AMENDED CLINICAL TRIAL PROTOCOL 02

Protocol title:	**A Phase 1b/2 study to evaluate the safety, pharmacokinetics, and preliminary efficacy of isatuximab (SAR650984) in patients awaiting kidney transplantation**
Protocol number:	**TED16414**
Amendment number:	**02**
Compound number (INN/Trademark):	**SAR650984 isatuximab/SARCLISA**
Study phase:	**Phase 1/Phase 2**
Short title:	**Safety, pharmacokinetics, and preliminary efficacy of isatuximab in patients awaiting kidney transplantation**
Sponsor name:	
Legal registered address:	
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 02	All	01 Feb 2022, version 1 (electronic 1.0)
Amended Clinical Trial Protocol 01	All	23 July 2020, version 1 (electronic 1.0)
Original Protocol		07 Nov 2019, version 1 (electronic 2.0)

Amended protocol 02 (01 FEB 2022)

This amended protocol 02 (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

To clarify throughout the protocol that the target cPRA is defined as achieving a 100% increase in the likelihood of finding a compatible donor.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis 3.0 Objectives and Endpoints 10.9 Desensitization response criteria	Criteria for cPRA reduction is corrected from “at least 50% increase of likelihood” to “at least 100% increase of likelihood”.	To correct inconsistencies and to align with Section 10.9, Table 13, which defines target cPRA as the reduction of cPRA required to achieve at least 100% increase in the likelihood of a compatible donor (LCD)
5.2 Exclusion criteria	E06: Editorial changes made to clarify that history of active or latent tuberculosis is relevant if within 24 weeks prior to IMP initiation, and “(peritoneal, etc)” are specific to the “deep tissue/space infection”.	Changes made to improve clarity on E06.
10.2 Clinical laboratory tests	Table 11, footnote “a” added to clarify that serology and viral load tests listed serve as a guidance, and study sites should determine which serology and viral load tests are required to confirm participant’s eligibility and to enable appropriate viral reactivation monitoring for HBV, HCV, HIV, EBV, and CMV as per protocol	Clarification on need for individual serology and viral load tests.
All document	Minor editorial and format changes.	Accuracy.

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1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Protocol title:

A Phase 1b/2 study to evaluate the safety, pharmacokinetics, and preliminary efficacy of isatuximab (SAR650984) in patients awaiting kidney transplantation

Short title:

Safety, pharmacokinetics, and preliminary efficacy of isatuximab in patients awaiting kidney transplantation

Rationale:

About 30% of the kidney transplant waitlist patients are sensitized to human leukocyte antigen (HLA). The HLA sensitized patients are at risk for early graft loss from antibody mediated rejection (AMR) due to the presence of alloantibodies or donor-specific antibodies (DSAs), leading to prolonged wait time because of the lower likelihood of finding a compatible donor compared to those who are not sensitized. Current desensitization therapies (not registered by competent health authorities) aim to overcome the humoral incompatibility by removing or reducing the strength of alloantibodies, but do not target the terminally differentiated antibody-secreting plasma cells which express high level of cluster of differentiation (CD) 38. Isatuximab, an immunoglobulin G1 (IgG1) monoclonal antibody (mAb) directed against CD38, has shown clinical response in relapsed/refractory multiple myeloma patients as a single agent and in combination with immunomodulatory agents, and is being developed in other advanced malignancies. In general, isatuximab is well-tolerated clinically with a manageable safety profile. This study is designed to explore whether isatuximab may have activity in desensitization of patients awaiting kidney transplantation.

Objectives and endpoints

Objectives	Endpoints
Primary	
• Phase 1: To characterize the safety and tolerability of isatuximab in kidney transplant candidates.	• Adverse events (AEs)/serious adverse events (SAEs) and laboratory abnormalities.
• Phase 2: To evaluate the efficacy of isatuximab in desensitization of patients awaiting kidney transplantation.	• Response rate (RR) defined as the proportion of participants meeting at least one of the predefined desensitization efficacy criteria, from baseline up to 26 weeks after treatment period, measured by single antigen bead (SAB) assay per central laboratory assessment as follows: - Reduction in calculated panel reactive antibodies (cPRA) resulting in at least 100%

Objectives	Endpoints
	increase of likelihood of finding a compatible donor (for target cPRA, see Section 10.9). - Reduction in antibody titer (≥75% reduction from baseline) to achieve target cPRA (see Section 10.9). - Elimination of ≥1 anti-HLA-antibody (ie, mean fluorescence intensity [MFI] reduced to <2000) as measured by a SAB assay, for antibodies with baseline MFI ≥3000.
Secondary	
• Phase 2: To characterize the safety profile of isatuximab in kidney transplant candidates. • To characterize the pharmacokinetic (PK) profile of isatuximab in kidney transplant candidates. • To evaluate the immunogenicity of isatuximab. • To assess the overall efficacy of isatuximab in desensitization of patients awaiting kidney transplantation.	• AEs/SAEs, and laboratory abnormalities. • PK parameters of isatuximab (see Table 7) • Incidence of anti-drug antibodies (ADA) against isatuximab. • Duration of response (DoR) per central laboratory assessment. • Proportions of participants and duration achieving target cPRA per local laboratory assessment. • Number of anti-HLA-antibody with baseline MFI ≥3000 reduced to <2000 as measured in a SAB assay per central laboratory assessment. • Transplantability including time to first transplant offer, time to transplant, and number of transplant offers, if applicable. • Time to first AMR episode and rate of AMR, if applicable. • Graft survival at 6 months post-transplant, if applicable.

Overall design:

This is a Phase 1b/2 open-label, non-randomized, multi-center study to evaluate the safety, PK, and preliminary efficacy of isatuximab in patients awaiting kidney transplantation. The study will be conducted in 2 phases (see Figure 1 for study design schema):

Phase 1 (safety run-in)

A minimum of 6 safety evaluable participants with cPRA ≥80% will be enrolled at the dose level to be tested without interruption in Phase 1. In order to be considered as safety evaluable, participants must have received at least 90% of the planned cumulative doses of the first cycle (unless they discontinue investigational medical product [IMP] due to pre-defined unacceptable toxicity).

Pre-defined unacceptable toxicity is defined as any verified Grade 4 AEs or laboratory abnormalities (except infusion reactions [IR]) occurring during the first cycle of treatment, unless

solely due to the underlying disease or due to a cause obviously unrelated to the IMP, if confirmed by the Sponsor and recruiting Investigators.

The totality of the safety findings, including all AEs occurring during treatment, unless solely due to the underlying disease or due to a cause obviously unrelated to IMP, will be taken into consideration for confirming the Phase 2 dose. Phase 2 of the study will be initiated after 6 safety evaluable participants have completed first cycle observation period where the dose level is determined to be sufficiently well-tolerated.

If the starting dose (SD) is determined not to be sufficiently well-tolerated, 6 additional (minimum) safety evaluable participants will be enrolled at dose level minus 1 (DL-1) (see Table 1 for details on the dose levels and schedule for Phase 1).

Overall safety monitoring will also be performed throughout the conduct of the study.

Upon completion of the first cycle safety observation period for each participant enrolled in Phase 1, participants will continue study procedures until study completion (see "Duration of study period [per participant]" in Figure 2).

Phase 2

In Phase 2, two cohorts will be included:

Cohort A: Participants with cPRA ≥99.90%; active candidates on the kidney waitlist. Up to 6 participants with living donor can be enrolled into Cohort A.

Cohort B: Participants with cPRA 80.00% to 99.89%; active candidates on the kidney waitlist with no living donor cleared for donation.

Disclosure Statement: This is a Single Group, Treatment study with 1 arm (2 cohorts) that is not masked. All participants will receive isatuximab monotherapy.

Number of participants:

In Phase 1, approximately 6 to 12 safety evaluable participants are expected to be enrolled (see Section 9.3 for definition of Safety Evaluable Population).

Approximately 24 to 36 participants (Phase 1 and Phase 2) are expected to be enrolled if the SD is retained as the Phase 2 dose or approximately 30 to 42 participants are expected to be enrolled if DL-1 is the Phase 2 dose.

A maximum of 6 replacements per cohort is allowed for participants who:

- enroll in Phase 1 and receive <90% of the planned cumulative doses within the first cycle (unless they discontinue IMP due to pre-defined unacceptable toxicity), or
- receive <75% of planned cumulative doses within 3 cycles, or
- have consecutive dose interruption of >28 days, or

- do not complete site visit follow-up period (FUP), after agreement with Medical Monitor.

Intervention groups and duration:

All participants will receive isatuximab monotherapy and the planned treatment duration is 3 cycles (each cycle is 28 days).

Starting dose and de-escalation design:

Starting dose is 10 mg/kg once weekly (QW) for 4 weeks followed by once every 2 weeks (Q2W). If the SD is determined not to be sufficiently well-tolerated, 6 additional (minimum) safety evaluable participants will be enrolled at DL-1. Dose levels and schedule for Phase 1 are detailed in Table 1.

Overall safety monitoring will also be performed throughout the conduct of the study.

Table 1 - Dose level and schedule in Phase 1

Dose Level	Isatuximab 1 cycle = 4 weeks (28 days)
SD	10 mg/kg QW × 4 for Cycle 1 → Q2W for cycles 2 and 3
DL-1	5 mg/kg QW × 4 for Cycle 1 → Q2W for Cycles 2 and 3

Abbreviations: DL-1 = dose level minus 1, QW = once weekly, Q2W = once every 2 weeks, SD = starting dose

Duration of study period (per participant):

The study will have a screening period of up to 28 days, a treatment period of up to 12 weeks, a site visit FUP of up to 26 weeks, and an extended FUP which include telephone contacts every 90 days and information collection until study cut-off, death, or lost to follow-up. The study cut-off is planned at 26 weeks after the last participant completes the treatment period, or when the last ongoing participant is lost to follow-up, whichever is earlier. The Sponsor may choose to extend the study cut-off date depending on the enrollment rate observed to facilitate adequate follow-up data collection. Participants who wish to proceed to transplantation when a compatible donor becomes available while on study must discontinue IMP immediately, and complete an early discontinuation (E/D) visit prior to transplantation if clinically feasible, and proceed to extended FUP. The study duration that involves site visit per participant (ie, screening, treatment, site visit FUP) will be approximately 42 weeks. The study duration including extended FUP per participant will be approximately 78 weeks (depending when the participant is enrolled).

Treatment period: The cycle duration is 28 days and a complete treatment period is comprised of 3 cycles of IMP treatment. Participants will continue treatment until receiving 3 cycles of IMP, unacceptable AE per Investigator's judgment, or participants' decision to stop the treatment.

Site visit FUP: Participants completing the treatment period and who are able to remain on study will return to the study sites for study procedures.

Extended FUP: The following participants will be followed-up every 90 days by phone calls until study cut-off date, death, or lost to follow-up, whichever comes first:

- Participants who completed or discontinued from site visit FUP
- Participants who proceed to transplantation during treatment period or site visit FUP.

During extended FUP, specified information per protocol will also be collected by the study site (see Schedule of Activities [SoA], Section 1.3).

Study interventions

Investigational medicinal product

Isatuximab:

- Formulation: Sterile 20 mg/mL concentrate for solution for infusion in single use vials containing 20 mg/mL (500 mg/25 mL) isatuximab in 20 mM histidine, 10% (w/v) sucrose, 0.02% (w/v) polysorbate 80, pH 6.0.
- Route of administration: Intravenous (IV) infusion.
- Dose regimen: Refer to the section above (Table 1) for Phase 1 dose regimen. Dose for Phase 2 will be determined based on the safety data from Phase 1. The Sponsor may decide to test an isatuximab dose of 20 mg/kg in case of inadequate efficacy and/or PK results.

Noninvestigational medicinal product

Premedication:

All participants will receive the following premedications to prevent or reduce the incidence or severity of IRs, approximately 15 to 30 minutes prior to isatuximab infusion (no longer than 60 minutes). Premedication is mandatory for the first 4 isatuximab infusions (see criteria below for subsequent infusions). The use of ranitidine or equivalent as part of IR premedication is left to the medical judgement of the Investigator. The standard premedication regimen will include:

- Acetaminophen 650 to 1000 mg oral route (PO) (or equivalent)
- Diphenhydramine 25 to 50 mg IV (or equivalent)
- Methylprednisolone 100 mg IV (or equivalent)
- Montelukast 10 mg PO (or equivalent)

Noninvestigational medicinal products (NIMP) will be locally sourced and the formulations may vary.

Premedication for prevention of IR has to be given for the first four isatuximab infusions, and the first infusion using fixed volume infusion following approval of Amended Protocol 01 (applicable for participants enrolled under original Protocol).

For a participant who has no IR upon 4 consecutive infusions, premedication for the subsequent infusions is optional at the Investigator's discretion.

Statistical considerations:

The participants treated at the Phase 2 dose during Phase 1 will be included in the efficacy analysis together with the participants in Phase 2.

- **Sample size calculations**

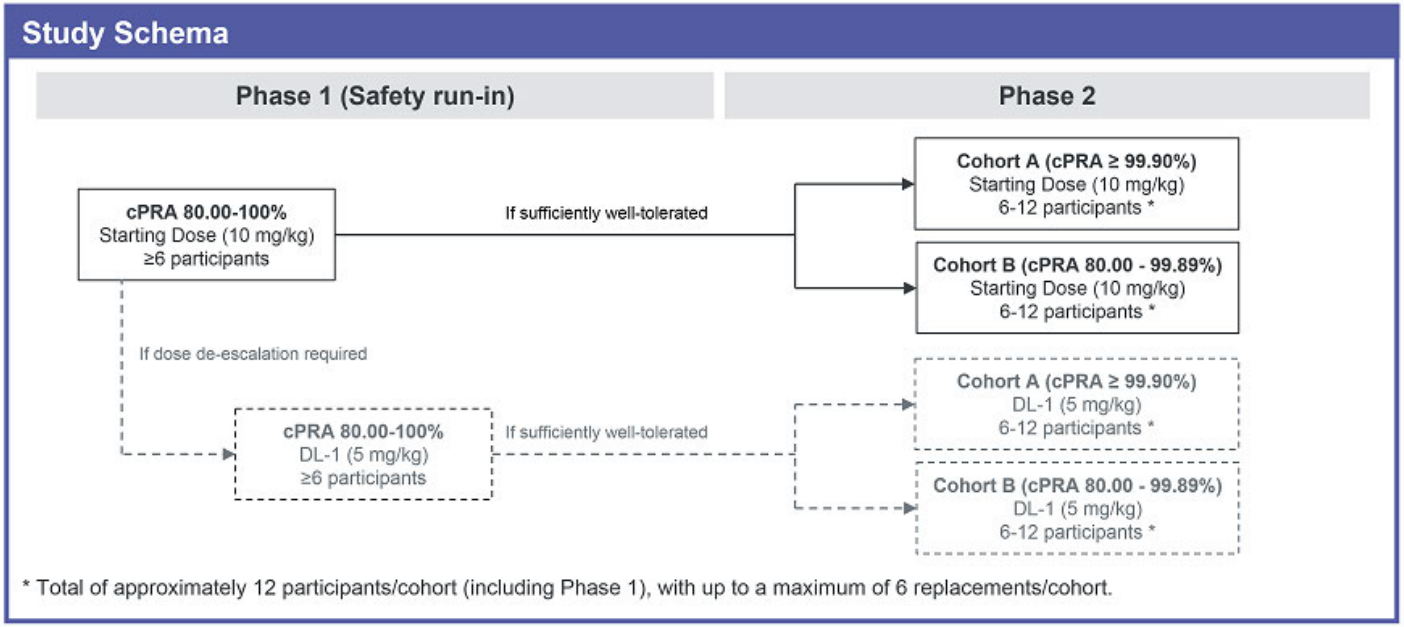
With a minimum sample size of 12 participants per cohort and 1-sided alpha of 0.025, the analysis will have at least 80% power to demonstrate that the RR is significantly better than [redacted] assuming the true RR is [redacted], based on exact test. A null hypothesis of [redacted] is selected representing placebo control as there is currently no approved or standard therapy for desensitization, and there is no expected decrease in anti-HLA antibody levels or cPRA in patients who do not undergo desensitization therapy.

- **Primary analysis:**
  - AEs and laboratory abnormalities in Phase 1 will be listed.
  - Response rate by cohort will be summarized using descriptive statistics. A 95% 2-sided confidence interval will be computed using the Clopper-Pearson method.
- **Analysis of secondary endpoints:**
  - All secondary (if applicable/possible) endpoints will be summarized descriptively and presented by cohort. Categorical variables (eg, rates and proportions) will be tabulated via frequency distributions. Continuous variables (eg, change from baseline) will be summarized by providing the number of observations (n), mean, median, standard deviation, minimum, and maximum. Duration of response (DoR) and other time to event variables will be analyzed using Kaplan-Meier method.
  - No hypothesis/significance testing will be performed.

