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AMENDED CLINICAL TRIAL PROTOCOL 06

Protocol title:	**A multicenter, open-label, non-randomized, Phase 1b/2 study to evaluate the safety, pharmacokinetics, and efficacy of subcutaneous isatuximab in adults with warm autoimmune hemolytic anemia**
Protocol number:	**ACT16832**
Amendment number:	**06**
Compound number (INN/Trademark)	**SAR650984 (isatuximab/SARCLISA)**
Study phase:	**Phase 1b/Phase 2**
Short title:	**Safety, pharmacokinetics, and efficacy of subcutaneous isatuximab in adults with warm autoimmune hemolytic anemia**
Sponsor name: **Legal registered address:**	**Sanofi-Aventis Recherche & Développement** **1 avenue Pierre Brossolette** **91380 Chilly-Mazarin, France** **Local Sponsor for US: Sanofi US Services Inc** **55 Corporate Drive, Bridgewater, NJ 08807, USA**

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PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE CHANGES

DOCUMENT HISTORY

Document	Country/Countries impacted by amendement	Date, version
Amended Clinical Trial Protocol 06	All	28 March 2022, version 1 (electronic 7.0)
Amended Clinical Trial Protocol 05	All	02 December 2021, version 1 (electronic 6.0)
Amended Clinical Trial Protocol 04	All	31 August 2021, version 1 (electronic 4.0)
Amended Clinical Trial Protocol 03	All	05 May 2021, version 1 (electronic 3.0)
Amended Clinical Trial Protocol 02	All	01 March 2021, version 1 (electronic 2.0)
Amended Clinical Trial Protocol 01	All	19 October 2020, version 1 (electronic 1.0)
Original Protocol		18 September 2020, version 1 (electronic 2.0)

AMENDED PROTOCOL 06 (28 Mar 2022)

This amended protocol (amendment 06) 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

Changes to inclusion/exclusion criteria for clarification and to address unnecessary eligibility requirements that may contribute to low enrollment rate.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
5.1 Inclusion criteria, criterion I02b	Total bilirubin changed to total or indirect/unconjugated bilirubin above upper limit of normal	Unconjugated bilirubin more specific for hemolysis
5.2 Exclusion criteria, criterion E17	Stable daily dose of steroids required for ≥ 15 days prior to study enrollment.	Decrease in required length of time to allow investigators more flexibility in changing steroid doses to treat ongoing disease prior to enrollment.
5.2 Exclusion criteria	E22 and E23 added	Clarification for immunomodulatory non-cytotoxic concurrent medications

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1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Protocol title: A multicenter, open-label, non-randomized, Phase 1b/2 study to evaluate the safety, pharmacokinetics, and efficacy of subcutaneous isatuximab in adults with warm autoimmune hemolytic anemia

Short title: Safety, pharmacokinetics, and efficacy of subcutaneous isatuximab in adults with warm autoimmune hemolytic anemia

Rationale:

Warm autoimmune hemolytic anemia (wAIHA) is a disease defined by the aberrant production of autoantibodies directed against red blood cells. The primary antibody-producing cell of the body is the plasma cell, which has a life span of months to years and is hypothesized to be responsible for the persistence of autoantibody production in individuals with refractory wAIHA. Plasma cells express a high density of CD38, and the anti-CD38 monoclonal antibody isatuximab is expected to deplete these antibody-producing cells, which are not targeted by glucocorticoids, antiproliferatives, or B-cell depletion by anti-CD20 therapy. This study will assess isatuximab in participants with wAIHA who have failed to respond to prior therapy. The first part of this study will assess safety and determine the isatuximab dose for patients with wAIHA, and the second part of the study will assess efficacy.

