal cell or squamous cell carcinoma of the skin or in situ carcinoma, unless they are successfully treated with curative intent for more than 3 years before entering the study.

E 03. Cardiomyopathy with ejection fraction <55%.

E 04. History of thrombophilic disease.

E 05. Eastern Cooperative Oncology Group (ECOG) performance status >2 or Lansky score <70 (see Section 10.6.2 and Section 10.6.3).

E 06. Total bilirubin >2.5 × upper limit of normal (ULN) unless the participant has Gilbert's syndrome or elevation related to acute leukemia.

E 07. Alanine aminotransferase, aspartate aminotransferase, or alkaline phosphatase >5 × ULN, unless considered due to the disease.

E 08. Serum creatinine >2 × ULN and/or estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2 (by revised Schwartz equation, Section 10.6.4).

E 09. Any serious active disease or comorbid condition (eg, infection or life threatening tumor lysis syndrome) if present at study entry or during the screening period that, in the opinion of the Investigator, may interfere with the safety of the study intervention or the compliance with the study protocol.

Prior/concomitant therapy

E 10. Participants must have been off prior treatment with immunotherapy/investigational agents 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 intervention administration. Exceptions are participants who need to receive cytoreductive chemotherapy in order to decrease tumor burden (the study treatment may start earlier if necessitated by the participant's medical condition [eg, rapidly progressive disease] following discussion with the Sponsor).

E 11. Prior stem cell transplant within 3 months and/or evidence of active systemic Graft versus Host Disease (GVHD) and/or immunosuppressive therapy for GVHD within 1 week before the first study intervention administration.

Prior/concurrent clinical study experience

E 12. Intolerance or contraindication to treatment with mAb or any other drug part of the study intervention.

Diagnostic assessments

E 13. Participants with LBL with BM blasts <5%.

E 14. Participants with Burkitt-type ALL.

E 15. Acute leukemia with testicular or CNS involvement alone.

E 16. Participants who have developed therapy-related acute leukemia.

Other exclusions

E 17. Individuals accommodated in an institution because of regulatory or legal order; prisoners or participants who are legally institutionalized.

E 18. Any country-related specific regulation that would prevent the participant from entering the study - see Appendix 8 (Section 10.8).

E 19. Participant not suitable for participation, whatever the reason, as judged by the Investigator, including medical or clinical conditions, or participants potentially at risk of noncompliance to study procedures.

E 20. Participants are dependent on the Sponsor or Investigator (in conjunction with Section 1.61 of the International Council for Harmonisation Good Clinical Practice (ICH GCP Ordinance E6).

E 21. Participants are employees of the clinical site or other individuals directly involved in the conduct of the study, or immediate family members of such individuals.

E 22. Any specific situation during study implementation/course that may raise ethics considerations.

E 23. Sensitivity to any of the study interventions, or components thereof, or drug or other allergy that, in the opinion of the Investigator, contraindicates participation in the study.

Criteria added in amended protocol

E 24. Live vaccine(s) within 30 days prior to the first IMP administration or plans to receive such vaccines during the study until 90 days after the last IMP administration.

E 25. Participants who are expected to have a superior benefit if treated with alternative established standard therapies (eg, blinatumomab or TKI-based regimes).

Criteria added as per amended protocol 04

E 26. Participants with white blood cell count >50 $x10^9$/L at the time of screening visit.

E 27. Participants who have been exposed to anti-CD38 therapies within 6 months prior to Day -1.

5.3 LIFESTYLE CONSIDERATIONS

Not applicable.

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently treated. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure reasons, eligibility criteria, and any SAEs.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened for as long as enrollment is open. Rescreened participants should be assigned a new participant number as for the initial screening.

5.5 CRITERIA FOR TEMPORARILY DELAYING OF ENROLLMENT/ADMINISTRATION OF STUDY INTERVENTION

During a regional or national emergency declared by a governmental agency, if the site is unable to adequately follow protocol mandated procedures, contingency measures proposed in Section 10.9: Contingency Measures for a regional or national emergency that is declared by a governmental agency should be considered for screening/enrollment/administration of study intervention.

6 STUDY INTERVENTION

Study intervention is defined as isatuximab and salvage chemotherapy intended to be administered to a study participant according to the study protocol. For chemotherapy, the body surface area used for dose determination is capped at 2 m^2.

6.1 STUDY INTERVENTION(S) ADMINISTERED

Table 4 - Overview of study interventions administered

Study intervention name	Isatuximab	Fludarabine
Dosage formulation	Concentrate for solution for intravenous infusion	Dependent on country sourcing
Unit dose strength(s)/Dosage level(s)	20 mg/mL (500 mg/25 mL and 100 mg/5 mL) of isatuximab in 20 mM histidine, 10% (w/v) sucrose, and 0.02% (w/v) polysorbate 80 at pH 6.0. Each vial will contain a nominal content of 500 or 100 mg isatuximab. The fill volume has been established to ensure removal of 25 or 5 mL.	Please refer to the product approved leaflet for further information.
Route of administration	Intravenous infusion	Intravenous infusion
Dosing instructions	**AML cohort:** 20 mg/kg weekly (this could be modified based on modeling and PK assessment on the first 20 participants) Days 1, 8, and 15 (mandatory for Cycles 1 and 2). **ALL cohorts:** 20 mg/kg weekly (this could be modified based on modeling and PK assessment on the first 20 participants) Days 1, 8, 15, 22, 29, 43, and 57.	**AML cohort only:** 30 mg/m², Days 8 to 12, inclusive (mandatory for Cycles 1 and 2).
Packaging and labeling	Each glass vial will be labeled as required per country requirement.	Each container will be labeled as required per country requirement.

Study intervention name	Cytarabine	Liposomal daunorubicin
Dosage formulation	Dependent on country sourcing.	Dependent on country sourcing
Unit dose strength(s)/Dosage level(s)	Please refer to the product approved leaflet for further information.	Please refer to the package insert for further information.
Route of administration	Intravenous infusion	Intravenous infusion
Dosing instructions	**AML cohort only:** 2 g/m², Days 8 to 12 inclusive (mandatory for Cycles 1 and 2).	**AML cohort only:** 60 mg/m², mandatory for Cycle 1 Day 8, optional for Cycle 1 Days 10 and 12, and optional for Cycle 2.
Packaging and labeling	Each container will be labeled as required per country requirement.	Each container will be labeled as required per country requirement.

Study intervention name	Idarubicin	Dexamethasone or equivalent
Dosage formulation	Dependent on country sourcing	Dependent on country sourcing
Unit dose strength(s)/Dosage level(s)	Please refer to the product approved leaflet for further information	Please refer to the product approved leaflet for further information.
Route of administration	Intravenous infusion	Intravenous infusion or Per os
Dosing instructions	**AML cohort only:** 10 mg/m², mandatory for Cycle 1 Day 8, optional for Cycle 1 Days 10 and 12, and optional for Cycle 2.	Dexamethasone, being part of both backbone treatment regimen and isatuximab premedication in ALL cohorts, before each administration of isatuximab, at least 15 to 30 minutes (but no longer than 60 minutes) prior to infusion, will be given as premedication for prevention of infusion associated reactions. When dexamethasone is administered at 10 mg/m² per os, it can be divided in two daily doses. This does not apply to dexamethasone administration as part of isatuximab premedication**.** **AML cohort:** Dexamethasone 10 mg/m² (maximum 20 mg) IV or PO optional on Days -3, -2, -1; premedication before isatuximab administration, on Days 1, 8, and 15 during the induction period (mandatory at Cycle 1 and before first isatuximab infusion at Cycle 2). **ALL cohorts:** Dexamethasone 10 mg/m² (maximum 20 mg) IV or PO on Days -3, -2, -1 before isatuximab administration, 1, 8, 15 to 19, 22, and 29 to 33 for the induction period and Days 43 to 47, and 57 during the consolidation period.
Packaging and labeling	Each container will be labeled as required per country requirement.	Each product will be labeled as required per country requirement.

Study intervention name	Doxorubicin	Mitoxantrone
Dosage formulation	Dependent on country sourcing	Dependent on country sourcing
Unit dose strength(s)/Dosage level(s)	Please refer to the product approved leaflet for further information.	Please refer to the product approved leaflet for further information.
Route of administration	Intravenous infusion	Intravenous infusion
Dosing instructions	**ALL cohorts only:** 25 mg/m² Days 10, 17, 24, and 31 of the induction period.	**ALL cohorts only**: 10 mg/m² Days 8 and 9 of the induction period.
Packaging and labeling	Each container will be labeled as required per country requirement	Each container will be labeled as required per country requirement.

Study intervention name	Vincristine	Pegaspargase or L-asparaginase (Erwinase)
Dosage formulation	Dependent on country sourcing	Dependent on country sourcing
Unit dose strength(s)/Dosage level(s)	Please refer to the product approved leaflet for further information.	Please refer to the product approved leaflet for further information.
Route of administration	Intravenous infusion	Intramuscular injection or intravenous infusion
Dosing instructions	**ALL cohorts only**: 1.5 mg/m² on Days 10, 17, 24, and 31 during the induction period (should not exceed 2 mg per infusion in any patient); Day 38 during the consolidation period. Vincristine should be given 3 to 24 hours before administration of pegaspargase in order to minimize the toxicity.	**ALL cohorts only**: Pegaspargase: 1000 IU/m² Days 10 and 24 during the induction period, Day 44 during the consolidation period. L-asparaginase (Erwinase): 25000 IU/m² on Days 8, 10, 12, 15, 17, 19, 22, 24, 26, 29, 31, 33 during induction and days 43, 45, 47, 50, 52, 54 during consolidation, only in case of confirmed hypersensitivity reaction to pegaspargase prior or during the study or loss of asparaginase and/or country availability and regulations. Hypersensitivity to pegaspargase and/or loss of asparaginase activity should be documented in the eCRF.
Packaging and labeling	Each container will be labeled as required per country requirement.	Each container will be labeled as required per country requirement.

Study intervention name	Cyclophosphamide	Etoposide
Dosage formulation	Dependent on country sourcing	Dependent on country sourcing
Unit dose strength(s)/Dosage level(s)	Please refer to the product approved leaflet for further information.	Please refer to the product approved leaflet for further information.
Route of administration	Intravenous infusion	Intravenous infusion
Dosing instructions	**ALL cohorts only**: 440 mg/m² on Days 50 to 54 inclusive, during the consolidation period.	**ALL cohorts only**: 100 mg/m² Days 50 to 54 inclusive, during the consolidation period.
Packaging and labeling	Each container will be labeled as required per country requirement.	Each container will be labeled as required per country requirement.
Study intervention name	**Methotrexate**	**Daunorubicin (nonliposomal)**
Dosage formulation	Dependent on country sourcing	Dependent on country sourcing
Unit dose strength(s)/Dosage level(s)	Please refer to the product approved leaflet for further information.	Please refer to the product approved leaflet for further information.
Route of administration	Intravenous infusion	Intravenous infusion
Dosing instructions	**ALL cohorts only**: 1000 mg/m² Day 43 during the consolidation period.	**AML cohorts only**: 60 mg/m^2, mandatory for Cycle 1 Day 8, optional for Cycle 1 Days 10 and 12, and optional for Cycle 2.
Packaging and labeling	Each container will be labeled as required per country requirement.	Each container will be labeled as required per country requirement.

Study intervention name	Filgrastim or equivalent (G-CSF)
Dosage formulation	Dependent on country sourcing
Unit dose strength(s)/Dosage level(s)	Please refer to the product approved leaflet for further information.
Route of administration	Subcutaneous or intravenous injection
Dosing instructions	**AML cohort only**: 200 μg/m² Days 7 to 12. G-CSF is optional for Cycles 1 and 2 and can be continued until neutrophil recovery.
Packaging and labeling	Each container will be labeled as required per country requirement.

AML = acute myeloid leukemia; ALL = acute lymphoblastic leukemia; EU = European Union; G-CSG = granulocyte colony stimulating factor; IV = intravenous(ly); PK = pharmacokinetic; PO = oral; ROW = rest of world; US = United States; w/v = water/volume.

INVESTIGATIONAL MEDICINAL PRODUCTS

Investigational medicinal products (IMPs) (except isatuximab) from available commercial supplies will be used for this study where applicable otherwise it will be relabeled by the Sponsor according to Good Manufacturing Practice (GMP) guidelines before supplies are provided to the sites.

On days when isatuximab is administered, the order of administration is recommended to be dexamethasone first, isatuximab second, and chemotherapy third.

NONINVESTIGATIONAL MEDICINAL PRODUCTS

Table 5 - Noninvestigational medicinal products

Noninvestigational medicinal products	Formulation[a]	Route of administration	Dose regimen
Paracetamol (acetaminophen)		PO	Paracetamol (acetaminophen) will be given 15 to 30 minutes (but no longer than 60 minutes) before isatuximab infusion and at dose per weight as follows: ≤10 kg: 7.5 mg/kg, >10 to 50 kg: 15 mg/kg, and >50 kg: 1 g.
Diphenhydramine or equivalent		IV	Diphenhydramine or equivalent will be given at a dose of 1 mg/kg, 15 to 30 minutes (but no longer than to 60 minutes) before isatuximab infusion.
Montelukast		PO	Montelukast should be given to a child under adult supervision, before isatuximab infusion. The recommended dosage for pediatric participants: • Montelukast is not recommended for participants less than 2 years of age • 4 mg for participants 2 to 5 years of age • 5 mg for participants of 6 to 14 years of age • 10 mg for participants ≥15 years of age.
Folinic acid (Leucovorin®)		PO, IM, or IV	Folinic acid should be administered 48 hours after the start of methotrexate infusion at a dose of 30 mg/m² PO, IM, or IV and 15 mg/m² at 54 hours. Folinate rescue can be extended at the Investigator's discretion.

Noninvestigational medicinal products	Formulation[a]	Route of administration	Dose regimen
Dexamethasone		PO or IV	Dexamethasone is part of isatuximab premedication in the AML cohort only, and will be given as premedication for prevention of infusion associated reactions before each administration of isatuximab, at least 15 to 30 minutes (but no longer than 60 minutes) prior to infusion. Dexamethasone 10 mg/m^2 (maximum 20 mg) IV or PO on Days 1, 8, and 15 during the induction period (mandatory for Cycle 1 and before first isatuximab infusion at Cycle 2).
Cyclophosphamide		PO or IV	Cyclophosphamide is a part of rescue cytoreductive chemotherapy up to 1 g/m^2 PO or IV for 1 day before first isatuximab treatment recommended for ALL
Hydroxyurea		PO	Hydroxyurea is a part of rescue cytoreductive chemotherapy 50-75 mg/kg/day PO for 4-5 days with or without steroids before first isatuximab treatment recommended for AML
Cytarabine		IV	Cytarabine is a part of rescue cytoreductive chemotherapy up to 1 g/m^2 IV every 12 hours for up to 2-3 days before Isatuximab administration recommended for AML

IM = intramuscular(ly); IV = intravenous(ly); PO = oral.

a Noninvestigational medicinal products will be locally sourced and the formulation may vary.

Noninvestigational medicinal products (NIMPs) from available commercial supplies will be used for this study where applicable otherwise it will be relabeled by the Sponsor according to GMP guidelines before supplies are provided to the sites.

For isatuximab, the rate of infusion should be initiated at 2.5 mg/kg/hour (maximum 175 mg/hour):

- First infusion: initiate infusion at 2.5 mg/kg/hour (maximum 175 mg/hour). In the absence of IRs after 1 hour of infusion, increase the infusion rate by 0.5 mg/kg/hour increments every 30 minutes, to a maximum of 5.5 mg/kg/hour (maximum 400 mg/hour).
- Subsequent infusions: initiate infusion at 2.5 mg/kg/hour (maximum 175 mg/hour). In the absence of IR after 1 hour of infusion, increase the infusion rate by 1.0 mg/kg/hour increments every 30 minutes, to a maximum of 5.5 mg/kg/hour (maximum 400 mg/hour).

A mandatory monitoring of patients after every isatuximab infusion for 2 hours after the infusion should be set up. Please see Section 8.2.2.

In case of the presence of IR, please see Section 6.6.1 for guidelines for the management of potential IRs.

Other IMPs should be prepared and administrated per the site's clinical practice unless otherwise indicated in the protocol.

In all 3 disease cohorts, participants will receive 1 administration of single-agent isatuximab on Day 1. Starting on Day 8, combination chemotherapy will be added.

All participants will receive the following premedication to prevent or reduce incidence or severity of IRs at least 15 to 30 minutes (but no longer than 60 minutes except for Montelukast that should be 2 hours) prior to the isatuximab infusion. For participants who do not experience an IR during the first 4 administrations of isatuximab, the need for premedication at the subsequent infusions may be reconsidered at the Investigator's discretion in consultation with the Sponsor, with the exception of dexamethasone administered as a part of study treatment in ALL cohorts (Days -3 to -1, 15 to 19, 29 to 33 and 43 to 47) that should be administered as planned, unless there are dose modifications related to toxicities.

The recommended isatuximab premedication agents are: montelukast, diphenhydramine (or equivalent), methylprednisolone, and acetaminophen (paracetamol) PO. Taking into consideration the disease context and the frequent use of steroids in acute leukemia, methylprednisolone will be replaced by dexamethasone.

Prophylaxis for tumor lysis syndrome and CNS relapse may be administered at the discretion of the treating physician during the treatment period. In case of CNS involvement, participant will be treated in parallel with IT chemotherapy as per the site's clinical practice. IT prophylaxis is mandatory for all cohorts; the drugs that will be used (methotrexate/aracytine/steroids) are per investigator discretion (only one drug, or two or all three).

In patients with high tumor burden (WBC counts higher than 20 x 10^9/L with or without pulmonary leukostasis, or significant organ involvement as per Investigator's judgement), a rescue cytoreductive chemotherapy before study treatment start is mandatory. In order to have rapid control of the tumor burden, in addition to dexamethasone pre-dose mandatory in ALL cohorts, the administration of following cytoreductive therapies are proposed (these are examples):

- cyclophosphamide up to 1 g/m² PO or IV for 1 day before first isatuximab treatment for ALL
- hydroxyurea 50-75 mg/kg/day PO for 4-5 days with or without steroids before first isatuximab treatment for AML
- cytarabine up to 1 g/m² IV every 12 hours for up to 2-3 days before first isatuximab treatment for AML

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

The dexamethasone in oral form may be supplied at the site or from the PI/site/Sponsor to the participant via a Sponsor-approved courier company where allowed by local regulations and agreed upon by the participant.

For a regional or national emergency declared by a governmental agency that results in travel restrictions, confinement, or restricted site access, contingency measures are included in

Section 10.9: Contingency Measures for a regional or national emergency that is declared by a governmental agency.

6.1.1 Acute myeloid leukemia combination therapies

AML combination therapies:

In the AML cohort, up to 2 cycles of induction will be given as defined in the SOA (Section 1.3). Dosing instructions and premedication are described in Section 6.1.

Cycle 2 (second induction):

If the BM aspiration performed 1 week after the end of induction treatment shows less than 20% blasts, a second cycle of combination therapy can be administered if neutrophils of $\geq 500/mm^3$ and platelets of $\geq 50\ 000/mm^3$, while keeping the same schedule and doses. Anthracyclines are optional in Cycle 2 (as well as Cycle 1 Days 10 and 12) and will be administered at the Investigator's discretion. The choice of anthracyclines is at the Investigator's discretion (either liposomal daunorubicin, nonliposomal daunorubicin, or idarubicin) and the same anthracycline should be used throughout the study.

6.1.2 T-ALL and B-ALL combination therapies

In the ALL cohorts, the treatment period will include 1 induction and 1 consolidation cycle. Dosing scheduled is defined in the SOA (Section 1.3). Dosing instructions and premedication are described in Section 6.1 (Table 4).

The choice of anthracyclines is at the Investigator's discretion (either doxorubicin or mitoxantrone) and the same anthracycline should be used throughout the study.

Prophylaxis for tumor lysis syndrome and CNS relapse may be administered at the discretion of the treating physician during the treatment period. In case of CNS involvement, the participant will be treated in parallel with IT chemotherapy as per the site's clinical practice.

Folinic acid (Leucovorin®) should be administered 48 hours after the start of methotrexate infusion at a dose of 30 mg/m^2 PO, IM, or IV and 15 mg/m^2 at 54 hours. Folinate rescue can be modified at the Investigator's discretion.

Before starting consolidation cycle, the patient must have neutrophils of $\geq 500/mm^3$ and platelets of $\geq 50\ 000/mm^3$.

In ALL patients treated with pegaspargase or L-asparaginase (Erwinase) daily monitoring of INR, PTT, fibrinogen and AT-III must be performed and fibrinogen and AT-III substituted, if necessary.

6.1.3 Mandatory evaluations on Day 1 prior to the first isatuximab administration

In order to thoroughly evaluate the patient's status on Day 1, before initiation of the first infusion of isatuximab, a chest X-ray, a hematology test including WBC with differential to rule out leukocyte elevation, and a biochemistry panel (including potassium, phosphorus, uric acid, corrected and ionized calcium) to exclude TLS should be performed and results assessed by an Investigator. If it is not possible to organize chest X-ray on Day 1 prior it can be done on Day -1 or Day -2. If it is not possible to assess potassium, phosphorus, uric acid, corrected and ionized calcium prior to the infusion on Day 1, it can be done on Day -1 or Day -2, and only in case this is not possible – on Day -3. Additional evaluations such as blood cultures would be performed if infection is suspected. Please see Section 1.3.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

Isatuximab concentrate for solution for infusion will be diluted in an infusion bag with 0.9% sodium chloride solution or 5% dextrose solution to achieve the appropriate drug concentration for infusion.

Infusion via a central line is preferred if available. In case of participants with local intolerance after peripheral IV infusion, the decision to use a central line is left to the Investigator. The final infusion volume corresponding to the dose of isatuximab will be administered by IV infusion for the period of time that depends on total dose administered.

Prior to dosing, each participant's dose will be individually prepared by the study pharmacist and labeled with the protocol number, participant number, and treatment description. The participant's weight should be measured prior to each treatment to allow calculation of the isatuximab dose. If the participant's weight on the day of the dose preparation is not available, the most recent participant's weight may be used, assuming it was assessed in a reasonable time frame and the participant did not have any events leading to significant weight loss (more than 10%) according to Investigator assessment. In such cases, the participant's weight should still be assessed on the day of administration to ensure the accuracy of the dose preparation.