Data Monitoring Committee: No

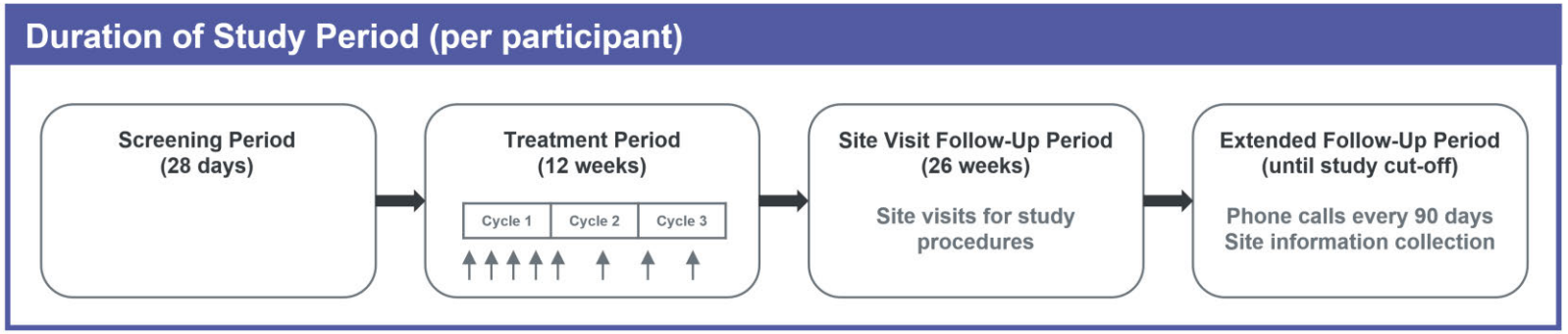
1.2 SCHEMA

Figure 1 - Graphical study design



Abbreviations: cPRA = calculated panel reactive antibodies, DL-1 = dose level minus 1

Figure 2 - Duration of study period (per participant)



1.3 SCHEDULE OF ACTIVITIES (SOA)

Procedure	Screening (up to 28 days before Day 1)	Treatment Period (12 weeks)								Site Visit FUP (26 weeks)[a]	E/D[b]	Extended FUP[c]	Notes All on-treatment procedures should be performed prior to IMP administration unless indicated otherwise
		Cycle 1 (28 Days)				Cycle 2 (28 days)		Cycle 3 (28 days)					
		D1	D8	D15	D22	D1	D15	D1	D15	D1 of every 4 weeks			
Time Window (days)		±1	±1	±1	±1	±2	±2	±2	±2	±7	±7	±7	
Informed consent	X												Informed consent may be signed prior to D-28
Inclusion and exclusion criteria	X												
Demography	X												Date or year of birth (depending on local regulation), sex, ethnicity, and race (if local regulation allows)
Medical, disease, and surgical history	X												Include start date of dialysis
Sensitizing events	X	←==========										==========→	Collect dates and types of relevant sensitizing events that can impact cPRA (eg, Blood transfusion)
HLA tissue typing (collect data on already available results is acceptable)	X												For screening (can be done prior to D-28), enter the most recent results if available
12-lead ECG	X												See Section 8.2.3

Procedure	Screening (up to 28 days before Day 1)	Treatment Period (12 weeks)								Site Visit FUP (26 weeks)[a]	E/D[b]	Extended FUP[c]	Notes
		Cycle 1 (28 Days)				Cycle 2 (28 days)		Cycle 3 (28 days)					All on-treatment procedures should be performed prior to IMP administration unless indicated otherwise
		D1	D8	D15	D22	D1	D15	D1	D15	D1 of every 4 weeks			
Time Window (days)		±1	±1	±1	±1	±2	±2	±2	±2	±7	±7	±7	
Echocardiography	X												Should be performed at dry weight, and/or on a non-dialysis day (see Section 8.2.4)
Full physical examination including height (screening only) and weight	X (≤7 days prior to first IMP)	X		X		X		X		X (Weeks 1 and 9 only)	X		See Section 8.2.1
Vital signs[d]	X	X	X	X	X	X	X	X	X	X (Weeks 1 and 9 only)	X		See Section 8.2.2)
Pregnancy test (WOCBP)	X (≤7 days prior to first IMP)					X		X		X[e] (Week 1, and 5 months after last dose)	X[e]		Serum pregnancy test at screening; serum or urine hCG pregnancy test at other time points See Section 10.2
HBV, HCV, HIV, CMV, EBV	X	As clinically indicated								X[f]	X[g]		See Section 10.2
Laboratory assessments (blood chemistry, hematology)	X (≤14 days prior to first IMP)	X[h]		X		X		X		X (Weeks 1 and 9 only)	X		See Section 10.2
Coagulation	X (≤14 days prior to first IMP)	As clinically indicated											See Section 10.2
Blood typing interference test[i]	X (≤14 days prior to first IMP)					X[i] (IAT)				X[i] (IAT)			See Section 10.10

Procedure	Screening (up to 28 days before Day 1)	Treatment Period (12 weeks)								Site Visit FUP (26 weeks)[a]	E/D[b]	Extended FUP[c]	Notes
		Cycle 1 (28 Days)				Cycle 2 (28 days)		Cycle 3 (28 days)					All on-treatment procedures should be performed prior to IMP administration unless indicated otherwise
		D1	D8	D15	D22	D1	D15	D1	D15	D1 of every 4 weeks			
Time Window (days)		±1	±1	±1	±1	±2	±2	±2	±2	±7	±7	±7	
cPRA and SAB assay (local laboratory assessment)	X	Perform as per local standard of practice											For unacceptable antigens, use MFI ≥2000 as positivity cut-off, and report cPRA to 2 decimal point (eg, 99.90%) See Section 8.1.2
Blood draw for cPRA and SAB assay (central laboratory assessment)		X[j]				X		X		X (every 4 weeks)[k]	X		Refer to laboratory manual for details
Blood draw for serum immunoglobulin levels (central laboratory assessment)		X[j]						X		X (Week 17 only)[k]	X[l]		Refer to laboratory manual for details
Blood draw for immune cell profiling (central laboratory assessment)		X[j]						X		X (Week 17 only)[k]	X[l]		Refer to laboratory manual for details
Blood draw for functional immune cell assay (central laboratory assessment)		X[j]						X		X (to be collected on Site Visit FUP Week 1 or E/D, if C3D1 sample not collected)			Refer to laboratory manual for details
Isatuximab		X	X	X	X	X	X	X	X				
PK/ADA		See Pharmacokinetic/ADA Flowchart											See Section 1.3.1

Procedure	Screening (up to 28 days before Day 1)	Treatment Period (12 weeks)								Site Visit FUP (26 weeks)[a]	E/D[b]	Extended FUP[c]	Notes
		Cycle 1 (28 Days)				Cycle 2 (28 days)		Cycle 3 (28 days)					All on-treatment procedures should be performed prior to IMP administration unless indicated otherwise
		D1	D8	D15	D22	D1	D15	D1	D15	D1 of every 4 weeks			
Time Window (days)		±1	±1	±1	±1	±2	±2	±2	±2	±7	±7	±7	
AE review	X	←==========							→	X (beyond 30 days after last dose of IMP: only ongoing related AEs, new related AEs until resolution/ stabilization)			Stabilization is defined as an AE ongoing without any change for at least 3 months
SAE review	X	←==========							→	X (beyond 30 days after last dose of IMP: only ongoing SAEs, new related SAEs until resolution/ stabilization)			
Prior/concomitant/post medication[m]	X	←==========							→	X	X	X	See Section 6.5
Participant/Transplant (if applicable) Status	X[n]	X[n]									X[o]	X[o]	

Abbreviations: ADA = anti-drug antibody, AE = adverse event, CMV = cytomegalovirus, cPRA = calculated panel reactive antibodies, D = Day, EBV = Epstein-Barr virus, ECG = electrocardiogram, E/D = early discontinuation, FUP = follow-up period, HBV = hepatitis B virus, hCG = human chorionic gonadotropin, HCV = hepatitis C virus, HIV = human immunodeficiency virus, HLA = human leukocyte antigen, ID = identification number, IMP = investigational medicinal product, MFI = mean fluorescence intensity, PK = pharmacokinetics, SAB = single antigen bead, SoA = Schedule of Activities, SAE = serious adverse event, WOCBP = women of childbearing potential.

a Week 1 visit for site visit FUP will occur 15 days after Cycle 3 Day 15 (±7 days), or 15 (±7) days after the last dose of IMP if participant discontinued IMP. Depending on local arrangements and preference of the Investigator, site visit FUP procedures may be performed at the study site or at the participant's home by a health care professional. Study procedures not performed at the study site must also be documented in the source documents and recorded in the appropriate pages of the eCRF by the study site.

b For E/D, study procedures will be performed 30±7 days after last IMP administration if discontinued study during treatment period, or within 30 days if discontinued during site visit FUP. Participants who discontinued IMP but remain on the study and proceed to complete site visit FUP do not need to complete E/D. Participants who wish to proceed to transplantation when a compatible donor becomes available while on study must discontinue IMP immediately, and complete an E/D visit prior to transplantation if clinically feasible, and proceed to extended FUP.

c In addition to the phone calls every 90 days, study site will collect information per the SoA throughout the extended FUP.

d Vital sign assessment includes blood pressure, pulse rate, temperature, and respiratory rate. During the treatment period, vital signs should be obtained prior to start of each IMP infusion, 1 hour after start of infusion, at the end of infusion, and during the infusion if clinically indicated.

e Pregnancy test can be performed at home for participants during the FUP or if date of test does not match with FUP visit and the site must record this in the source document. Test should be performed at the end of isatuximab treatment (ie, Week 1 of site visit FUP or E/D visit [±7 days]), and 5 months (±7 days) after the last dose of IMP.

f Post-treatment tests are only applicable for HBV, CMV, and EBV, and only has to be performed at Site Visit FUP Week 9 if baseline result is positive or as clinically indicated. In case HBV vaccination will be started before first study treatment administration, anti-HBs should be monitored at approximately 1, 2, and 3 months after end of vaccination (±7 days, or at the next blood sampling). For participants with positive anti-HBc and negative HBsAg and undetectable HBV deoxyribonucleic acid (DNA) at study entry (past resolved infection, resolving acute infection, or receiving antiviral treatment with controlled infection), close monitoring of viral reactivation (greater than 1log10 IU/mL increase in HBV DNA or reappearance of HBsAg or detection of HBV DNA in patients with resolved infection) throughout and following the end of study

treatment should be proposed (alanine aminotransferase [ALT], aspartate aminotransferase [AST], and HBV DNA at Site Visit FUP Week 9 and Week 25, or until initiation of further desensitization therapy/transplant surgery). In case of viral reactivation during study treatment (greater than 1log10 IU/mL increase in HBV DNA or reappearance of HBsAg or detection of HBV DNA in participants with resolved infection), close monitoring of ALT and AST approximately every month (may coincide with the next scheduled blood sampling ±7 days), up to study treatment discontinuation. HBV DNA to be done as per Investigator's and/or specialist advice.

g Only if screening result is positive and not tested during site visit FUP.

h Assessment not required to be repeated prior to Cycle 1 Day 1, if screening assessments were performed within 7 days prior to the first IMP infusion and met the entry criteria. Window for assessment is within 1 working day prior to IMP infusion.

i Blood type (if not already done) and phenotype (according to the site protocol). Recommended phenotype includes Rh system (C/c and E/e), Kell system (K/k); Duffyn system (Fya/Fyb); Kidd system (Jka/Jkb); MNS system (M/N, S/s), and indirect antiglobulin test (IAT; indirect Coombs test). Blood type card will be kept by the participant with the study card. Blood type and blood product transfusions are to be recorded in the electronic case report form. The blood bank needs to be informed that the participant is receiving a treatment with an anti-CD38 and a potential interference with the Coombs test is possible (see Section 10.10). IAT (indirect Coombs test) to be repeated at C2D1 (if not performed at this visit, it can be done at the next blood sampling); if post-treatment (ie, C2D1) IAT (indirect Coombs test) is positive, subsequent tests to be performed at site Visit FUP Weeks 1, 13, and 25, and E/D if discontinued during Site Visit FUP.

j Blood sample must be collected prior to IMP administration. Window for assessment is within 1 working day prior to IMP infusion.

k Blood draw time points that do not coincide with site visits may be collected at the local facility or at the participant's home by a health care professional (depending upon local arrangements and preference of the Investigator), provided that samples are collected with designated tubes and per laboratory manual. Blood drawn should be performed prior to dialysis (if dialysis is performed on the same day).

l Only if site visit FUP sample (ie, Week 17) not collected.

m Include any desensitization therapy. For participants who proceed to transplantation after E/D, or completion of treatment and/or site visit FUP, also collect immunosuppression regimen.

n Collect the following information: Start and end date(s) when listed as active candidate on the waitlist for kidney transplant, waitlist ID and transplant center code (if applicable, and if local regulation allows and in line with the most recent participant signed informed consent form), virtual or donor-specific cross matching results, and dates of all transplant offers (if any, indicate whether offers were accepted and reasons of rejecting offers).

o Collect the following information: Start and end date(s) when listed as active candidate on the waitlist for kidney transplant (if status has changed), virtual or donor-specific cross matching results, dates of all transplant offers (if any, indicate whether offers were accepted and reasons of rejecting offers), solid organ transplant surgery, participant survival status, graft survival status, dates of biopsy proven acute rejection episodes (antibody mediated and/or T-cell mediated), and estimated glomerular filtration rate (eGFR) using the Modification of Diet in Renal Disease (MDRD) equation.

1.3.1 Pharmacokinetic/anti-drug antibodies (ADAs) flowchart

1.3.1.1 Treatment period: Cycle 1 (rich sampling)

Procedure	Treatment Period							
	Cycle 1							
	D1			D4	D8	D15		D22
IV infusion	X----------X				X	X----------X		X
Sample RNT (hours) Ref: isatuximab SOI	SOI	EOI	EOI + 1 h	72 h	168 h (SOI C1D8)	SOI	EOI	SOI
Sample time window	(-24 h, SOI)	±10 min	+30 min	±5 h	(-24 h, SOI)	(-24 h, SOI)	±10 min	(-24 h, SOI)
PK sample ID	P00[a]	P01	P02	P03	P04[a, b]	P05[a]	P06	P07[a]
ADA sample ID	AB00[a]					AB01[a]		

AB = antibody, ADA = anti-drug antibody, C1D8 = Cycle 1 Day 8, D = Day, EOI = end of infusion, h = hours, ID = identification, IV = intravenous, min = minutes, P = plasma, PK = pharmacokinetics, Ref = reference, RNT = relative normal time, SOI = start of infusion

a Sample must be collected strictly before the start of isatuximab infusion.

b Sample must be collected even if the infusion planned on C1D8 is not done or delayed.

Note: The sampling time points for PK and ADA may be modified during the course of the study based on the updated knowledge of isatuximab behavior, upon notification from the Sponsor. Depending on local arrangements, PK/ADA sample may be collected at the participant's home by a health care professional if sampling time point does not coincide with site visit.

1.3.1.2 Treatment period: Cycle 2 and beyond (sparse sampling)

Procedure	Treatment Period				Site Visit FUP
	Cycles 2 and 3				26 weeks
	D1			D15	D60 (site visit FUP Week 9)
IV infusion	X----------		X	X	
Sample RNT (hours) Ref: isatuximab SOI	SOI	EOI	EOI + 1 h	SOI	
Sample time window	(-24 h, SOI)	±10 min	±10 min	(-24 h, SOI)	±7 days
PK sample ID	P00[a]	P01	P02	P03[a]	P00
ADA sample ID	AB00[a]				AB00[b]

AB = Antibody in plasma, ADA = anti-drug antibody, C1D8 = Cycle 1 Day 8, D = Day, EOI = end of infusion, FUP = follow-up period, h = hours, ID = identification, IV = intravenous, min = minutes, P = plasma, PK = pharmacokinetics, Ref = reference, RNT = relative normal time, SOI = start of infusion

a PK and ADA samples to be collected predose.

b If a participant discontinues the study early, an ADA sample must be collected 60 days after last dose of isatuximab (±7 days).

Note: The sampling time points for PK and ADA may be modified during the course of the study based on the updated knowledge of isatuximab behavior, upon notification from the Sponsor. Depending on local arrangements, PK/ADA sample may be collected at the participant's home by a health care professional if sampling time point does not coincide with site visit.

2 INTRODUCTION

In the United States (US), close to 800 000 patients have end stage renal disease (ESRD), and the number of cases continues to rise by about 20 000 cases per year (1). Approximately 100 000 patients are currently on the waitlist for kidney transplantation (2), but only about 20% of these patients will proceed to transplantation due to donor organ shortage (3). Approximately 30% of the kidney transplant patients on the waitlist are sensitized to HLA with cPRA ≥20% (cPRA is reciprocally proportional to the likelihood of finding a matching donor) (4, 5). Human leukocyte antigen sensitization can occur as a result of previous pregnancies, blood transfusions, or previous transplants. The HLA sensitized patients are at risk for rapid graft loss from AMR by pre-existing donor-specific alloantibodies, decreasing chances of finding a matching donor and hence leading to prolonged wait times as compared to those who are not sensitized.

Desensitization therapy aims to overcome the humoral incompatibility by removing or reducing the presence of reactive antibodies, thereby increasing the chance of finding compatible or acceptable donors for transplantation. However, the current most common desensitization protocols involve plasmapheresis, intravenous immunoglobulin (IVIG), and/or rituximab which do not target the terminally differentiated antibody-secreting plasma cells that are responsible for alloantibody production in the bone marrow and are hence often associated with a quick rebound effect (6, 7).

Isatuximab is an IgG1 monoclonal antibody directed against CD38, a receptor antigen expressed on hematopoietic cells. In particular, CD38 is highly expressed in plasma cells - the primary source of antibody production (8, 9). Isatuximab is currently being developed for treatment of multiple myeloma, and other advanced malignancies including solid tumors and lymphomas, and may have clinical utility in desensitization for kidney transplantation.