Objectives and endpoints

Objectives	Endpoints
Primary	
• Part A: To evaluate the safety and tolerability of subcutaneous injections of isatuximab in adults with wAIHA.	• Standard clinical and laboratory parameters and adverse events.
• Part B: To evaluate the efficacy of the selected dose in adults with wAIHA.	• Overall response rate (response (R) or complete response (CR)) at Day 85. R is defined as an increase in hemoglobin by ≥2 g/dL from baseline and an absence of transfusion in the last 7 days and absence of rescue medications in the past 4 weeks. Biochemical evidence of hemolysis may still be present. CR is defined as hemoglobin ≥11 g/dL (women) or ≥12 g/dL (men), no evidence of hemolysis (normal bilirubin, LDH, haptoglobin, and reticulocytes), absence of transfusion in the last 7 days and absence of rescue medication in the past 4 weeks.

Objectives	Endpoints
Secondary	
Part A (Cohorts 2 and 3 only)	
• To evaluate the efficacy of isatuximab in adults with wAIHA.	• Overall response rate (response (R) or complete response (CR)) at Day 85. R is defined as an increase in hemoglobin by ≥2 g/dL from baseline and an absence of transfusion in the last 7 days and absence of rescue medications in the past 4 weeks. Biochemical evidence of hemolysis may still be present. CR is defined as hemoglobin ≥11 g/dL (women) or ≥12 g/dL (men), no evidence of hemolysis (normal bilirubin, LDH, haptoglobin, and reticulocytes), and absence of transfusion in the last 7 days and absence of rescue medication in the past 4 weeks.
• To evaluate the durability of response to isatuximab and time to response.	• Proportion of participants with durable hemoglobin response by Day 169. Durable response is defined as Hb level ≥10 g/dL with an increase from baseline of ≥2 g/dL on three consecutive evaluable visits during the study period; with absence of transfusion and no rescue medication during the period of 3 consecutive visits and for at least 7 days (transfusions) and 4 weeks (rescue medication) prior to the first consecutive visit. • Overall response rate at Day 169, median time to R or CR, median time to loss of R or CR (loss of R defined as hemoglobin <10 g/dL at two consecutive visits at least 7 days apart and initiation of new treatment for anemia or increase in steroid dose; loss of CR is defined as hemoglobin <11 g/dL (women) or <12 g/dL (men) at two consecutive visits at least 7 days apart), proportion of participants requiring rescue therapy (any wAIHA-directed therapy other than prednisone or transfusion) or splenectomy.
• To evaluate the impact of isatuximab treatment on fatigue.	• FACIT-fatigue scale score at Day 85 and Day 169.
Part B	
• To evaluate the safety and tolerability of isatuximab in adults with wAIHA.	• Standard clinical and laboratory parameters and adverse events.
• To evaluate the durability of response to isatuximab and time to response.	• Proportion of participants with durable hemoglobin response by Day 169. Durable response is defined as Hb level ≥10 g/dL with an increase from baseline of ≥2 g/dL on three consecutive evaluable visits during the study period; with absence of transfusion and no rescue medication during the period of 3 consecutive visits and for at least 7 days (transfusions) and 4 weeks (rescue medication) prior to the first consecutive visit. • Overall response rate at Day 169, median time to R or CR, median time to loss of R or CR (loss of R defined as hemoglobin <10 g/dL at two consecutive visits at least 7 days apart and initiation of new treatment for anemia or increase in steroid dose; loss of CR is defined as hemoglobin <11 g/dL (women) or <12 g/dL (men) at two consecutive visits at least 7 days apart), proportion of participants requiring rescue therapy (any wAIHA-directed therapy other than prednisone or transfusion) or splenectomy.

Objectives	Endpoints
• To evaluate the impact of isatuximab treatment on fatigue.	• FACIT-fatigue scale score at Day 85 and Day 169.
Parts A (all Cohorts) and B	
• To evaluate the effect of isatuximab on markers of hemolysis.	• Change from baseline in LDH, haptoglobin, reticulocytes, and total bilirubin at 1, 2, 4, 8, 12, and 24 weeks.
• To characterize the pharmacokinetic profile of isatuximab in adults with wAIHA.	• PK parameters after subcutaneous administrations (including C_{max} and $AUC_{0\text{-}2\ week}$).
• To evaluate the immunogenicity of isatuximab.	• Incidence and titer (if relevant) of anti-isatuximab antibodies.