For infusion, an IV tubing administration set with a 0.20 µm in-line filter will be used; if an in−line filter is unavailable, a 0.20 µm filter unit may be attached to the administration set before administration. Further details are provided in the Pharmacy Manual.

For other IMPs, please refer to the product approved leaflet for further information.

The following conditions for drug storage and accountability apply:

1. The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area

in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.

3. The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
4. Further guidance and information for the final disposition of unused study interventions are provided in the pharmacy manual.

Any quality issue noticed with the receipt or use of isatuximab (deficiency in condition, appearance, pertaining documentation, labeling, expiration date, etc) must be promptly notified to the Sponsor. Some deficiencies may be recorded through a complaint procedure (see Section 8.3.6).

A potential defect in the quality of isatuximab 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 isatuximab and eliminate potential hazards.

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

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

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

Isatuximab is to be stored at +2°C to +8°C (36°F to 46°F), is not to be frozen, and is to be protected from light. All containers 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.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

This is a nonrandomized and noncontrolled study. No blinding or randomization will be used for this study.

6.4 STUDY INTERVENTION COMPLIANCE

Administration of the IMPs will be supervised by the Investigator or sub-Investigator.

The person responsible for drug dispensing is required to maintain adequate records of the IMPs. These records include the date IMPs are received from the Sponsor, dispensed to the participant, and destroyed or returned to the Sponsor. The packaging batch number and the treatment number must be recorded on the drug accountability form. The person responsible for drug administration to the participant will record precisely the date and the time of the drug administration to the participant.

Deviation(s) from the prescribed dosage regimen should be recorded in the eCRF.

6.5 CONCOMITANT THERAPY

Participants should receive full supportive care, including transfusions of blood and blood products, antibiotics, antiemetics, allopurinol, etc, when appropriate. Prophylaxis and treatment for tumor lysis syndrome are recommended (see Section 6.6.4).

The mandatory cytoreductive chemotherapy drugs should be administered before isatuximab infusion in patient with high tumor burden at screening are cyclophosphamide (ALL), hydroxyurea (AML), or cytarabine (AML) and dexamethasone. Refer to Section 6.5.1 for details.

Treatment with hormones or other chemotherapeutic agents must not be administered except for steroids given for adrenal failure; and hormones administered for nondisease-related conditions (eg, insulin for diabetes).

Steroids may be used to treat and/or prevent hypersensitivity reactions or transfusion reactions. Brief use of corticosteroids as antiemetics is permitted but not recommended in these immunocompromised participants. Their use must be reported in participant records.

In the ALL cohorts, myeloid growth factors should not be used routinely or prophylactically but are permitted as indicated by the American Society of Clinical Oncology guidelines for neutropenic participants with prognostic factors that are predictive of clinical deterioration such as pneumonia, hypotension, multi-organ dysfunction (sepsis syndrome) or fungal infection. The use of G-CSF (filgrastim, polyethylene glycol [PEG]-filgrastim, etc) must be documented and reported in the participant's records.

In the ALL cohorts, folinic acid is to be administered after methotrexate infusion in the consolidation period, at 48 and 54 hours. Folinate rescue can be modified at the Investigator's discretion.

The use of epoetin or darbepoetin in this protocol is permissible but not recommended.

Pneumocystis prophylaxis should be provided as per the site's clinical practice.

Antimicrobial prophylaxis (bacterial, viral, and fungal) as per the National Comprehensive Cancer Network (NCCN) guidelines or site's clinical practice is recommended.

Prophylactic heparin therapy is recommended for participants receiving pegaspargase, as well as use of anti-allergy premedication as per site clinical practice in order to decrease the risk of allergic reactions.

Effect of coadministered drugs on isatuximab: Isatuximab is a mAb and is likely to be eliminated by proteolytic degradation. Thus, drugs that impact cytochrome P450 (CYP) or transporter expressions are not anticipated to alter the PK of isatuximab.

Effect of isatuximab on other drugs: Direct drug-drug interactions (DDI) via CYP enzymes or transporters is not expected because isatuximab is a therapeutic mAb. However, potential risks of DDI caused by isatuximab due to the alteration of cytokine levels were taken into consideration. The activity of drug metabolizing enzymes, such as CYPs, can be modified during altered immunological states (eg, inflammation), and modulators of proinflammatory cytokines have been shown to affect both CYP expression and enzyme activity. However, based on a physiologically based PK (PBPK) model, transient elevation of cytokines, such as interlukin-6 and interferon-γ, is predicted to have only a limited effect on CYP activities with low potential for DDIs.

Hepatitis B vaccination could be considered, following investigator's discretion, for patients with negative HBsAg, total anti-HBc, anti-HBs and HBV-DNA. At least 3 doses of vaccine will be administered at monthly intervals, the first one 1-2 weeks before start of study treatment. Anti-HBs should be monitored at 1, 2 and 3 months after end of vaccination. Anti-HBs above 100 mU/mL will indicate a good seroconversion, between 10 and 100 mU/mL moderate seroconversion that can be limited in time, less than 10 mU/mL will indicate no response to vaccination.

If antiviral therapy for HBV or HCV was started before initiation of IMP and patient was eligible for the trial, the antiviral therapy for HBV or HCV should continue throughout the treatment period as recommended by specialist. In case of trial testing combo, to check that there is no DDI with the drug associated with isatuximab.

Patient not having been tested for HBV/HCV at screening that are still on treatment at the time of the amended protocol 4 will need to be tested additionally for HBsAg, anti HBs, anti-HBc (total and IgM), anti-HCV, HCV RNA level.

In case of viral reactivation during study treatment (greater than 1 $\log_{10}$ IU/mL increase in HBV DNA or reappearance of HBsAg or detection of HBV DNA in patients with resolved infection*), (*defined as previous known history of acute or chronic hepatitis B or the presence of total anti HBc Ab with/without anti-HBs Ab; HBsAg negative; undetectable serum HBV DNA; and normal ALT levels) study treatment will be held, and specialist consulted for initiation of anti-viral treatment and monitoring of the patient. Restart of study treatment should be agreed between the Sponsor, the Investigator and specialist (hepatologist) if infection is controlled. ALT and AST will be closely monitored every month up to study treatment discontinuation. HBV DNA to be done as per specialist advice.

Administration of any live vaccine from 30 days before the first IMP administration until 90 days after the last IMP administration is forbidden.

6.5.1 Rescue medicine

In patients with high tumor burden (WBC count higher than 20 x 10^9/L or significant organ involvement as per Investigator's judgement), a rescue cytoreductive chemotherapy before study

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

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

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

In case of Grade 2 or higher CRS event, anti-IL6 therapy (for example, tocilizumab) may be started as a rescue therapy. For more details, see Section 6.6.3 (guidelines for CRS management).

6.6 DOSE MODIFICATION

Dose modifications different from those stated in the protocol should only be made in consultation with the Sponsor unless required for immediate participant safety.

Isatuximab: within a cycle (induction or consolidation), an isatuximab administration can be delayed for up to 1 day in case of weekly administration or 2 days for every 2 weeks administration. 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.

Administration of other IMPs in the study intervention will be discontinued/modified in the event of a treatment-emergent AE (TEAE) that persists despite appropriate dose modifications or any other AE that, in the opinion of the Investigator, warrants discontinuation or dose modification.

If there is a suspicion of anaphylaxis of any degree, every effort should be made to distinguish it from other IRs. If the suspicion of anaphylaxis persists or is confirmed, isatuximab (or any other product causally responsible for anaphylaxis) should be permanently disontinued.

The final decision will be per Investigator's judgment for the best interest of the participant.

In case of Grade 3 or 4 neurotoxicity or autoimmune events under fludarabine, no rechallenge with fludarabine is allowed.

In case of eGFR between 30 and 70 mL/min/1.73 m^2, the fludarabine dose will be reduced to 20 mg/m^2.

In case of hypersensitivity, allergy or non-allergic reaction to pegaspargase monitoring and treatment will be administered as per the site's clinical practice or NCCN guidelines.

Pegaspargase IV infusion should last at least 2 hours, infusion of normal saline and use of anti-allergy premedication (such as montelukast, hydrocortisone, diphenhydramine, paracetamol) should be administered, in order to reduce the incidence and severity of adverse events and the need for substitution with L-asparaginase (Erwinase).

For further information, please refer to the products' product approved leaflet.

The term IR indicates only a specific temporal relationship with the infusion and does not specify a particular mechanism underlying the signs or symptoms. Note that an IR is different from the diagnostic terms 'anaphylactic reaction' 'anaphylactoid reaction' or 'cytokine release syndrome (CRS), which does imply a specific pathophysiologic mechanism, and may or may not be an IR (see Section 6.6.2 for anaphylaxis and see Section 6.6.3 for CRS).

This study has specific instructions for IRs, CRS, and anaphylactic reaction.

6.6.1 Guidelines for the management of potential infusion reactions

Participants should routinely receive premedication prior to isatuximab infusion as detailed in Section 6.1 to reduce the risk and severity of IRs commonly observed with mAbs. Infusion reactions are defined as AEs related to isatuximab with onset within 24 hours from the start of the infusion and assessed as related to an IMP (National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] Version 5.0 term "allergic/hypersensitivity reactions" or "cytokine release syndrome/acute infusion reaction"). For the NCI Consensus Guideline for cytokine release syndrome is in Section 6.6.3.

Please refer to the current edition of the IB for IR manifestations reported in participants treated with isatuximab.

In case of an IR while receiving or after isatuximab administration, additional medication can be provided for symptom treatment as per the Investigator's judgment including epinephrine, diphenhydramine 1 mg/kg IV (or equivalent; maximum of 25 mg) and methylprednisolone 2 mg/kg IV (maximum of 100 mg), IV fluids, vasopressors, oxygen, bronchodilators, and acetaminophen (paracetamol). These participants must be informed of the potential risk of recurrent IRs.

Further treatment with isatuximab (subsequent infusions) is to be started at 2.5 mg/kg/hour and follow the same rule in case of an IR.

Once a Grade 2 IR leading to interruption has improved to Grade ≤1, the infusion may be restarted at one-half (1.25 mg/kg/hour) of the initial infusion rate. If symptoms do not recur after 30 minutes, the infusion rate may be increased in 0.50 mg/kg/hour increments every 30 minutes, to a maximum of 5.5 mg/kg/hour (maximum of 400 mg/hour).

Participants with a Grade 3 or 4 IR must follow rules described in the Table 6 and appropriate supportive therapy should be administered.

Grade 1 IRs lasting more than 24 hours and Grade 2 or higher IRs, regardless of duration, must be reported as AEs of special interest (AESIs) (see Section 8.3).

Recommendations for management of IRs are described in Table 6.

If there is a suspicion of anaphylaxis of any degree, every effort should be made to distinguish it from other IRs. If the suspicion of anaphylaxis persists or is confirmed, isatuximab (or any other product causally responsible for anaphylaxis) will be permanently discontinued.

The final decision will be per Investigator's judgment for the best interest of the participant.

Table 6 - Management of infusion reactions

NCI-CTCAE Version 5 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 participant's clinical status. Isatuximab infusion may be stopped at any time if deemed necessary. If stopped, the IR will be classified as Grade 2 as per NCI-CTCAE Version 5.0. Grade 1 IRs lasting more than 24 hours must be reported as AESIs.
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 diphenhydramine 1 mg/kg IV (or equivalent; maximum of 25 mg) and/or methylprednisolone 2 mg/kg IV (maximum of 100 mg) as needed. Isatuximab may be resumed only after participant recovery, with a slower infusion rate and with close monitoring. All Grade 2 IRs must be reported as AESIs.
Severe Grade 3 **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	If a Grade 3 infusion-related AE occurs, the isatuximab infusion must be interrupted, and the patient observed carefully and treated as needed until the AE either resolves or improves to Grade 1. Then, at the investigator's discretion, the infusion may be restarted at half the infusion rate before the interruption. The infusion rate may be increased subsequently, at the investigator's discretion. Please refer to Section 6.6.2. If after restarting the infusion, the severity of an infusion-related AE returns to Grade 3, the infusion can be interrupted and restarted again (as described above) at the investigator's discretion. If the same Grade 3 infusion-related AE occurs for a third time, treatment with isatuximab will be permanently discontinued for that patient. All Grade 3 IRs must be reported as AESIs.
Severe or life-threatening (Grade 4) Grade 4: life-threatening consequences; urgent intervention indicated	Stop isatuximab infusion. Give additional premedication with diphenhydramine 1 mg/kg IV (or equivalent; maximum of 25 mg), and/or methylprednisolone 2 mg/kg IV (maximum of 100 mg), and/or epinephrine as needed. Definitive treatment discontinuation. For signs or symptoms of anaphylaxis, please refer to Section 6.6.2. All Grade 4 IRs must be reported as AESIs.

AE = adverse event; AESI = adverse event of special interest; IAR = infusion associated reaction; IR = infusion reaction; IV = intravenous; NCI-CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; NSAIDs = nonsteroidal antiinflammatory drugs.
Infusion should be completed within 16 hours from the end of infusion preparation or a new infusion should be prepared with the remaining dose to be administered the same day.

In case of allergic reactions to pegaspargase, or L-asparaginase (Erwinase), either these NCCN guidelines or the site's clinical practice should be followed.

6.6.2 Guidelines for the management of anaphylaxis

Evidence-based guidelines for the diagnosis and management anaphylaxis has been published by the National Institute of Allergy and Infectious Disease (36). Analogous guidelines for the diagnosis and management of anaphylaxis have been published by the European Academy of Allergy and Immunology and the European Society for Oncology (37).

Anaphylaxis is a severe, potentially life-threatening systemic hypersensitivity reaction, only Grade 3 and Grade 4 are defined in the NCI-CTCAE v 5.0 (38) as a disorder characterized by an acute inflammatory reaction resulting from the release of histamine and histamine-like substances from mast cells, causing a hypersensitivity immune response. Clinically, it presents with breathing difficulty, dizziness, hypotension, cyanosis and loss of consciousness and may lead to death. It is characterized by being rapid in onset with life-threatening airway, breathing, or circulatory problems and is usually, although not always associated with skin and mucosal skin changes. Please see Table 7 below for the clinical criteria for diagnosing anaphylaxis (36).

Table 7 - Clinical criteria for diagnosing anaphylaxis

Anaphylaxis is highly likely when anyone of the following criteria is fulfilled:

1. Acute onset during or after treatment exposure of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips–tongue–uvula AND AT LEAST ONE OF THE FOLLOWING
   a) Respiratory compromise (eg, dyspnea, wheeze–bronchospasm, stridor, reduced PEF, hypoxemia)
   b) Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)
2. Two or more of the following that occur rapidly after treatment exposure:
   a) Involvement of the skin–mucosal tissue (eg, generalized hives, itch-flush, swollen lips–tongue–uvula
   b) Respiratory compromise (eg, dyspnea, wheeze–bronchospasm, stridor, reduced PEF, hypoxemia)
   c) Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)
   d) Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)

Notes: PEF, peak expiratory flow; BP, blood pressure.
*Low systolic blood pressure for children is defined as<70 mmHg from 1 month to 1 year, less than (70 mmHg+[2*age]) from 1 to10 years and<90 mmHg from 11 to 17 years.

Anaphylaxis should lead to immediate interruption of ongoing infusion, and to permanent discontinuation of isatuximab and any chemotherapy suspected of inducing the anaphylactic reaction.

Management should be prompt and may include but is not limited to administration of epinephrine, IV fluids, antihistamines, oxygen, vasopressors, corticosteroids, as well as increased monitoring of vital signs as medically indicated, until the participant recovers.

Note that these guidelines place **epinephrine as the first intervention for anaphylaxis**. It is stated that there is no absolute contraindication to treatment with epinephrine in a patient experiencing anaphylaxis (37).

6.6.3 Cytokine-release syndrome (CRS)

CRS should be suspected in a participant with fever, which may be accompanied by tachypnea, tachycardia, hypotension, hypoxia or other findings. The diagnosis of CRS requires fever (≥38.0°C), with or without hypotension, hypoxia, and/or organ dysfunction that can start within hours or days after IMP treatment. CRS may also occur within minutes of or after the infusion start and therefore may overlap with an anaphylactic reaction, an infusion reaction of unknown mechanism, TLS, infections, sepsis. Other causes that could mimic CRS should be excluded. The Investigator should use his clinical judgement for making the correct diagnosis.

Early signs of cytokine release syndrome should also prompt a thorough clinical assessment to identify the involvement of a specific organ system, including neurological system to identify potential immune effector cell-associated neurotoxicity syndrome (ICANS) see Section 10.6.7.

Laboratory tests are not required to diagnose CRS, however, since CRP and ferritin levels are usually elevated in patients with CRS, they will be collected to distinguish CRS from other conditions. Cytokine levels will be assessed as part of safety markers and investigations to exclude infection. Potassium, corrected calcium, phosphorus, uric acid, blood urea nitrogen, and serum creatinine should be evaluated to differentiate from TLS and repeated daily. Grade 1 CRS with flu-like symptoms can also be reported as Grade 1 or Grade 2 flu-like symptoms depending on severity of the symptoms as per NCI-CTCAE v 5.0 (38). Flu-like symptoms are similar to those observed in patients with the flu influenza and includes fever, chills, body aches, malaise, loss of appetite and dry cough.

Since these recommendations concern CRS induced by therapeutics other than chimeric antigen receptor T (CAR-T) cells, NCI-CTCAE v 5.0 grading will be used. While fever is absolutely required, it must not be attributable to any other cause. In participants who develop CRS and receive antipyretic and anti-cytokine therapy, fever is no longer required to grade CRS toxicity and grading is driven by hypotension and/or hypoxia (39).

Although there is limited data tocilizumab us in the management of CRS induced by therapeutics other than CAR-T cell therapy, it appears that it may be less effective than steroids in these settings (39).

Observation in intensive care unit (ICU) is required in case a participant develops hemodynamic or respiratory compromise and ICU should be staffed by a critical care physician who has experience in treating CRS.

In case a CRS event occurs, chest X-ray and WBC counts must be repeated daily. Please refer to Section 1.3 for other biological parameters.

Guidelines for management CRS events according to severity grading are provided in Table 8.

Table 8 - Guidelines for the management of Cytokine Release Syndrome (CRS)

Event severity (NCI-CTCAE v 5.0 criteria)	Recommended IMP dose modification and supportive care guidelines
Mild Grade 1 Fever, with or without constitutional symptoms	Continuation of an IMP infusion is as per the judgment of the Investigator under close monitoring of the participant's clinical status. IMP infusion may be stopped at any time if deemed necessary. If stopped, IMP may be resumed only after participant's recovery, with a slower infusion rate and with close monitoring. Appropriate symptomatic treatment may include but is not limited to IV fluids (care should be taken to not excessively hydrate if evidence of vascular leak), antihistamines, nonsteroidal anti-inflammatory drugs (NSAID) and acetaminophen. Close direct monitoring of the patient's clinical status. Clinical and laboratory monitoring should initially be performed daily, then less frequently as the participant improves. A blood sample should be collected to measures cytokines.
Moderate Grade 2 Hypotension responding to fluids. Hypoxia responding to <40 percent FiO_2	Temporarily interrupt IMPs, if the events occur during the infusion. If an event of CRS of Grade 2, isatuximab will be permanently discontinued. Additional appropriate medical therapy may include but is not limited to IV fluids (care should be taken to not excessively hydrate if evidence of vascular leak), antihistamines, NSAIDs and acetaminophen. Monitoring of vital signs, cardiac and other organ functions closely as medically indicated should be increased until the participant recovers. Transfer to ICU may be required. For patients with comorbidities, older age, or with oxygen requirement, hypotension, or patients in whom symptoms (eg, high grade fever) that do not respond to antipyretics within 72 hours treatment with corticosteroids and/or tocilizumab may be considered. IMP (except isatuximab) may be resumed when clinical symptoms have resolved or improved to Grade 1 and corticosteroid taper. No dose modification is required but decreasing to half the infusion rate can be considered. A blood sample should be collected to measures cytokines.
Severe or Life-threatening Grade 3 Hypotension managed with one vasopressor. And/or hypoxia responding to ≥40 percent FiO2	If CRS Grade 3, isatuximab should be permanently discontinued. Temporarily interrupt other IMPs, if the events occur during the infusion. The participant can continue treatment with other IMPs without dose modification. IV corticosteroids should be initiated, and tocilizumab may be considered, and/or epinephrine or another vasopressor should be administered as needed. Participants with severe CRS may require management in intensive care setting, with monitoring of clinical status and laboratory tests performed at least daily. As the participant improves, the intensity of the monitoring and setting can be decreased, but the participant should not be discharged from the hospital until clinically stable. Corticosteroids can then be administered IV or orally every 8 hours for up to 3 days, then tapered over 4 days. In general, tapering of steroids can start when vasopressors and high-flow oxygen are no longer needed.

Event severity (NCI-CTCAE v 5.0 criteria)	Recommended IMP dose modification and supportive care guidelines
	CRS is considered resolved when there is a sustained resolution of fever and there is no longer a need for oxygen supplementation to relieve hypoxia nor vasopressors to maintain blood pressure; however, normalization of temperature alone does not define resolution of CRS. If no clinical improvement in oxygenation, hypotension, fever, and other CRS manifestations is observed within 24 to 72 hours, management for persistent or worsening CRS should be initiated. Re-evaluation of other contributing conditions should be done, such as infection, cardiac, thromboembolic and other complications. Intravenous Tocilizumab at 8 mg/kg (for patients weighing ≥30 kg) or 12 mg/kg (for patients weighing <30 kg) should be considered, and steroids should be administered concurrently. If still no improvement in oxygenation, hypotension, fever and other manifestations is observed after the first dose of tocilizumab, it may be repeated after an interval of at least 8 hours and should not exceed 4 doses in total. A blood sample should be collected to measures cytokines.
Grade 4 Life-threatening consequences; urgent intervention indicated	If CRS Grade 4, all IMPs should be permanently discontinued. In addition to recommendations listed for Grade 3 for participants with severe CRS who fail to improve after repetitive treatment with both tocilizumab and steroids, alternative options should be discussed with clinical site specialists. A blood sample should be collected to measures cytokines.

6.6.4 Guidelines for the management of tumor lysis syndrome

Tumor lysis syndrome may occur and is a life-threatening event. Hydration is recommended for all participants prior to Cycle 1 infusions and is left to Investigator judgment for further cycles.

The participants at greatest risk of tumor lysis syndrome (TLS) are, as an example, those with high tumor burden prior to treatment, elevated uric acid level, receiving intensive cytoreductive therapy, poor hydration or tumor infiltration of the kidney.