2.1 STUDY RATIONALE

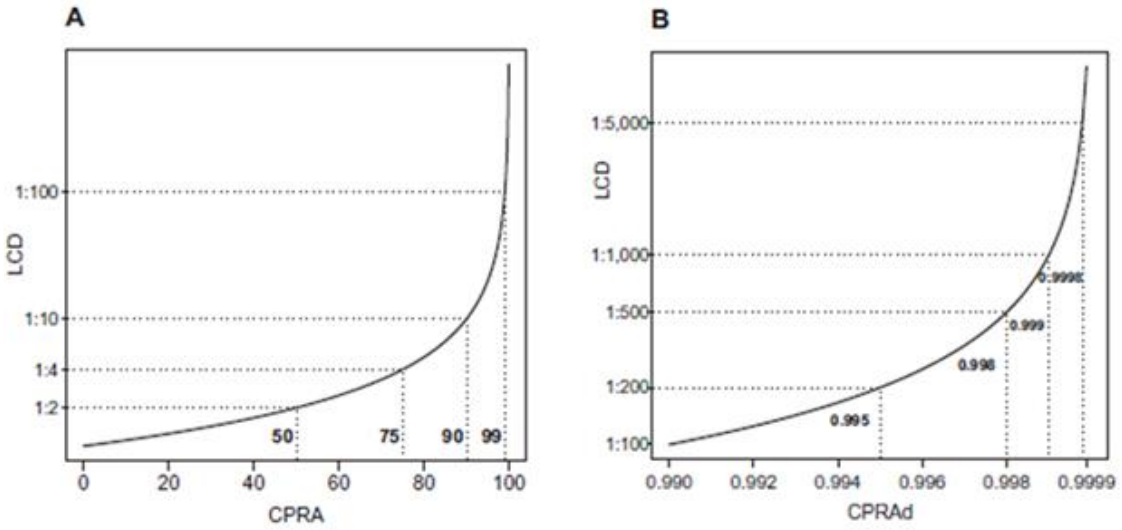
2.1.1 HLA sensitized patients: Unmet medical need

For patients with ESRD, transplantation is associated with decreased mortality, better quality of life, and lower expenditures, compared to chronic dialysis treatment (10, 11). Unfortunately, HLA sensitized patients have prolonged wait time for transplant and may never find a compatible donor depending on the extent of sensitization. This is attributed to the presence of anti-HLA antibodies that bear a high risk of causing rapid rejection of a new organ and therefore limit a candidate's possibilities to accept organ offers (12, 13). Even for patients with living donors, transplantation may not be possible due to positive cross-match with their willing donors. For kidney transplant candidates waitlisted for deceased donor organs, the likelihood of finding a compatible donor is highly dependent on their cPRA score. The cPRA (in the US cPRA is established by the Organ Procurement and Transplantation Network) provides a standardized evaluation of the degree of sensitization of a transplant candidate to HLA antigens. Use of cPRA has increased the allocation efficiency and access for sensitized patients waiting for a kidney transplant, particularly for patients with a cPRA ≥80% (14, 15). Much of the literature focuses on "broadly" or "highly"

sensitized patients who have been variably defined using cPRA cut-off values of 50+, 80+, or higher. However, even patients with cPRA values as low as 30 theoretically require a greater number of match runs to have a 95% chance of finding an acceptable donor as compared to candidates with cPRA of 10 and 20 (16). Of note, a positive correlation between cPRA and DSA has been observed, and DSA may confer immunologic risk (17, 18, 19, 20). A meta-analysis of 7 retrospective cohort studies revealed a nearly 2-fold risk of AMR (relative risk: 1.98, 95% confidence interval: 1.36 – 2.89) and 76% increased risk of graft failure associated with the presence of DSA as compared to the absence of DSA (21). Therefore, a higher cPRA implies a higher likelihood of positive cross-matches between the donor pool and the waitlisted patient, and therefore a lower likelihood of finding a compatible donor. It has been reported that cPRA with decimals (cPRAd) is inversely related to the likelihood of finding a compatible donor, as described by the following equation and Figure 3 (22).

$$LCD = 1\ in\ \frac{1}{1 - cPRA}$$

Figure 3 - Relationship between cPRA and likelihood of finding a compatible donor



Abbreviations: cPRA = calculated panel reactive antibodies, cPRAd = calculated panel reactive antibody with decimals, LCD = likelihood of compatible donor

The median waiting time to transplantation in the US was reported to be 4 years, while sensitized patients often endure waiting times exceeding 5 years (3, 23). With the introduction of the Kidney Allocation System (KAS) in December 2014 giving highly sensitized patients additional points, the deceased donor transplantation rate became more balanced across different cPRA compared to pre-KAS (increased transplantation rate in patients with cPRA 90% to 99.9%) (24). However, access to transplant remains considerably lower post-KAS for candidates with cPRA >99.9% who are considered as “difficult-to match” patients (25). In addition, the transplant rate for cPRA 80% to 89% candidates decreased, and the waitlist mortality continued to increase for very highly sensitized patients with cPRA ≥98% compared to other patients (24). The long-term risk of death is significantly lower in patients who undergo transplantation compared to patients who remain on the waitlist and continue dialysis (relative risk 0.32; P <0.001) (26). In addition, prolonged

dialysis has resulted in shorter patient and graft survival after transplantation (27, 28). An unintended consequence of KAS is the disproportionate allocation of highest quality of kidneys (kidney donor profile index ≤20) in highly sensitized patients (cPRA ≥99%) which is correlated with survival, which created a disadvantage for the majority of other kidney transplant waitlist candidates (cPRA <99%) (29). National prioritization access programs similar to KAS have been implemented by ex-US countries (eg, ETKAS by Eurotransplant, PATHI in Spain). While it may be unattainable to achieve a system with absolutely no undesirable disparities in access to transplantation, a standardized desensitization therapy that can effectively convert HLA sensitized patients to lower cPRA levels (eg, non-sensitized or less sensitized) would help to further resolve the imbalance in kidneys allocation, and/or reduce the need to transport donor organs across long distance for those who requiring expanded access to match with a compatible donor organ.

Pre-transplantation desensitization can reduce alloantibody titers to a level that is sufficiently low, resulting in an acceptable cross-match which allows for transplantation with low risk of AMR. A study on desensitization in HLA-incompatible kidney recipients and survival demonstrated significant survival benefits of pre-transplantation desensitization in patients who underwent HLA-incompatible live-donor kidney transplantation (30). The 8-year survival rate for desensitized patients was 80.6% compared to 30.5% for the dialysis group and 49.1% for the dialysis-or-transplantation group (P <0.0001). Therefore, desensitization is an important option for HLA sensitized patients to increase access to kidney transplantation, as this confers to better clinical outcome in addition to being more cost-effective than chronic dialysis treatment.

2.1.2 Current desensitization therapies

Currently, there is no approved or standard therapy for desensitization in patients awaiting kidney transplantation. The landscape of current desensitization therapies in use by physicians has been extensively reviewed (5, 31, 32, 33).

Plasmapheresis is one of the oldest techniques used in removing circulating antibodies. Plasmapheresis must be performed on a daily basis as a standalone treatment as antibody rebound occurs after each session (31). In practice, plasmapheresis is usually used in conjunction with other desensitization agents, and most commonly with IVIG.

The exact mechanism of IVIG is not thoroughly understood; however, possibilities include regulation of B-cell antibody production, neutralization of circulating anti-HLA antibodies, inhibition of complement mediated inflammation, and various pro-inflammatory cytokines (5). The clinical utility of IVIG in kidney transplant desensitization was demonstrated in the randomized, double-blinded, placebo-controlled NIH IG02 trial (34). Patients who received IVIG 2 mg/kg have shown significant reduction in panel reactive antibody levels (p <0.033) and higher transplant rate compared to placebo (35% versus 17%). However, similar to plasmapheresis, IVIG alone does not durably suppress anti-HLA antibody levels and is associated with antibody rebound. Nevertheless, IVIG remains the backbone in current desensitization protocols. As mentioned above, a study on desensitization in HLA-incompatible kidney recipients and survival demonstrated significant survival benefits in patients treated with plasmapheresis and low dose IVIG prior to kidney transplantation (30). It was also reported that the use of IVIG and rituximab in highly sensitized patients successfully reduced mean panel reactive antibody (PRA) by 44%

from baseline (p <0.001) (35). Nevertheless, similar to plasmapheresis, efficacy of IVIG is limited with additional cycles, and antibody rebound remains a major problem for this approach (36, 37).

Rituximab is a chimeric mAb targeting CD20. It is approved in the US and Europe for multiple indications including Non-Hodgkin's lymphoma, chronic lymphocytic leukemia, and rheumatoid arthritis. The rationale for using rituximab in kidney transplant desensitization is to deplete CD20 positive B-cells, including precursors for plasma cells (32). Rituximab has been widely accepted in desensitization protocols, in combination with plasmapheresis and/or IVIG. While eliminating B-cells may prevent recurrence of antibodies to some extent, rituximab was not able to eliminate DSA-producing long-lived plasma cells that reside in the bone marrow niche as such plasma cells typically do not express CD20 (23, 33).

Bortezomib was recently explored as a desensitization agent with the aim to deplete plasma cells. Bortezomib was approved in the US and Europe for treatment of multiple myeloma and mantle cell lymphoma. Studies have reported the use of bortezomib in combination with other classical desensitization protocols resulting in significant decrease in HLA antibody MFI and reversal of acute rejection (7). This is likely attributed to its ability to trigger apoptosis of CD138+CD20- bone marrow derived plasma cells, thereby blocking anti-HLA antibody production. However, bortezomib was not well-tolerated, making it difficult to incorporate into desensitization protocols (5). Nevertheless, the clinical experience with bortezomib supported targeting long-lived plasma cells could be a viable strategy in effective removal of alloantibodies and potentially sustain reduction in DSA levels (7).

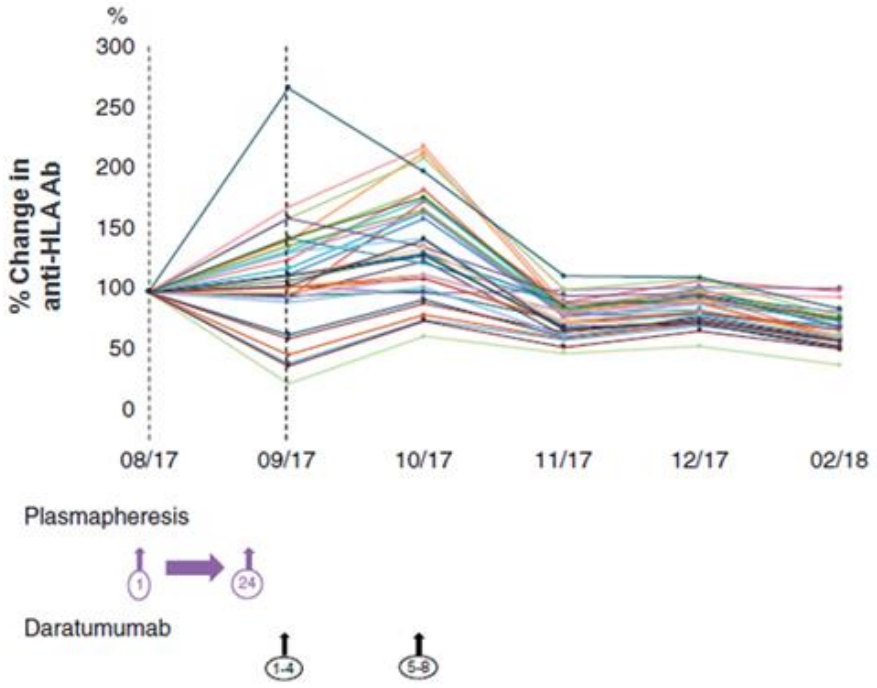
2.1.3 Targeting CD38 for plasma cell depletion as a desensitization strategy

Short-lived plasma cells rise rapidly in the spleen following antigen exposure, allowing for immediate production of antibody in response to acute infections. For sustained humoral immune response, selection of antigen-exposed B-cells occurs within the germinal center which eventually mature into long-lived plasma cells within the bone marrow, producing over 80% of antibodies detectable in the serum (38, 39). The CD38 is expressed on germinal center B-cells and differentiated plasma cells. In particular, plasma cell differentiation is associated with high positivity of CD38, where CD38 expression of normal plasma cells is much higher compared to other CD38 positive hematopoietic cells in the peripheral blood and bone marrow including monocytes, natural killer cells (NK-cells), activated T-cells, and B-cell progenitors (8, 39, 40). Therefore, CD38 is a rational target for depleting plasma cells that produce alloantibodies or DSAs, which is potentially a more effective strategy in desensitization for kidney transplantation.

Anti-CD38 monoclonal antibodies currently in clinical development include daratumumab (approved in the US and Europe for use in multiple myeloma), isatuximab (Phase 3 development), and MOR202 (development terminated in China). To date, there is no clinical study to systematically evaluate the use of anti-CD38 monoclonal antibodies in desensitization for solid organ transplant. A recent study reported the use of daratumumab in desensitization in a heart transplant candidate (41). Multiple courses of plasmapheresis, high-dose IVIG, and rituximab result in no significant changes in cPRA (cPRA=98%) with deterioration of clinical condition. Following 8 weekly injections of daratumumab (16 mg/kg), the patient's cPRA significantly decreased to 62% and subsequently enabled heart transplantation (Figure 4). The decrease in

anti-HLA antibody was associated with high depletion of peripheral CD38+ plasma cells. Anti-CD38 monoclonal antibody was also shown to effectively treat AMR in a clinical case of refractory AMR in a combined heart and kidney transplant recipient, where histologic analysis revealed T-cell mediated rejection (TCMR) and AMR with plasma cell predominant infiltration. Conventional therapy such as high dose steroid pulses, plasmapheresis, anti-thymocyte globulin, rituximab, and high dose IVIG was ineffective in treating the AMR. Following treatment with daratumumab combined with eculizumab, de novo DSA was dramatically declined and allograft functions were significantly improved. While 2 of the 9 DSAs reascended 20 weeks after daratumumab treatment, retreatment with daratumumab decreased the DSAs significantly. Another study of daratumumab for treatment of AMR in a kidney transplant recipient also reported similar effect of daratumumab in treating resistant AMR in a highly sensitized HLA-incompatible kidney transplant recipient (42). The effectiveness of daratumumab in removing harmful antibodies was also demonstrated in a patient who developed pure red-cell aplasia that is refractory to standard treatments following allogenic stem cell transplantation (43). After first dose of daratumumab at 16 mg/kg (total 6 weeks of treatment), transfusion dependence was fully resolved with subsequent complete removal of anti-A antibodies and sustained normal differential blood count. Importantly, at 10-month follow-up, no graft-versus-host-disease (GVHD) or opportunistic infection was observed.

Figure 4 - Desensitization of heart transplant candidate with daratumumab

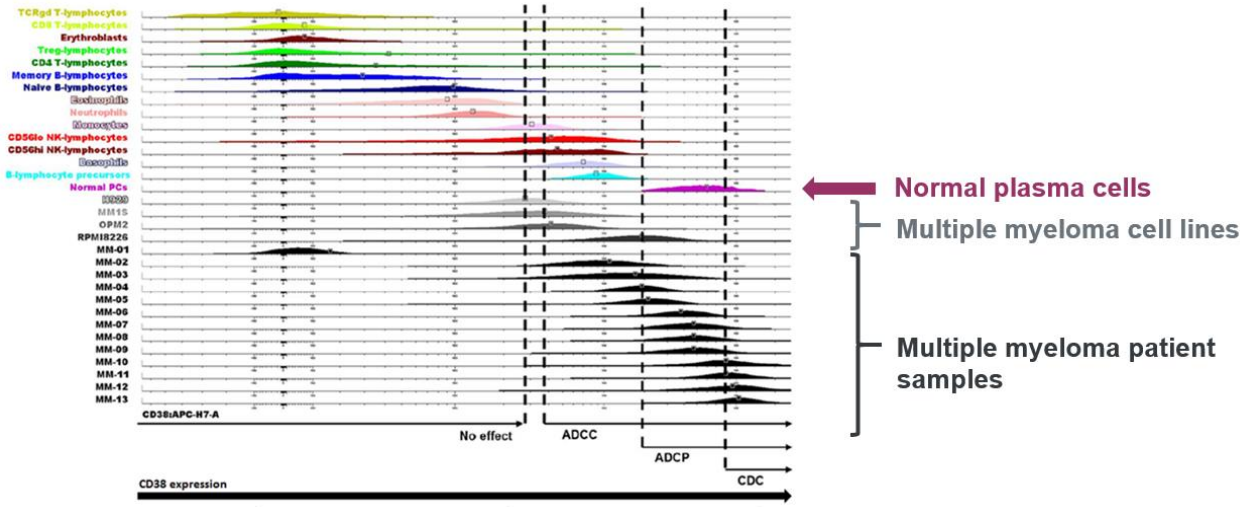


Abbreviations: Ab = antibody, HLA = human leukocyte antigen

Similar to daratumumab, isatuximab targets CD38 positive cells. To date, clinical studies have demonstrated activity in multiple myeloma patients (see Investigator's Brochure for details), and has recently met primary endpoint of prolonging progression-free survival in patients with relapsed/refractory multiple myeloma in its first randomized Phase 3 trial (44). It was reported

that isatuximab induces the above mechanisms of action depending on the CD38 expression on the target cells (Figure 5) (8). Direct apoptosis, antibody-dependent cellular cytotoxicity (ADCC), antibody-dependent cellular phagocytosis (ADCP), and complement dependent cytotoxicity (CDC) could be triggered depending on the CD38 expression on target cells. Although isatuximab activity was not directly tested in normal plasma cells, it is expected that isatuximab can effectively deplete normal plasma cells based on the extremely high expression of CD38 on these cells. The authors also demonstrated that isatuximab depletes CD38 high B-cell precursors and NK-cells ex vivo, which have lower CD38 expression than normal plasma cells.