Overall design:

This is a Phase 1b/2 open-label, non-randomized, multicenter study to evaluate the safety, pharmacokinetics, and efficacy of subcutaneous isatuximab in adults with wAIHA. The study will be conducted in 2 parts: Part A for safety and dose-finding, and Part B for assessment of the efficacy of the selected dose regimen. Approximately 17 to 23 participants are expected to be enrolled, depending on the number of participants in Part A who receive the regimen chosen for Part B.

Part A will have 2 to 3 cohorts. Cohort 1 consists of 3 participants who will receive 2 doses of isatuximab 140 mg (1 mL) SC administered 2 weeks apart. Cohort 2 can open following a review of available safety, pharmacokinetic (PK), and pharmacodynamic (PD) data after the 3 participants in Cohort 1 complete the Day 43 visit. Cohort 2 will consist of 3 participants who will receive isatuximab SC given every 2 weeks through Day 71 (total of 6 doses). The dose for Cohort 2 may be 70 mg (0.5 mL), 140 mg (1 mL), or 280 mg (2 mL), determined based on the safety profile, PK, and PD observed in Cohort 1.

Once the 3 participants in Cohort 2 have completed the Day 85 visit, an analysis of the available safety, PK, and PD data will be performed, and a decision will be made to either enroll 3 participants as an additional optional dose-finding cohort (Cohort 3) in which a dose up to 560 mg (4 mL) can be investigated, or to open Part B. If Cohort 3 is enrolled, Part B will open once available safety, PK, and PD data through the Day 85 visit from those participants have been reviewed.

Participants in Cohort 1 who experience no response by the end of the treatment period, or a response that subsequently wanes while still in follow up, can be retreated with 6 administrations of the dose selected for Cohort 2, Cohort 3, or Part B. Such participants will continue to be followed for at least 24 weeks from the first retreatment dose, but their response to the additional doses will not be included for efficacy analyses.

For the review of data between each cohort, the safety data will consist of clinical and laboratory parameters and adverse events. Unacceptable toxicity is defined as any verified Grade 4 AE or laboratory abnormality (except infusion reactions [IRs]) occurring during the treatment period, unless due to the underlying disease or due to a cause unrelated to the Investigational Medicinal Product (IMP), if confirmed by the Sponsor and Investigators. PK data will include standard PK parameters, with a focus on isatuximab exposure (C_{max} and $AUC_{0\text{-}2\ week}$). PD data will include hemoglobin levels, markers of hemolysis, and immune cell profiling.

A decision to de-escalate the dose between cohorts will primarily be based on safety signals, while a decision to dose escalate will primarily be based on an insufficient hemoglobin response. Additional PD and PK data will be used to help guide these decisions. While it is anticipated that dose selection for each cohort will occur after all participants in the previous cohort have completed the Day 43 (Part A, Cohort 1) or Day 85 (Part A, Cohorts 2 and 3) visits, in certain circumstances such decisions may be made earlier if clear safety or efficacy signals emerge. All decisions regarding dose levels and the opening of new cohorts will be made by Sponsor representatives and the Principal Investigator at dose selection meetings.

Part B will consist of 8 to 14 participants who will receive isatuximab SC every 2 weeks for a total of 6 doses, at a dose to be determined by the totality of safety, PK, an PD data available from all participants in Part A. The maximum allowable dose in Part B is 560 mg. Approximately 14 participants in the study will receive the isatuximab regimen selected for Part B. Thus, the number of participants in Part B may range from 8 to 14, depending on the number of participants in Part A who received that same regimen in the second or third cohort.

Disclosure Statement: This is a single group treatment study that is not blinded.

Number of participants:

Approximately 17 to 23 participants are expected to be enrolled, depending on the number of participants in Part A who receive the regimen chosen for Part B.