These participants should be monitored closely, and appropriate precautions should be taken (such as systematic use of prophylactic uric acid lowering agents [eg, allopurinol or rasburicase], regular measurement of electrolytes).

Prophylaxis against TLS may be required depending on the participant's risk for TLS, as described below.

Low risk is defined as:

- Participants with low tumor burden (WBC $\leq 50 \times 10^9$/L and normal lactic acid dehydrogenase [LDH] level)
- Participants receiving low intensity cytoreductive therapy

- Normal preexisting uric acid
- Adequate hydration
- No tumor infiltration in the kidney

High risk is defined as:

- Hematological malignancies with high proliferative rate
- High tumor burden (WBC >50 × 109/L and high LDH level)
- Elevated uric acid level
- Participants receiving intensive cytoreductive therapy
- Poor hydration
- Leukemia infiltration of the kidney

Recommendations for IV hydration during isatuximab treatment in participants at high risk for TLS include the following:

- Normal saline solution 3 L/m^2/d, unless no symptoms of acute renal dysfunction and oliguria
- Maintain urine output >100 mL/m^2/h
- Diuretics may be required to maintain urine output at >100 mL/m^2/h: mannitol 0.5 mg/kg or furosemide 0.5 to 1.0 mg/kg

For high-risk participants, prophylactic treatment with allopurinol should begin 2 to 3 days before the start of antineoplastic therapy and continue for 10 to 14 days, as described:

- Allopurinol:
  - 100 mg/m^2/dose q8 hour (10 mg/kg/d divided q8 hour) oral (maximum 800 mg/d) or 200 to 400 mg/m^2/d in 1 to 3 divided doses IV (maximum 600 mg/d)
  - Reduce dose by 50% or more in renal failure
  - Adjust doses of drugs metabolized by P450 hepatic microsomal enzymes with concomitant allopurinol
- Rasburicase:
  - Avoid in glucose-6-phosphate dehydrogenase deficient participants
  - Immediate and permanent stop of treatment if methemoglobinemia is result
  - 0.05 to 0.20 mg/kg IV over 30 minutes
  - To measure uric acid levels, place blood sample immediately on ice to avoid continual pharmacological ex vivo enzymatic degradation
  - 10% incidence of antibody formation

Rasburicase is indicated for participants with the following features:

- High risk of TLS development
- Urgent need to initiate therapy in a participant with a high bulk of malignant disease
- In a situation where adequate hydration may be difficult or impossible
- Acute renal failure

Recommendations regarding the selection of allopurinol and/or rasburicase are summarized in Table 9.

Table 9 - Recommendations on selection of hypouricemic agents

	Allopurinol	**Rasburicase**
Uric acid level	Normal	Elevated
Tumor type	Nonhematological Hodgkin's lymphoma, Chronic myeloid leukemia	Burkitt's lymphoma, lymphoblastic lymphoma, ALL, AML
Tumor burden		
WBC count	≤50 × 10^9/L	>50 × 10^9/L
Lactic acid dehydrogenase	≤2 × normal	>2 × normal
Cytoreductive intensity	Mild	Aggressive
Kidney tumor infiltration	Absent	Present

ALL = acute lymphoblastic leukemia; AML = acute myeloid leukemia; WBC = white blood cell

Tumor lysis syndrome has to be managed according to the site's usual practice. Table 10 provides some parameters to be checked in case of TLS suspicion and high-level recommendations for TLS management. Abnormalities listed in Table 10 do not exclusively support TLS diagnosis and any differential diagnosis also needs to be assessed, if appropriate.

After recovery, study intervention can be re-administered as planned at the same dose.

Table 10 - Management of tumor lysis syndrome

TLS diagnosis	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 (<0.3 mmol/L)[a].	Omit study intervention 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 intervention 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, paresthesia, 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.	

TLS = tumor lysis syndrome.

a The corrected calcium level in milligrams per deciliter = measured calcium level in milligrams per deciliter + 0.8 × (4-albumin in grams per deciliter). The ionized calcium level in milligrams per deciliter = measured calcium level in milligrams per deciliter (total calcium) + 0.02*(40 – albumin in grams per deciliter).

6.6.5 Guidance in case of hepatitis B reactivation occurring under study treatment

In case of viral reactivation during study treatment (greater than 1 $\log_{10}$ IU/mL increase in HBV DNA or reappearance of HBsAg or detection of HBV DNA in patients with resolved infection) study treatment will be held and specialist consulted for initiation of anti-viral treatment and monitoring of the patient. Resolved infection means previous known history of acute or chronic hepatitis B or the presence of total anti-HBc Ab with/without anti-HBs Ab; HBsAg negative; undetectable serum HBV DNA; and normal ALT levels. Restart of study treatment should be agreed between the Sponsor, the Investigator and specialist (hepatologist) if infection is controlled. ALT and AST will be closely monitored every month up to study treatment discontinuation. HBV DNA to be done as per specialist advice.

6.7 INTERVENTION AFTER THE END OF THE STUDY

The IMPs will not be provided after the end of the treatment period.

The participant's treatment after discontinuation of the last IMP will be at the discretion of the treating physician.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

7.1.1 Definitive discontinuation

The study intervention should be continued whenever possible.

In case the IMP is stopped, it should be determined whether the interruption is temporary; definitive IMP discontinuation should be a last resort.

For the details of dose modification in the study intervention, please refer to Section 6.6.

Any IMP discontinuation must be fully documented in the eCRF. In any case, the participant should remain in the study as long as possible.

Definitive intervention discontinuation is any intervention discontinuation associated with the definitive decision from the Investigator not to re-expose the participant to the IMP at any time during the study, or from the participant not to be re-exposed to the IMP whatever the reason.

See the SOA for data to be collected at the time of intervention discontinuation and follow-up and for any further evaluations that need to be completed (Section 1.3).

Withdrawal from the intervention with IMPs may occur if, in the Investigator's opinion, continuation of the study intervention would be detrimental to the participant's well-being, such as:

- Disease progression
- Unacceptable AE
- Poor compliance to the study protocol
- Pregnancy (see Section 10.4)
- Any other reason such as intercurrent illness that prevents further administration of study intervention (will be specified)
- Participant is lost to follow-up

Any abnormal laboratory value or electrocardiogram (ECG) parameter will be immediately rechecked for confirmation before making a decision of definitive discontinuation of the IMP for the concerned participant.

Handling of participants after definitive intervention discontinuation

Participants will be followed up according to the study procedures specified in this protocol up to the scheduled date of study completion, or up to recovery or stabilization of any AE to be followed up as specified in this protocol, whichever comes last.

If possible, and after the definitive discontinuation of intervention, the participants will be assessed using the procedure normally planned for the last dosing day with the IMP including a PK sample, if appropriate.

All cases of definitive intervention discontinuation must be recorded by the Investigator or designee in the appropriate pages of the eCRF when considered as confirmed.

7.1.2 Temporary intervention discontinuation

Temporary intervention discontinuation may be considered by the Investigator because of suspected AEs or disruption of the clinical trial due to a regional or national emergency declared by a governmental agency (Section 10.9: Contingency Measures for a regional or national emergency that is declared by a governmental agency). For all temporary intervention discontinuations, duration should be recorded by the Investigator in the appropriate pages of the eCRF.

For dose modifications or dose delays, please refer to Section 6.6.

7.1.3 Rechallenge

For a regional or national emergency declared by a governmental agency, contingency measures are included in Section 10.9: Contingency Measures for a regional or national emergency that is declared by a governmental agency.

Reinitiation of intervention with the IMP will be done under close and appropriate clinical/and or laboratory monitoring once the Investigator will have considered according to his/her best medical judgment that the responsibility of the IMP(s) in the occurrence of the concerned adverse event was unlikely and if the selection criteria for the study are still met (refer to Section 5).

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants (or the LAR to the participants) may withdraw or discontinue the study for the following reasons:

- A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons.
- If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.
- See the SOA (Section 1.3) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

If participants no longer wish to take the IMP, they will be encouraged to remain in the study.

The Investigators should discuss with the participants the key visits to attend. The value of all their study data collected during their continued involvement will be emphasized as important to the public health value of the study.

Participants who withdraw from the study intervention should be explicitly asked about the contribution of possible AEs to their decision, and any AE information elicited must be documented.

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

In addition, a participant may withdraw his/her consent to stop participating in the study. Withdrawal of consent for intervention should be distinguished from withdrawal of consent for follow-up visits and from withdrawal of consent for nonparticipant contact follow-up, eg, medical record checks. The site should document any case of withdrawal of consent.

Participants who have withdrawn from the study cannot be re-enrolled in the study. Their inclusion and intervention numbers must not be reused.

7.3 LOST TO FOLLOW UP

Please refer to the SOA (Section 1.3).

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the site.

The following actions must be taken if a participant fails to return to the site for a required study visit:

- The site must attempt to contact the participant or the LAR to the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed "lost to follow-up", the Investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

8 STUDY ASSESSMENTS AND PROCEDURES

The following apply to all study assessments and procedures:

- Study procedures and their timing are summarized in the SOA (Section 1.3). Protocol waivers or exemptions are not allowed.
- Adherence to the study design requirements, including those specified in the SOA (Section 1.3), is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, BM assessment) and obtained before signing of the Informed Consent Form (ICF) may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within 1 month before Day 1 (Section 1.3).
- For a regional or national emergency declared by a governmental agency, contingency measures are included in Section 10.9: Contingency Measures for a regional or national emergency that is declared by a governmental agency.

8.1 EFFICACY ASSESSMENTS

To assess response, BM aspiration (or biopsy if clinically indicated), computed tomography (CT) of chest with IV contrast or positron emission tomography (PET)-CT or PET-MRI scans will be performed for extramedullary disease assessment, and peripheral blood sampling at the time points indicated in the flowchart (Section 1.2) and as summarized hereafter.

Bone marrow aspiration will be performed in accordance with the SOA (Section 1.3). In case hematological recovery cannot be reached for any reason, in both AML and ALL participants, BM aspiration could be done at any time if investigator does not expect any more hematological change and/or urgent need for therapeutic strategy decision. Any additional BM aspirations will be performed at the Investigator's discretion and should be reported in the eCRF. In case BM aspiration fails, BM biopsy could be an option. No BM assessment is necessary if nonresponse or progressive disease can be diagnosed with peripheral blood evaluation, or if a WBC $<300/mm^3$, or if the BM assessment is considered noncontributory by the Investigator. The BM assessment will be performed locally.

Extramedullary assessments are optional. For the extramedullary assessment of ALL, CT, PET-CT or PET-MRI scan are suggested to be performed as defined in the SOA (Section 1.3) if lymphomatous involvement is suspected. If not done, PET-CT or PET-MRI scan is suggested to be performed at screening if lymphomatous involvement is present. If positive at screening, the PET-CT or PET-MRI scan will be repeated at the time of CR in BM.

Extramedullary assessment of AML will be performed by physical examination if radiology assessment cannot be performed. A CT or PET-CT or PET-MRI scan can be performed if clinically indicated for the AML cohort.

Assessment of extramedullary disease will be performed locally.

Lumbar puncture with IT chemotherapy will be performed at time points indicated in the SOA (Section 1.3) and when clinically indicated. The assessment of CNS involvement by the lumbar puncture will be performed locally.

For ALL, MRD assessments are to be performed with BM aspiration at screening and with peripheral blood samples at the end of induction, at the time of hematological recovery, and/or at the time of each BM aspiration for disease assessment if CR or CRi is achieved. For AML, MRD assessments are to be performed with BM aspiration samples at the time of hematological recovery, and/or at the time of each BM aspiration for disease assessment if CR or CRi is achieved. Minimal residual disease assessments will be performed by central laboratories.

8.2 SAFETY ASSESSMENTS

Planned time points for all safety assessments are provided in the SOA (Section 1.3).

The NCI-CTCAE version 5.0 will be used in this study to grade the severity of clinical and laboratory AEs.

The safety profile will be mainly based on incidence, severity, and cumulative nature of TEAEs. Treatment-emergent AEs are defined as AEs that develop or worsen in grade or become serious during the on-treatment period.

Adverse events will be coded to a lower level term (LLT), preferred term (PT), high level term (HLT), high group level term, and associated primary system organ class (SOC) using the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events will be summarized with respect to the type, frequency, severity, seriousness, and relatedness.

The safety profile will be assessed from the findings of physical examination (preferably by the same physician), laboratory tests, etc, and will be based on incidence, severity, and cumulative nature of AEs.

8.2.1 Physical examinations

The following should be assessed during physical examinations:

- Examination of major body systems will include neurological examination, digestive, skin/mucosae, mediastinal, testicular involvements, respiratory, hepatomegaly, splenomegaly, and lymphadenopathy. Body weight and ECOG or Lansky score will also be measured and recorded. Height will be recorded only at screening.
- Testicular involvement should be assessed for male participants with ALL.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.
- Any new finding or worsening of a previous finding should be reported as a new AE.

8.2.2 Vital signs

Temperature, heart rate, respiratory rate, and blood pressure will be assessed at screening and preinfusion, to be measured just before starting infusion of isatuximab, 1 hour after starting the infusion, at the end of infusion, in 2 hours after every isatuximab infusion and as clinically indicated.

In case of high tumor burden at screening requiring cytoreductive chemotherapy or occurrence of CRS event, continuous monitoring of vital signs is required as per site clinical practice.

8.2.3 Electrocardiograms

A 12-lead ECG will be obtained as outlined in the SOA (Section 1.3), using an ECG machine that automatically calculates the heart rate and measures heart rate, QRS, QT, and QTc intervals. Clinically significant abnormalities should be reported as an AE, except for at the screening assessment if the detected finding is linked to a preexisting condition. In that case, the diagnosis should be recorded in the participant's medical history.

8.2.4 Cardiac assessment

Left ventricular ejection fraction measurement will be performed by echocardiogram, cardiac scintigraphy, or multigated acquisition scan at baseline, as clinically indicated during the study treatment period, and at the end of Cycle 2 (second induction for AML or consolidation for ALL).

8.2.5 Chest X-ray

Chest X-ray should be done at screening and as well mandatory done and assessed prior to the first infusion on Day 1. If it is not possible to organize on Day 1 prior it can be done on Day -1 or Day -2. In case of high tumor burden at screening requiring cytoreductive chemotherapy or occurrence of CRS event, chest X-ray must be repeated every day until the event is improved to Grade 1. CT-scan can also be used based on site's clinical practice.

8.2.6 Clinical safety laboratory assessments

See Appendix 2 (Section 10.2) for the list of clinical laboratory tests to be performed and to the SOA (Section 1.3) for the timing and frequency.

Hematology test is mandatory for all patients prior to the first isatuximab infusion on Day 1. Hematology test including WBC counts with differential should be assessed prior to the first isatuximab infusion. In case of high tumor burden at screening requiring cytoreductive chemotherapy or occurrence of CRS event, white blood cell count with differential must be repeated every day.

Please refer to sections Section 6.2 and Section 6.6.3 for CRS and for Section 6.6.4 for TLS guidance.

Where possible, blood volume sampling for each visit will be minimized to less than approximately 1% of total blood volume and less than approximately 3% of total blood volume over a 4-week period. If necessary, blood sampling related to patient safety and the primary endpoint of the study should be prioritized. Additional blood samples may be collected at the Investigator's discretion for participant safety monitoring.

- The Investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents. A vital sign or ECG abnormality or laboratory value is reported as an AE if it meets the definition of AE. See Appendix 3 (Section 10.3)
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 14 days the last dose of study intervention should be repeated until the values return to normal or baseline or stabilized or are no longer considered clinically significant by the Investigator or medical monitor
  - The etiology should be identified by the Investigator and the Sponsor notified.
  - All protocol-required laboratory assessments, as defined in Appendix 2 (Section 10.2), must be conducted in accordance with the Laboratory Manual and the SOA (Section 1.3).
  - If laboratory values from non-protocol-specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the Investigator (eg, SAE or AE or dose modification), then the results must be recorded in the eCRF.

8.2.6.1 Blood type phenotyping/genotyping

Blood typing and complete blood phenotyping (C,c; E,e; Kell. Kidd; Duffy; S,s is recommended, if not available, the site's standard will be followed) and indirect antiglobulin test (IAT) will be assessed in accordance with the SOA (Section 1.3). After the start of the study treatment, a new IAT assessment will be performed once. If the second test is positive, a dithiothreitol (DTT) test should be performed only if transfusions are required (in accordance with Section 10.6.6). Results of IAT (and DTT test, if applicable) will be recorded in the eCRF, including those performed prior to any transfusion during study intervention.

Transfusions are to be recorded in the eCRF. The transfusion service should be made aware that the participant is receiving an antiCD38 treatment (isatuximab). During the study intervention, 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 participant card. Participants should keep their study participant card with their blood type card together throughout the duration of the study intervention.

8.2.7 Suicidal risk monitoring

Not applicable.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

Adverse event of special interest

An AESI is an AE (serious or nonserious) of scientific and medical concern specific to the isatuximab program, for which ongoing monitoring and immediate notification by the Investigator to the Sponsor within 24 hours is required. Such AESIs 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 a protocol amendment.

- Pregnancy of a female participant entered in a study as well as pregnancy occurring in a female partner of a male participant entered in a study with IMP/NIMP;
  - Pregnancy occurring in a female participant entered in the study or in a female partner of a male participant entered in the study. It will be qualified as an SAE only if it fulfills one of the seriousness criteria (see Appendix 3 [Section 10.3]).
  - In the event of pregnancy in a female participant, the IMP should be discontinued.
  - Follow-up of the pregnancy in a female participant or in a female partner of a male participant is mandatory until the outcome has been determined (see Appendix 4 [Section 10.4]).
- Symptomatic overdose (serious or nonserious) with the IMP/NIMP.
  - An overdose (accidental or intentional) with the IMP is an event suspected by the Investigator or spontaneously notified by the participant (not based, for example, on systematic pills count) and defined as:
    - Infusion: increase of at least 30% of the dose to be administered in the specified duration or if the dose is administered in less than half the recommended duration of administration.
    - Oral: increase of at least 30% of the dose to be taken.
    - An overdose of the IMP or NIMP that meets the definition of an SAE.
- Of note, asymptomatic overdose should be reported as a standard AE.
- Infusion reaction: an IR is an AE related to isatuximab typically with onset within 24 hours from the start of the isatuximab infusion:
  - Infusion reaction of Grade 1 lasting more than 24 hours
  - Infusion reaction of Grade 2 or higher, regardless of duration.
- Seizures equal or greater than Grade 3

The definitions of an AE or SAE can be found in Appendix 3 (Section 10.3).

AE will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative. The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study intervention (see Section 7).

8.3.1 Time period and frequency for collecting AE and SAE information

All AEs and SAEs will be collected from the signing of the ICF until the last follow-up visit at the time points specified in the SOA (Section 1.3).

All SAEs, AESIs, and updated SAE data will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours of the data being available, as indicated in Appendix 3 (Section 10.3).

Investigators are not obligated to actively seek AEs or SAEs after conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the Investigator must promptly notify the Sponsor.

8.3.2 Method of detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3 (Section 10.3).

8.3.3 Follow-up of AEs and SAEs

After the initial AE/AESI/SAE report, the Investigators are required to proactively follow each participant at subsequent visits/contacts. At the prespecified study end-date, all SAEs, and nonserious AESIs (as defined in Section 8.3), will be followed until resolution, stabilization, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is given in Appendix 3 (Section 10.3).

8.3.4 Regulatory reporting requirements for SAEs

The following apply to the reporting of SAEs:

- Prompt notification by the Investigator to the Sponsor of any SAE is essential so that regulatory obligations and ethical responsibilities towards the safety of participants and the safe use of a study intervention under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs), and Investigators.
- Expected serious adverse reactions are specified in the Reference Safety Information (Section 8 of the isatuximab IB).

- Suspected unexpected serious adverse reactions (SUSARs) are reported to regulatory authorities, Investigators, and IRBs/IECs as follows (Note: A serious adverse reaction is considered "unexpected," if it is not listed in the Investigator Brochure in the section on Reference Safety Information):
  - For SUSARs that are life-threatening or result in death, reporting is no later than 7 days after first knowledge by the Sponsor, with all relevant follow-up information subsequently reported within an additional 8 days.
  - For SUSARs, other than those that are life-threatening or result in death, reporting is no later than 15 days after first knowledge by the Sponsor.
- An Investigator who receives a safety report describing an SAE, SUSAR, or any other specific safety-related information (eg, summary or listing of SAEs), from the Sponsor will review and file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements. It is the responsibility of the Sponsor to assess whether an event meets the criteria for a SUSAR, and therefore, is expedited to regulatory authorities.

8.3.5 Pregnancy

Details of all pregnancies in female participants and, if indicated, female partners of male participants will be collected after the start of study intervention and until 6 months after the last dose of isatuximab, or 12 months after the last dose of cyclophosphamide or start of another anticancer therapy.

If a pregnancy is reported, the Investigator should inform the Sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 4 (Section 10.4).

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, and ectopic pregnancy) are considered SAEs.

8.3.6 Guidelines for reporting product complaints

Any defect in the IMP/NIMP/device must be reported as soon as possible by the Investigator to the Monitoring Team that will complete a product complaint form within the required timelines.

Appropriate information (eg, samples, labels, or documents like pictures or photocopies) related to product identification and to the potential deficiencies may need to be gathered. The Investigator will assess whether or not the quality issue has to be reported together with an AE or SAE.

8.4 TREATMENT OF OVERDOSE

Symptomatic overdose (serious or nonserious) of study intervention: an overdose (accidental or intentional) with the study intervention is an event suspected by the Investigator or spontaneously notified by the participant and defined as an increase of at least 30% of the dose to be administered in the specified duration or if the dose is administered in less than half the recommended duration of administration.

Symptomatic overdose must be reported as an AESI.

8.5 PHARMACOKINETICS

8.5.1 Sampling time

The following blood collection time points are defined to measure isatuximab concentrations and conduct the PK analysis:

- The sampling times for blood collection can be found in the PK and immunogenicity flowchart (Section 1.3).
- It is of utmost importance to collect all blood samples at the specified times and according to the specifications.
- Samples missed or lost for any reason should be recorded. Actual dates and times of blood collection should be recorded in the eCRF. Actual dates and times of drug administration should also be precisely recorded.

8.5.2 Pharmacokinetic sample handling procedure

Detailed instructions for collection, sample preparation, storage, and shipment will be provided to the sites in a separate Laboratory Manual.