Figure 5 - Schematic representation of the different mechanisms of action possibly triggered by isatuximab according to the levels of CD38 expression in normal and tumor cells



Abbreviations: ADCC = antibody-dependent cellular cytotoxicity, ADCP = antibody-dependent cellular phagocytosis, CD = cluster of differentiation, CDC = complement dependent cytotoxicity

Based on the above, it is hypothesized that isatuximab (anti-CD38 monoclonal antibody) can target long-lived plasma cells and result in sustained removal of alloantibodies and DSA by depleting their production source. Consequently, desensitization with isatuximab in patients awaiting transplantation may increase access to transplantation for this immunologically disadvantaged group of HLA sensitized patients, decrease wait and dialysis time, and potentially achieve better clinical outcome.

The primary objectives of this study are to assess safety and PK of isatuximab in patients awaiting kidney transplantation, and to assess its ability to decrease anti-HLA antibodies and cPRA.

2.2 BACKGROUND

Isatuximab (SAR650984) is an IgG1 class naked mAb binding selectively the human CD38 membrane protein. Isatuximab has been approved, in some countries, in combination with pomalidomide and dexamethasone, for the treatment of adult patients with multiple myeloma who have received at least two prior therapies including lenalidomide and a proteasome inhibitor (bortezomib or carfilzomib or ixazomib). Isatuximab is also being developed for the treatment of a number of hematological malignancies and solid tumors.

Depending on the CD38 expression level, isatuximab has the capacity to kill CD38 positive tumor cells by a combination of 4 distinct biological mechanisms:

- ADCC
- ADCP
- CDC
- Pro-apoptotic activity

As of cut-off date of 05 January 2020, an estimated 1652 patients were treated with isatuximab in multiple myeloma and other malignancies, including 147 patients with various solid tumors known to bear minimal tumor CD38. In general, isatuximab is well-tolerated clinically with a manageable safety profile. The most common adverse reactions are IRs which are clinically manageable. Infusion reactions are not dose-dependent and tend to occur most frequently during the first infusion. Overall, the most current findings from the clinical experience acquired from multiple clinical studies with isatuximab in multiple indications have not identified any potential safety risks or concerns in addition to those described in the Investigator's Brochure 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 the efficacy and PK/pharmacodynamic (PD) analyses, 20 mg/kg given QW for the first 28-day cycle, and Q2W after Cycle 1 is the selected dose for the single agent study in the multiple myeloma indication. In other clinical studies, isatuximab 10 mg/kg is the selected dose when combining with other anticancer therapies.

Refer to isatuximab Investigator's Brochure for the most updated nonclinical and clinical studies of isatuximab.

2.3 BENEFIT/RISK ASSESSMENT

2.3.1 Benefits

Refer to Section 2.1.

2.3.2 Potential and identified risks

2.3.2.1 Isatuximab

Isatuximab has been investigated either as monotherapy or in combination in participants with hematological malignancies and other advanced malignancies. The safety profile of isatuximab monotherapy has been assessed by a pooled analysis of completed monotherapy studies TED10893 (Phase 1 and Phase 2 Stage 1, including 181 participants with multiple myeloma), and TED14154 (relapsed/refractory multiple myeloma) where the most common treatment emergent adverse events (TEAE), excluding the AEs corresponding to laboratory abnormalities, include

IRs, fatigue, nausea, anemia, cough, upper respiratory infection, diarrhea, headache and dyspnea. Infusion reactions occurred in 53.8% of the 212 participants assessed.

The IRs associated with isatuximab in participants who are administered appropriate primary prophylaxis (see also Section 2.3.3) are most common with the first administration of the drug, are not dose-dependent, are Grade 1 to 2 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, 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.

Another identified risk is that isatuximab binds to endogenous CD38 found at low levels on red blood cells and may interfere with routine blood bank compatibility testing and cross-matching, with false-positive indirect Coombs test. This interference is limited to the minor blood groups (not affect the ABO and Rh typing). See Section 10.10 for details.

The CD38 antigen is expressed on normal immune cells. Isatuximab could modulate cell survival and differentiation of both lymphoid and myeloid cells in patients. This modulation could have decreased all CD38+ cells and their lineage cells as an identified risk of opportunistic infections in patients with chronic kidney disease (CKD). In addition, suppression of immune system (with its ability to detect and destroy cancer cells) may increase the risk of second primary malignancies.

Please refer to the current version of the isatuximab Investigator's Brochure for more detailed information about the known risks of isatuximab.

2.3.2.2 Potential risk of desensitization therapies in patients awaiting transplantation

Desensitization therapies are immunosuppressive in nature, infection (especially cytomegalovirus [CMV] and polyoma virus) and malignancy maybe a potential risk (33). Conflicting results have been published on whether desensitization therapies such as rituximab would result in higher rate and severity of infections (5, 33, 45). A single-center retrospective study dedicated to understanding infectious complications from desensitization treatment was conducted (46). In this study, a total of 361 patients were included in the analysis. After an average of 18-month follow-up, patients who received rituximab plus IVIG for desensitization were found to have similar infection rates compared to patients who did not receive desensitization treatment. According to the authors, the infection rates observed were also similar to that reported in the literature. In a systematic review of the use of rituximab for desensitization in renal transplantation, no statistically significant higher incidence of infectious complications in patients treated with rituximab was observed (47). Lower rates of CMV viremia and viral infections were identified, and may be attributed to fewer episodes of rejection and associated steroid therapy.

A couple of publications have reported potential immunomodulatory effects of anti-CD38 mAb such as T-regulatory cell suppression and T-cell activation in multiple myeloma patients (48, 49). It is unknown whether these immunomodulatory effects observed in multiple myeloma patients would translate into potential concern for TCMR in patients post transplantation. While individual reports have suggested use of anti-CD38 may lead to TCMR (41, 42), further investigation is warranted to assess the benefit/risk ratio. Nevertheless, the main cause of kidney transplant failure is usually

attributed to AMR, which is strongly associated with graft loss, whereas TCMR was not (50, 51). It should be noted that no GVHD was observed in the clinical case that reported the use of daratumumab to desensitize a patient who received ABO-mismatched stem cell transplantation (43).

2.3.3 Preventive measures to minimize the risk of isatuximab

To minimize the risk of IRs, all participants treated with isatuximab should routinely receive primary prophylactic treatment with diphenhydramine 25 to 50 mg IV (or equivalent), methylprednisolone 100 mg IV (or equivalent), acetaminophen (paracetamol) 650 to 1000 mg orally (or equivalent), and montelukast 10 mg orally (or equivalent), approximately 15 to 30 minutes (and never longer than 60 minutes) prior to the isatuximab infusion to minimize the incidence and severity of IR commonly observed with certain mAbs. It is recommended that prescribing information of each of these medications to be considered in the context of each patient's clinical situation.

In an attempt to further mitigate the incidence and severity of IRs, infusion of isatuximab is administered in a titrated manner (see Section 6.1). In the event of a mild or moderate hypersensitivity reaction, the isatuximab infusion should be interrupted and may subsequently resume after recovery, at a slower infusion rate, under close monitoring and with supportive care as needed. Prior to restarting the infusion, participants may receive additional medication per the judgment of the Investigator; recommended medications consist of diphenhydramine 25 mg IV and methylprednisolone 100 mg IV (or equivalent). In the event of a severe hypersensitivity reaction, treatment with isatuximab is to be immediately and permanently discontinued. Detailed management guidelines for IRs are also provided in Section 6.6.4.

Isatuximab infusion administered in units of mL per hour has been evaluated in Study TCD14079 Part B. A total of 47 patients were included in this study. The primary endpoint of the study was achieved as no Grade ≥3 IRs were reported, therefore confirming the feasibility of the fixed volume infusion method of isatuximab administration. The overall incidence of IRs was 40.4%.

For the risk of neutropenia and infections, Investigators are recommended to monitor complete blood cell counts periodically during the treatment. Antibiotics, antifungal, and antiviral prophylaxis can be considered during the treatment. Patients with neutropenia should be monitored for signs of infection. No dose reductions of isatuximab are recommended. Dose delays and the use of colony stimulating factors (eg, granulocyte-colony stimulating factor [G-CSF]) may be required to allow improvement of neutrophil count.

To mitigate potential risk of infections in patients receiving isatuximab, participants with active, recurrent, or chronic infections requiring treatment are excluded from the study. Furthermore, participants with positive hepatitis core antigen but hepatitis B surface antigen (HBsAg) negative must receive prophylactic antiviral therapy prior to IMP initiation, and should continue therapy until end of site visit FUP or early discontinuation. Potential viral reactivation (including hepatitis B virus [HBV], CMV, and Epstein-Barr virus [EBV]) in participants will be monitored pre- and post-treatment with isatuximab.

To avoid potential problems with blood transfusion, the American Association of Blood Banks recommends that patients being treated with anti-CD38 antibodies have blood type and screen

tests performed prior to treatment (ie, at screening see Section 1.3). After the treatment and each time before blood transfusion, the antibody screen test (indirect Coombs test) should be performed. After a patient begins taking anti-CD38 antibodies, ABO/RhD typing can be performed normally; for antibody detection and identification, dithiothreitol (DTT)-treated cells can be used to eliminate the interference (see Section 10.10 for details).

In regard to the aforementioned potential risk of TCMR, participants who received isatuximab and subsequently proceed to solid organ transplantation are recommended to receive anti-thymocyte globulin (as indicated for prophylaxis of acute rejection) and steroids maintenance as part of the post-transplant immunosuppression regimen. During extended FUP, post-transplant status including rejection episodes and graft survival will be collected.

Additionally, careful monitoring of AEs and laboratory abnormalities, continuous direct communication between the Investigators and the monitoring team, and the adherence to the dose modification rules specified in the study protocol, are the continuous measures that will minimize the risks in study participants.

Overall, the anticipated benefit/risk ratio of isatuximab supports the conduct of study TED16414 in participants diagnosed with CKD awaiting kidney transplantation.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of isatuximab may be found in the Investigator's Brochure.

3 OBJECTIVES AND ENDPOINTS

Table 2 - Objectives and endpoints

Objectives	Endpoints
Primary	
• Phase 1: To characterize the safety and tolerability of isatuximab in kidney transplant candidates. • Phase 2: To evaluate the efficacy of isatuximab in desensitization of patients awaiting kidney transplantation.	• Adverse events (AEs)/serious adverse events (SAEs) and laboratory abnormalities. • Response rate (RR) defined as the proportion of participants meeting at least one of the predefined desensitization efficacy criteria, from baseline up to 26 weeks after treatment period, measured by single antigen bead (SAB) assay per central laboratory assessment as follows: - Reduction in calculated panel reactive antibodies (cPRA) resulting in at least 100% increase of likelihood of finding a compatible donor (for target cPRA, see Section 10.9). - Reduction in antibody titer (≥75% reduction from baseline) to achieve target cPRA (see Section 10.9). - Elimination of ≥1 anti-HLA-antibody (ie, mean fluorescence intensity [MFI] reduced to <2000) as measured by a SAB assay, for antibodies with baseline MFI ≥3000.
Secondary	
• Phase 2: To characterize the safety profile of isatuximab in kidney transplant candidates. • To characterize the pharmacokinetic (PK) profile of isatuximab in kidney transplant candidates. • To evaluate the immunogenicity of isatuximab. • To assess the overall efficacy of isatuximab in desensitization of patients awaiting kidney transplantation.	• AEs/SAEs, and laboratory abnormalities. • PK parameters of isatuximab (see Table 7) • Incidence of anti-drug antibodies (ADA) against isatuximab. • Duration of response (DoR) per central laboratory assessment. • Proportions of participants and duration achieving target cPRA per local laboratory assessment. • Number of anti-HLA-antibody with baseline MFI ≥3000 reduced to <2000 as measured in a SAB assay per central laboratory assessment. • Transplantability including time to first transplant offer, time to transplant, and number of transplant offers, if applicable. • Time to first AMR episode and rate of AMR, if applicable. • Graft survival at 6 months post-transplant, if applicable.

Objectives	Endpoints
Tertiary/exploratory	
• To assess other preliminary efficacy of isatuximab in desensitization of patients awaiting kidney transplantation.	[redacted]
• To assess the biological effects of isatuximab on immune cell populations and identify potential predictive and/or PD biomarkers	[redacted]
• To perform PK/PD analysis.	[redacted]

3.1 APPROPRIATENESS OF MEASUREMENTS

Each of the efficacy and safety assessments chosen for use in this study is considered well established and relevant in the renal transplant setting. In addition, suitable steps have been built into each of these assessments to ensure their reliability and accuracy and to minimize any risks to patient safety.

Safety and tolerability are the primary objectives of the Phase 1 with endpoints including AEs/SAEs and laboratory abnormalities. The safety objective is extended as a secondary objective for Phase 2. Monitoring of safety data is described in detail in Section 8.3 and Section 10.3.

Efficacy of isatuximab in desensitization is the primary objective for Phase 2. Participants are considered as responders if meeting at least one of the predefined desensitization efficacy criteria as outlined in Section 3. The predefined desensitization efficacy criteria are designed to capture the ability of isatuximab in removing/reducing circulating anti-HLA antibody. Calculated panel reactive antibody is a standardized parameter to estimate the unacceptable risk against the national donor population, based upon unacceptable HLA antigens which the transplant candidates have antibodies against. The SAB assay is the most widely accepted method for precisely identifying the anti-HLA antibodies due to its much-improved sensitivity and specificity compared to older methods such as cytotoxicity or flow cytometry. The assay is considered to be acceptable as a semi-quantitative assay (negative or positive), with MFI of <2000 may be considered negative at multiple kidney transplant centers. The MFI variability has been reported as up to 62%; while standardized operating procedure could reduce variability to <25% even across centers and with different reagents (52, 53). The TED16414 study utilizes a central laboratory for primary efficacy assessment and the MFI variability is expected to be <25%. As a conservative approach to mitigate false positive RR, the third predefined efficacy criterion (ie, elimination of ≥1 anti-HLA antibody) is only applicable to antibodies with baseline MFI ≥3000 to account for possible assay variability. Moreover, reduction in anti-HLA antibody strengths are being evaluated by antibody dilution (ie, second criterion) instead of quantifying MFI values (54, 55).

Duration of response (assessed both locally and centrally) is included as a secondary endpoint to address potential antibody rebound concern, which is commonly observed with current desensitization protocols. If applicable, transplantability and post-transplant outcomes will also be captured as secondary endpoints.

4 STUDY DESIGN

4.1 OVERALL DESIGN

This is a Phase 1b/2 open-label, non-randomized, multi-center study to evaluate the safety, PK, and preliminary efficacy of isatuximab in patients awaiting kidney transplantation. The study will be conducted in 2 phases (see Figure 1 for study design schema):

Phase 1 (safety run-in)

A minimum of 6 safety evaluable participants with cPRA ≥80% will be enrolled at the dose level to be tested without interruption in Phase 1. In order to be considered as safety evaluable, participants must have received at least 90% of the planned cumulative doses of the first cycle (unless they discontinue IMP due to pre-defined unacceptable toxicity).

Pre-defined unacceptable toxicity is defined as any verified Grade 4 AEs or laboratory abnormalities (except IRs) occurring during the first cycle of treatment, unless solely due to the underlying disease or due to a cause obviously unrelated to IMP, if confirmed by the Sponsor and recruiting Investigators.

The totality of the safety findings, including all AEs occurring during treatment, unless solely due to the underlying disease or due to a cause obviously unrelated to IMP, will be taken into consideration for confirming the Phase 2 dose. Phase 2 of the study will be initiated after 6 safety evaluable participants have completed first cycle observation period where the dose level is determined to be sufficiently well-tolerated.

If the SD is determined not to be sufficiently well-tolerated, 6 additional (minimum) safety evaluable participants will be enrolled at DL-1 (see Table 4 for details on the dose levels and schedule for Phase 1).

Overall safety monitoring will also be performed throughout the conduct of the study.

Upon completion of the first cycle safety observation period for each participant enrolled in Phase 1, participants will continue study procedures until study completion (see “Duration of study period [per participant]” in Figure 2).

Phase 2

In Phase 2, two cohorts will be included:

Cohort A: Participants with cPRA ≥99.90%; active candidates on the kidney waitlist. Up to 6 participants with living donor can be enrolled into Cohort A.

Cohort B: Participants with cPRA 80.00% to 99.89%; active candidates on the kidney waitlist with no living donor cleared for donation.

The study will have a screening period of up to 28 days, a treatment period of up to 12 weeks, a site visit FUP of up to 26 weeks, and an extended FUP which include telephone contacts every 90 days and information collection until study cut-off, death, or lost to follow-up. The study cut-off is planned at 26 weeks after the last participant completes the treatment period, or when the last ongoing participant is lost to follow-up, whichever is earlier. The Sponsor may choose to extend the study cut-off date depending on the enrollment rate observed to facilitate adequate follow-up data collection. Participants who wish to proceed to transplantation when a compatible donor becomes available while on study must discontinue IMP immediately, and complete an E/D visit prior to transplantation if clinically feasible, and proceed to extended FUP. The study duration that involves site visit per participant (ie, screening, treatment, site visit FUP) will be approximately 42 weeks. The study duration including extended FUP per participant will be approximately 78 weeks (depending when the participant is enrolled).

Treatment period: The cycle duration is 28 days and a complete treatment period is comprised of 3 cycles of IMP treatment. Participants will continue treatment until receiving 3 cycles of IMP, unacceptable AE per Investigator's judgment, or participants' decision to stop the treatment.

Site visit FUP: Participants completing the treatment period and who are able to remain on study will return to the study sites for study procedures.

Extended FUP: The following participants will be followed-up every 90 days by phone calls, until study cut-off date, death, or lost to follow-up, whichever comes first:

- Participants who completed or discontinued from site visit FUP
- Participants who proceed to transplantation during treatment period or site visit FUP.

During extended FUP, specified information per protocol will also be collected by study site (see Section 1.3).