Note: "Enrolled" means a participant's, or their legally acceptable representative's, agreement to participate in a clinical study following completion of the informed consent process. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled.

Intervention groups and duration:

All participants will receive isatuximab subcutaneously. The screening period is up to 28 days, followed by a treatment period of 42 days (6 weeks) for Cohort 1 or 84 days (12 weeks) for the other participants in the trial. All participants will be followed for at least 24 weeks from the first isatuximab dose. The total length of the study, including screening, is 28 weeks.

Study interventions

Investigational medicinal products

Isatuximab

- Formulation: Solution at a concentration of 140 mg/mL.
- Route of administration: subcutaneous injection.
- Dose regimen: Subcutaneous every 2 weeks. The 3 participants in the first cohort of Part A will receive 2 doses; all other participants will receive 6 doses. The following dose levels are planned: 140 mg in the first cohort of Part A; 70 mg, 140 mg, or 280 mg in the second cohort of Part A, depending on the results of the first cohort. The dose level in the

optional third cohort in Part A and the Part B cohort will determined based on analyses of safety, PK, and PD from prior cohorts.

- An isatuximab dose up to a maximum of 560 mg SC may be administered in this study.

Non-investigational medicinal products

- Pre-medication for infusion reactions: To be administered approximately 15 to 30 minutes (and never >60 minutes) prior to the first two isatuximab administrations
  - Montelukast 10 mg orally
  - Acetaminophen/paracetamol 650 to 1000 mg orally
  - Famotidine 40 mg orally (or equivalent)
  - Diphenhydramine 25-50 mg orally (or equivalent)

Statistical considerations:

- **Main analysis populations:**
  - **Efficacy population** and **Safety population:** All participants exposed to the IMP (regardless of the amount of treatment administered).
- **Analysis of primary endpoint:**
  - For Part A, the safety analysis will focus primarily on the treatment emergent period, defined as the time from the first IMP administration up to 30 days after the last IMP administration. Descriptive summaries of Treatment-Emergent Adverse Events and potentially clinically significant abnormalities for standard clinical and laboratory parameters will be provided in the safety population by dose level group.
  - For Part B, the proportion of overall response will be computed at Day 85 together with its exact 95% confidence interval using Clopper-Pearson method in the efficacy population. Participants whose response at Day 85 is not evaluable, whatever the reason (eg, early discontinuation), will be considered as non-responders.
- **Analysis of main secondary endpoints:**
  - For Part A, secondary endpoints will be described by dose level group.
  - For Part B, safety analysis will be conducted using a similar approach as detailed for Part A above. The proportion of overall response at Day 169 and its exact 95% confidence interval using Clopper-Pearson method will be computed. In addition, a mixed-effect model for repeated measures will be implemented on the FACIT-fatigue scale score providing estimates and 95% confidence intervals at Day 85 and Day 169. Other secondary endpoints will be described.

Data Monitoring Committee: There will not be a data monitoring committee for this study. Decisions regarding the dose for Cohorts 2 and 3 in Part A and for Part B will be made at dose selection meetings comprised of Sponsor representatives and the Principal Investigator.