8.5.3 Bioanalytical methods

Bioanalytical methods are summarized in Table 11.

Table 11 - Bioanalytical methods for isatuximab pharmacokinetic analysis

Analyte	Isatuximab
Matrix:	Plasma
Analytical technique:	ELISA
Assay volume:	100 µL
Lower limit of quantification:	0.500 ng/mL
Site of bioanalysis:	Refer to PK Manual

ELISA = enzyme-linked immunosorbent assay; PK = pharmacokinetic.

8.5.4 Pharmacokinetic parameters

8.5.4.1 Population pharmacokinetic approach for isatuximab

Plasma concentrations of isatuximab will be used for population PK analysis by nonlinear 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 population PK parameters and interparticipant PK variability. Empirical Bayesian estimation of individual parameters and of individual exposure (AUCs, C_{max}, and C_{trough}) will also be performed. The PK estimates will then be investigated as prognostic factors for clinical outcome, including safety and efficacy endpoints, if possible.

8.6 PHARMACODYNAMICS

Pharmacokinetic and pharmacodynamics (PK/PD) parameters will be investigated as prognostic factors for clinical outcomes including safety and efficacy endpoints, if possible.

8.7 GENETICS

Not applicable.

8.8 BIOMARKERS

8.8.1 CD38 expression, receptor density, and receptor occupancy

CD38 expression, receptor density (RD) and receptor occupancy (RO) will be assessed and correlated with clinical response. Blood samples will be collected once on Day 1 predose and once on Day 15 predose. The testing will be limited to European countries and North America.

8.9 IMMUNOGENICITY ASSESSMENTS

Human antidrug antibody (ADA) to isatuximab will be assessed throughout the study. The sampling times for blood collection will be according to the schema and flowcharts in Section 1.2 and Section 1.3.

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

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 intervention administration should also be precisely recorded.

Detailed instructions for collection, sample preparation, storage, and shipment will be provided to the sites in a separate Laboratory Manual.

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

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 intervention administration.
- The ADA on-study observation period will be defined as the time from the first study intervention administration until the end of the study.
- Once a participant is off treatment, ADA samples will be collected 30 and 90 days after the last isatuximab administration. No additional ADA samples will be collected, regardless of the result of these samples (negative, positive or inconclusive).

Participants with at least 1 evaluable ADA result during the ADA pretreatment period will be considered as evaluable at baseline. Participants with at least 1 evaluable ADA result during the ADA on-study observation period will be considered evaluable during the on-study observation period.

8.10 HEALTH ECONOMICS

Not applicable.

8.11 DATA COLLECTION AFTER PREMATURE STOP OF THE STUDY IN CASE OF SPONSOR DECISION DUE TO STAGE 2 CRITERIA ARE NOT MET FOR ONE OF THE COHORTS

If the IA criteria are not met to move to Stage 2 and one of the cohorts is stopped only ongoing related AE/SAE data will be collected. Patients will be followed by phone for survival until final cut-off.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

T-ALL:

- Null hypothesis: complete response (CR + CRi) rate ≤60%
- Alternative hypothesis: CR rate ≥80%

B-ALL and AML:

- Null hypothesis: complete response (CR + CRi) rate ≤70%
- Alternative hypothesis: CR rate ≥85%

9.2 SAMPLE SIZE DETERMINATION

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

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

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

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

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

9.3 POPULATIONS FOR ANALYSES

For purposes of analysis, the following populations are defined (Table 12):

Table 12 - Populations for analyses

Population	Description
Enrolled	All participants who signed the ICF, regardless of whether the study intervention was received or not.
All-treated	The AT population will include all participants who received at least 1 dose (even incomplete) of study intervention. This population is the primary population for the analyses of safety parameters.
Evaluable	The evaluable population will include participants from the AT population who received at least 1 full dose of isatuximab in Cycle 1 and who had at least one valid response value that is evaluable. This population is the primary population for the analyses of efficacy parameters.
PK	The PK population will include all participants from the AT population with at least one available concentration post-baseline (whatever the cycle and even if dosing is incomplete) with adequate documentation of dosing and sampling dates and times.
ADA evaluable	The ADA evaluable population will include all participants from the AT population with at least 1 nonmissing ADA result during the on-study observation period.

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

For a regional or national emergency declared by a governmental agency, contingency measures are included in Section 10.9: Contingency Measures for a regional or national emergency that is declared by a governmental agency.

9.4 STATISTICAL ANALYSES

The statistical analysis plan will be developed and finalized before database lock and will describe the participant populations to be included in the analyses and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of primary, secondary, and other endpoints.

General statistical approach

Data from participants enrolled in 3 cohorts (T-ALL, B-ALL, and AML) will be analyzed separately.

Unless otherwise specified, analyses will be descriptive and performed on the AT population, except for the analyses of efficacy endpoints that will utilize the evaluable population. The baseline for a given parameter is defined as the last assessment for this parameter before the first study intervention administration.

Continuous data will be summarized using the number of available observations, mean, SD, median, minimum, and maximum by cohort and overall (where applicable). Categorical and

ordinal data will be summarized using the number and percentage of participants by cohort and overall (where applicable).

Planned date for analysis cut-off:

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

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

9.4.1 Efficacy analyses

All efficacy analyses (summarized in Table 13) will be performed based on the evaluable population for each ALL and AML cohort.

Response to treatment that will be analyzed is the response after 1 full dose of isatuximab in Cycle 1 (induction).

Table 13 - Efficacy analyses

Endpoint	Statistical analysis methods
Primary	
Complete response rate (CR + CRi)	Descriptive statistics and Clopper-Pearson method
Secondary	
DOR, EFS and OS	Kaplan-Meier method
MRD status	Descriptive statistics
ORR	Descriptive statistics and Clopper-Pearson method

CR = complete response: CRi = complete response with incomplete peripheral recovery; DOR = duration of response; EFS = event free survival; MRD = minimal residual disease; ORR = overall response rate; OS = overall survival.

9.4.1.1 Analysis of primary efficacy endpoint

The primary efficacy endpoint is the CR rate, defined in this study as the proportion of participants with CR or CRi.

The CR rate will be summarized with descriptive statistics on all evaluable population. An 80% confidence interval will be computed using the Clopper-Pearson method.

9.4.1.2 Analysis of secondary efficacy endpoints

The following secondary efficacy endpoints will be analyzed:

- Duration of response (DOR), event free survival (EFS), and OS will be analyzed using the Kaplan-Meier method. The Kaplan-Meier estimates of the 25th, 50th, and 75th percentiles and the 95% confidence intervals of median will also be computed. The Kaplan-Meier curves will be plotted.
- Minimal residual disease: Among participants who achieved CR or CRi, the number and percentage of participants by MRD status (negative and positive) will be provided in the evaluable population.
- Overall response rate, defined as the proportion of participants with a CR, CRi, or PR, will be summarized with descriptive statistics. An 80% confidence interval will be computed using Clopper-Pearson method.

9.4.2 Safety analyses

All safety analyses (Table 14) will be performed on the AT population for each ALL and AML cohort, and overall.

Table 14 - Safety analyses

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

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

9.4.2.1 Analyses of adverse events

The observation period will be divided into 3 segments: screening, on-treatment, and post-treatment:

- The screening period is defined as the time from when informed consent is signed until the first IMP administration.
- The on-treatment period is defined as from the time of the first IMP administration until the time of hematological recovery or new anticancer therapy is started or 30 days after the last IMP, whichever is first.
- The post-treatment period is defined as the time following the on-treatment period.

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

Post-treatment AEs are defined as AEs that are reported during the post-treatment period. Related AEs and any SAE ongoing at the end of treatment must be followed until resolution or stabilization. Any AEs or SAEs assessed as related to IMP that are new during the follow-up period will be reported and followed until recovery or stabilization.

The TEAEs will be coded according to the MedDRA dictionary. Adverse events will be graded according to the NCI-CTCAE Version 5.0. The grade will be taken into account in the summary. For participants with multiple occurrences of the same PT within an observation period, the maximum grade will be used.

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

- Treatment-emergent AEs
- Treatment-emergent adverse events of Grade ≥3
- Treatment-related TEAEs
- Serious TEAEs
- Serious treatment-related TEAEs
- Treatment-emergent AEs with a fatal outcome
- Treatment-emergent AEs leading to permanent treatment discontinuation
- Infusion reactions and other AESIs

The number and percentage of participants 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, AESIs, TEAEs leading to permanent or premature discontinuation, TEAEs leading to dose modification, serious TEAEs, TEAEs with fatal outcome, and AEs/SAEs occurring during the post-treatment dosing period.

Sorting within tables should ensure the same presentation for the set of all AEs within the observation period (screening, on-treatment, and post-treatment). For that purpose, the table of all

TEAEs will be presented by SOC and PT sorted by internationally agreed order unless otherwise specified.

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

9.4.2.2 Deaths

A summary of the number and proportion of participants who died by study period (screening, on-treatment period, and post-treatment) and cause will be generated. A listing of deaths will be provided.

9.4.2.3 Clinical laboratory evaluations

All laboratory abnormalities will be graded according to NCI-CTCAE Version 5.0, when applicable. Number (%) of participants with laboratory abnormalities (ie, all grades and by grade) using the worst grade during the on-treatment period will be provided for the AT population.

9.4.2.4 Vital signs

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

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

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

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

9.4.3 Immunogenicity

The observation period for ADA will be divided into 2 periods: pretreatment and on-study observation period:

- The ADA pretreatment period will be defined as the time from informed consent signature until the first isatuximab administration.
- The ADA on-study observation period will be defined as the time from the first isatuximab administration until the end of the study.

Participants with at least 1 evaluable ADA result during the ADA pretreatment period will be considered as evaluable at baseline. Participants with at least 1 evaluable ADA result during the ADA on-study observation period will be considered evaluable during the on-study observation period.

The following notions will be derived:

- Preexisting 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 participants without preexisting ADA (including participants without pretreatment samples).
- Transient ADA response:
  - Treatment-induced ADA detected only at 1 sampling time point during the treatment or follow-up observation period (excluding the last sampling time point) OR
  - Treatment-induced ADA detected at 2 or more sampling time points during the treatment (including follow-up period if any), where the first and last ADA-positive samples (irrespective of any negative samples in between) are separated by a period less than 16 weeks, and the participant's last sampling time point is ADA negative.
- Persistent ADA response: treatment induced detected at 2 or more sampling time points during the treatment (including follow-up period if any), where the first and last ADA-positive samples (irrespective of any negative samples in between) are separated by at least 16 weeks.
- Indeterminate ADA response:
  - Only the last sampling time point is positive OR
  - The last 2 samples, separated by a period less than 16 weeks, are positive.
- Treatment-boosted ADA, defined as preexisting ADA with a significant increase in the ADA titer during ADA on-study observation period compared with the baseline titer.
- ADA-positive participants, defined as participants with at least 1 treatment-induced or treatment-boosted ADA positive sample at any time following the first isatuximab administration.
- ADA prevalence, defined as the sum of the number of participants with preexisting ADA and the number of participants with treatment-induced ADAs, divided by the number of evaluable participants.
- ADA incidence, defined as the number of ADA-positive participants divided by the number of evaluable participants.

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

9.4.4 Pharmacokinetic analysis

The population PK analyses will be described in the population PK analysis plan provided by Pharmacokinetics and Drug Metabolism Modeling and Simulation group.

9.4.5 Biomarkers analysis

The PD and biomarker analyses will be described in the statistical analysis plan finalized before database lock.

CD38 receptor density (RD) and occupancy (RO) data will be presented in summary statistics by cohort. The data by groups of responders versus non-responders in best overall response will also be summarized.

9.5 INTERIM ANALYSES

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

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

The statistical analysis plan will describe the planned interim analyses in greater detail (see Section 10.1.5 for the committee structure).

9.5.1 Data monitoring committee

Close safety monitoring of each participant is planned, and an independent DMC will regularly monitor participant safety. A first safety review by the DMC is planned after the first 10 participants have completed at least 1 induction cycle. See Section 10.1.5 for details of the DMC.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 APPENDIX 1: REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 Regulatory and ethical considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and the applicable amendments and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH GCP Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants
- The Investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations
- The Sponsor will be responsible for the following:
  - Submitting to the regulatory authorities for notification and approval any change(s) of the protocol that are deemed as “substantial” (ie, changes which are likely to have a significant impact on the safety or physical or mental integrity of the clinical trial participants or on the scientific value of the trial)
  - Notifying IRBs/IECs and competent authorities of the Member States the reason for, and the content of, any substantial amendments

10.1.2 Financial disclosure

Investigators and sub-Investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3 Informed consent process

For informed consent:

- The Investigator or his/her representative will explain the nature of the study to the participant or his/her LAR and answer all questions regarding the study
- Participants and LAR must be informed that their participation is voluntary. The LAR will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB/IEC or site. Participants are encouraged to sign an assent form, if possible
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF
- Legally acceptable representatives or participants who reach the legal age of majority as defined by local regulation during the course of the study must be reconsented to the most current version of the ICF(s) during their participation in the study
- A copy of the ICF(s) must be provided to the participant or the participant's LAR
- Participants who are rescreened are required to have their LAR sign a new ICF
- The ICF will contain a separate section that addresses the use of remaining mandatory samples for optional oncohematology exploratory research. The Investigator or authorized designee will explain to each participant the objectives of the exploratory research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a participant's agreement to allow any remaining specimens to be used for exploratory research. Participants who decline to participate in this optional research will not provide this separate signature.
- For a regional or national emergency declared by a governmental agency, contingency measures are included in Section 10.9: Contingency Measures for a regional or national emergency that is declared by a governmental agency.

10.1.4 Data protection

All personal data collected related to participants, Investigators, or any person involved in the study, which may be included in the Sponsor's databases, shall be treated in compliance with all applicable laws and regulations including the Global Data Protection Regulation.

Data collected must be adequate, relevant, and not excessive, in relation to the purposes for which they are collected. Each category of data must be properly justified and in line with the study objective.

Participant race and ethnicity will be collected in this study because these data are required by regulatory agencies (eg, on Afro American population for the Food and Drug Administration or on Japanese population for the Pharmaceuticals and Medical Devices Agency in Japan).

- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- When archiving or processing personal data pertaining to the Investigator and/or to the participants, the Sponsor shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

10.1.5 Committees structure

An independent DMC, consisting of external independent experts, not associated with the conduct of the study, will meet regularly to:

- Review the progress of the trial.
- Review the safety data.
- Advise the Sponsor on potential modifications or communications that may be necessary to ensure the participant safety or protect the scientific integrity of the trial. The Sponsor will make the final decision(s).

The first meeting will be set up to review early safety results (eg, after approximately 10 participants have completed at least one induction period), and then periodically. Ad hoc DMC meetings may also be held if a significant safety issue or issue deemed important for discussion arises on this or any other isatuximab studies. After each meeting, the DMC will advise the Sponsor’s representatives on recommendations regarding the continued safety of treating ongoing and future study participants, as well as the course of action regarding the conduct of the trial.

One interim analysis is planned, and, after review of the results by cohort, the DMC will make recommendations on continuation of the study or not.

10.1.6 Dissemination of clinical study data

Sanofi shares information about clinical studies and results on publicly accessible websites, based on company commitments, international and local legal and regulatory requirements, and other clinical study disclosure commitments established by pharmaceutical industry associations. These websites include clinicaltrials.gov, EU clinicaltrialregister (eu.ctr), and sanofi.com, as well as some national registries.

In addition, results from clinical studies in participants are required to be submitted to peer-reviewed journals following internal company review for accuracy, fair balance, and intellectual property. For those journals that request sharing of the analyzable data sets that are reported in the publication, interested researchers are directed to submit their request to clinicalstudydatarequest.com.

Individual participant data and supporting clinical documents are available for request at clinicalstudydatarequest.com. While making information available we continue to protect the privacy of participants in our clinical studies. Details on data sharing criteria and process for requesting access can be found at this web address: clinicalstudydatarequest.com.

10.1.7 Data quality assurance

For data quality insurance:

- All participant data relating to the study will be recorded on printed or eCRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in separate study documents.
- The Sponsor assumes accountability for actions delegated to other individuals (eg, Contract Research Organizations).
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 25 years after the signature of the final study report unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.8 Source documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.

Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

10.1.9 Study and site closure

The Sponsor or designee reserves the right to close the site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Sites will be closed upon study completion. A site is considered closed when all required documents and study supplies have been collected and a site closure visit has been performed.

The Investigator may initiate site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for study termination by the sponsor, as well as reasons for the early closure of a site by the Sponsor or Investigator may include but are not limited to:

- For study termination:
  - Information on the product leads to doubt as to the benefit/risk ratio.
  - Discontinuation of further study intervention development.
- For site termination:
  - Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines.
  - Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the Investigator.
  - Total number of participants included earlier than expected.

10.1.10 Publication policy

The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2 APPENDIX 2: CLINICAL LABORATORY TESTS

The tests detailed in Table 15 will be performed by the local laboratories with the exceptions of PK, ADA, RO/RD, MRD analyses, pro-inflammatory cytokine panel (including IL2, IL6, IL8, IL10, IFN γ, TNF alpha) which will be performed at the central laboratory.

Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.

Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.

Table 15 - Protocol-required safety laboratory assessments

Laboratory assessments	Parameters			
Hematology	Platelet count Red blood cell count Hemoglobin Hematocrit		White blood cell count with differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils Blasts	
Clinical chemistry[a]	Blood urea nitrogen	Potassium	Aspartate aminotransferase(AST)/Serum glutamic-oxaloacetic transaminase	Total and direct bilirubin
	Creatinine	Sodium	Alanine aminotransferase (ALT)/Serum glutamic-pyruvic transaminase	Total protein
	Glucose (fasting)	Total Calcium	Amylase	Albumin
	Uric acid	Phosphorus	Lactic acid dehydrogenase	Alkaline phosphatase
	Free T4	Free/total T3	Thyroid-stimulating hormone	
	Ferritin	CRP		

Laboratory assessments	Parameters			
Coagulation[a]	D-dimers AT-III	Fibrinogen	Prothrombin time and international normalized ratio	Partial thromboplastin time
Routine urinalysis	• pH, glucose, protein, blood, ketones, by dipstick			
Other screening tests	• Highly sensitive urine human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)[b] • Serology (HIV antibody, hepatitis B surface antigen [HBsAg] anti-HBc total and IgM, [HBV DNA testing by PCR in case of anti-HBc positive], anti-HBs, anti-HCV and HCV RNA)[c] • All study-required laboratory assessments will be performed by a local laboratory, with the exception of PK, ADA, RO/RD and MRD. The results of each test must be entered into the eCRF			

ADA = antidrug antibody; eCRF = electronic case report form; DNA = deoxyribonucleic acid; HIV = human immunodeficiency virus; IEC = Independent Ethics Committee; INR = international normalized ratio; IRB = Institutional Review Board; ISI = international sensitivity index; MRD = minimal residual disease; PK = pharmacokinetics; PT_{normal} = normal prothrombin time; PT_{test} = prothrombin time in the participant; RD = receptor density; RNA = ribonucleic acid; RO = receptor occupancy; SAE = serious adverse event; ULN = upper limit of normal.

NOTES :

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

b Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC.

c For patients with positive anti-HBc and negative HBsAg and undetectable HBV DNA at study entry (past resolved infection, resolving acute infection or receiving antiviral treatment with controlled infection), close monitoring of viral reactivation (greater than 1 log_{10} IU/mL increase in HBV DNA or reappearance of HBsAg or HBV DNA in resolved infection) throughout and following the end of study treatment should be proposed (ALT, AST, and HBV DNA every 3 months, up to 6 months after treatment discontinuation or initiation of further anticancer therapy). In case of viral reactivation during study treatment (greater than 1 log_{10} IU/mL increase in HBV DNA or reappearance of HBsAg or detection of HBV DNA in patients with resolved infection [see definition in Section 6.5]), close monitoring of ALT and AST every month, up to study treatment discontinuation. HBV DNA to be done as per specialist advice. In case HBV vaccination will be started before first study treatment administration, anti-HBs should be monitored at 1, 2 and 3 months after end of vaccination.

In ALL patients on treatment with pegaspargase or L-asparaginase (Erwinase) daily monitoring of international normalized ratio (INR), partial thromboplastin time (PTT), fibrinogen and antithrombin III (AT-III) must be performed and fibrinogen and AT-III substituted if necessary.

Investigators must document their review of each laboratory safety report.

10.3 APPENDIX 3: ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

DEFINITION OF AE

AE definition

- An AE is any untoward medical occurrence in a participant or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.
- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events meeting the AE definition

- Any abnormal laboratory results which impact the study treatment, leads to treatment discontinuation, or fulfill the definition of an SAE.
- Any safety assessments (eg, ECG, radiological scans, or vital sign measurements) including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator.
- Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected DDI.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.
- "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

Events NOT meeting the AE definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

DEFINITION OF SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:

A) Results in death

B) Is life-threatening

The term “life-threatening” in the definition of “serious” refers to an event in which the participant 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.

C) Requires inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician’s office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether “hospitalization” occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.

D) Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person’s ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

E) Is a congenital anomaly/birth defect

F) Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

RECORDING AND FOLLOW-UP OF AE AND/OR SAE

AE and SAE recording

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information in the eCRF.

- It is not acceptable for the Investigator to send photocopies of the participant's medical records to the Monitoring Team in lieu of completion of the AE/SAE eCRF page.
- There may be instances when copies of medical records for certain cases are requested by the Monitoring Team. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the Monitoring Team.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of intensity

The Investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the severity categories as defined by the NCI-CTCAE Version 5.0.

An AE is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of causality

- The Investigator is obligated to assess the causal relationship between study intervention and each occurrence of each AE/SAE, as a YES or NO evaluation.
- A "reasonable possibility" of a causal relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The Investigator will use clinical judgment to determine the causal relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The Investigator will also consult the IB and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report to the Monitoring Team. However, **it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data.**
- The Investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during the follow-up period, the Investigator will provide sanofi with a copy of any postmortem findings including histopathology.
- New or updated information will be recorded in the originally completed eCRF.
- The Investigator will submit any updated SAE data to the Monitoring Team within 24 hours of receipt of the information.
- All AEs/SAEs will be followed until resolution, stabilization, or the participant is lost to follow-up.

REPORTING OF SAES

SAE reporting to the Monitoring Team via an electronic data collection tool

- The primary mechanism for reporting an SAE to the Monitoring Team will be the electronic data collection tool.
- If the electronic system is unavailable for more than 24 hours, then the site will use the paper SAE data collection tool (see next section).
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the Monitoring Team by telephone.
- Contacts for SAE reporting will be informed by the Monitoring Team.