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

This is a Phase 1b/2 open-label, non-randomized, multi-center study to evaluate the safety, preliminary efficacy, and PK of isatuximab (SAR650984) in patients awaiting kidney transplantation.

The HLA sensitized patients with high cPRA have low likelihood of finding a compatible donor. Currently no approved or standard therapy is available for desensitization. An effective desensitization therapy with a durable response has the potential to increase the likelihood for transplant candidates to find a compatible donor, reduce time on dialysis, and a better clinical outcome.

As the safety profile of isatuximab is well-established, Phase 1 (safety run-in) is designed to characterize the safety and tolerability of isatuximab in patients with CKD, and to confirm the Phase 2 dose in this patient population.

Phase 2 is designed to assess preliminary efficacy of isatuximab in desensitizing HLA sensitized patients awaiting kidney transplantation, which includes assessing change in cPRA and anti-HLA antibody levels.

The patient population enrolled in the Phase 1 and Phase 2 is identical, which allows for inclusion of patients enrolled in the Phase 1 treated with Phase 2 dose in efficacy analysis.

4.3 JUSTIFICATION FOR DOSE

In the case where oncology drugs are used in desensitization protocols or clinical studies exploring efficacy in desensitization for solid organ transplant, the full therapeutic doses (ie, doses approved in oncology or other indications) were commonly utilized (5, 33). Rituximab (375 mg/m^2 or 1 g; approved for use in Non-Hodgkin's lymphoma and rheumatoid arthritis) is widely accepted for the use in desensitization protocols including combination with IVIG and/or plasmapheresis for kidney transplantation (56). For instance, in a study where highly sensitized patients were allocated to intervention group versus control group (57), the intervention group received 2 doses of high dose IVIG, a single dose of rituximab (375 mg/m^2 on Day 1), and a single cycle of bortezomib (1.3 mg/m^2, on Days 15, 18, 21, and 24), for which the short courses of rituximab and bortezomib are of the same dose levels used in their corresponding approved oncology indications (375 mg/m^2 rituximab for Non-Hodgkin's lymphoma, or 375 mg/m^2 rituximab on Day 1 in combination with 1.3 mg/m^2 bortezomib on Days 1, 4, 8, and 11 for mantle cell lymphoma). The regimen was well-tolerated and the AEs were consistent with that expected for the monotherapy drugs.

Based on safety, efficacy, PK, and PK/PD data analyses, the dose/schedule of isatuximab when used as monotherapy for the treatment of multiple myeloma is 20 mg/kg QW × 4 followed by Q2W. In multiple myeloma patients, isatuximab displays nonlinear PK with target-mediated drug disposition. Isatuximab undergoes elimination by parallel linear and nonlinear pathways. In the range of plasma concentrations achieved with a 10 mg/kg QW/Q2W dose and schedule, linear clearance is the predominant elimination pathway as it represents approximately 90% of total clearance at steady state, indicative of the saturation of the target. As a large protein, isatuximab is expected to be eliminated by non-saturable proteolytic catabolism processes. Renal excretion and hepatic enzyme-mediated metabolism of intact isatuximab are unlikely to play a major role in the elimination of isatuximab. Thus, variations/modifications in renal and hepatic function are unlikely to affect the elimination of isatuximab (58). From population PK analysis (n=476 multiple myeloma patients), mild (n=192), moderate (n=163), and severe (n=12) renal impairment, and mild hepatic impairment (n=65) had no impact on isatuximab PK.

In CKD patients without multiple myeloma disease, less target-mediated drug disposition is anticipated compared to multiple myeloma patients. Isatuximab monotherapy demonstrated activity at doses ≥10 mg/kg with no clear dose response between 10 mg/kg and 20 mg/kg, clinical safety data also supported that 10 mg/kg is sufficiently well-tolerated in patients with advanced cancer who received more than 1 year of treatment. Therefore, 10 mg/kg QW × 4 followed by Q2W over a 12-week period is proposed to be tested in this study.

4.4 END OF STUDY DEFINITION

A participant is considered to have completed the study if he/she has completed all phases of the study including the last visit (including extended FUP), or at study cut-off, death, or lost to follow-up.

The study cut-off is defined as 26 weeks after the last participant completes the treatment period, or when the last ongoing participant is lost to follow-up, whichever is earlier. The Sponsor may choose to extend the end of the study depending on the enrollment rate observed to facilitate adequate follow-up data collection.

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:

Age

I 01. Participant must be 18 to 70 years of age inclusive, at the time of signing the informed consent.

Type of participant and disease characteristics

I 02. Diagnosis of CKD and active candidate on the kidney waitlist at the time of screening.

For Participants in Cohort A:

I 03. cPRA ≥99.90% within 4 weeks of IMP initiation as per local laboratory assessment (unacceptable antigens defined as MFI ≥2000), and stable within 6 months prior to IMP initiation based on medical history or samples, if available.

For participants in Cohort B:

I 04. cPRA 80.00% to 99.89% within 4 weeks of IMP initiation as per local laboratory assessment (unacceptable antigens defined as MFI ≥2000), and stable within 6 months prior to IMP initiation based on medical history or samples, if available.

I 05. Participant with no living donor cleared for donation at the time of screening.

Weight

I 06. Body mass index (BMI) ≤40 kg/m^2.

Sex

I 07. Male or Female

Contraceptive use by men or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

a) Male participants

Male participants with female partners of childbearing potential are required to use effective contraceptive methods as detailed in Appendix 4 (Section 10.4) of this protocol starting 2 weeks before IMP administration, during treatment period, and until 5 months after last dose of isatuximab.

b) Female participants

Female participants of childbearing potential are required to use effective contraceptive methods as detailed in Appendix 4 (Section 10.4) of this protocol starting 2 weeks before IMP administration, during treatment period, and until 5 months after last dose of isatuximab. Female participants of childbearing potential must be willing or able to be tested for pregnancy (see Section 10.4 for details).

Informed Consent

I 08. Capable of giving signed informed consent as described in Appendix 1 (Section 10.1) which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

5.2 EXCLUSION CRITERIA

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

Medical conditions

E 01. Known malignancy requiring active treatment within 3 years prior to IMP initiation, with the exception of complete resection of basal cell carcinoma or squamous cell carcinoma of the skin, an in situ malignancy, or low-risk prostate cancer after curative therapy.

E 02. History of significant cardiac dysfunction such as New York Heart Association classification for chronic heart failure III-IV, symptomatic cardiovascular disease, major clinically significant electrocardiogram (ECG) abnormality, left ventricular ejection fraction <40%, clinically significant ventricular arrhythmias, myocardial infarction within 6 months prior to IMP initiation, or unstable or poorly controlled angina pectoris despite treatment.

E 03. In the opinion of Investigator, participant with severe autonomic dysfunction leading to chronic hypotension.

E 04. Evidence of active mucosal or internal bleeding.

E 05. History of 2 or more events of pulmonary embolism or deep-vein thrombosis.

E 06. Known active, recurrent or chronic infection requiring parenteral or oral anti-infective treatment; including primary or secondary immunodeficiency, a history of active or latent

tuberculosis or history of deep tissue/space infection (peritoneal, etc) within 24 weeks prior to IMP initiation, or any serious infection within 8 weeks prior to IMP initiation.

E 07. Participants on peritoneal dialysis with a history of peritoneal infection at any time during the 12 weeks prior to IMP initiation.

E 08. Participants on peritoneal dialysis with a positive culture or high cell count numbers on peritoneal fluid indicative of confirmed or suspected infection at the time of screening.

E 09. Known active hepatitis B or C viral infection, or human immunodeficiency virus (HIV).

- Participants with positive hepatitis B core antigen (anti-HBc or HBcAb) but HBsAg negative who received prophylactic antiviral therapy prior to IMP initiation are eligible and should continue therapy until end of treatment period or E/D visit. Participants with negative HBsAg and positive HBV deoxyribonucleic acid (DNA) observed during screening period will be evaluated by a specialist or Investigator for start of antiviral treatment: study treatment could be proposed if HBV DNA becomes negative and all the other study criteria are still met.
- Participants 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. Participants with positive anti-HCV and undetectable HCV ribonucleic acid (RNA) without antiviral therapy for HCV are eligible.

E 10. Participants with active lupus or uncontrolled diabetes, per Investigator's judgment.

Prior/concomitant therapy

E 11. Prior treatment with an agent (approved or investigational) that blocks CD38 (patients who had previously participated in a study with an anti-CD38 but have written confirmation they were on control arm are allowed).

E 12. Prior treatment with biological therapy, major surgery, desensitization therapy, or immunosuppressive therapy (up to 10 mg prednisone/day or equivalent is allowed) within 28 days from initiation of IMP.

E 13. Recipients of any live attenuated vaccine(s) within 4 weeks of IMP initiation.

E 14. Received treatment with rituximab or obinutuzumab within 6 months from initiation of IMP.

E 15. Received prior liver, heart, or lung transplantation.

E 16. Received cell transplantation or cell therapy within 5 years prior to IMP initiation.

Prior/concurrent clinical study experience

E 17. Prior treatment with any investigational drugs within 28 days from initiation of IMP or concomitant enrollment in any other clinical study involving an investigational study treatment.

Diagnostic assessments

E 18. Inadequate organ and bone marrow function at the Screening Visit:

- Absolute neutrophil count (ANC) <1500/mm^3 (1.5×10^9/L),
- Platelets <90×10^9/L (platelet transfusion is not allowed within 7 days before the screening hematological test),
- Hemoglobin <9 g/dL or <5.6 mmol/L (without transfusion 7 days before the screening hematological test),
- Total bilirubin >1.5 upper limit of normal (ULN),
- Aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) >3 × ULN,
- Alkaline phosphatase (ALP) >2.5 × ULN.

Other exclusions

E 19. Pregnant or breastfeeding women or women who intend to become pregnant during participation in the study.

E 20. Known intolerance or hypersensitivity to any component of isatuximab or premedications.

E 21. Participant not suitable for participation, whatever the reason (including medical, ethical, or clinical conditions), as judged by the Investigator, or participants potentially at risk of noncompliance to study procedures.

E 22. Participants are dependent on the Sponsor or Investigator (in conjunction with Section 1.61 of the International Council for Harmonisation [ICH] Good Clinical Practice [GCP] Ordinance E6).

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 SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once.

- A participant who is rescreened ≤56 days (ie, 2 × the 28-day screening period) from the most recent consent form signature date, and for whom several procedures are still valid, the participant does not need to sign another consent form and this is considered as temporary screen failure. Investigator should ensure the willingness of the participant to continue and repeat any out of protocol window screening procedures. This verbal agreement should be documented in the participant's chart and all the tests out of protocol window should be repeated and entered in the additional eCRF pages.
- If screening window will be prolonged for >56 days, and the individual becomes eligible for the study, then rescreening is allowed, but in this situation patient must sign a new consent form and all screening procedures must be repeated. A different participant identification will be issued, while the other identification for this participant should be recorded as Screen Failure. There is no requirement for a waiting period between a screen failure date and the rescreening date.

6 STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

6.1 STUDY INTERVENTION(S) ADMINISTERED

Table 3 - Overview of study interventions administered

Intervention name	Isatuximab	Premedications (see description after this table for NIMP)
Type	Drug	See description after this table for NIMP
Dose formulation	Concentrated solution for infusion	See description after this table for NIMP
Unit dose strength(s)	20 mg/mL (500 mg/25 mL) isatuximab in 20 mM histidine, 10% (w/v) sucrose, 0.02% (w/v) polysorbate 80, pH 6.0	See description after this table for NIMP
Dosage level(s)	See Table 4 for details on the dose levels and schedule	See description after this table for NIMP
Route of administration	IV infusion See below for rate and duration of infusion	See description after this table for NIMP
IMP and NIMP	IMP	NIMP
Packaging and labeling	Isatuximab will be provided in 1 glass vial per box. Each vial and box will be labeled as required per country requirement	Each treatment container will dependent on country sourcing. Each container will be labeled as required per country requirement

Abbreviations: IMP = investigational medicinal product, IV = intravenous, NIMP = noninvestigational medicinal product.

Between the protocol-scheduled on-site visits, interim visits may be required for IMP dispensing. As an alternative to these visits, isatuximab may be supplied from the site to the participant via a Sponsor-approved courier company where allowed by local regulations and approved by the participant.

Starting dose of investigational medicinal product (isatuximab) and de-escalation design

The SD of IMP is 10 mg/kg QW for 4 weeks followed by Q2W. If the SD is determined not to be sufficiently well-tolerated, 6 additional (minimum) safety evaluable participants will be enrolled at DL-1 (ie, 5 mg/kg QW for 4 weeks followed by Q2W) (see Table 4 for details on the dose levels and schedule for Phase 1).

Overall safety monitoring will also be performed throughout the conduct of the study.

Table 4 - Dose level and schedule in Phase 1

Dose Level	Isatuximab 1 cycle = 4 weeks (28 days)
SD	10 mg/kg QW × 4 for Cycle 1 → Q2W for cycles 2 and 3
DL-1	5 mg/kg QW × 4 for Cycle 1 → Q2W for Cycles 2 and 3

Abbreviations: DL-1 = dose level minus 1, QW = once weekly, Q2W = once every 2 weeks, SD = starting dose

The totality of the safety findings, including all AEs occurring during treatment, unless solely due to the underlying disease or due to a cause obviously unrelated to IMP, will be taken into consideration for confirming the Phase 2 dose. Phase 2 of the study will be initiated after 6 safety evaluable participants have completed first cycle observation period where the dose level is determined to be sufficiently well-tolerated.

Rate and duration of infusion

The rates of isatuximab infusion are as follows:

- **First infusion:** Initiate infusion at 25 mL/hour. In the absence of IRs after 1 hour of infusion, increase infusion rate by 25 mL/hour increments every 30 minutes, to a maximum of 150 mL/hour.
- **Second infusion:** Initiate infusion at 50 mL/hour. In the absence of IRs after 30 minutes of infusion, increase rate to 100 mL/hour for 30 minutes, and then to 200 mL/hour until the total volume is infused.
- **Third and subsequent infusions:** Initiate infusion at a fixed infusion rate of 200 mL/hour, until the total volume is infused.
- In the presence of IR: See Section 6.6.4.

For details of IMP preparation and administration, refer to pharmacy manual.

Noninvestigational medicinal products (Premedications)

All participants will receive the following premedications to prevent or reduce the incidence or severity of IRs, approximately 15 to 30 minutes prior to isatuximab infusion (no longer than 60 minutes). Premedication is mandatory for the first 4 isatuximab infusions (see criteria below for subsequent infusions). The use of ranitidine or equivalent as part of IR premedication is left to the medical judgement of the Investigator. The standard premedication regimen will include:

- Acetaminophen 650 to 1000 mg PO (or equivalent)
- Diphenhydramine 25 to 50 mg IV (or equivalent)
- Methylprednisolone 100 mg IV (or equivalent)
- Montelukast 10 mg PO (or equivalent)

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

Premedication for prevention of IR has to be given for the first four isatuximab infusions, and the first infusion using fixed volume infusion following approval of Amended Protocol 01 (applicable for participants enrolled under Original Protocol).

For a participant who has no IR upon 4 consecutive infusions, premedication for the subsequent infusions is optional at the Investigator's discretion.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

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).

Any quality issue noticed with the receipt or use of an IMP/NIMP (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 8.3.8).

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

Under no circumstances will the Investigator supply IMP to a third party (except for direct-to-patient shipment, for which a courier company has been approved by the Sponsor), allow the IMP to be used other than as directed by this clinical trial protocol, or dispose of IMP in any other manner.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

Not applicable.

6.4 STUDY INTERVENTION COMPLIANCE

Administration of the study intervention will be supervised by the Investigator or Sub-Investigator.

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

Deviation(s) from the prescribed dosage regimen should be recorded in the electronic case report form (eCRF).

6.5 CONCOMITANT THERAPY

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

Prohibited concomitant medications:

Prohibited concomitant medications (until end of Site Visit FUP, or E/D, or participant undergoes transplantation) are described below:

- Concurrent treatment with any desensitization procedure or anti-neoplasm therapy not specified in the protocol, including chemotherapy, immunotherapy, hormonal therapy, targeted therapy, biological therapy, other investigational drug, or curative radiotherapy.
- Concomitant treatment with immunosuppression medications are prohibited, except for:
  - use in premedication defined in the study protocol,

- treatment of any life-threatening emergency,
- low dose corticosteroids (eg, up to 10 mg prednisone/day or equivalent) as needed for Investigator's judgment, and
- a brief course (≤7 days) of systemic corticosteroid for prophylaxis (eg, contrast dye allergy) or for the treatment of non-autoimmune conditions (eg, delayed-type hypersensitivity reactions cause by contact allergen).

- Investigational therapy (other than protocol-mandated study intervention) is prohibited within 28 days prior to initiation of IMP, during treatment period, and during site visit FUP.
- Live vaccines should be avoided. However, given the increased risk of infection, routine vaccinations are recommended for the participants and their contacts. Prophylactic vaccination is recommended for influenza A and B virus, pneumococci, and haemophilus influenza.
- Phase 1 only: Prophylactic use of hematopoietic growth factors (eg, G-CSF, granulocyte macrophage-colony stimulating factor [GM-CSF]) during the first cycle observation period. Curative treatment and prophylactic use of erythropoietin is allowed.

Other concomitant medication may be considered on a case-by-case basis by the Investigator in consultation with the Medical Monitor if required.

HBV 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 approximately 1, 2 and 3 months after end of vaccination (±7 days, or at the next blood sampling). 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 or Investigator.

See Section 6.6.3 in case of hepatitis B viral reactivation (sub section "Guidance in case of hepatitis B reactivation occurring under study treatment").

6.5.1 Rescue Medicine

The Sponsor will not supply any rescue medication. The site will use standard and locally acceptable rescue medications in line with current box labeling, as appropriate. However, the risk-benefit of use of such medications must be assessed case-by-case by the Investigator or his team. The date and time of rescue medication administration as well as the name and dosage regimen of the rescue medication must be recorded.

6.6 DOSE MODIFICATION

6.6.1 General rules

Cycle delay (ie, delay of IMP for Cycle 2 and 3), dose delay, or dose omission (ie, omission within a cycle) are permitted in case of toxicity.

Administration of the IMP will be discontinued in the event of a TEAE that persists despite appropriate dose modifications or any other AE that, in the opinion of the Investigator, warrants discontinuation.

There will be no dose reduction for isatuximab.

Any changes to IMP administration must be recorded in the eCRF.

6.6.2 Dose delay and dose omission

Within a cycle, the treatment window is ±1 day for each of the weekly administrations and ±2 days for each of the Q2W administrations. Within a cycle, a dose is deemed to have been delayed if the treatment is ≥2 days beyond the theoretical day of treatment for weekly dose, or ≥3 days beyond the theoretical day of treatment for Q2W dose. The reason for dose delay must be captured. The participant will receive the next infusion/cycle after recovery from the AE.

If infusion has been delayed within a cycle, the next dose of IMP should be administered at the planned time interval between the 2 administrations (eg, if Cycle 1 Day 15 administration was administered on Day 17, the planned Day 22 should be administered on Day 24 ±1 day).

Participants may have dose delay, cycle delay, or dose omission if an AE occurs and does not recover according to the following rules:

- In Cycle 1 (for weekly administration) if an AE occurs and the participant does not recover on the day of planned infusion or within the following 3 days, infusion of isatuximab (Day 8, Day 15, or Day 22) may be omitted.
- In Cycles 2 and 3:
  - For Day 1 infusions: If an AE occurs and the participant does not recover on the day of planned infusion, the cycle may be delayed up to a maximum of 2 weeks.
  - For Day 15 infusions: If an AE occurs and the participant does not recover on the day of planned infusion or within the following 7 days, infusion of isatuximab may be omitted.
- If the AE is not recovered within 14 days:
  - IMP may be delayed up to 56 days.
  - After a cycle delay of >14 days and ≤56 days, it is per Investigator's decision to restart the treatment or the IMP that is omitted, if a clear benefit from therapy is observed and after consultation with the Medical Monitor.
  - The IMP must be definitively permanently discontinued if the dose/cycle delay is longer than 56 days.

6.6.3 General guidelines for the management of adverse events

Guidelines for isatuximab dose modifications and treatment discontinuation due to hematological and non-hematological AEs in general are outlined in Table 5.

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

Table 5 - General management guidelines for adverse events

Adverse Event (NCI-CTCAE version 5.0 criteria)	Management of Isatuximab	Action and Guildeines
Hematological AE		
Grade 1, 2, 3	No change in dose	Participant should be given supportive care and monitored closely.
Grade 3 Thrombocytopenia lasting >7 days or associated with bleeding	Delay the dose/cycle until bleeding is controlled and platelet >50 000/mm³. Restart treatment with the same dose and schedule.	Participant should be given supportive care and monitored closely. Permanent discontinuation should be considered if AE does not resolve/recover within 56 days of last infusion.
Grade 4	Delay the dose/cycle until ANC >1000/mm³, or platelet >50 000/mm³, or hemoglobin >8 g/dL. Restart treatment with the same dose and schedule. Grade 4 lymphopenia: no change in dose.	
Febrile neutropenia and/or neutropenic infection	Delay the dose/cycle until fever and infection recovered and ANC >1000/mm³. Restart treatment with the same dose and schedule.	
Non-hematological AE		
Grade 1	No change in dose	Not applicable
Grade 2	Delay the dose/cycle until improves to Grade ≤1 or baseline. Restart treatment with the same dose and schedule.	If the treatment interruption is >14 days, before restarting the treatment, Investigator must discuss with the Sponsor; if it is determined that it is for the best interest of the patient, treatment may be restarted. If the interruption is longer than 56 days, the treatment must be definitively discontinued
Grade 3	Delay the dose/cycle until improves to Grade ≤1 or baseline. Restart treatment with the same dose and schedule	
Grade 4	Permanently discontinue treatment for treatment related AEs. For treatment unrelated AEs, delay the dose/cycle until improves to Grade ≤1 or baseline. Restart treatment with the same dose and schedule.	
Infusion Reaction: see Table 6 for management guideline		

Abbreviations: AE = adverse event, ANC = absolute neutrophil count, CTCAE = common terminology criteria for adverse events, IV = intravenous, NCI = National Cancer Institute

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 hold and specialist should be consulted for initiation of anti-viral treatment and monitoring of the patient. Re-start of study treatment should be agreed between sponsor, investigator and specialist (hepatologist) if controlled infection. Close monitoring of ALT and AST approximately every month (may coincide with the next scheduled blood sampling ±7 days) up to study treatment discontinuation. HBV DNA to be done as per Investigator's or specialist advice.

** Previous known history of acute or chronic hepatitis B or the presence of total anti-HBc with/without anti-HBs; HBsAg negative; undetectable serum HBV DNA; normal ALT levels.*

6.6.4 General guidelines for the management of infusion reactions

Participants should routinely receive premedications prior to isatuximab infusion as detailed in Section 6.1 to reduce the risk and severity of IRs commonly observed with mAbs.

Infusion reactions typically occur within 24 hours from the start of the infusion.

If an IR is observed, participants must also be informed of the potential risk of recurrent similar reactions at subsequent infusions. The guidelines for management of IRs are summarized in Table 6.

Participants may receive additional medication per the judgment of the Investigator. Additional recommended medications are: diphenhydramine 25 mg IV (or equivalent) and methylprednisolone 100 mg IV (or equivalent).

Participant who experience Grade 2 IRs, or first/second Grade 3 IR, may resume isatuximab infusion after temporary interruption, under close monitoring and with therapy as needed.

Once the Grade 2 IR or first/second Grade 3 IR has improved or resolved according to Table 6, the infusion may be restarted as follows at the Investigator's discretion:

- **First infusion:** Infusion could be restarted at one-half (12.5 mL/hour) of the initial infusion rate when the IR improves to Grade ≤1. If symptoms do not recur after 30 minutes, the infusion rate may be increased by 25 mL/hour increments every 30 minutes, until the total volume is infused or reaching 150 mL/hour, whichever is earlier.
- **Second infusion:** Infusion could be restarted at one-half (25 mL/hour) of the initial infusion rate when the IR improves to Grade ≤1. If symptoms do not recur after 30 minutes, the infusion rate may be increased by 50 mL/hour increments every 30 minutes, until the total volume is infused or reaching 200 mL/hour, whichever is earlier.
- **Third and subsequent infusions:** Infusion could be restarted at one-half (100 mL/hour) of the initial infusion rate when the IR improves to Grade ≤1. If symptoms do not recur

after 30 minutes, the infusion rate may be increased by 50 mL/hour increments every 30 minutes, until the total volume is infused or reaching 200 mL/hour, whichever is earlier.

Participants with Grade 3 IR (third Grade 3, or do not fulfil criteria to restart infusion as per Table 6) or Grade 4 IR must permanently discontinue the treatment with isatuximab.

Grade 3 or higher IRs for isatuximab must be reported as adverse event of special interests (AESIs) (see Section 8.3). Study personnel should consult the Medical Monitor for further guidance regarding retreatment of participants with IRs and regarding issues of premedication management (eg, alternative medications for participants allergic or intolerant to premedication agents), or to determine if locally used equivalent medications are acceptable.

Table 6 - Management guidelines for infusion reaction

Infusion related reaction grading (NCI-CTCAE version 5.0 criteria)	Recommendation
Grade 1 Mild transient reaction; infusion interruption not indicated; intervention not indicated.	**Continuation of isatuximab infusion is per the judgment of the Investigator** following close direct monitoring of the participant's clinical status.
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 medication(s) with IV diphenhydramine 25 mg (or equivalent) and/ or IV methylprednisolone 100 mg (or equivalent), and/or other supportive care as needed. **Isatuximab[a] may be resumed only after participant recovery, with reduced infusion rate and with close monitoring.**
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.	**Stop isatuximab infusion.** Give additional medication(s) with diphenhydramine 25 mg IV (or equivalent) and/or IV methylprednisolone 100 mg (or equivalent) and/or epinephrine as needed until resolution of the AE or until the AE improves to Grade 1. Only then, the infusion may be restarted at the Investigator's discretion: if so, the infusion rate should be half of the initial infusion rate, and it may be increased subsequently, at the Investigator's discretion. If the severity of an infusion-related AE returns to Grade 3 after the restart of the infusion, the same procedure described above may be repeated at the Investigator's discretion. If a Grade 3 infusion-related AE occurs for a 3rd time, treatment with isatuximab will be definitively discontinued for that participant. If symptoms do not resolve rapidly, do not improve after interruption of the isatuximab infusion, they recur after initial improvement with appropriate medications, or they require hospitalization, treatment with isatuximab should be definitively discontinued. Report as AESI.

Infusion related reaction grading (NCI-CTCAE version 5.0 criteria)	Recommendation
Grade 4 Life-threatening consequences; urgent intervention indicated.	**Definitive discontinuation of isatuximab**. Give additional premedication with diphenhydramine 25 mg IV (or equivalent) and/or IV methylprednisolone 100 mg (or equivalent) and/or epinephrine as needed. Report as AESI.

Abbreviations: AESI = adverse event of special interest, CTCAE = common terminology criteria for adverse events, IR = infusion reaction, IV = intravenous, NCI = National Cancer Institute, NSAIDS = nonsteroidal anti-inflammatory drugs.

a Isatuximab: the 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.

6.6.5 Retreatment of participants

The participants must have recovered to National Cancer Institute (NCI) common terminology criteria for adverse events (CTCAE) Grade ≤1 or to the baseline status before initiation of the next cycle at the same dose level.

In the event of an AE causing a delay, in order for participants to be retreated, see Section 6.6.1 to Section 6.6.4 for recommendations.

6.7 INTERVENTION AFTER THE END OF THE STUDY

The IMP will not be provided after the end of the treatment period. The participant's treatment after study discontinuation will be at the discretion of the treating physician.

For participants who received isatuximab treatment and subsequently proceed to solid organ transplantation, it is recommended to include the following as part of the post-transplant immunosuppression regimen:

- Anti-thymocyte globulin (rabbit) as indicated for prophylaxis of acute rejection.
- Steroids during maintenance phase, with tapering if applicable.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

Refer to Section 7.1 and Section 7.2 for details regarding discontinuation of study intervention and participant discontinuation.

7.1 DISCONTINUATION OF STUDY INTERVENTION

7.1.1 Definitive discontinuation

In rare instances, it may be necessary for a participant to permanently discontinue study intervention. If study intervention is permanently discontinued (except in the case of discontinuation due to transplantation), the participant will remain in the study to be evaluated as per the assessments planned for site visit FUP. See the SoA (Section 1.3) for data to be collected at the time of discontinuation of study intervention.

The IMPs should be continued until end of treatment period whenever possible.

In case the IMP is stopped, it should be determined whether the stop can be made temporarily. Any IMP discontinuation must be fully documented in the eCRF.

Pregnancy will lead to definitive treatment discontinuation in all cases.

Treatment with the IMP should be discontinued in any of the following cases:

- At the participant's request, at any time and irrespective of the reason (participant's decision), or at the request of their legally authorized representative without any effect on their care. "Legally authorized representative" is considered to be an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective patient to the patient's participation in the procedure(s) involved in the research.
- If, in the Investigator's opinion, continuation of the IMP would be detrimental to the participant's well-being, such as:
  - unacceptable AE,
  - poor compliance to the study protocol,
  - any other reason such as intercurrent illness that prevents further administration of IMP (will be specified).
- Participant is lost to follow-up.
- Completion of the 3 cycles of treatment period.

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.

Any abnormal laboratory value or ECG parameter will be immediately rechecked for confirmation (per Investigators discretion) before making a laboratory/ECG abnormality-driven 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.

In the case of participants discontinuing IMP during treatment period due to transplantation, the participants should complete an E/D visit (30±7 days after last IMP) if clinically feasible, and proceed to extended FUP.

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

7.1.2 Temporary discontinuation

Temporary intervention discontinuation may be considered by the Treating Investigator because of suspected AEs or disruption of the clinical trial due to a regional or national emergency declared by a governmental agency (Appendix 13 [Section 10.13]). For all temporary intervention discontinuations, duration should be recorded by the Investigator in the appropriate pages of the eCRF.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

- 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. This is expected to be uncommon.
- At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoA (Section 1.3). See SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.
- The participant will be permanently discontinued from the study intervention if discontinued from the study at that time.
- 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.

If participants no longer wish to take the IMP, they will be encouraged to remain in the study (ie, continue participation in site visit FUP and extended FUP).

The Investigators should discuss with them 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 non-participant 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 reallocated (treated) in the study. Their inclusion and intervention numbers must not be reused.

7.3 LOST TO FOLLOW UP

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 study site.

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

- The site must attempt to contact 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.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix 1 (Section 10.1).

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.
- Adherence to the study design requirements, including those specified in the SoA, 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, blood count) and obtained before signing of the 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.
- The total volume of blood required for all assessments as per protocol is expected to be within the recommended safe limit for human in clinical trials by the local Institutional Review Boards and Ethics Committees.
- For a regional or national emergency declared by a governmental agency, contingency measures are included in Appendix 13 (see Section 10.13).
- In exceptional cases, under regional or national emergencies (eg, natural disaster, epidemic/pandemic, terrorist attack), onsite visits may be replaced with telephone/remote visits. For example, patient interview for medical history/prior medications could be performed by phone, local safety labs and some efficacy assessments could be performed off-site/at the participant's home (eg, home nursing) if agreed by patient and permissible per local regulations. In such circumstances, visit window may be expanded, if needed (eg, ±14 days for visits).

8.1 EFFICACY ASSESSMENTS

8.1.1 Efficacy assessment - Central laboratory assessments

The primary efficacy endpoint, selective secondary, and exploratory efficacy endpoints will be assessed by the central laboratory using the SAB assay (see Section 10.9). For the purpose of cPRA and anti-HLA antibody determination, unacceptable antigens are defined as those with MFI ≥2000. The cPRA will be computed based on cPRA calculator developed by the Organ Procurement and Transplantation Network, with values to be provided with 2 decimal places.

Refer to the laboratory manual for details regarding sample collection, processing, storage, and shipment.

8.1.2 Efficacy assessment - Local laboratory assessment

The cPRA levels assessed by the local laboratory will be captured for the analysis of one of the secondary efficacy endpoints. Frequency of assessment will be performed as per the local standard of practice. If possible, cPRA levels should be reported to 2 decimal points (eg, 99.99%) based on cPRA calculator developed by the Organ Procurement and Transplantation Network, in addition to locally reported cPRA, with unacceptable antigens defined as those with MFI ≥2000.

8.2 SAFETY ASSESSMENTS

Planned time points for all safety assessments are provided in the SoA.

8.2.1 Physical examinations

- A complete physical examination will include, at a minimum, assessments of the major body systems. Height (only at screening) and weight will also be measured and recorded.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.
- Any new finding or worsening of previous finding should be reported as a new AE.

8.2.2 Vital signs

- During the treatment period, vital signs are to be monitored just before starting infusion of the IMP, 1 hour after the start of the infusion, at the end of infusion, and during the infusion if clinically indicated.
- Temperature, pulse rate, respiratory rate, and blood pressure will be assessed.
- Blood pressure and pulse measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (eg, television, cell phones).

8.2.3 Electrocardiogram

A single 12-lead ECG will be obtained at screening using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals.

8.2.4 Echocardiography

Two-dimensional echocardiography coupled with Doppler flow studies will be performed at screening to evaluate the left ventricular ejection fraction and other relevant cardiac function assessments, as needed. Echocardiography should be performed at dry weight, and/or on a non-dialysis day.

8.2.5 Clinical safety laboratory assessments

- See Appendix 2 (Section 10.2) for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.
- 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. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator or Medical Monitor.
  - If such values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified 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.
  - 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.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

Adverse event of special interest (AESI)

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

- 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 clinical trial or in a female partner of a male participant entered in the clinical trial. 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, 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 IMP/NIMP
  - An overdose (accidental or intentional) with isatuximab is defined as increase of at least 30% of the intended administered dose at each infusion (expressed in unit per body weight) to be administered in the specified duration or if the dose is administered in less than half the recommended duration of administration.
  - An overdose (accidental or intentional) with NIMP is defined as increase of at least 30% of the intended administered dose at each administration,
  - In case of accidental or intentional overdose with IMP/NIMP, even not fulfilling a seriousness criterion, is to be reported to the Sponsor immediately (within 24 hours) using the AE form together with the SAE complementary form to be entered in the eCRF.
  - Of note, asymptomatic overdose has to be reported as a standard AE.
- Other project specific AESI
  - Grade ≥3 IRs. An IR occurs typically within 24 hours from the start of the infusion.

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 time points specified in the SoA (Section 1.3).

Beyond 30 days after the last dose of IMP, only ongoing related AEs, ongoing SAEs, and new related AEs/SAEs will be followed up until resolution/stabilization.

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

Investigators are not obligated to actively seek AE or SAE 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

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

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

8.3.3 Follow-up of AEs and SAEs

After the initial AE/AESI/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. Beyond 30 days after the last dose of IMP, only ongoing related AEs, ongoing SAEs, and new related AEs/SAEs will be followed up until resolution/stabilization, the event is otherwise explained, 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

- Prompt notification by the Investigator to the Sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety 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.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.
- Adverse events that are considered expected will be specified in the reference safety information.
- An Investigator who receives an Investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.5 Pregnancy

- Details of all pregnancies in any female participant and any female partner of male participant who becomes pregnant 2 weeks before the first dose of isatuximab treatment, while the male participant is in the study, and within 5 months after the last dose of isatuximab treatment will be collected.