SAE reporting to the Monitoring Team via paper CRF

- Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the Monitoring Team.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the Investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- Contacts for SAE reporting will be informed by the Monitoring Team.

10.4 APPENDIX 4: CONTRACEPTIVE GUIDANCE AND COLLECTION OF PREGNANCY INFORMATION

DEFINITIONS:

Woman of childbearing potential

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP

- Premenarchal
- Premenopausal female with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

    For individuals with permanent infertility due to an alternate medical cause other than the above (eg, mullerian agenesis, androgen insensitivity), Investigator discretion should be applied to determining study entry.

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

CONTRACEPTION GUIDANCE

Participants who receive cyclophosphamide should use a highly effective method of contraception for 1 year after the last dose of cyclophosphamide.

Male participants

- Male participants with female partners of childbearing potential are eligible to participate if they agree to 1 of the following during the protocol-defined time frame in Section 5.1:
  - Are abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent
  - Agree to use a male condom plus partner use of a contraceptive method with a failure rate of <1% per year as described in Table 16 when having penile-vaginal intercourse with a woman of childbearing potential who is not currently pregnant.
- In addition, male participants must refrain from donating sperm for the duration of the study and for 6 months after the last dose of isatuximab, 12 months after the last dose of cyclophosphamide, and at least 6 months after other IMPs discontinuation (vincristine, pegaspargase, L-asparaginase (Erwinase), methotrexate, etoposide, doxorubicin, mitoxantrone, fludarabine, cytarabine), whatever occurs last and with the longest recommended period of contraception.

- Male participants with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration for the duration of the study and for 6 months after the last dose of isatuximab, 12 months after the last dose of cyclophosphamide, and at least 6 months after other IMPs discontinuation (vincristine, pegaspargase, L-asparaginase (Erwinase), methotrexate, etoposide, doxorubicin, mitoxantrone, fludarabine, cytarabine), whatever occurs last and with the longest recommended period of contraception.

Female participants

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception as described in Table 16, consistently and correctly from 2 weeks prior to the first dose and 6 months after the last dose of isatuximab, 12 months after the last dose of cyclophosphamide, and at least 6 months after other IMPs discontinuation (vincristine, pegaspargase, L-asparaginase (Erwinase), methotrexate, etoposide, doxorubicin, mitoxantrone, fludarabine, cytarabine), whatever occurs last and with the longest recommended period of contraception.

Since an indirect interaction between components of the oral contraception and asparaginase cannot be ruled out, oral contraceptives are not considered sufficiently safe in such clinical situation. A method other than oral contraceptives should be used in women of childbearing potential using pegaspargase or L-asparaginase (Erwinase).

Table 16 - Highly effective contraceptive methods

Highly effective contraceptive methods that are user dependent[a]
Failure rate of <1% per year when used consistently and correctly.
Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation[b]. Participants taking hormonal contraception should take only progesterone while being treated with polyethylene glycol-asparaginase. • Oral. • Intravaginal. • Transdermal.
Progestogen only hormonal contraception associated with inhibition of ovulation • Oral. • Injectable.
Highly effective methods that are user independent[a]
Implantable progestogen only hormonal contraception associated with inhibition of ovulation[b]. • Intrauterine device. • Intrauterine hormone-releasing system. • Bilateral tubal occlusion.
Vasectomized partner A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
Sexual abstinence Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

a Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies.

b Hormonal contraception may be susceptible to interaction with the study intervention, which may reduce the efficacy of the contraceptive method. In this case, 2 highly effective methods of contraception should be utilized during the treatment period and for at least 6 months after the last dose of isatuximab or 12 months after the last dose of cyclophosphamide.

PREGNANCY TESTING:

- Women of childbearing potential should only be included after a confirmed menstrual period and a negative highly sensitive urine or serum pregnancy test 2 weeks prior to the first dose of study intervention.
- Additional pregnancy testing is required monthly during the treatment period on Day 1 of each cycle prior to the dose, and up to 6 months after the last dose of isatuximab, or 12 months after the last dose of cyclophosphamide and as required locally (see the corresponding protocol-defined time frame in the SOA [Section 1.3]).
- Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected.

Note: For adolescent participants of childbearing potential, specific contraceptive counseling is recommended to ensure understanding of these requirements.

COLLECTION OF PREGNANCY INFORMATION:

Male participants with partners who become pregnant

- The Investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive study intervention.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female participants who become pregnant

- The Investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of a participant's pregnancy. The participant will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the Sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- Any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such. Any poststudy pregnancy-related SAE considered reasonably related to the study intervention by the Investigator will be reported to the Sponsor as described in Section 8.3.4 of the protocol. While the Investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will be withdrawn from the study.

10.5 APPENDIX 5: GENETICS

Not applicable.

10.6 APPENDIX 6: OTHER ASSESSMENTS AND SAFETY ITEMS

10.6.1 Response criteria

The following response criteria are from the NCCN Guidelines Version 1.2018.

10.6.1.1 Acute lymphoblastic leukemia

Response Criteria for Blood and BM:

- Complete response:
  - No circulating blasts or extramedullary disease.
  - No lymphadenopathy, splenomegaly, skin/gum infiltration/testicular mass/central nervous system involvement.
  - Trilineage hematopoiesis and <5% blasts.
  - Absolute neutrophil count (ANC) >1000/μL.
  - Platelets >100 000/μL.
  - RBC transfusion independence: If the physician documents transfusion dependency related to study treatment and not to the patient's underlying disease, CRi can be reported.
- Complete response with incomplete blood count recovery:
  - Meet all criteria for CR except platelet count and/or ANC.
- Overall response rate (ORR = CR + CRi+PR).
- Refractory disease:
  - Failure to achieve CR at the end of induction.
- Progressive disease:
  - Increase of at least 25% in the absolute number of circulating or bone marrow blasts or development of extramedullary disease.
- Relapsed disease:
  - Reappearance of blasts in blood or bone marrow (>5%) or in any extramedullary site after a CR.

Response Criteria for Mediastinal Disease (CT of chest with IV contrast and PET imaging should be performed to assess):

- Complete response:
  - Complete resolution of mediastinal enlargement by CT. For participants with a previous positive PET scan, a post-treatment residual mass of any size is considered a CR as long as it is PET negative.

- Partial response:
  - >50% decrease in the sum of the product of the greatest perpendicular diameters (SPD) of the mediastinal enlargement.
  - For participants with a previous positive PET scan, a post-treatment PET must be positive in at least 1 previously involved site.
- Progressive disease:
  - >25% increase in the SPD of the mediastinal enlargement.
  - For participants with a previous positive PET scan, a post-treatment PET must be positive in at least 1 previously involved site.
- No response:
  - Failure to qualify for PR or progressive disease.
- Relapse:
  - Recurrence of mediastinal enlargement after achieving CR. For participants with a previous positive PET scan, a post-treatment PET must be positive in at least 1 previously involved site.

Response criteria for CNS disease:

- Central nervous system remission:
  - Achievement of CNS-1 status in a patient with CNS-2 or CNS-3 at diagnosis (see Table below).
- Central nervous system relapse:
  - New development of CNS-3 status or clinical signs of CNS leukemia without other explanation. New development of CNS-2 status on 2 consecutive lumbar punctures (between 2 to 4 weeks apart).

Definition of CNS Disease	Criteria
NS 1	No blasts seen on cytocentrifuge (CNS negative)
NS 2	Total Nucleated Cell Count <5 x 10^6/L, but blasts seen on cytocentrifuge
NS 3	Total Nucleated Cell Count ≥ 5 x 10^6/L with blasts on cytocentrifuge and/or signs of CNS leukemia (eg, cranial nerve palsy)

10.6.1.2 Acute myeloid leukemia

For AML, a morphologic leukemia-free state is defined as:

- <5% blasts in a BM aspirate with spicules.
- No blasts with Auer rods or persistence of extramedullary disease.

A CR is defined as:

- Morphologic CR - participant independent of transfusions
  - <5% blasts in a BM aspirate with spicules
  - No blasts with Auer rods or persistence of extramedullary disease
  - ANC ≥1000/μL
  - Platelets ≥100 000/μL
  - No residual evidence of extramedullary disease
  - Red blood cell transfusion independence; If the physician documents transfusion dependency related to study treatment and not to the patient's underlying disease, CRi can be reported

A CRi is defined as:

- Same criteria as for CR, except neutrophils and/or platelets recovery (ANC <1000/μL or platelets <100 000/μL)

A partial remission is defined as a decrease of at least 50% in the percentage of blasts to between 5% to 25% in the BM aspirate and the normalization of blood counts as defined for CR.

A relapse is defined as, following a CR, the reappearance of leukemic blasts in the peripheral blood or the finding of more than 5% blasts in the BM, not attributable to another cause (eg, BM regeneration after consolidation therapy) or extramedullary relapse.

As induction failure is defined as the failure to attain CR following exposure to at least 2 courses of intensive induction therapy.

10.6.2 Eastern cooperative oncology group performance status scale

ECOG PS (40)

0 – Fully active, able to carry on all predisease performance without restriction

1 – Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work)

2 – Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours

3 – Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours

4 – Completely disabled; cannot carry on any selfcare; totally confined to bed or chair

5 – Death

10.6.3 Lansky score scale

Lansky scores (41):

- 100 – fully active, normal
- 90 – minor restrictions in strenuous physical activity
- 80 – active, but tires more quickly
- 70 – both greater restriction and less time spent in active play
- 60 – up and around, but minimal active play; keeps busy with quieter activities
- 50 – gets dressed, but lies around much of the day; no active play; able to participate in all quiet play and activities
- 40 – mostly in bed; participates in quiet activities
- 30 – in bed; needs assistance even for quiet play
- 20 – often sleeping; play entirely limited to very passive activities
- 10 – no play; does not get out of bed
- 0 – unresponsive

10.6.4 Revised Schwartz equation to estimate GFR in children

eGFR* (mL/min/1.73 m^2) = 0.413 × Height(cm) / Serum Creatinine (mg/dL) (42).

*eGFR: estimated glomerular filtration rate.

10.6.5 Types of infusion reactions and typically associated symptoms

Please refer to the IB of isatuximab for the list of infusion reactions and typically associated symptoms. Common symptoms and infusion reactions from Study TED10893 are detailed below.

TED10893 (Phases 1 and 2 - Stage 1): Most frequent symptoms (≥5%) of infusion associated reaction in participants exposed to isatuximab

	Isatuximab (N=186)	
Preferred term	**All grades, n (%)**	**Grade ≥3, n (%)**
Any event	93 (50.0)	13 (7.0)
Infusion related reaction	87 (46.8)	4 (2.2)
Chills	25 (13.4)	0
Dyspnoea	22 (11.8)	1 (0.5)
Nausea	22 (11.8)	0
Chest discomfort	17 (19.1)	0
Flushing	11 (5.9)	0
Headache	10 (5.4)	0

Only rows with frequency of at least 5% in isatuximab in the all grades column are shown.

10.6.6 CD38 blood test interference guideline

The AABB issued the following bulletin (Association Bulletin #16-02, Dated 15 January 2016) to mitigate the anti-CD38 interference with serologic testing.

https://www.aabb.org/programs/publications/bulletins/Documents/ab16-02.pdf

Association Bulletin #16-02

Date: 15 January 2016

To: AABB Members

From: [redacted]President

[redacted]—Chief Executive Officer

Re: Mitigating the Anti-CD38 Interference with Serologic Testing

Summary

A new class of therapeutic agents for multiple myeloma, CD38 mAbs, can result in interference with blood bank serologic tests and thereby cause delays in issuing red blood cell (RBC) units to participants receiving these agents. To minimize these delays, hospitals should set up procedures to inform the transfusion service when participants start receiving these agents. Considerations for the transfusion service, both before and after initiation of anti-CD38 therapy, are detailed below.

The AABB Clinical Transfusion Medicine Committee has developed this bulletin to provide background information and guidance to members regarding anti-CD38 interference with serologic testing. The bulletin includes recommendations for its prevention and treatment.

Association Bulletins, which are approved for distribution by the AABB Board of Directors, may include announcements of standards or requirements for accreditation, recommendations on emerging trends or best practices, and/or pertinent information. This bulletin contains information and recommendations. No new standards are proposed.

Background

CD38 mAbs are a new treatment for multiple myeloma CD38, an integral membrane protein that is highly expressed on myeloma cells, has been identified as an effective target antigen for mAb therapies. In November 2015, the first therapeutic CD38 mAb (daratumumab [Darzalex, Janssen Biotech, Horsham, PA]) was approved by the Food and Drug Administration[1]. Other CD38 mAbs are under development.

CD38 mAbs interfere with blood bank serologic tests

CD38 is weakly expressed on red cells. Anti-CD38 binds to CD38 on reagent RBCs, causing panreactivity in vitro.[2, 3] Plasma samples from anti-CD38-treated participants consistently cause positive reactions in IATs, antibody detection (screening) tests, antibody identification panels, and

antihuman globulin (AHG) crossmatches. Agglutination due to anti-CD38 may occur in all media (eg, saline, low ionic strength saline, and polyethylene glycol), and with all IAT methods (eg, gel, tube, and solid phase). Agglutination reactions caused by antiCD38 are usually weak (1+), but stronger reactions (up to 4+) may be seen in solid-phase testing. However, anti-CD38 does NOT interfere with ABO/RhD typing, or with immediate-spin crossmatches.

Other notes on anti-CD38 serologic interference:

- Adsorptions using either untreated or ZZAP-treated cells fail to eliminate the interference.
- Anti-CD38 variably interferes with direct antiglobulin tests (DATs) and antibody identification panel auto controls.
- Some rare Lu(a–b–) cells are not reactive in the presence of anti-CD38, potentially giving the false impression that the participant has a Lutheran-related antibody.[4, 5]
- Positive IATs can be observed for up to 6 months after anti-CD38 is discontinued.[1, 3]
- Anti-CD38 may cause a small decrease in hemoglobin in vivo (approximately 1 g/dL), but severe hemolysis has not been observed among treated participants.[3, 6]

Anti-CD38 interference can cause delays in issuing RBCs

If the transfusion service is unaware that a participant has received anti-CD38, the following scenario may occur when the participant's sample is tested:

1. ABO/RhD typing: no issues
2. Antibody detection (screening) test: all cells positive
3. Antibody identification panel: all cells positive (auto control may be negative)
4. DAT: positive or negative
5. AHG crossmatches: positive with all RBC units tested
6. Adsorptions: panreactivity cannot be eliminated.

This leads to delays in issuing RBCs to the participant. In some cases, the anti-CD38 interference could mask the presence of a clinically significant alloantibody.

Recommendations

To avoid problems with transfusions, hospitals should set up procedures to inform the transfusion service whenever any participant is scheduled to begin taking anti-CD38.

BEFORE a participant begins taking anti-CD38:

- A baseline type and screen should be performed.
- In addition, a baseline phenotype or genotype is recommended.

AFTER a participant begins taking anti-CD38:

- ABO/RhD typing can be performed normally.

- For antibody detection (screening) and identification, DTT-treated cells can be used to eliminate the interference[2, 7].
  - Because DTT treatment destroys Kell antigens, K-negative units should be provided unless the participant is known to be K-positive.
  - Antibodies against other DTT-sensitive blood group antigens (anti-k, anti-Yta, anti-Doa/Dob, etc) will not be detectable when the antibody screen with DTT-treated cells is performed; however, such antibodies are encountered infrequently.

Crossmatch

- For participants with a negative antibody screen using DTT-treated cells, an electronic or immediate-spin crossmatch with ABO/RhD-compatible, K-matched units may be performed.
- For participants with known alloantibodies, phenotypically or genotypically matched RBC units may be provided.[6, 8]
  - As some typing antisera require the use of AHG, phenotyping should be performed before the participant receives anti-CD38.
  - Genotyping can be performed either before or after the participant receives anti-CD38.
  - AHG crossmatches with phenotypically or genotypically matched units will still be incompatible.
  - Some clinically significant antibodies may be missed with the use of uncrossmatched phenotypically or genotypically matched units, although this will occur infrequently.
- Alternatively, an AHG crossmatch may be performed using DTT-treated donor cells.
- If an emergency transfusion is required, uncrossmatched ABO/RhD-compatible RBCs may be given per local blood bank practices.

Future/alternative approaches to mitigating the anti-CD38 interference

It is possible to neutralize anti-CD38 in plasma and eliminate the interference using either recombinant soluble human CD38 or daratumumab idiotype antibody.[2, 3] Neither reagent is widely available at this time, and additional validation would be needed. In principle, soluble CD38 could be used to neutralize any anti-CD38, while different idiotype antibodies would be needed to neutralize different CD38 therapeutic antibodies. Finally, antigen-typed cord cells have been used for the antibody screen as an alternative to DTT-treated cells.[9]

References for Section 10.6.6

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10.6.7 Grading system and mitigation strategy for ICANS, based on 2019 ASTCT consensus guidelines

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
Impact, Confidence, and Ease (ICE) score for children age ≥12 years*	7-9	3-6	0-2	0 (patient is unarousable and unable to perform ICE)
Cornell Assessment of Pediatric Delirium (CAPD) score for children age <12 years	1-8	1-8	≥9	Unable to perform CAPD
Depressed level of consciousness†	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Unarousable or requires vigorous or repetitive tactile stimuli to arouse; stupor or coma
Seizure (any age)	N/A	N/A	Any clinical seizure focal or generalized that resolves rapidly or nonconvulsive seizures on EEG that resolve with intervention	Life-threatening prolonged seizure (>5 min); or Repetitive clinical or electrical seizures without return to baseline in between
Motor weakness (any age)‡	N/A	N/A	N/A	Deep focal motor weakness, such as hemiparesis or paraparesis
Elevated ICP/ cerebral edema (any age)	N/A	N/A	Focal/local edema on neuroimaging§	Decerebrate or decorticate posturing, cranial nerve VI palsy, papilledema, Cushing's triad, or signs of diffuse cerebral edema on neuroimaging

ICANS grade is determined by the most severe event (ICE or CAPD score, level of consciousness, seizure, motor findings, raised intracranial pressure (ICP)/cerebral edema) not attributable to any other cause. Baseline CAPD score should be considered before attributing to ICANS.

* A patient with an ICE score of 0 may be classified as grade 3 ICANS if awake with global aphasia, but a patient with an ICE score of 0 may be classified as grade 4 ICANS if unarousable.

† Depressed level of consciousness should be attributable to no other cause (eg, no sedating medication).

‡ Tremors and myoclonus associated with immune effector cell therapies may be graded according to CTCAE v5.0, but they do not influence ICANS grading.

§ Intracranial hemorrhage with or without associated edema is not considered a neurotoxicity feature and is excluded from ICANS grading. It may be graded according to CTCAE v5.0

Data source: Lee et al. ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells Biol Blood Marrow Transplant 25 (2019) 625-638 (43)

10.6.8 Encephalopathy Assessment Tools for Grading of ICANS Immune Effector Cell-Associated Encephalopathy (ICE) score

[redacted]

10.6.9 Encephalopathy assessment for children age <12 years using the CAPD score

[redacted]

10.7 APPENDIX 7: MEDICAL DEVICE INCIDENTS: DEFINITION AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

Not applicable.

10.8 APPENDIX 8: COUNTRY-SPECIFIC REQUIREMENTS

For German sites coagulation test will be done twice a week and if clinically indicated. For the rest of the world, it will remain once a week and if clinically indicated.

10.9 APPENDIX 9: CONTINGENCY MEASURES FOR A REGIONAL OR NATIONAL EMERGENCY THAT IS DECLARED BY A GOVERNMENTAL AGENCY

Continuation of the study in the event of a regional or national emergency declared by a governmental agency:

A regional or national emergency declared by a governmental agency (eg, public health emergency, natural disaster, pandemic, terrorist attack) may prevent access to the clinical trial site.

Contingency procedures are suggested for an emergency that prevents access to the study site, to ensure the safety of the participants, to consider continuity of the clinical study conduct, protect trial integrity, and assist in maintaining compliance with Good Clinical Practice in Conduct of Clinical Trials Guidance. Sponsor agreement MUST be obtained prior to the implementation of these procedures for the duration of the emergency.

During the emergency, if the site will be unable to adequately follow protocol mandated procedures, alternative treatment outside the clinical trial should be proposed, and screening/enrollment/administration of study intervention may be temporarily delayed.

Attempts should be made to perform all assessments in accordance with the approved protocol to the extent possible. In case this is not possible due to a temporary disruption caused by an emergency, focus should be given to assessments necessary to ensure the safety of participants and those important to preserving the main scientific value of the study.

Procedures to be considered in the event of a regional or national emergency declared by a governmental agency:

- If onsite visits are not possible visit windows may be extended for assessment of safety and/or efficacy data that cannot be obtained remotely. Possibility of visit extension must be discussed on a case by case basis with the Sponsor considering first subject’s safety and best interests.

If onsite visits are possible and there is a need to reduce the time spent on site to a minimum, the focus should be on IMP infusion/administration, collection of safety information (vital signs, adverse events) and safety blood collection (mainly biochemistry, hematology and ADA, if planned for the visit). However, all efforts should be made to perform the measurements of key

parameters for efficacy endpoints. These would include bone marrow aspirations and optional extramedullary disease assessments: CT, PET-CT or PET-MRI for this study.

For ongoing patients unable to come to the study site, administration of isatuximab and other study drugs (dexamethasone, fludarabine, cytarabine, anthracycline, IT chemotherapy for AML; dexamethasone, mitoxantrone or doxorubicin, vincristine, pegaspargase, L-asparagase, IT chemotherapy for ALL induction; dexamethasone, methotrexate, cyclophosphamide, etoposide, vincristine, pegaspargase, L-asparagase, IT chemotherapy for ALL consolidation cycle) requiring IV infusion need to occur in investigator site hospital, consequently these infusions will be delayed until the moment when regular study visits will be conducted again at the study site.

During a regional or national emergency declared by a governmental agency, reinitiation of IMP can only occur once the Investigator has determined, according to his/her best judgement, that the contribution of the IMP(s) to the occurrence of the epidemic event (eg, COVID-19) was unlikely.

The following contingencies may be implemented for the duration of the emergency (after Sponsor agreement is obtained) to make clinical supplies available to the participant for the duration of the emergency:

The dexamethasone in oral form may be supplied at the site or from the PI/site/Sponsor to the participant via a Sponsor-approved courier company where allowed by local regulations and agreed upon by the participant.