- 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, ectopic pregnancy) are considered SAEs.

8.3.6 Cardiovascular and death events

Cardiovascular and death events should be reported as per the protocol. See Section 8.3 for details.

8.3.7 Disease-related events and/or disease-related outcomes not qualifying as AEs or SAEs

Disease-related events (DREs) are typically associated with disease progression under the study according to the Investigator's opinion, and that the Investigator deem to be obviously unrelated to the IMP.

NOTE: However, if either of the following conditions applies, then the event must be recorded and reported as an AE or SAE (instead of a DRE):

- *The event is, in the Investigator's opinion, of greater intensity, frequency, or duration than expected for the individual participant.*

OR

- *The Investigator considers that there is a reasonable possibility that the event was related to study intervention.*

In addition, death occurred beyond 30 days after the last IMP administration that is not due to an AE related to IMP, or is unrelated to ongoing AE/SAE, will not be reported as an SAE even though the event may meet the definition of a SAE.

8.3.8 Guidelines for reporting product complaints

Any defect in the IMP must be reported as soon as possible by the Investigator to the monitoring team that will complete a product complaint form within 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

There is no information on specific recommendations regarding overdose with isatuximab. In case of overdose, participants should be closely monitored for signs and symptoms of adverse reactions, and appropriate symptomatic treatment should be instituted.

In the event of an overdose, the Investigator should:

1. Contact the Medical Monitor immediately.
2. Closely monitor the participant for any AE/SAE and laboratory abnormalities.
3. Document the quantity of the excess dose as well as the duration of the overdose in the eCRF.

Decisions regarding dose interruptions or delays will be made by the Investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

8.5 PHARMACOKINETICS

Blood samples will be collected for the measurement of isatuximab concentrations in plasma as described in the PK flowcharts (see Section 1.3.1). Instructions for the collection and handling of biological samples will be provided by the Sponsor in a separate laboratory manual. The actual date and time of each sample will be recorded. These samples will be tested by the Sponsor's designee.

8.5.1 Non-compartmental analysis

Pharmacokinetic parameters will be calculated using the non-compartmental methods from isatuximab plasma concentrations. The parameters will include, but may not be limited to the following (Table 7):

Table 7 - List of pharmacokinetic parameters and definitions

Parameters	Definition
C_{eoi}	Concentration observed at the end of intravenous infusion
C_{max}	Maximum concentration observed after the first infusion
t_{max}	Time to reach C_{max}
C_{last}	Last concentration observed above the lower limit of quantification after the first infusion
t_{last}	Time of C_{last}
C_{trough}	Concentration observed just before treatment administration during repeated dosing
$AUC_{0\,T}$	Area under the plasma concentration versus time curve calculated using the trapezoidal method over the dosing interval $_T$ (168 hours)

8.5.2 Population approach

Population PK approaches may be used. If done, the data generated will be reported in a separate report(s).

8.6 PHARMACODYNAMICS

Refer to Section 8.8 for PD biomarkers.

8.7 GENETICS

Genetics are not evaluated in this study.

8.8 BIOMARKERS

- Collection of samples for other biomarker research is also part of this study. Blood samples for biomarker research are required and will be collected from all participants in this study as specified in the SoA.
- Samples will be tested for the presence and/or function of specific immune cells especially CD38 expression cells as well as total immunoglobulin to evaluate their association with the observed clinical responses in reduced anti-HLA antibodies to anti-CD38 treatment.

Detailed instructions for sample preparation and shipping for the biomarkers will be provided to the study sites in a separate laboratory manual.

8.8.1 Immune cell profiling

Blood samples will be collected from all participants for the flow cytometric analysis of immune cells before and after the treatment with isatuximab. The blood sampling time points are depicted in the SoA (Section 1.3). Sample preparation and analysis will be conducted by the Sponsor's designee. Blood immune cells will be incubated with mAbs which detect specific cell surface and intracellular proteins. Based on the combination of bound antibodies to the immune cells distinct cell populations and specific cell types can be identified. One major aim is to determine the alteration of percentage and cell count of CD38 expressing cells in blood upon isatuximab treatment. Other immune cell populations may also be examined.

8.8.2 Functional B-cell assay

Blood samples will be collected to enable possible functional assessment of memory B-cells depletion. Blood sampling time points before and after treatment with isatuximab are depicted in the SoA (Section 1.3). Sample preparation and analysis will be conducted by the Sponsor's designee(s). Peripheral B-cells will be processed for subsequent analysis of anti-HLA alloreactivity upon isatuximab treatment.

8.8.3 Determination of serum total immunoglobulin levels

Blood samples will be collected from all participants for the measurement of total immunoglobulin levels before and after the treatment with isatuximab. The blood sampling time points are depicted in the SoA (Section 1.3). Sample preparation and analysis will be conducted

by the Sponsor's designee. In particular the levels of ImmunoglobulinG are of interest in order to estimate the efficacy of isatuximab treatment.

Additional analysis, not specified in the protocol but related to the drug action and/or effect of IMP, may be conducted on the remaining samples pending evolving literature.

8.9 IMMUNOGENICITY ASSESSMENTS

Blood samples will be collected for assessing the presence of ADA against isatuximab in plasma from all participants as described in the PK/ADA flowcharts (see Section 1.3.1). These samples will be tested by the Sponsor's designee.

Refer to the laboratory manual for details regarding sample collection, processing, storage, and shipment.

Plasma samples will be screened for antibodies binding to isatuximab and the titer of confirmed positive samples will be reported.

8.10 HEALTH ECONOMICS OR MEDICAL RESOURCE UTILIZATION AND HEALTH ECONOMICS

Not applicable.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

Phase 1: There is no formal statistical hypothesis.

Phase 2:

- Null hypothesis: True RR [redacted]
- Alternative hypothesis: True RR[redacted]

9.2 SAMPLE SIZE DETERMINATION

In Phase 1, approximately 6 to 12 safety evaluable participants are expected to be enrolled (see Section 9.3 for definition of Safety Evaluable Population).

Approximately 24 to 36 participants (Phase 1 and Phase 2) are expected to be enrolled if the SD is retained as the Phase 2 dose or approximately 30 to 42 participants are expected to be enrolled if DL-1 is the Phase 2 dose.

A maximum of 6 replacements per cohort is allowed for participants who:

- enroll in Phase 1 and receive <90% of the planned cumulative doses within the first cycle (unless they discontinue IMP due to pre-defined unacceptable toxicity), or
- receive <75% of planned cumulative doses within 3 cycles, or
- have consecutive dose interruption of >28 days, or
- do not complete site visit follow-up period (FUP), after agreement with Medical Monitor.

Phase 2:

- With a minimum sample size of 12 participants per cohort and 1-sided alpha of 0.025, the analysis will have at least 80% power to demonstrate that RR is significantly better than [redacted] assuming the true RR is [redacted], based on exact test.
- A null hypothesis of [redacted] is selected representing placebo control as there is currently no approved or standard therapy for desensitization, and there is no expected decrease in anti-HLA antibody levels or cPRA in patients who do not undergo desensitization therapy.

The participants treated at the Phase 2 dose during Phase 1 will be included in the analysis together with the participants in Phase 2.

9.3 POPULATIONS FOR ANALYSES

For purposes of analysis, the following populations are defined (Table 8):

Table 8 - Populations for analyses

Population	Description
Screened	All participants who sign the ICF.
All Treated	Includes all participants who receive at least 1 dose of isatuximab. This population is the primary population for the analyses of safety parameters, unless otherwise noted. All analyses using this population will be based on the dose level actually received.
Safety Evaluable (Phase 1)	Includes all participants enrolled in Phase 1 who receive ≥90% planned cumulative doses of isatuximab within Cycle 1 (unless IMP is discontinued due to pre-defined unacceptable toxicity).
Efficacy Evaluable	Includes All Treated Population who fulfill the study eligibility criteria, with an evaluable baseline and at least 1 evaluable postbaseline efficacy assessment, and receive ≥75% of planned cumulative doses. This is the primary population for efficacy analyses.
PK	Includes All Treated Population with at least 1 available concentration result post-treatment (whichever the cycle and even if dosing is incomplete) with adequate documentation of date and time of dosing and date and time of sampling.
ADA	Includes All Treated Population with at least 1 available ADA result (negative, positive, or inconclusive) post-treatment (whichever the cycle and even if dosing is incomplete).

Abbreviations: ADA = anti-drug antibody, ICF = informed consent form, IMP = investigational medicinal product, PK = pharmacokinetic.

9.4 STATISTICAL ANALYSES

The statistical analysis plan (SAP) will be developed and finalized before the database lock and will describe the participant populations to be included in the analyses and procedures for accounting for missing, unused, and spurious data. For a regional or national emergency declared by a governmental agency, contingency measures are included in Appendix 13 (Section 10.13). This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

9.4.1 Efficacy analyses

Analysis of primary efficacy endpoint:

- In Phase 2, the RR by cohort will be summarized using descriptive statistics. A 95% 2-sided confidence interval will be computed using the Clopper-Pearson method (Table 9).

Analyses of secondary endpoints:

- All secondary endpoints (if applicable) during Phase 2 will be summarized descriptively and presented by cohort. Categorical variables (eg, rates and proportions) will be tabulated

via frequency distributions. Continuous variables (eg, change from baseline) will be summarized by providing the number of observations (n), mean, median, standard deviation, minimum, and maximum. Duration of response and other time to event variables will be analyzed using the Kaplan-Meier method (Table 9). Participants not reaching an event will be censored at their last follow-up visit.

- No hypothesis/significance testing will be performed.

Table 9 - Efficacy analyses

Endpoint	Statistical Analysis Methods
Primary: Response rate (per central laboratory)	Descriptive statistics and Clopper-Pearson method
Secondary:	
• Rate/Proportion of participants: - achieving target cPRA (per local laboratory) - with AMR (if applicable) - with graft survival at 6 months post-transplant (if applicable)	Descriptive statistics
• Number of: - anti-HLA-antibody eliminated (per central laboratory) - transplant offers (if applicable)	Descriptive statistics
• Duration of: - response (DoR) (based on central laboratory) - achieving target cPRA (based on local laboratory)	Kaplan-Meier method
• Time to event: - first transplant offer - transplant (if applicable) - first AMR episode (if applicable)	Kaplan-Meier method
Tertiary/Exploratory	Will be described in the SAP and finalized before the database lock.

Abbreviations: AMR = antibody mediated rejection, cPRA = calculated panel reactive antibodies, DoR = duration of response, HLA = human leukocyte antigen, SAP = statistical analysis plan.

9.4.2 Safety analyses

All safety analyses will be performed on the Safety Evaluable Population for Phase 1 and All Treated Population for Phase 2.

For safety analyses, the observation period will be divided into 3 segments:

- The pretreatment period is defined as the time from when the participants give informed consent to the first administration of the IMP.

- The on-treatment period is defined as the time from the first dose of IMP up to 30 days after the last dose of IMP.
- The post-treatment period is defined as the time starting 31 days after the last dose of IMP to study cut-off.

Analyses of adverse events

Adverse events will be coded according to Medical Dictionary for Regulatory Activities (MedDRA) and graded according to NCI-CTCAE (version 5.0 criteria).

An overall summary of TEAEs will be provided. The number (%) of participants experiencing TEAEs by primary system organ class (SOC) and preferred term (PT) will be summarized by CTCAE grade (all grades and Grade ≥3). Similar summary tables will be generated for treatment related TEAEs, AESIs, TEAEs leading to treatment discontinuation, serious TEAEs, and TEAEs with fatal outcome. Post-treatment AEs will be analyzed separately.

Clinical laboratory evaluations

All laboratory abnormalities will be graded according to NCI-CTCAE, when applicable. The number (%) of participants with laboratory abnormalities (ie, all grades and grade ≥3) will be tabulated using the worst grade during on-treatment period.

Table 10 - Safety analyses

Endpoint	Statistical Analysis Methods
Primary: AEs/SAEs, and laboratory abnormalities in Phase 1	Will be listed
Secondary: AEs/SAEs, and laboratory abnormalities in Phase 2	Will be summarized using descriptive statistics
Exploratory	Not applicable

Abbreviations: AE = adverse event, SAE = serious adverse event

9.4.3 Analyses of immunogenicity

Immunogenicity analyses and the potential impact on PK will be described in the SAP, and will be performed on the ADA population.

9.4.4 Pharmacokinetic analyses

The non-compartmental PK analysis will be described in the SAP, and will be performed on the PK population.

If applicable, the population PK analyses will be described in the Population PK analysis plan (PAP) provided by PKDM Modeling and Simulation group and the results will be described in a separate report.

9.4.5 Other analyses

The biomarker exploratory analyses will be described in the SAP and finalized before the database lock.

9.5 INTERIM ANALYSES

No interim analyses are planned.

9.5.1 Data Monitoring Committee (DMC)

Not applicable.

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, Investigator Brochure, 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 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

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

- The Investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative 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 (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- 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.
- Participants must be re-consented 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 legally authorized representative.

Participants who are rescreened (except for temporary screen failure) are required to sign a new ICF (see Section 5.4 for details).

The ICF will contain a separate section that addresses the use of remaining mandatory samples for optional 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 Appendix 13 (see Section 10.13).

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 GDPR (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 [FDA] 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

Study Committee

Composition of the Study Committee will vary based on the matter discussed, but it will generally include Sponsor representatives and at least 2 key Investigators. The Study Committee will convene ad hoc when required, to review data (including Phase 1) and provide strategic recommendations on study medical decisions.

10.1.6 Dissemination of clinical study data

Sanofi shares information about clinical trials and results on publicly accessible websites, based on company commitments, international and local legal and regulatory requirements, and other clinical trial 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 trials in patients 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 trials. 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

- All participant data relating to the study will be recorded on 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 electronically signing the case report form (CRF).
- 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 or designee is responsible for the data management of this study including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (eg, Contract Research Organizations).
- 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 study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The Investigator may initiate study-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 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

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 11 will be performed by the local laboratory.

- The results must be entered into the eCRF.
- 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 the local regulations.
- For women of childbearing potential (WOCBP), a serum pregnancy test will be performed at screening. For all other planned time points (see Section 1.3), a serum or urine human chorionic gonadotropin (hCG) pregnancy test will be performed. Pregnancy test can be performed at home for participants during the FUP or if date of test does not match with FUP visit and the site must record this in the source document. Test should be performed at Screening (ie, ≤7 days prior to first IMP), C2D1, C3D1, at the end of isatuximab treatment (ie, Week 1 of site visit FUP or E/D visit [±7 days]), and 5 months (±7 days) after the last dose of IMP.

Table 11 - Protocol-required safety laboratory assessments

Laboratory assessments	Parameters
Hematology	
	Platelet count
	RBC count
	Hemoglobin
	Hematocrit
	WBC count with differential:
	Neutrophils (absolute neutrophil count))
	Lymphocytes
	Monocytes
	Eosinophils
	Basophils
Clinical chemistry	
	Urea or BUN
	Uric acid
	Creatinine
	eGFR (MDRD)
	Glucose fasting
	Hemoglobin A1c (screening, site visit FUP Week 9, E/D visit; and as clinically indicated)
	Potassium
	Chloride
	Sodium
	Magnesium
	Phosphate
	Calcium
	Bicarbonate (screening, site visit FUP Week 9, E/D visit; and as clinically indicated)

Laboratory assessments	Parameters
	AST/SGOT ALT/SGPT Alkaline phosphatase Total and direct bilirubin LDH Total protein Albumin PTH assessment (screening, site visit FUP Week 9, E/D visit; and as clinically indicated)
Other tests	• Coagulation: prothrombin time or INR, and activated PTT • Blood typing interference test (see Section 1.3, footnote *i*) • Serology[a]: HBV (HBsAg, anti-HBc [total and IgM], anti-HBs), HCV (anti-HCV), HIV (HIV antibody), CMV (IgG and IgM), EBV (early antigen, VCA-IgG, VCA-IgM, nuclear antigen antibody) • Viral load[a]: HBV DNA, HCV RNA, EBV DNA, CMV DNA The results of each test must be entered into the eCRF

Abbreviations: anti-HBc = antibody to hepatitis B core antigen; anti-HBs = antibody to hepatitis B surface antigen; ALT = alanine aminotransferase, AST = aspartate aminotransferase, BUN = blood urea nitrogen, CMV = cytomegalovirus, EBV = Epstein-Barr virus, eCRF = electronic case report form, E/D = early discontinuation, eGFR = estimated glomerular filtration rate, DNA =deoxyribonucleic acid, FUP = follow-up period, HBV = hepatitis B virus, HBsAg = hepatitis B surface antigen, HCV = hepatitis C virus, HIV = human immunodeficiency virus, IgG= immunoglobulin G, IgM = immunoglobulin M, INR = international normalized ratio, LDH = lactic acid dehydrogenase, MDRD = Modification of Diet in Renal Disease, PTH = parathyroid hormone, PTT = partial thromboplastin time, RBC = red blood cell, RNA = ribonucleic acid, SGOT = serum glutamic-oxaloacetic transaminase, SGPT = serum glutamic-pyruvic transaminase, VCA = viral capside antigen, WBC = white blood cell.

NOTES: Blood chemistry, hematology: assessments are not required to be repeated prior to Cycle 1 Day 1 if the screening laboratory assessments were performed within 7 days prior to first the IMP administration and met entry criteria. The window for blood chemistry and hematology is within 1 working day prior to IMP administration.

a Study sites should determine which serology and viral load tests are required to confirm participant's eligibility and to enable appropriate viral reactivation monitoring for HBV, HCV, HIV, EBV, and CMV as per protocol. The tests listed serve as a guidance and may not require all tests to be performed if selective results are conclusive on participant's viral infection status and sufficiently support safety monitoring.