Contingencies implemented due to emergency will be documented.

For a regional or national emergency declared by a governmental agency, contingency procedures may be implemented for the duration of the emergency. The participant or their legally authorized representative should be verbally informed prior to initiating any changes that are to be implemented for the duration of the emergency (eg, study visit delays/treatment extension, use of local labs).

The impact of the regional or national emergency if any declared by a governmental agency on study conduct will be summarized (eg, study discontinuation or discontinuation/delay/omission of the intervention due to the emergency). Any additional analyses and methods required to evaluate the impact on efficacy (eg, missing data due to the emergency) and safety will be detailed in the SAP.

10.10 APPENDIX 10: ABBREVIATIONS

ADA:	antidrug antibody
AE:	adverse event
AESI:	adverse events of special interest
AHG:	antihuman globulin
ALL:	acute lymphoblastic leukemia
AML:	acute myeloid leukemia
ANC:	absolute neutrophil count

AT:	all-treated
AT-III:	antithrombin III
AUC:	area under the curve
AUC_{last}:	area under the curve from time 0 to the last measurable concentration
B:	B-cell
B-ALL:	B-cell acute lymphoblastic leukemia
BM:	bone marrow
CAPD:	Cornell Assessment of Pediatric Delirium
CAR-T:	chimeric antigen receptor T cells
CFR:	Code of Federal Regulations
CIOMS:	Council for International Organizations of Medical Sciences
CL:	linear clearance
CL_{inf}:	time-independent clearance
C_{max}:	maximum serum concentration reached by the drug after a dose
CNS:	central nervous system
CONSORT:	Consolidated Standards of Reporting Trials
CR:	complete response
CRi:	complete response with incomplete peripheral recovery
CRP:	C-reactive protein
CRS:	cytokine release syndrome
CT:	computed tomography
C_{trough}:	lowest serum concentration reached by a drug before the next dose is administered
CYP:	cytochrome P450
D:	day
DAT:	direct antiglobulin test
DDI:	drug-drug interactions
DFS:	disease-free survival
DLT:	dose-limiting toxicity
DMC:	data monitoring committee
DNA:	deoxyribonucleic acid
DOR:	duration of response
DTT:	dithiothreitol
ECG:	electrocardiogram
ECOG:	Eastern Cooperative Oncology Group
eCRF:	electronic case report form
EFS:	event free survival
eGFR:	estimated glomerular filtration rate
FDA:	Food and Drug Administration
FLAG:	Fludarabine, Aracytine, G-CSF
GCP:	Good Clinical Practice
G-CSF:	granulocyte colony-stimulating factor
GMP:	Good Manufacturing Practice
GVHD:	Graft versus Host Disease
HBs:	hepatitis B surface
HBsAg:	hepatitis B surface antigen

HBV:	hepatitis C virus
HCV:	hepatitis C virus
HIV:	human immunodeficiency virus
HLT:	high level term
HSCT:	hematopoietic stem cell transplantation
IAT:	indirect antiglobulin test
IB:	Investigator's Brochure
ICE:	Impact, Confidence, and Ease
ICF:	Informed Consent Form
ICH:	International Council for Harmonisation
ICP:	intracranial pressure
ICU:	intensive care unit
IEC:	Independent Ethics Committee
IFN:	interferon
IgG:	immunoglobulin G
IgM:	immunoglobulin M
IL:	interleukin
IMP:	investigational medicinal product
INR:	international normalized ratio
IR:	infusion reaction
IRB:	Institutional Review Board
IT:	intrathecal
IV:	intravenous(ly)
LAR:	legally acceptable representative
LBL:	lymphoblastic lymphoma
LDH:	lactic acid dehydrogenase
LLT:	lower level term
mAb:	monoclonal antibody
MDS:	myelodysplasia
MedDRA:	Medical Dictionary for Regulatory Activities
MM:	multiple myeloma
MRD:	minimal residual disease
NCCN:	National Comprehensive Cancer Network
NCI-CTCAE:	National Cancer Institute Common Terminology Criteria for Adverse Events
NIMP:	noninvestigational medicinal product
NSAID:	nonsteroidal anti-inflammatory drugs
ORR:	overall response rate
OS:	overall survival
PBPK:	physiologically based pharmacokinetic
PCR:	polymerase chain reaction
PCSA:	potentially clinically significant abnormality
PD:	pharmacodynamics(s)
PEG:	polyethylene glycol
PET:	positron emission tomography
Ph:	Philadelphia chromosome
PK:	pharmacokinetic(s)

PO:	oral administration
PT:	preferred term
PTT:	partial thromboplastin time
Q2W:	once every 2 weeks
QW:	once a week
R/R:	relapsed or refractory
RBC:	red blood cell
RD:	receptor density
RNA:	ribonucleic acid
RO:	receptor occupancy
SAE:	serious adverse event
SD:	standard deviation
SOA:	Schedule of Activities
SOC:	system organ class
SPD:	sum of the product of the greatest perpendicular diameters
SUSAR:	suspected unexpected serious adverse reactions
T:	T-cell
T-ALL:	T-cell acute lymphoblastic leukemia
TEAE:	treatment-emergent adverse event
T-LBL:	T-cell lymphoblastic lymphoma
TLS:	tumor lysis syndrome
TLS:	tumor lysis syndrome
TNF:	tumor necrosis factor
TSH:	thyroid-stimulating hormone
ULN:	upper limit of normal
WBC:	white blood cell
WOCBP:	woman of childbearing potential

10.11 APPENDIX 11: PROTOCOL AMENDMENT HISTORY

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

10.11.1 Amended protocol 04 (24 November 2020)

This amended protocol (Amendment 04) is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

OVERALL RATIONALE FOR THE AMENDMENT

The primary driver for this amendment is to implement DMC recommendations following the occurrence of first fatal case as an outcome of a Cytokine Release Syndrome (CRS) event.

On 01 October 2020, due to the occurrence of first fatal CRS event, the study data monitoring committee (DMC) has evaluated the safety profile of the first 9 treated patients and recommended the continuation of the study with changes to be implemented in an amendment to the protocol.

The main changes are:

- White blood cell (WBC) counts should be below 20 x 10^9/L before isatuximab administration.
- Patients with high WBC counts between 20 and 50 x 10^9/L at screening and with high tumor burden in relation to extramedullary disease should receive a rescue cytoreductive therapy with a short half-life in order to potentially reach the 20 x 10^9/L WBC threshold before first isatuximab administration.
- As consequence the list of cytoreductive drugs with suggested doses are proposed in this amendment in order to have less heterogeneity in the participants' cytoreductive therapy management across participating sites.
- Guidance is added to clarify the CRS events with inclusion of a specific section and table describing criteria for diagnosis, grading, as well as management of these events. Prospective determinations of CRS biomarkers at different time points are included.
- Cytokines panel, ferritin, and C-reactive protein (CRP) are added at baseline and at different time points in order to better assess events like CRS, hemophagocytic lymphohistiocytosis (HLH), infections, etc. Moreover, specific guidance for hematology, vital signs, radiology are added in case of high tumor burden or CRS events.
- Anti-IL6 as concomitant or rescue medication in case of CRS Grade 2 or above is added.
- Seizures ≥ Grade 3 should be reported as adverse events of special interest (AESI).

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Section 1.1, Section 4.1.2, Section 5.1, 5.2, Section 6.1, Section 6.5, Section 6.5.1, Section 8.2.2 and Section 8.2.6	For patients with high tumor burden, cytoreductive chemotherapy should become mandatory, before the study treatment start. Threshold for tumor burden and types of chemotherapy are provided. Inclusion criterion 05 was added to reflect these changes.	Clarification on cytoreductive chemotherapy and modification of inclusion and exclusion criteria to address DMC recommendations.
Section 4.1.2	For patients with WBC count <20 x 10^9/L at screening, but higher than 20 x 10^9/L on Day 1, a cytoreductive chemotherapy should be started as recommended in order to decrease their WBC count and the screening period will be extended without a deviation.	Clarification on cytoreductive chemotherapy for with WBC count <20 x 10^9/L at screening.

Section # and Name	Description of Change	Brief Rationale
Sections 1.1, Section 1.2, Section 1.3, Section 6.1, Section 6.1.2	Erwinase is the treatment of choice that should be used to replace PEG-Asparaginase in case of hypersensitivity or loss of activity and/or country availability and regulations; infusion should last at least 2 hours. Instructions were added for daily monitoring of INR, PTT, and related to fibrinogen and AT-III parameters for ALL patients treated with pegaspargase or L-asparginase.	Clarification on L-asparaginase (Erwinase) use conditions and treatment procedures.
Section 1.2	Patients may experience intolerance to PEG-asparaginase during study treatment period. They may switch to Erwinase, the rules on the switch process are provided.	Clarification on the use of L-Asparaginase (Erwinase) and switch from PEG-Asparaginase during treatment to all cohorts.
Section 2.3	Instructions for screening with serological tests was modified	Serological tests during screening are now mandatory
Section 1.3, Section 10.2 (appendix 2)	Cytokines panel, ferritin, CRP are added at baseline and at different time points in case of CRS. Moreover, specific guidance for hematology, vital signs, radiology was added in case of high tumor burden or CRS events.	Addition of some clinical, radiological and biological parameters needed for specific events assessments.
Section 5.2	As cytoreductive therapy is requested for some participants, the exclusion criterion E10 is updated in order to allow these prior treatments.	To update according to DMC recommendations the exclusion criteria E10.
Sections 1.1, Section 6.1, Section 6.5.1, Section 4.1.2	Cytoreductive chemotherapy is non-IMP, added as a rescue therapy for patients with high tumor burden at screening.	To add according to DMC recommendations the possibility of cytoreductive chemotherapy and clarify these are non-IMP products.
Section 6.5.1	Added anti-IL6 as concomitant or rescue medication in case of CRS event of Grade 2 or above as a rescue therapy.	CRS risk has been identified for this study, consequently treatment and guidance are provided.
Section 8.3	Added seizures $\geq$ Grade 3 as AESI.	Two cases of Grade 3 seizures have been identified among the first 9 treated patients. DMC recommended to add these events as AESI.
Section 5.2	An exclusion criterion E09 has been modified to clarify that patients with infection or life-threatening tumor lysis syndrome if present at study entry or during the screening period cannot participate in the study.	The exclusion criteria E09 has been modified to exclude patients with infections and life-threatening tumor lysis syndrome if present at study entry or during the screening period to prevent avoidable risks for participants.
Section 5.2	Additional exclusion criterion was added as regard to WBC count threshold. Participants with white blood cell count > $50x10^9$/L at the time of screening visit are not allowed.	An additional exclusion criterion E26 to define the WBC count threshold at screening visit.

Section # and Name	Description of Change	Brief Rationale
Section 5.2	Additional exclusion criterion was added to exclude participants who have been exposed to anti-CD38 therapies within 6 months prior to Day 1.	An additional exclusion criterion E27 to exclude prior treatment with anti-CD38 therapies as prior exposure may decrease CD38 expression within 6 months.
Section 6.6.1	Definition of IR has been added, Table 6 - Management of infusion reactions have been updated.	To prevent avoidable risks for participants.
Added Section 6.6.2	Guidance for Anaphylaxis management is provided. In case of anaphylaxis of any grade isatuximab (or other product) will be permanently discontinued.	To prevent avoidable risks for participants.
Added Section 6.6.3	Guidance for CRS management are provided. In case of any event of CRS of Grade 2 or higher isatuximab will be permanently discontinued.	CRS risk has been identified for this trial, consequently treatment and guidance are provided.
Section 8.2.1	Guidance for physical exam in case of CRS with potential occurrence of ICANS was added.	CRS may complicate with neurological symptoms that need specific grading and guidance.
Section 1.3, Section 8.2.2	Vital signs monitoring after every isatuximab infusion in case of high tumor burden or CRS event added.	Vital signs need intensive monitoring after every isatuximab infusion in case of CRS for subjects' safety follow up.
Section 1.3, and, added Section 8.2.5	Guidance on pulmonary imaging was added in case of high tumor burden or CRS event.	Risk of leukostasis is high in case these events occur, consequently, more intensive chest X-ray monitoring was added.
Section 8.2.6	Safety laboratory section updated.	To be consistent with different protocol sections.
Section 9.3	Definition of all treated and evaluation patients were modified.	To add more clarification.
Section 9.4.2.1	Definition of On-treatment period was modified.	To add more clarification.
Section 10.6.7	The 2014 CRS grading is replaced with 2019 ASTCT ICANS grading. Encephalopathy Assessment Tools for Grading of ICANS Immune Effector Cell-Associated Encephalopathy (ICE) score and Encephalopathy Assessment for Children Age <12 Years Using the CAPD score were added.	As CRS grading is already added into the protocol as a specific section, appendix will include these neurological events ASTCT ICANS grading and its assessments tolls.
Section 1.3	Cardiac assessment and ECG has been added to hematological recovery visit and at "EOT visit" also to AML cohort.	Correction of an inconsistency.
Section 1.3	Instructions were added to assess Potassium, phosphorus, uric acid, corrected and ionized calcium.	To rule out tumor lysis syndrome.
Table 1 and Table 2 in Section 1.3	Sample for CD38 RO/RD test should be collected just before isatuximab administration or up to 3 days prior to it.	Some flexibility to CD38 RO/RD test collection has been added.

Section # and Name	Description of Change	Brief Rationale
Section 1.3, Section 4.1.3, Section 6.5	HBV/HCV serological tests are mandatory for all patients at study entry. Patient not having been tested for HBV/HCV at screening that are still on treatment at the time of the amended protocol 4 will need to be tested additionally for HBsAg, anti HBs, anti-HBc (total and IgM), anti-HCV, HCV RNA level.	Clarification.
Section 6.6.1, Section 6.6.2	If there is a suspicion of anaphylaxis of any degree, every effort should be made to distinguish it from other IRs. If the suspicion of anaphylaxis persists or is confirmed, isatuximab (or any other product causally responsible for anaphylaxis) should be permanently discontinued.	Clarification that repeated IMP administration regardless of the grade of anaphylaxis must be prevented.
Section 10.4	Since an indirect interaction between components of the oral contraception and asparaginase (Erwinase) cannot be ruled out, oral contraceptives are not considered sufficiently safe in such clinical situation. A method other than oral contraceptives should be used in women of childbearing potential using pegaspargase or L-asparaginase (Erwinase).	Clarification on contraception for WOCBP receiving pegaspargase or L-asparaginase (Erwinase).
Section 1.3, Section 10.2, Section 6.1.2	In ALL patients on treatment with pegaspargase or L-asparaginase (Erwinase) daily monitoring of international normalized ratio (INR), partial thromboplastin time (PTT), fibrinogen and antithrombin III (AT-III) must be performed and fibrinogen and AT-III substituted if necessary. Pegaspargase IV infusion should last at least 2 hours.	To improve surveillance of participants receiving pegaspargase or L-asparaginase (Erwinase).
Added Section 6.1.3, Section 1.3, Section 4.1.3, Section 8.2.5, Section 8.2.6	Mandatory evaluations (hematology test including WBC with differential, Chest X-ray, potassium, phosphorus, uric acid, albumin, and calcium must be repeated every day) on Day 1 (or on schedule of evaluations provided) prior to the first isatuximab administration have been added.	To prevent avoidable risks in participants.
Section 6.1	Mandatory monitoring of patients after every isatuximab infusion is set up for 2 hours.	To prevent avoidable risks in participants.
Section 10.11	Summary of changes to last version of protocol has been added.	To provide summary of changes introduced in the last amended protocol v3.

10.11.2 Amended protocol 03 (30 July 2020)

This amended protocol (Amendment 03) is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

OVERALL RATIONALE FOR THE AMENDMENT

The primary driver for this amendment is to implement changes following health Authorities comments and to mitigate the risk of hepatitis reactivation identified in the SAR650984 Investigator's Brochure edition 11 (30-Apr-2020).

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities (SoA); 2.3 Benefit/Risk Assessment; 10.2 Appendix 2: Clinical laboratory tests	Additional hepatitis-related serology tests to be performed at screening.	A risk of hepatitis reactivation has been identified.
1.3 Schedule of Activities (SoA); 10.2 Appendix 2: Clinical laboratory tests	Hepatitis viral serology to be performed during treatment period as clinically indicated.	A risk of hepatitis reactivation has been identified.
5.2 Exclusion criteria	Hepatitis-related exclusion criteria clarified.	A risk of hepatitis reactivation has been identified.
5.2 Exclusion criteria; 6.5 Concomitant therapy	Exclusion of live vaccines from 30 days before first IMP administration until 90 days after last IMP administration.	To prevent potential safety risks.
6.5 Concomitant therapy; 10.2 Appendix 2: Clinical laboratory tests	Procedure for HBV vaccination and antiviral therapy defined.	A risk of hepatitis reactivation has been identified.
6.5 Concomitant therapy; 6.6.3 Guidance in case of hepatitis B reactivation occurring under study treatment; 10.2 Appendix 2: Clinical laboratory tests	Description of monitoring of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) in case of viral reactivation.	A risk of hepatitis reactivation has been identified.
2.3 Benefit/Risk Assessment; 6.5 Concomitant therapy; 6.6.3 Guidance in case of hepatitis B reactivation occurring under study treatment; 10.2 Appendix 2: Clinical laboratory tests	Description of study treatment discontinuation and restart procedure in case of viral reactivation.	A risk of hepatitis reactivation has been identified.

Section # and Name	Description of Change	Brief Rationale
5.5 Criteria for temporarily delaying of enrollment/administration of study intervention; 6.1 Study intervention(s) administered; 7.1.2 Temporary intervention discontinuation; 7.1.3 Rechallenge; 8 Study assessments and procedures; 9.3 Populations for analyses; 10.1.3 Informed consent process; 10.9 Appendix 9: Contingency Measures for a regional or national emergency that is declared by a governmental agency	The specific contingency measures in case of regional or national emergency that is declared by a governmental agency (eg, remote visits, use of local laboratory, temporary treatment discontinuation) have been added.	To ensure the safety of the participants, to consider continuity of the clinical study conduct, protect trial integrity, and assist in maintaining compliance with Good Clinical Practice in Conduct of Clinical Trials Guidance.
1.1 Synopsis; 3 Objectives and Endpoints	Secondary endpoints: CD38 receptor density will be assessed at baseline and CD38 receptor occupancy on Day 15.	Clarification.
1.1 Synopsis; 4.1.3 Study treatment period	Earlier initiation of chemotherapy is allowed if required.	During pre-phase with isatuximab alone, some patients may aggravate their clinical condition in absence of intensive associated treatment; only for these patients, chemotherapy may be started earlier than Day 8, without change in isatuximab infusions.
1.1 Synopsis; 1.3 Schedule of Activities (SoA); 4.1.3 Study treatment period; 4.1.5 Study duration; 8.1 Efficacy Assessments	Flexibility is added to bone marrow aspiration at the time of hematological recovery.	For medical reasons, some patients cannot reach hematological recovery.
1.1 Synopsis; 1.2 Schema; 1.3 Schedule of Activities (SoA); 5.2 Exclusion criteria; 6.1 Study intervention(s) administered; 6.6 Dose modification	L-asparaginase (Erwinase) can be used in case of intolerance to pegaspargase prior or during the study as per local clinical practice.	Many patients may have experienced or will present during the trial intolerance to pegaspargase; excluding this option may significantly decrease recruitment and does not provide any option for participants who will experience this issue during the trial.
1.1 Synopsis; 6.1 Study intervention(s) administered	Dose of vincristine should not exceed 2 mg per infusion in any patient.	Clarification.

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities (SoA); 4.1.2 Screening; 6.1 Study intervention(s) administered	IT prophylaxis is mandatory for all cohorts; the drugs that will be used (methotrexate/aracytine/steroids) are per investigator discretion.	Clarification.
5.2 Exclusion criteria	Exclusion for cardiomyopathy is defined as ejection fraction <55%.	New York Heart Association Grade 3 and 4 does not apply to pediatric population.
6.1 Study intervention(s) administered	Mandatory monitoring of first infusions of isatuximab.	To prevent and treat infusion reactions.
6.1 Study intervention(s) administered	Timing of premedication with montelukast was changed.	Montelukast activity is observed after 2 hours.
1.1 Synopsis; 4.1.2 Screening; 6.1 Study intervention(s) administered	When dexamethasone is administered at 10 mg/m^2 per os, it can be divided in two daily doses, except for administration as part of isatuximab premedication.	Clarification.
1.1 Synopsis; 6.1 Study intervention(s) administered	Ranitidine or equivalent are deleted from premedication list.	According to Investigator's Brochure edition 11.
5.1 Inclusion criteria; 10.4 Appendix 4: Contraceptive guidance and collection of pregnancy information	Change in duration of contraception depending on the last treatment discontinued and considering the longest recommended duration of contraception.	To cover recommended duration of contraception for all study treatments.
7.1.1 Definitive discontinuation	Mention that pregnancy will result in treatment discontinuation.	Consistency.
1.3 Schedule of Activities (SoA); 8.2.4 Cardiac assessment	ECG and cardiac assessment to be performed at the end of Cycle 2.	It is not possible to rule out a relationship between isatuximab concentration and heart rate.
8.8.1 CD38 expression, receptor density, and receptor occupancy	CD38 testing will be limited to European countries and North America.	Clarification.
1.3 Schedule of Activities (SoA); 10.2 Appendix 2: Clinical laboratory tests	Addition of thyroid panel to the clinical chemistry tests.	To prevent potential safety risks.
1.3 Schedule of Activities (SoA); 10.2 Appendix 2: Clinical laboratory tests	Addition of alkaline phosphatase to the clinical chemistry tests.	Correction of an inconsistency.
1.3 Schedule of Activities (SoA)	Risk groups were clarified	To provide examples of what will be consider as risk factor for final analysis.
1.1 Synopsis; 6.1.1 Acute myeloid leukemia combination therapies; 6.1.2 T ALL and B ALL combination therapies	Conditions for second induction include neutrophils of ≥500/mm^3 and platelets of ≥50,000/mm^3.	Typo.

Section # and Name	Description of Change	Brief Rationale
5.2 Exclusion criteria	Participants who are expected to have a superior benefit if treated with alternative established standard therapies are excluded.	In the interest of the patient.
1.1 Synopsis; 9.1 Statistical hypotheses; 9.2 Sample size determination	Complete response (CR) rate in statistical analysis defined as CR + complete response with incomplete peripheral recovery (CRi) rate.	Consistency with primary endpoint.
1.1 Synopsis; 9.3 Populations for analyses	Definition of pharmacokinetic population was clarified.	Clarification.
9.4.5 Biomarkers analysis	The analysis of CD38 receptor density and occupancy was clarified.	Clarification.
10.1.3 Informed consent process	Consent process for optional onco-hematology research is described.	Clarification.
Whole document	Correction of typos and minor inconsistencies.	

10.11.3 Amended protocol 02 (04 December 2019)

This amended protocol (amendment 02) is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

OVERALL RATIONALE FOR THE AMENDMENT

The objectives of this amendment were:

- To bring clarifications on the definition of complete response, in order to avoid patients being ‘not evaluable’ if still dependent on red blood cell transfusions.
- To include dexamethasone as an IMP for ALL cohort as part of study treatment. To further clarify the difference that for AML cohort dexamethasone is optional, except as premedication for isatuximab.
- To update the duration for contraception.
- To add Montelukast as a systematic premedication, the objective being to decrease the incidence and severity of IRs; it should not be at Investigator's discretion.
- To add hematological criteria for ALL patients before starting the consolidation period.
- To simplify some procedures in order to be closer to clinical practice.
- To add recommendations in case of pegaspargase hypersensitivity.
- To add analysis of CD38 receptor density and occupancy, in order to better understand the response profile at the end of the trial.

- To bring more clarification on the first interim analysis that will be performed on first 20 patients.
- To perform administrative and editorial updates and corrections to the protocol.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Short title	The short title of the study has been updated to include the following name of the study: Isatuximab in Combination with Chemotherapy in Pediatric Patients with Relapsed/Refractory Acute Lymphoblastic Leukemia or Acute Myeloid Leukemia **(ISAKIDS).**	To include the new approved short title.
Section 1.1 Synopsis, Section 3 Objectives and Endpoints, Section 4.1.2 Screening	The following primary endpoint has been updated in Section 1.1 and Section 3: For AML: CR: bone marrow blasts lower than 5%; No blasts with Auer rods or persistence of extramedullary disease; ~~absolute~~ ANC higher than 1000/mm^3, platelets higher than 100 000/mm^3; **red blood cells** transfusion independence**. If the physician documents transfusion dependency related to study treatment and not to the patient's underlying disease, CRi can be reported.** For B-ALL and T-ALL: CR: bone marrow blasts lower than 5%, no circulating blasts or lymphoblasts in CSF or extramedullary disease; ANC higher than 1000/mm^3, platelets higher than 100 000/mm^3; **red blood cells transfusion independence. If the physician documents transfusion dependency related to study treatment and not to the patient's underlying disease, CRi can be reported.**	Avoid having patients recruited and not evaluated in case they still require red blood cell transfusions.
	The following secondary endpoint has been updated in Section 1.1 and Section 3: The overall response rate is defined as the proportion of participants with CR or CRi for blood and bone marrow disease; PR based on the NCCN guideline will be considered ~~in case of lymphomatus extramedullary disease for participants with T-ALL~~.	PR as response doesn't apply only for T-ALL, also for AML assessment.
	A new secondary objective/endpoint has been added to Section 1.1 and Section 3: **Relationship between clinical effects and CD38 receptor density and occupancy: CD38 receptor density and occupancy will be assessed at baseline and at Day 15 and correlated with clinical endpoints.**	Relationship between clinical effects and CD38 receptor density and occupancy will be evaluated to better understand the response profile at the end of the trial.

Section # and Name	Description of Change	Brief Rationale
	The following text has been updated in synopsis and Section 4.1.2: In order to have rapid control of the tumor burden, the administration of cyclophosphamide 200 mg/m² **is allowed (optional for both AML and ALL cohorts)**~~.and/or~~ Dexamethasone 10 mg/m²/day (or equivalent) before the first study intervention administration (at least 3 times, on Days -3, -2, and -1) is **(mandatory for ALL** ~~in all~~ cohorts **as a part of study treatment and optional for AML cohort). Administration of dexamethasone on Day 1 is mandatory in both cohorts as part of isatuximab premedication.**	Based on clinical practice, dexamethasone will be mandatory and consequently IMP only in ALL cohort; in both cohorts it will replace methylprednisolone as isatuximab premedication.
Section 1.1 Synopsis, Section 6.1.1 AML combination therapies, Section 6.1.2 T-ALL and B-ALL combination therapies	The following text has been added in AML combination therapies in synopsis: **Refer to Figure 1 and Section 1.3 for days of investigational medicinal product (IMP) administration**. Cycle 2 (second induction) text has been modified in synopsis and Section 6.1.1: If the BM aspiration performed 1 week after the end of induction treatment shows less than 20% blasts, a second cycle of combination therapy can be administered **if neutrophils of ≥ 0.5/mm³ and platelets of ≥ 50/mm³**~~after complete hematological recovery (ie, absolute neutrophil count >1000/µL and platelets 100 000/ µL)~~, while keeping the same schedule and doses. The following text has been added after the consolidation cycle for TALL and B-ALL combination therapies in the synopsis and Section 6.1.2: **Before starting consolidation cycle, the patient must have neutrophils of ≥0.5/mm³ and platelets of ≥50/mm³.**	Inconsistency corrected as presence of < 20% bone marrow blasts cannot correspond with complete hematological recovery. Minimal hematological function recovery is needed before starting a second induction treatment in AML.
Section 1.1 Synopsis, Section 4.1.1 Study participants and cohorts, Section 4.3 Justification of dose, Section 6.1 Study interventions administered, Section 9.5 Interim analyses	The dose regimen for dexamethasone or equivalent Investigational medicinal product for the AML cohort has been updated in the synopsis table and Section 6.1 (Table 4): Dexamethasone ~~being~~ is part of ~~both backbone treatment regimen and~~ isatuximub premedication **in the AML cohort only**, **and will be given as premedication for prevention of infusion associated reactions** before each administration of isatuximab, at least 15 to 30 minutes (but no longer than 60 minutes) prior to infusion~~, will be given as premedication for prevention of infusion associated reactions~~. Dexamethasone 10 mg/m² (maximum 20 mg) IV or PO on ~~Days -3, -2, and -1 before isatuximab administration, and~~ Days 1, 8, and 15 during the induction period (mandatory for Cycle 1 and **before first isatuximab infusion Cycle 2). It could be optionally used for rapid control of tumor burden on Days -3, -2 and -1.**	Based on clinical practice, dexamethasone will be mandatory and consequently IMP only in ALL cohort; in both cohorts it will replace methylprednisolone as isatuximab premedication.

Section # and Name	Description of Change	Brief Rationale
	Noninvestigational Medicinal Products: The following text has been added in the synopsis and Section 6.1: **The recommended isatuximab premedication agents are: montelukast, diphenhydramine (or equivalent), methylprednisolone, ranitidine (or equivalent), and acetaminophen (paracetamol) PO. Taking into consideration the disease context and the frequent use of steroids in acute leukemia, methylprednisolone will be replaced by dexamethasone.** The following text has been modified in the synopsis and Section 6.1 (Table 5): Montelukast is to be given to a child under adult supervision, before isatuximab infusion, ~~upon the Investigator's decision~~. Dexamethasone has been added to the noninvestigational products table in the synopsis and Section 6.1 (Table 5): Route of administration: **PO or IV** Dose regimen: **Dexamethasone is part of isatuximab premedication ~~only~~ in the AML cohort only, and will be given as premedication for prevention of infusion associated reactions before each administration of isatuximab, at least 15 to 30 minutes (but no longer than 60 minutes) prior to infusion. Dexamethasone 10 mg/m^2 (maximum 20 mg) IV or PO on Days 1, 8, and 15 during the induction period (mandatory for Cycle 1 and before first isatuximab infusion at Cycle 2).**	
	The following subgroup PK analysis age group has been modified in the synopsis, Section 4.1.1, Section 4.3, and Section 9.5: at least 5 participants in the age groups of 2 to 4~~-10~~ years, ~~5 to 11 years and 12 to 18 years~~ **including approximately 3 patients between 2 and 5 year-old**.	Based on PK simulations, the threshold of 2 year-old has been identified as a potential risk for dose adaptation, and the population of interest for this analysis would focus on patients younger than 10 years; consequently, for interim analysis purposes, at least 5 patients would be needed between 2 and 10 year-old and no further stratification is needed. The current version is not consistent, as it requests the same minimal sample size by age subgroup as for the whole population at the end. This change is also in relation with the important challenges in patients' recruitment, due to the epidemiology of the diseases
Section 1.1 Synopsis and Section 9.4.5 Biomarkers analysis	The following text was added to synopsis and Section 9.4.5: Receptor density and occupancy data: The descriptive statistics of receptor density and receptor occupancy will be summarized by cohort and overall as well as for best overall response (responders versus non-responders) will be calculated.	Relationship between clinical effects and CD38 receptor density and occupancy will be evaluated to better understand the response profile at the end of the trial.

Section # and Name	Description of Change	Brief Rationale
Section 1.3 Schedule of Activities (SOA), Section 4.1.5 Study duration, Section 5.1 Inclusion criteria, Section 8.3.5 Pregnancy, Section 10.4 (Appendix 4) Contraceptive guidance and collection of pregnancy information	Physical examination has been added to the EOT visit for the AML cohort. CD38 biomarker added to the AML and ALL cohorts; consolidation and follow-up. Duration updated for bone marrow for disease assessment and MRD assessment (from Days 36~~7~~ to 43) for ALL cohorts consolidation and follow-up. The following footnotes were updated in Section 1.3: c-Past and current medical condition: date of initial diagnosis, type of disease (T-ALL/T-LBL, B-ALL, B-LBL, AML, immunophenotyping and cytogenetic, molecular profile), previous antileukemia treatment (reason for discontinuation, date of relapse, and best overall response to prior treatments), risk group **as per site institutional practice**, and prior transplant. e-Pregnancy testing should be carried out in WOCBP as follows: for ALL induction: within 2 weeks prior to first dose, Day 1 (predose), and Day 30 (predose). For ALL consolidation: on Day 57 (predose), end of treatment (30 days after last dose), and monthly during the follow up period for 180 days (6 months) after the last dose **of isatuximab, or 12 months after the last dose of cyclophosphamide**. For AML: within 2 weeks prior to first dose, Cycle 1 Day 1 (predose), Cycle 2 Day 1 (predose), end of treatment (30 days after last dose), and monthly during the follow up period for 180 days (6 months) after the last dose of **isatuximab, or 12 months after the last dose of cyclophosphamide**. This text is also updated in Section 4.1.5, Section 5.1 (I 03), Section 8.3.5, and Section 10.4 (Appendix 4). g-Hematology: Hemoglobin, hematocrit, white blood cell count with differential, percentage of blasts, platelet count (please see Table 13 for a complete list). **Hematology sample collection is recommended every 2 days, but mandatory at least weekly.** j- Urinalysis: Dipstick only. **If other analytes are collected based on clinical context, they must be reported in the eCRF**. m-Bone marrow for disease assessment: No BM assessment is necessary if nonresponse or progressive disease can be diagnosed with peripheral blood evaluation, ~~or, if a white blood cell count <300/mm^3~~, or if the BM assessment is considered noncontributory by the Investigator. Any additional BM aspirations will be performed at the Investigator's discretion and should be reported in the eCRF. **If BM aspirate fails, BM biopsy could be an option.** o-Extramedullary disease assessment: For ALL, CT or PET-CT **(preferred)** scans are suggested to be performed at screening and at hematological recovery or	Clarifications and simplifications on some procedures and visits were needed in order to be more compatible with clinical practice. Pregnancy testing is updated based on the use of cyclophosphamide.

Section # and Name	Description of Change	Brief Rationale
	at EOT (if no hematological recovery) if lymphomatous involvement is suspected. **If not done**, PET-CT scan is suggested to be performed at screening if lymphomatous involvement is present. If positive at screening, PET-CT will be repeated at the time of CR in BM. For AML, ~~by~~ physical examination **may be used for specific locations when imaging is not appropriate (ex cutaneous location)**.	
	The following procedure has been added to PK flowcharts: **Pharmacodynamics: CD38 receptor density and occupancy in blood**.	
Section 2.2 Background	The following text has been updated: The half-life associated to the linear elimination was ~~18.6~~ **28** days	Half-life for Isatuximab has been corrected.
Section 2.3 Benefit/risk assessment	The following text has been modified: **At the cut-off date of 05 January 2019, the clinical development program with isatuximab consisted of Phase 1/2/3 studies of isatuximab as a single agent or in various therapeutic combinations with other agents. A total of 1301 patients have been exposed to isatuximab thus far in the completed studies**~~As of 05 January 2018, the clinical development program with isatuximab consists of Phase 1, Phase 2, and Phase 3 studies of isatuximab as a single agent or in various therapeutic combinations with other agents. A total of 675 participants have been exposed to isatuximab so far in company sponsored trials.~~ During the dose escalation phase (Phase 1) of the TED10893 study **(monotherapy in relapsed-refractory multiple myeloma [R/R MM] and other hematological malignancies)**, dose-limiting toxicities (DLTs) consistent with IRs (which were initially included in the definition of DLTs), occurred at Cycle 1 in 2 participants with MM. **Based on the efficacy results from a pooled analysis of completed monotherapy studies TED10893 (Phase 1 and Phase 2 Stage 1) and TED14154 (monotherapy in RRMM, Part A) (N = 212)**~~From June 2010 to August 2016, a total of 89 participants with CD38+ hematological malignancies were treated with isatuximab monotherapy in the TED10893 study. ,~~ ~~O~~overall response rate ~~(≥ partial response [PR]) according to Investigator assessment by the European Society for Blood and Marrow Transplantation criteria among the 84 MM treated participants~~ was **19.8**~~20.2~~% ~~(1 CR, 16 PRs)~~. Clinical benefit response (≥ minimal response) was ~~26.2~~**28.3%** and best response was stable disease in ~~42.9~~**39.2%** of the ~~MM~~ treated participants.	To be consistent with the latest version of IB (edition 10).

Section # and Name	Description of Change	Brief Rationale
Section 4.1.2 Screening	The following text has been modified: The screening assessment data obtained prior to the informed consent may be accepted if performed within ~~3 weeks~~ **1 month** prior to Day 1.	More flexibility for screening testings.
Section 5.1 Inclusion criteria and Section 5.2 Exclusion criteria	Numbering of the eligibility criteria has been corrected.	Minor formatting error corrections.
Section 5.2 Exclusion criteria	The following text has been added to E01: **Human immunodeficiency virus, hepatitis B, and hepatitis C virus serology testing to be performed and collected in database only in countries where requested by local regulations**. The E 12 has been clarified: Intolerance **or contraindication** to treatment with mAb or any other drug part of the study intervention.	To anticipate specific regulatory requests in some countries. Clarification on exclusion criteria related to prior drug administrations.
Section 5.2 Exclusion criteria	The Exclusion criterion 13 has been clarified: E 13 - Participants with LBL with BM blasts <~~20~~**5**%.	Clarification on exclusion criteria: typo has been corrected.
Section 6.1 Study interventions administered	Dosing instructions for Vincristine have been updated to include the following text: **Vincristine should be given 3 to 24 hours before administration of** ~~Asparaginase~~**pegaspargase in order to minimize the toxicity.** The following text has been updated: For participants who do not experience an IR during the first 4 administrations of isatuximab, the need for premedication at the subsequent infusions may be reconsidered at the Investigator's discretion in consultation with the Sponsor, **with the exception of dexamethasone administered as a part of study treatment in ALL cohorts (Days -3 to -1, 15 to 19, 29 to 33 and 43 to 47) that should be administered as planned, unless there are dose modifications related to toxicities.**	Clarification on IMP administration.
Section 6.5 Concomitant therapy	The following text has been updated: Pneumocystis prophylaxis ~~can~~ **should** be provided as per the site's clinical practice. Prophylactic heparin therapy is recommended for participants receiving ~~PEG asparaginase~~**pegaspargase, as well as use of anti-allergy premedication as per site clinical practice in order to decrease the risk of allergic reactions.**	Supportive care was updated in order to be compliant with clinical practice and international guidelines.
Section 6.6 Dose modification	The following texts have been updated: Administration of other IMPs in the study intervention will be discontinued/**modified** in the event of a treatment emergent AE (TEAE) that persists despite appropriate dose modifications or any other AE that, in the opinion of the Investigator, warrants discontinuation **or dose modification.**	Clarification on IMP dose modification.

Section # and Name	Description of Change	Brief Rationale
	In case of ~~Grade 3 or 4~~ hypersensitivity, **allergy or non-allergic reaction to pegaspargase**~~PEG asparaginase, no rechallenge with this drug is allowed. M~~monitoring and treatment will be administered as per the site's clinical practice or **NCCN guidelines. Slowing infusion to ≥2 hours, infusion of normal saline and use of anti-allergy premedication (such as hydrocortisone, diphenhydramine) can reduce the incidence and severity of these reactions and the need for substitution with Erwinia.**	Provide guidelines for asparaginase administration in order to avoid substitution with other equivalents that are less effective.
Section 6.6.1 Guidelines for the management of potential infusion reaction	Severe Grade 3 NCI CTCAE version 5 criteria definition has been modified with the following intervention recommendation: 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 - **If a Grade 3 infusion-related AE occurs, the isatuximab infusion must be interrupted, and the patient observed carefully and treated as needed until the AE either resolves or improves to Grade 1. Then, at the investigator's discretion, the infusion may be restarted at half the infusion rate before the interruption. The infusion rate may be increased subsequently, at the investigator's discretion. If after restarting the infusion, the severity of an infusion-related AE returns to Grade 3, the infusion can be interrupted and restarted again (as described above) at the investigator's discretion. If a Grade 3 infusion-related AE occurs for a third time, treatment with isatuximab will be permanently discontinued for that patient. All Grade 3 IRs must be reported as AESIs.**	Modification of guidelines in case of isatuximab Grade 3 IRs, in order to avoid early discontinuation of the drug.
8.1 Efficacy assessments	The following text has been modified: Extramedullary assessment of AML will be performed by physical examination **if radiology assessment cannot be performed**. A CT or PET CT scan can be performed if clinically indicated for the AML cohort. ~~Analysis~~ **Assessment** of extramedullary ~~assessment~~ **disease** will be performed locally. The following sentence has been added: **Minimal residual disease assessments will be performed by central laboratories.**	Editorial update.
8.2.5.1 Blood type phenotyping/genotyping	After the start of the study treatment, a new IAT assessment will be performed once. If the second test is positive, a dithiothreitol (DTT) test should be performed **only if transfusions are required** (in accordance with Section 10.6.6).	Clarification on dithiothreitol (DTT) test.

Section # and Name	Description of Change	Brief Rationale
New Section 8.8.1 CD38 expression, receptor density, and receptor occupancy added	The following text has been added: **CD38 expression, receptor density (RD) and receptor occupancy (RO) will be assessed and correlated with clinical response. Blood samples will be collected once on Day 1 predose and once on Day 15 predose.**	Addition of RO and RD analysis in order to identify subgroups of patients who may benefit from treatment.
Section 8.9 Immunogenicity assessments	Immunogenicity assessment has been updated as a separate heading.	Updated formatting.
New Section 9.4.4 Pharmacokinetic analysis added	The following text has been added to the new section 9.4.4 pharmacokinetic analysis: **The population PK analyses will be described in the Population PK analysis plan provided by Pharmacokinetics and Drug Metabolism Modeling and Simulation group.**	Clarification on PK analysis.
Section 9.4.5 Biomarkers analyses	The section heading and the text has been updated: ~~Other~~ **Biomarkers** analys~~e~~s: The ~~PK~~, PD and biomarker ~~exploratory~~ analyses will be described in the statistical analysis plan finalized before database lock, if applicable. The ~~population PK analysis and~~ PD analyses **and biomarker** will be presented separately from the main clinical study report.	
Section 10.2 Appendix 2: Clinical laboratory tests	The following heading and text has been updated: **Flowchart** Appendix 2: Clinical laboratory tests. The tests detailed in Table 13 will be performed by the local laboratories with the exceptions of PK, ADA, **RO/RD** and MRD analyses, which will be performed at the central laboratory.	Clarification on central and local laboratory tests.
Section 10.6.1.1 Acute lymphoblastic leukemia	Response criteria have been added for blood and BM: **RBC transfusion independence: If the physician documents transfusion dependency related to study treatment and not to the patient's underlying disease, CRi can be reported.** **Response criteria for CNS disease have been added:** • **Central nervous system remission: Achievement of CNS-1 status in a patient with CNS-2 or CNS-3 at diagnosis (see Table below)** • **Central nervous system relapse: New development of CNS-3 status or clinical signs of CNS leukemia without other explanation. New development of CNS-2 status on 2 consecutive lumbar punctures (between 2 to 4 weeks apart).** **Definition of CNS Disease Criteria** **CNS 1-No blasts seen on cytocentrifuge (CNS negative)**	CNS disease assessment have been added to be in line with international guidance.

Section # and Name	Description of Change	Brief Rationale
	CNS 2-Total Nucleated Cell Count < 5 x 10^6/L, but blasts seen on cytocentrifuge **CNS 3-Total Nucleated Cell Count ≥ 5 x 10^6/L with blasts on cytocentrifuge and/or signs of CNS leukemia (eg, cranial nerve palsy).**	
Section 10.6.1.2 Acute myeloid leukemia	Definition of CR has been updated to add the following points: • **<5% blasts in a BM aspirate with spicules** • **No blasts with Auer rods or persistence of extramedullary disease** • **Red blood cell transfusion independence: If the physician documents transfusion dependency related to study treatment and not to the patient's underlying disease, CRi can be reported.** The following text has been modified: ANC ≥>1000/µL CRi definition has been updated as follows: • **Same criteria as for CR, except neutrophils and/or platelets recovery (ANC <1000/µL or platelets <100 000/µL)**	Clarification to be in line with international guidance and clinical practice.
	~~•<5% BM blasts~~ ~~•Either ANC <1000/µL or platelets <100 000/µL~~ ~~•Transfusion independence but with persistence of cytopenia (usually thrombocytopenia)~~	
Throughout	Generic drug name pegaspargase updated to replace Polyethylene glycol (PEG) asparaginase and product approved leaflet updated to replace package insert.	Clarifications in order to allow available generics and be more compatible with clinical practice.
Throughout	Editorial changes and/or typographical errors.	To improve text clarity, consistency, and readability and address typographical errors.