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 patient 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 test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (ie, not related to progression of underlying disease), eg:
  - Leading to IMP discontinuation or modification of dosing, and/or
  - Fulfilling a seriousness criterion, and/or
  - Defined as an AESI
- Exacerbation of a chronic or intermittent pre-existing 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 drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.

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 pre-existing 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).

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

a) Results in death

c) 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.

d) 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 pre-existing condition that did not worsen from baseline is not considered an AE.

e) 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.

f) Is a congenital anomaly/birth defect

g) 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 Sponsor 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 Sponsor. 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 Sponsor.
- 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 NCI-CTCAE version 5.0 will be used to assess the severity of AEs/SAEs

Assessment of causality

- The Investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a 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 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 Investigator's Brochure 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 Sponsor. 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 to Sponsor**
- The Investigator may change his/her opinion of causality in light of follow-up information and send a 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 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.

- New or updated information will be recorded in the originally completed CRF.
- The Investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

REPORTING OF SAES

SAE reporting to Sponsor via an electronic data collection tool

- The primary mechanism for reporting an SAE to Sponsor will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours.
- 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 Sponsor by telephone.
- Contacts for SAE reporting can be found in the Investigator Study File.

SAE reporting to Sponsor via paper CRF

- Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the Sponsor if the electronic system is unavailable.
- 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 can be found in the Investigator Study File.

10.4 APPENDIX 4: CONTRACEPTIVE GUIDANCE AND COLLECTION OF PREGNANCY INFORMATION

DEFINITIONS:

Woman of childbearing potential (WOCBP)

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

1. Premenarchal
2. 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.

3. Postmenopausal female
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
   - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
   - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

CONTRACEPTION GUIDANCE:

Females of childbearing potential or male participants with female partners of childbearing potential are required to use effective contraceptive methods starting 2 weeks before IMP administration, during treatment period, and until 5 months after last dose of isatuximab.

Male participants

- Male participants with heterosexual partners of reproductive potential (WOCBP) are eligible to participate if they agree to use the following during the protocol defined timeline:
  - Refrain from donating sperm

and

- At least 1 of the following conditions applies:

  Are and agree to remain abstinent from penile-vaginal intercourse on a long-term and persistent basis, when this is their preferred and usual lifestyle,

  or

  Agree to use a male condom plus an additional contraceptive method with a failure rate of <1% per year (see table for female participants).

- Male participants with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom for the time defined in the protocol.

Female participants

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in Table 12.

Table 12 - 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] • 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 (IUD) • Intrauterine hormone-releasing system (IUS) • 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 woman of childbearing potential (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.*

NOTES:

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 intervention period and for at least 3 months after the last dose of study intervention

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 2 weeks before the first dose of isatuximab treatment, while the male participant is in the study, and within 5 months after the last dose of isatuximab treatment.
- 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. If applicable, the follow-up will be approximately at least 1 year after the birth. 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 2 weeks before the first dose of isatuximab treatment, while participating in the study, and within 5 months after the last dose of isatuximab treatment. 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. If applicable, the follow-up will be approximately at least 1 year after the birth. 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 post-study 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. 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 discontinue study intervention or be withdrawn from the study.

10.5 APPENDIX 5: GENETICS

Not applicable.

10.6 APPENDIX 6: LIVER SAFETY: SUGGESTED ACTIONS AND FOLLOW-UP ASSESSMENTS

Not applicable.

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

Not applicable.

10.9 APPENDIX 9: DESENSITIZATION RESPONSE CRITERIA

The target cPRA (ie, reduction of cPRA required to achieve at least 100% increase of likelihood of compatible donor [LCD]) is calculated according to the following equation (22). Examples of target cPRA reduction are presented in Table 13.

$$LCD = 1\ in\ \frac{1}{1 - cPRA}$$

Table 13 - Examples of target cPRA reduction

Baseline		Target	
cPRA	**LCD**	**cPRA**	**LCD**
99.99%	1:10000	**99.98%**	1:5000
99.90%	1:1000	**99.80%**	1:500
99.80%	1:500	**99.60%**	1:250
99.60%	1:250	**99.20%**	1:125
99.50%	1:200	**99.00%**	1:100
99.00%	1:100	**98.00%**	1:50
97.50%	1:40	**95.00%**	1:20
95.00%	1:20	**90.00%**	1:10
90.00%	1:10	**80.00%**	1:5
80.00%	1:5	**60.00%**	1:2.5

Abbreviations: cPRA = calculated panel reactive antibodies, LCD = likelihood of compatible donor

Participants with baseline cPRA 100.00% will be assigned with cPRA 99.99% for computational purpose.

Antibody titer is defined as the last dilution of serum at which positive results is obtained (eg, MFI ≥2000) (54). Examples of antibody titer based on MFI are illustrated in Table 14.

Table 14 - Examples of antibody titer

	Neat Serum	1:2	1:4	1:8	1:16	1:32	Titer
Antigen 1 MFI	13430	12492	6250	3123	1550	790	**8**
Antigen 2 MFI	18320	20820	10501	5206	2604	1302	**16**
Antigen 3 MFI	11020	5493	2750	1384	688	360	**4**

Abbreviations: MFI = mean fluorescence intensity

Using similar concept, Table 16 illustrates an example in which the second predefined desensitization criterion (ie, ≥75% reduction in antibody titer from baseline to achieve target cPRA, see Table 15) may be met. In this example, participant's baseline cPRA is measured by SAB as 97.50%, the target cPRA is therefore 95.00% as defined in Table 13. Through serial dilution of the serum collected at baseline, titer required to achieve target cPRA is 16 (ie, achieved at 1:16 dilution). Subsequent post-treatment serum is therefore diluted at 1:4 (ie, 75% reduction from 1:16) to determine whether target cPRA is achieved. At Cycle 3 Day 1, target cPRA is reached at 1:4 dilution therefore meeting the aforementioned predefined desensitization criterion.

Table 15 - 75% reduction in antibody titer from baseline

Baseline		75% Reduction	
Titer	**Dilution**	**Titer**	**Dilution**
2	1:2	**1**	Neat
4	1:4	**1**	Neat
8	1:8	**2**	1:2
16	1:16	**4**	1:4
32	1:32	**8**	1:8
64	1:64	**16**	1:16
128	1:128	**32**	1:32
256	1:256	**64**	1:64
512	1:512	**128**	1:128

Table 16 - Example of ≥75% reduction in antibody titer from baseline to achieve target cPRA

	Neat Serum	1:2 Titer = 2	1:4 Titer = 4	1:8 Titer = 8	1:16 Titer = 16	Response Criterion Met
Baseline cPRA	97.50%	97.50%	97.50%	96.00%	95.00% (target cPRA)	
C2D1 cPRA	96.00%		96.00%			**No**
C3D1 cPRA	96.00%		95.00% (target cPRA)			**Yes**

Abbreviations: C2D1 = Cycle 2 Day 1, C3D1 = Cycle 3 Day 1, cPRA = calculated panel reactive antibodies

10.10 APPENDIX 10: CLUSTER OF DIFFERENTIATION 38 BLOOD TEST INTERFERENCE GUIDELINE

Advancing Transfusion and Cellular Therapies Worldwide

Association Bulletin #16-02

Date: January 15, 2016
To: AABB Members
From: Donna M. Regan, MT(ASCP)SBB—President
Miriam A. Markowitz—Chief Executive Officer
Re: Mitigating the Anti-CD38 Interference with Serologic Testing

Summary

A new class of therapeutic agents for multiple myeloma, CD38 monoclonal antibodies, can result in interference with blood bank serologic tests and thereby cause delays in issuing Red Blood Cell (RBC) units to patients receiving these agents. To minimize these delays, hospitals should set up procedures to inform the transfusion service when patients 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 monoclonal antibodies 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 monoclonal antibody therapies. In November 2015, the first therapeutic CD38 monoclonal antibody [daratumumab (Darzalex, Janssen Biotech, Horsham, PA)] was approved by the Food and Drug Administration.[1] Other CD38 monoclonal antibodies are under development.

CD38 monoclonal antibodies 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 patients consistently cause positive reactions in indirect antiglobulin tests (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, polyethylene glycol),

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and with all IAT methods (eg, gel, tube, solid phase). Agglutination reactions caused by anti-CD38 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 autocontrols.
- Some rare Lu(a–b–) cells are not reactive in the presence of anti-CD38, potentially giving the false impression that the patient has a Lutheran-related antibody.[4,5]
- Positive IATs can be observed for up to six months after anti-CD38 is discontinued.[1,3]
- Anti-CD38 may cause a small decrease in hemoglobin in vivo (~1 g/dL), but severe hemolysis has not been observed among treated patients.[3,6]

Anti-CD38 interference can cause delays in issuing RBCs

If the transfusion service is unaware that a patient has received anti-CD38, the following scenario may occur when the patient'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 (autocontrol 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 patient. In some cases, the anti-CD38 interference could mask the presence of a clinically significant alloantibody.

Recommendations

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

BEFORE a patient begins taking anti-CD38:

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

AFTER a patient begins taking anti-CD38:

- ABO/RhD typing can be performed normally.
- For antibody detection (screening) and identification, dithiothreitol (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 patient is known to be K-positive.
    - Antibodies against other DTT-sensitive blood group antigens (anti-k, anti-Yt^a, anti-Do^a/Do^b, etc) will not be detectable when the antibody screen with DTT-

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treated cells is performed; such antibodies are encountered infrequently, however.

Crossmatch

- For patients 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 patients 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 patient receives anti-CD38.
    - Genotyping can be performed either before or after the patient 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]

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10.11 APPENDIX 11: ABBREVIATIONS

ADA:	anti-drug antibody
ADCC:	antibody-dependent cellular cytotoxicity
ADCP:	antibody-dependent cellular phagocytosis
AE:	adverse event
AESI:	adverse event of special interest
ALT:	alanine aminotransferase
AMR:	antibody mediated rejection
ANC:	absolute neutrophil count
AST:	aspartate aminotransferase
CD:	cluster of differentiation
CDC:	complement dependent cytotoxicity
CKD:	chronic kidney disease
CMV:	cytomegalovirus
CONSORT:	Consolidated Standards of Reporting Trials
cPRA:	calculated panel reactive antibodies
CRF:	case report form
CTCAE:	common terminology criteria for adverse events
DL-1:	dose level minus 1
DNA:	deoxyribonucleic acid
DoR:	duration of response
DRE:	Disease-related event
DSA:	donor-specific antibody
E/D:	early discontinuation
EBV:	Epstein-Barr virus
ECG:	electrocardiogram
eCRF:	electronic case report form
ESRD:	end stage renal disease
FSH:	follicle stimulating hormone
FUP:	follow-up period
GCP:	Good Clinical Practice
G-CSF:	granulocyte-colony stimulating factor
GVHD:	graft-versus-host-disease
HBsAg:	hepatitis B surface antigen
HBV:	hepatitis B virus
HIV:	human immunodeficiency virus
HLA:	human leukocyte antigen
HRT:	hormonal replacement therapy
IAT:	indirect antiglobulin test
ICF:	informed consent form
ICH:	International Council for Harmonisation
IEC:	Independent Ethics Committee
IgG1:	immunoglobulinG1
IMP:	investigational medical product

IR:	infusion reactions
IRB:	Institutional Review Board
IV:	intravenous
IVIG:	intravenous immunoglobulin
KAS:	Kidney Allocation System
LCD:	likelihood of compatible donor
mAb:	monoclonal antibody
MFI:	mean fluorescence intensity
NCI:	National Cancer Institute
NIMP:	noninvestigational medicinal product
NK-cell:	natural killer cell
PD:	pharmacodynamic
PK:	pharmacokinetic
PO:	oral route
Q2W:	once every 2 weeks
QW:	once weekly
RNA:	ribonucleic acid
RR:	response rate
SAB:	single antigen bead
SAE:	serious adverse event
SAP:	statistical analysis plan
SD:	starting dose
SoA:	Schedule of Activities
TCMR:	T-cell mediated rejection
TEAE:	treatment emergent adverse events
ULN:	upper limit of normal
US:	United States
WOCBP:	women of childbearing potential

10.12 APPENDIX 12: PROTOCOL AMENDMENT HISTORY

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

10.12.1 Amended protocol 01 (23 July 2020)

This amended protocol 01 (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

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis; 2.3.3 Preventive measures to minimize the risk of isatuximab; 6.1 Study intervention(s) administered	Ranitidine is removed from standard premedication regimen and will be considered as per medical judgement of the Investigator. Criteria for optional premedication is simplified to base on no IR upon 4 consecutive infusions.	To provide option to adapt the premedication depending on individual situation.
1.3 SoA (footnote f); 5.2 Exclusion criteria; 6.5 Concomitant therapy; 6.6.3 General guidelines for the management of adverse events; 10.2 Appendix 2 Clinical laboratory tests	Included detailed guidance relating to viral reactivation monitoring and risks. As a new footnote "f" was implemented, numbering of following footnotes were shifted accordingly.	To clarify monitoring and risks related to viral reactivation.
1.3 SoA (footnote i)	Added indirect Coombs tests after treatment period during Site Visit follow-up period (FUP) if C2D1 is positive.	To investigate duration of blood typing interference following termination of isatuximab treatment.
1.3 SoA (Blood draw for functional immune cell assay)	Add sample collection during Site Visit FUP Week 1 or E/D if C3D1 sample not collected.	To ensure a post-treatment sample is collected in case C3D1 sample is not collected or if patient discontinued treatment prior to C3D1.
1.3.1.1 Treatment period: Cycle 1 (rich sampling)	C1D1 EOI+4h (± 30 min) timepoint is modified to EOI+1h (+30 min) timepoint.	Modification of sample collection timepoint to reduce wait time/burden for study participants.
1.3.1.1 Treatment period: Cycle 1 (rich sampling) 1.3.1.2 Treatment period: Cycle 2 and beyond (sparse sampling)	Addition of allowing PK/ADA sample to be collected at participant's home by a health care professional (depending on local arrangements).	To provide flexibility and potentially reduce site visit for study participants.
2.2 Background	Updates of isatuximab approval status and number of treated patients.	To provide updates aligned with updates of isatuximab IB ed11.
2.3.3 Preventive measures to minimize the risk of isatuximab; 6.1 Study intervention(s) administered; 6.6.4 General guidelines for the management of infusion reactions	Updated infusion rates based on fixed volume infusion method.	Switching to faster infusion schedule with a fixed distribution volume will reduce hospital chair time (particularly in some specific challenging situations like pandemic restrictions) and increase convenience for patients and sites.

Section # and Name	Description of Change	Brief Rationale
5.1 Inclusion criteria	For participants in Cohort B (I04): cPRA upper limit corrected from 99.80% to 99.89%.	Correction of typographical error.
5.2 Exclusion criteria	E14: Added obinutuzumab to require 6 months washout period.	Inclusion of obinutuzumab in E14 as it has similar mechanism of action as rituximab which is mentioned in the original E14.
7.1.2 Temporary discontinuation 8.0 Study assessments and procedures 9.4 Statistical analyses 10.1.3 Informed consent process 10.13 Appendix 13. Contingency measures for a regional or national emergency that is declared by a governmental agency.	The following text was added: "Temporary intervention discontinuation may be considered by the Treating Investigator because of suspected AEs or disruption of the clinical trial due to a regional or national emergency declared by a governmental agency (Section 10.13). For all temporary intervention discontinuations, duration should be recorded by the Investigator in the appropriate pages of the eCRF". "Onsite visits" changed to "telephone/remote visits" for flexibility to continue the trial during regional or national emergency such as covid-19 pandemic. Contingency Measures for a regional or national emergency are added.	Include flexibility and ease of continuation of study during regional or national emergency such as Covid-19.
6.6.4 General guidelines for the management of infusion reactions	Updated management guideline on Grade 2 and 3 IR including permanent discontinuation of study treatment at third IR.	Clinical management of Grade 3 infusion reaction was updated to align with isatuximab IB ed11. Re-infusion rates following grades 2 and 3 infusion reactions were updated to align with the faster infusion protocol.
8.3.7 Disease-related events and/or disease-related outcomes not qualifying as AEs or SAEs	"AE or" was added to the sentence: "However, if either of the following conditions applies, then the event must be recorded and reported as an AE or SAE (instead of a DRE):"	Clarification.
10.2 Appendix 2 Clinical laboratory tests	Pregnancy test frequency is corrected to be consistent with SoA.	Pregnancy test frequency was not consistent with Section 1.3 SoA (Screening, C2D1, C3D1 were missing).
All document	Minor editorial and format changes. List of abbreviations updated.	Accuracy.

10.13 APPENDIX 13: 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, epidemic/pandemic, terrorist attack) may prevent access to the clinical trial site.

Contingency procedures are suggested below and in Section 8 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 and administration of study intervention may be temporarily delayed.

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

- If onsite visits are not possible, remote visits (eg, with home nurses, home health vendor, etc.) may be planned for the collection of possible safety and/or efficacy data. For example, patient interview for medical history/prior medications could be performed by phone, local safety labs and some efficacy assessments could be performed off-site/at the participant's home (eg, home nursing) if agreed by patient and permissible per local regulations.
- If onsite visits are not possible visit windows may be extended for assessment of safety and/or efficacy data that cannot be obtained remotely, if needed (eg, ±14 days for visits).
- Use of local clinic or laboratory locations may be allowed.

Contingencies implemented due to emergency will be documented.

The impact of the regional or national emergency 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.

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).

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