10.11.4 Amended protocol 01 (11 March 2019)

This amended protocol (Amendment 01) is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment

The objectives of this amendment were:

- To clarify suspected unexpected serious adverse reactions and sponsor responsibilities to submit any change(s) considered substantial to the regulatory authorities for notification and approval.

- To clarify contraception and pregnancy testing for females and males of childbearing potential, as well as clarification of the criteria for discontinuation of the study by the Sponsor.
- To update the pharmacokinetic follow-up assessment from 60 to 90 days after last isatuximab administration to align with other isatuximab studies.
- To improve the feasibility of the study procedures.
- To perform administrative and editorial updates and corrections to the protocol.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Throughout	Editorial changes and/or typographical errors.	To improve text clarity, consistency, and readability and address typographical errors.
Section 1.1 (Synopsis), Section 4.1.1 (Study participants and cohorts); Section 4.3 (Justification for dose); Section 9.5 (Interim analyses)	Subgroup pharmacokinetic analysis re-stratified by age group. The following change has been made in Section 1.1, and performed with the same intent for Sections 4.1.1, 4.3, and 9.5: **"**A subgroup PK analysis will be performed after the first 20 participants ~~(approximately 10 participants in each ALL and AML cohorts)~~ of 2 years of age or more **(at least 5 participants in the age groups of 2 to 4 years, 5 to 11 years and 12 to 18 years)** are exposed to isatuximab. The dosage for ~~younger age~~ **participants aged less than 2 years** will be reassessed based on the results. **"**	To include more patients in the lower age range. The inclusion of younger patients improves the possibility of supporting dosing in children below 2 years of age.
Section 1.1 (Synopsis); Section 1.3 (Schedule of activities); Section 6.1 (Study intervention[s] administered)	Granulocyte colony-stimulating factor administration updated to be optional during the study.	To add flexibility to the product administration, in accordance with the Investigator's discretion and participant's clinical status and history. Clinical standards for granulocyte colony-stimulating factor administration vary between countries.
Section 1.2 (Schema)	Figures **re**-designed.	Figures have been re-designed to improve clarity and consistency with the remaining updates.
Section 1.3 (Schedule of activities); Section 8.1 (Efficacy assessments)	~~The following updates have been made to Section 1.3, footnote n:~~	Specimen collection and time of collection have been updated for minimal residual disease assessment, to be consistent with the specifications of the assays used to assess minimal residual disease.

Section # and Name	Description of Change	Brief Rationale
	"~~Bone marrow for~~ MRD assessment: ~~To~~ **For ALL, to** be performed with BM aspiration ~~samples~~ at screening~~,~~ **and with peripheral blood samples** at the end of induction ~~for ALL~~ **(between Days 36 and 43),** at the time of hematological recovery, and/or at the time of each BM ~~aspirate~~ **aspiration** for disease assessment if CR or CRi is achieved. ~~For ALL only, if BM aspirates are not available (biopsy not allowed), peripheral blood samples could be used for these assessments except for the screening period.~~ **For AML, to be performed with BM aspiration samples at the time of hematological recovery between Days 22 and 29 (optional), and/or at the time of each BM aspiration for disease assessment if CR or CRi is achieved**". Also in Section 1.3, the minimal residual disease assessments schedule was updated to include the first week of the consolidation phase **"from Days 37 to 43"**. Section 8.1 has also been updated to reflect these changes.	
Section 1.3 (Schedule of activities); Section 6.1 (Study intervention[s] administered)	The following updates have been made regarding anthracycline administration in the AML cohort. In Section 1.3, footnote p: "Anthracycline: The choice of anthracycline (~~DaunoXome~~,**liposomal daunorubicin, nonliposomal** daunorubicin, or idarubicin) is at the Investigator's discretion **and the same anthracycline should be used throughout the study. The administration of Day 8 in Cycle 1 is mandatory. Other administrations of anthracycline, including Day 8 in Cycle 2, are at the Investigator's discretion**". In Section 6.1, Table 4, dosing instructions for liposomal daunorubicin, nonliposomal daunorubicin, or idarubicin were updated so that doses would be mandatory for Cycle 1 Day 8, optional for Cycle 1 Days 10 and 12, and optional for Cycle 2.	To add flexibility to the product administration, in accordance with the Investigator's discretion and participant's clinical status and history. Anthracycline administration will depend on previous participant's exposure and history of transplant.
Section 1.3 (Schedule of activities)	Contraception and pregnancy testing updated to include the period 2 weeks prior to treatment, and on a monthly basis during treatment and 6 months after treatment.	To ensure compliance with the European Medicines Agency Clinical Trial Facilitation Group Recommendations related to contraception and pregnancy testing in clinical trials.
Section 1.1 (Synopsis), Section 6.1 (Study intervention[s] administered)	Polyethylene glycol-asparaginase updated to include intravenous mode of administration.	To add flexibility to the product administration, in accordance with the approved package insert and Investigator's discretion. Intravenous route was also included to account for the increased risk of thrombocytopenia in these participants, which does not allow for subcutaneous administration.

Section # and Name	Description of Change	Brief Rationale
Section 1.1 (Synopsis), Section 6.1 (Study intervention[s] administered)	Formulation, packaging, and labeling information for all investigational medicinal products (except for isatuximab) has been removed. In its place, the approved package inserts of these products have been referred.	This information may be dependent on country sourcing and respective instructions should be performed in accordance with the approved package insert.
Section 1.3 (Schedule of activities)	Lumbar puncture and intrathecal chemotherapy in the acute lymphoblastic leukemia induction changed from Days 1 to 8.	The original text was incorrect.
Section 1.3 (Schedule of activities)	Day 37 moved from the acute lymphoblastic leukemia induction schedule to the consolidation schedule.	Day 37 is part of treatment Week 6, outside of the induction period (5 weekly isatuximab infusions for the acute lymphoblastic leukemia cohort).
Section 1.3 (Schedule of activities); Section 8.1 (Efficacy assessments)	It has been clarified that extramedullary assessments are optional. In addition, it has been added that computed tomography (CT) or positron emission tomography (PET)-CT scans should be performed if lymphomatous involvement is suspected, whereas if lymphomatous involvement is present, PET-CT scan should be performed. In Section 1.3 footnote o, the following updates have been made: "Extramedullary disease assessment: For ALL, ~~A CT of neck/chest/abdomen/pelvis with IV contrast at baseline;~~**CT or** PET-CT **scans are suggested to be performed at screening and at hematological recovery or at EOT (if no hematological recovery) if lymphomatous involvement is suspected. PET-CT** scan ~~should~~ **is suggested to be** performed at screening if lymphomatous involvement ~~suspected~~ **is present**. If positive **at screening**, ~~to be~~ **PET-CT will be** repeated at the time of CR **in BM**. For AML, by physical examination. CT or PET-CT can be performed if clinically indicated". In Section 8.1, the following updates have been made: "**Extramedullary assessments are optional.** For **the** extramedullary assessment of ALL, CT or PET-CT ~~scan should~~ **scans are suggested** to be performed ~~at screening and at hematological recovery or at EOT (if no hematological recovery). A CT of neck/chest/abdomen/pelvis with IV contrast will be performed at screening. In case of~~ **as defined in the SOA (Section 1.3)** if lymphomatous involvement **is** suspected. **If lymphomatous involvement is present at screening,** a PET-CT scan ~~should~~ **is suggested** to be performed~~, instead~~. If positive **at screening**, the PET-CT scan will be repeated at the time of CR in BM".	To clarify the extramedullary assessment procedures for this study and to decrease the participant's exposure to radiations, as systematic PET-CT is not standard in European countries.

Section # and Name	Description of Change	Brief Rationale
Section 1.1 (synopsis), Section 1.3 (Schedule of activities); Section 4.1.3 (study treatment period)	For the acute myeloid leukemia cohort, it has been clarified that bone marrow aspirations (with optional minimal residual disease assessment) were to be performed once between Days 22 and 29. The following updates have been made to Section 1.3 footnote m, and updates in accordance have been made to, Section 1.1, and Section 4.1.3: **"**Bone marrow for disease assessment: To be performed **once** at ~~baseline~~ **screening**, **once** between Days 8 and 15 (optional), **once at the** end of induction for ALL (first week of consolidation ~~± 1 week~~), **once between Days 8 and 15 (optional), once** between Days 22 and 29 for AML, and **once** at the time of complete hematological recovery ~~in case bone marrow aspirate failed, bone marrow biopsy could be an option. If recovery from aplasia~~ (**at least 48 hours after the last injection of G-CSF, when neutrophils reach 1 G/L and platelet count 100 G/L). No BM assessment is necessary if nonresponse or progressive disease can be diagnosed with peripheral blood evaluation, or, if a white blood cell count <300/mm^3, or if the BM assessment is considered noncontributory by the Investigator. Any additional BM aspirations** will ~~show persistence of peripheral leukemic blasts, bone marrow aspirate is not mandatory~~ **be performed at the Investigator's discretion and should be reported in the eCRF**". Also in Section 1.3, the bone marrow assessments schedule was updated to include the first week of the consolidation phase **"from Days 37 to 43"**.	To clarify the bone marrow aspiration requirement for the acute myeloid leukemia cohort.
Section 1.3 (Schedule of activities)	Blood type phenotyping/genotyping text updated as follows: "**Blood typing and complete blood phenotyping (C,c; E,e; Kell. Kidd; Duffy; S,s is recommended, if not available, the site's standard will be followed) if not already done, and antibody screening (IAT) to be obtained prior to the start of the study treatment. After the start of the study treatment, a new IAT assessment will be performed once. If the second test is positive, a DTT test should be performed (in accordance with Section 10.6.6). Results of IAT (and DTT test, if applicable) will be recorded in the eCRF, including those performed prior to any transfusion during study intervention. Transfusions are to be recorded in the eCRF.** ~~If not previously performed, blood type phenotyping (or genotyping) and screen to be done after enrollment in the study and prior to first study treatment intervention administration~~"	To clarify AABB guidance on managing antiCD38 interference with blood bank serologic testing.

Section # and Name	Description of Change	Brief Rationale
Section 1.3 (Schedule of activities)	For glucose assessments, fasting is necessary. When the participant has not fasted overnight, glucose should not be measured. The following changes have been made in Section 1.3 footnote i "Biochemistry: "glucose (fasting**; if the participant has not fasted overnight, glucose should not be measured**)".	To clarify that participants must fast overnight for glucose to be measured.
Section 1.3 (Schedule of activities) – PK flowchart for AML cohort	Immunogenicity follow-up assessment ABF1 changed from 60 to 90 days after last isatuximab administration (±5 days).	Half-life of endogenous immunoglobulin G (IgG) is 21 to 25 days. Therefore, an IgG transient response is expected to be eliminated at the end of 5 times the half-life (approximately 16 weeks).
Section 1.3 (Schedule of activities) – PK flowchart for ALL cohorts	Immunogenicity follow-up assessment ABF1 changed from 60 to 90 days after last isatuximab administration (±5 days).	Half-life of endogenous IgG is 21 to 25 days. Therefore, an IgG transient response is expected to be eliminated at the end of 5 times the half-life (approximately 16 weeks).
Section 1.3 (Schedule of activities) – PK flowchart for ALL cohorts	Footnote d of Table 1 has been updated as follows: "~~At EOT, if participant~~ **If the ABF1 ADA result** is positive or inconclusive ~~for ADA~~, **no** additional ADA are required ~~every visit until sample is negative (sample ID: ABF2, ABF3, etc)~~".	Follow-up immunogenicity assessments will not be required after ABF1 to reduce the participants' burden.
Section 1.3 (Schedule of activities) – PK flowchart for AML cohort	The following footnote has been added to Table 1: "**Note: In case a Cycle 2 (second induction) is administered, PK samples must be taken only at predose on Days 1 and 15.**"	In case of second induction, pharmacokinetic sampling times are not the same as during Cycle 1.
Section 1.3 (Schedule of activities) – PK flowchart for AML cohorts	Footnote d of Table 1 has been updated as follows: "~~At EOT, if participant~~ **If the ABF1 ADA result** is positive or inconclusive ~~for ADA~~, **no** additional ADA are required ~~every visit until sample is negative (sample ID: ABF2, ABF3, etc)~~".	Follow-up immunogenicity assessments will not be required after ABF1 to reduce the participants' burden.
Section 4.1.2 (Screening)	The following text has been added "**The screening assessment data obtained prior to the informed consent may be accepted if performed within 3 weeks prior to Day 1**".	To clarify that data obtained prior to the informed consent can be accepted, as long as within the 3-week period prior to Day 1.
Section 5.1 (Inclusion criteria)	Changes described below have been made to I 05: "A) Male participants: A male participant with a female partner of childbearing potential must agree to use contraception as detailed in Appendix 4 (Section 10.4) of this protocol during the ~~intervention~~ **treatment** period and for at least ~~3~~ **6** months after the last dose of study intervention and refrain from donating sperm during this period (…) A WOCBP who agrees to follow the contraceptive guidance in Appendix 4 (Section 10.4) during the ~~intervention~~ **treatment** period and for at least ~~3~~ **6** months after the last dose of study intervention."	Participants must follow the contraceptive guidance for at least 6 months after the last dose of study intervention.

Section # and Name	Description of Change	Brief Rationale
Section 6.1 (Study intervention[s] administered)	Manufacturer row has been removed from Table 4 (Overview of study interventions administered).	Removed, as the product sourcing can change during the course of the study.
Section 6.1.1 (AML combination therapies)	Text listing the assessments to be performed on Cycle 1 has been removed. Instead, all assessments have been referred to the schedule of activities.	To reduce repetition of information.
Section 6.1.1 (AML combination therapies)	The following text has been added "**The choice of anthracyclines is at the Investigator's discretion (either liposomal daunorubicin, nonliposomal daunorubicin, or idarubicin) and the same anthracycline should be used throughout the study**".	To clarify that only 1 anthracycline compound is allowed per participant.
Section 6.1.2 (T-ALL and B-ALL combination therapies)	Text listing the assessments to be performed has been removed. Instead, all assessments have been referred to the schedule of activities.	To reduce repetition of information.
Section 6.1.2 (T-ALL and B-ALL combination therapies)	The following text has been added: "**The choice of anthracyclines is at the Investigator's discretion (either doxorubicin or mitoxantrone) and the same anthracycline should be used throughout the study**".	To clarify that only 1 anthracycline compound is allowed per participant.
Section 6.2 (Preparation/handling/ storage/accountability)	The following text has been added: "**If the participant's weight on the day of the dose preparation is not available, the most recent participant's weight may be used, assuming it was assessed in a reasonable time frame and the participant did not have any events leading to significant weight loss according to Investigator assessment. In such cases, the participant's weight should still be assessed on the day of administration to ensure the accuracy of the dose preparation**".	Word added to add flexibility on the determination of participant weight on dosing days.
Section 8 (Study assessments and procedures)	The following text has been removed: "~~Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention~~".	Any discontinuation is left to the Principal Investigator's medical judgment.
Section 8 (Study assessments and procedures)	The following text has been updated: "Procedures conducted as part of the participant's routine clinical management (eg, ~~blood count~~ **BM assessment**) and obtained before signing of the Informed Consent Form (ICF) may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within ~~the time frame defined in the SOA~~ **1 month before Day 1** (Section 1.3)".	To reduce the participants' burden, by decreasing the need to repeat routine clinical examinations.
Section 8.2.1 (Physical examinations)	The following text has been removed: "~~A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal and neurological systems~~".	To reflect the correct procedures and keep consistency with the schedule of activities.

Section # and Name	Description of Change	Brief Rationale
	The following text has been added: "**Examination of major body systems will include neurological examination, digestive, skin/mucosae, mediastinal, testicular involvements, respiratory, hepatomegaly, splenomegaly, and lymphadenopathy**".	
Section 8.2.2 (Vital signs)	Text corrected to reflect that vital signs are to be taken just before starting infusion of isatuximab, 1 hour after starting the infusion, at the end of infusion, and as clinically indicated. In addition, the following sentence has been removed "~~The measurements will also be performed at the EOT visit and post treatment follow up visits~~".	To reflect the correct procedures and keep consistency with the schedule of activities.
Section 8.2.5 (Clinical safety laboratory assessments)	The following text has been added: "**Where possible, blood volume for sampling for each visit will be minimized to less than approximately 1% of total blood volume and less than approximately 3% of total blood volume over a 4-week period. If necessary, blood sampling related to patient safety and the primary endpoint of the study should be prioritized. Additional blood samples may be collected at the Investigator's discretion for participant safety monitoring**".	Text added to clarify the desirable amount of blood to be collected from each participant clarify which procedures requiring blood sampling should be prioritized.
Section 8.2.5 (Clinical safety laboratory assessments)	Details on vital signs, electrocardiogram abnormalities or laboratory values meeting the definition of adverse event have been removed from this section and referred to Section 10.3. Changes are shown below: "A vital sign or ECG abnormality or laboratory value is reported as an AE **if it meets the definition of AE. See Appendix 3 (Section 10.3**).~~:~~ ~~- Is associated with a sign or symptom~~ ~~- Requires treatment~~ ~~- Leads to treatment discontinuation~~ ~~- Leads to dose modification~~ ~~- Fulfills a seriousness criterion~~ ~~- Is defined as an AESI~~".	To clarify and centralize the definition of vital signs, electrocardiogram abnormalities or laboratory values meeting the definition of adverse event, to avoid redundancy and inconsistencies.
Section 8.2.5.1 (Blood type phenotyping/genotyping)	New section added, describing the blood phenotyping/genotyping and indirect antiglobulin tests to be performed in this study, in alignment with the Schedule of Activities.	Section added to better clarify these assessments.
Section 8.3.4 (Regulatory reporting requirements for SAEs)	The deadlines for unexpected serious adverse events (SUSARs) reporting by the Sponsor to the authorities have been included in the protocol, as below: • For SUSARs that are life-threatening or result in death: 7 days after first knowledge, with follow-up information reported within an additional 8 days. • For other SUSARs: 15 days after first knowledge.	Details provided for compliance with Directive 2001/20/EC.

Section # and Name	Description of Change	Brief Rationale
Section 8.3.5 (Pregnancy)	The following change has been made "Details of pregnancies in female participants and, if indicated, female partners of male participants will be collected after the start of study intervention and until ~~3~~ **6** months after the last administration…".	Pregnancy data collection limit changed from 3 months after last administration to 6 months.
Section 8.4 (Treatment of overdose)	The following sentence has been removed: "~~Asymptomatic overdose should be reported as standard AE (See Section 8.3)~~".	Text deleted as it is not aligned with the electronic case report form completion guide (overdose electronic case report form page will be used).
Section 8.8.1 (Immunogenicity assessments)	The following sentence has been removed: "~~At 30 days after the last study treatment administration, if a participant is positive or inconclusive for ADA, additional ADAs are required to be collected and assessed at every follow-up visit until the sample is negative~~". The following sentence has also been added: "**Once a participant is off treatment, ADA samples will be collected 30 and 90 days after the last isatuximab administration. No additional ADA samples will be collected, regardless of the result of these samples (negative, positive or inconclusive)**".	Follow-up immunogenicity assessments will not be required after ABF1 to reduce the participants' burden.
Section 10.1.1 (Regulatory and ethical considerations)	Text included to clarify that the Sponsor will submit any change(s) considered substantial to the regulatory authorities for notification and approval: • "The Sponsor will be responsible for the following: - Submitting to the regulatory authorities for notification and approval any change(s) of the protocol that are deemed as "substantial" (ie, changes which are likely to have a significant impact on the safety or physical or mental integrity of the clinical trial participants or on the scientific value of the trial). - Notifying IRBs/IECs and competent authorities of the Member States the reason for, and the content of, any substantial amendments."	To clarify the Sponsor responsibilities on the notification of substantial amendments.
Section 10.1.3 (Informed consent process)	The following sentence has been removed: "~~A participant who reaches the legal age of majority as defined by local regulation during the course of the study must sign a new ICF~~".	This sentence has been removed for redundancy, as it is already reflected in the following text "Legally acceptable representatives or participants who reach the legal age of majority as defined by local regulation during the course of the study must be reconsented to the most current version of the ICF(s) during their participation in the study".

Section # and Name	Description of Change	Brief Rationale
Section 10.1.4 (Data protection)	The following text has been added: "**Participant race and ethnicity will be collected in this study because these data are required by regulatory agencies (eg, on afro American population for the Food and Drug Administration or on Japanese population for the Pharmaceuticals and Medical Devices Agency in Japan)**".	Text added to clarify the reason for collecting race and ethnicity information.
Section 10.1.7 (Data quality assurance)	The following bullets have been added: • "Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in separate study documents. • The Sponsor assumes accountability for actions delegated to other individuals (eg, Contract Research Organizations)".	To clarify monitoring strategies and accountabilities for this study.
Section 10.1.9 (Study and site closure)	Text changed as follows: "Reasons for **study termination by the Sponsor, as well as** reasons for the early closure of a study site by the sponsor or Investigator may include but are not limited to: • For study termination: - Information on the product leads to doubt as to the benefit/risk ratio - Discontinuation of further study intervention development • For site termination: - Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines - Inadequate **or no** recruitment **(evaluated after a reasonable amount of time)** of participants by the Investigator - Total number of participants included earlier than expected".	To further clarify the criteria for study and site closure

Section # and Name	Description of Change	Brief Rationale
Section 10.4 (Contraceptive guidance and collection of pregnancy information)	The following text has been added to the definition of women of childbearing potential: "**If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered**". The following text has been added to the definition of women not considered of childbearing potential: "**For individuals with permanent infertility due to an alternate medical cause other than the above (eg, mullerian agenesis, androgen insensitivity), Investigator discretion should be applied to determining study entry**".	Text added to further clarify the definition of women of childbearing potential.
Section 10.4 (Contraceptive guidance and collection of pregnancy information)	The following changes have been made to the text: "In addition, male participants must refrain from donating sperm for ~~3~~ **6** months after **the last dose** of study ~~completion~~ **intervention**." "Male participants with a pregnant or breastfeeding partner must agree to remain abstinent from penile vaginal intercourse or use a male condom during each episode of penile penetration **for the duration of the study and for 6 months after the last dose of study treatment** (during the protocol-defined time frame)." "Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception **as described in Table 14**, consistently and correctly ~~as described in~~ **from 2 weeks prior to the first dose and 6 months after the last dose of study treatment**."	
Section 10.6.1.1 (Acute lymphoblastic leukemia)	In the response criteria for blood and bone marrow, "no recurrence for 4 weeks" has been removed from the complete response criteria.	Criterion removed because it is not practical in clinical trials.

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