1.2 SCHEMA

Figure 1 - Graphical study design

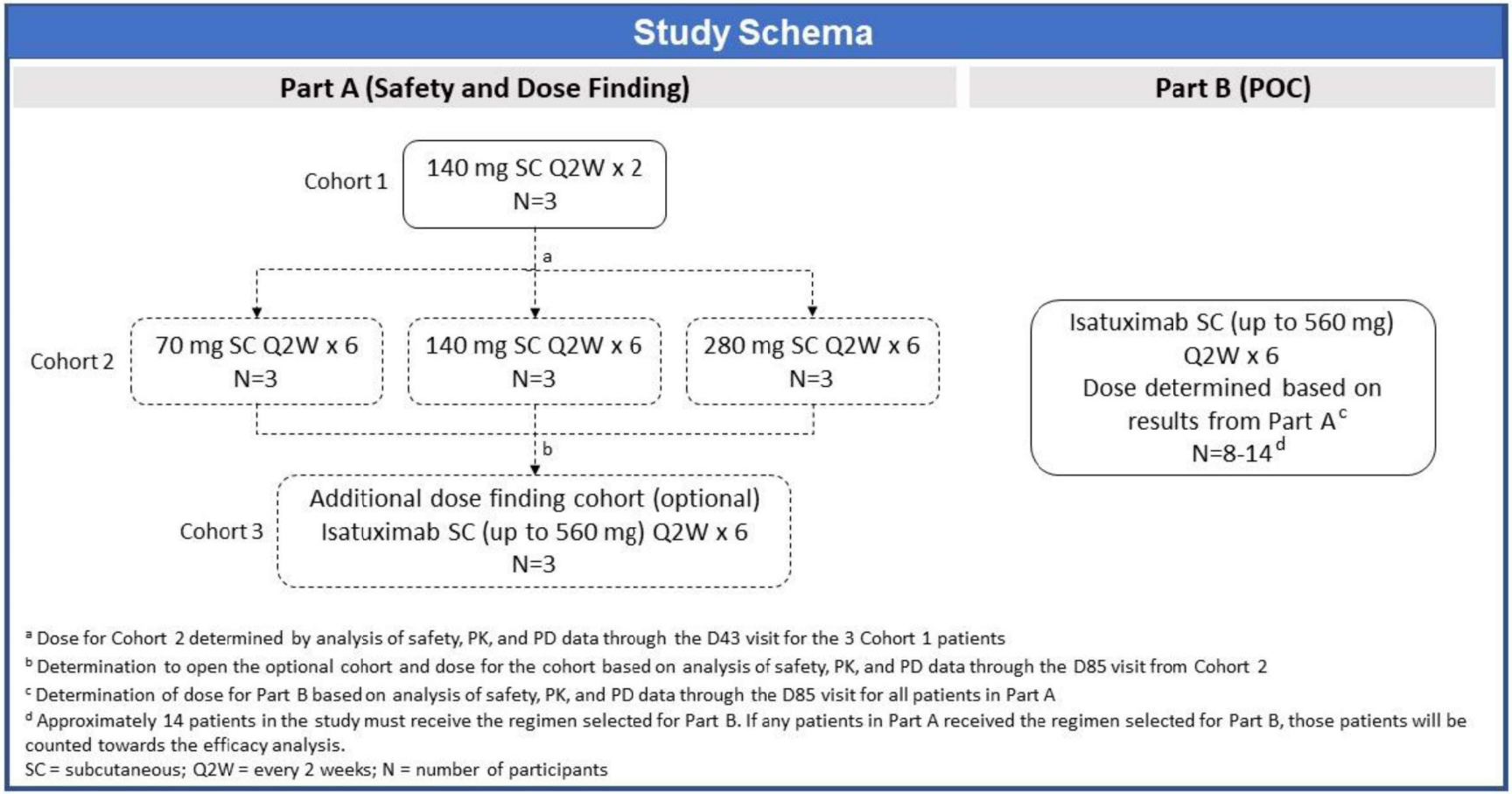


Figure 2 - Study periods for Part A Cohort 1

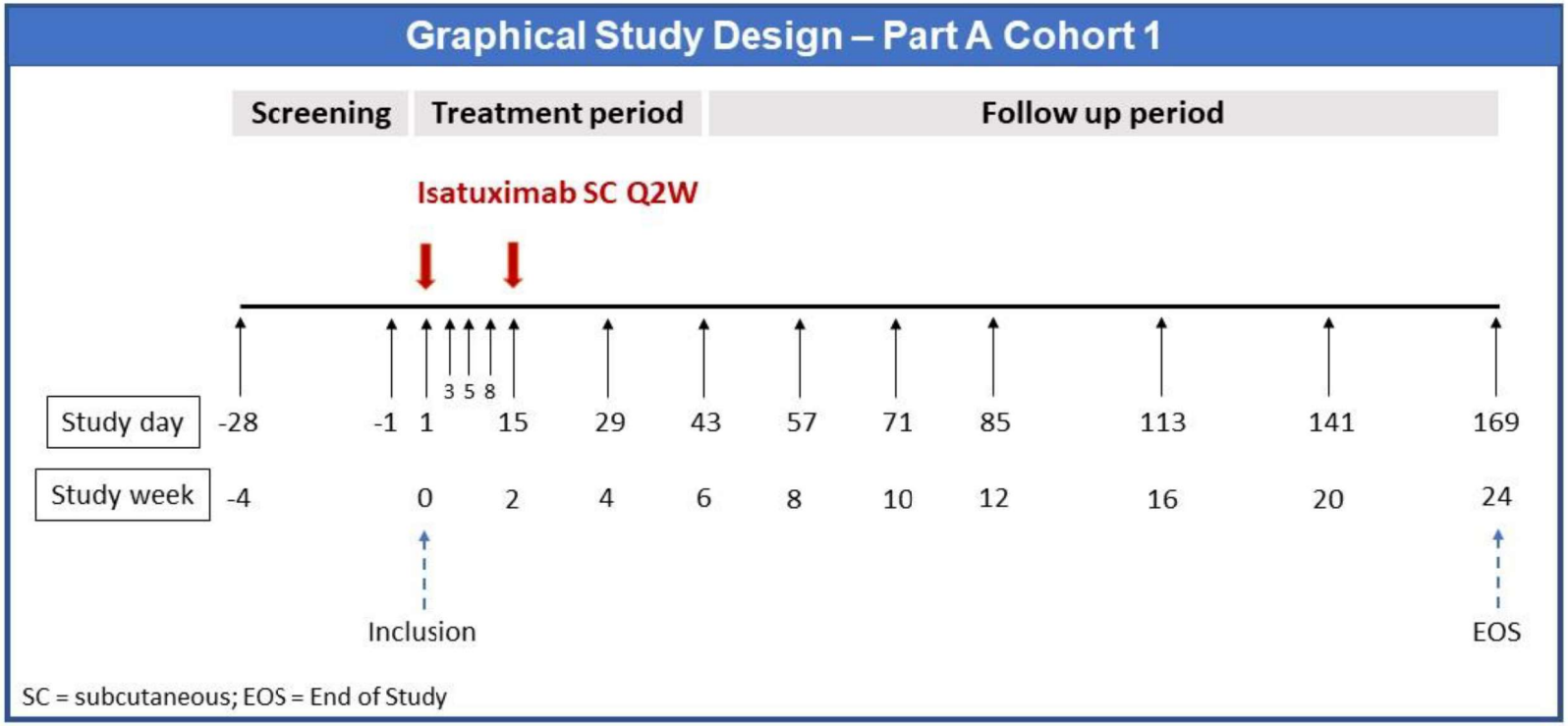
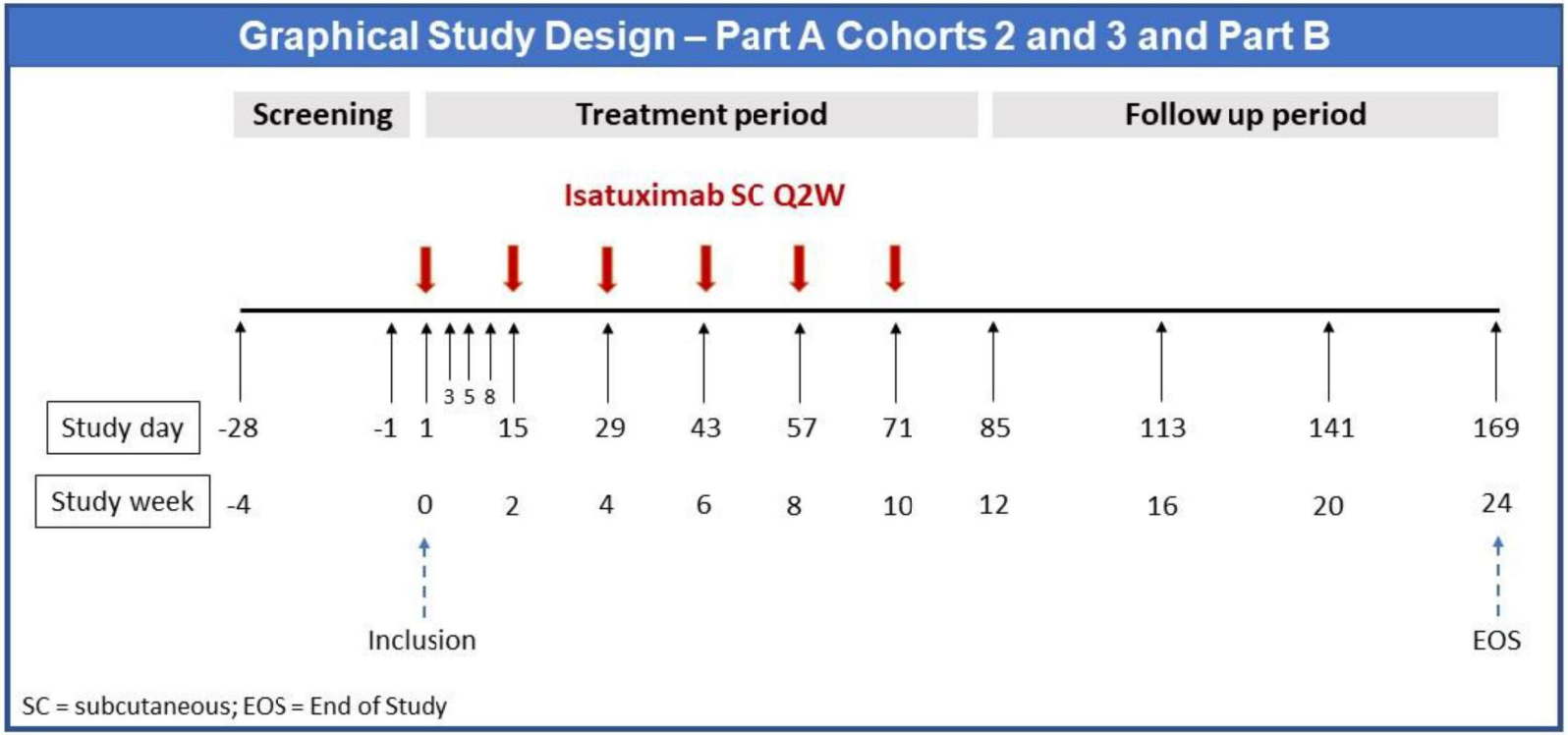


Figure 3 - Study periods for Part A Cohorts 2 and 3 and Part B



1.3 SCHEDULE OF ACTIVITIES (SOA)

Procedure	Screening (up to 28 days before Day 1)	Intervention period										Follow-up period			ED	Notes
		D1	D3[a]	D5[a]	D8[a]	D15	D29	D43	D57	D71	D85	D113	D141	D169		ED = Early Discontinuation
					W1	W2	W4	W6	W8	W10	W12	W16	W20	W24		
Visit window			±5 h	±5 h	±8 h	±1 d	±1 d	±2 d	±2 d	±2 d	±2 d	±7 d	±7 d	±7 d		
Nominal time		0 H	48 H	96 H	168 H											
Informed consent	X															
Inclusion and exclusion criteria	X	X[j]														
Demography	X															
Past and current medical conditions[b]	X															
Physical exam[c]	X	X					X		X			X		X	X	
Vital signs[d]	X	X				X	X	X	X	X		X		X		
IMP/NIMP administration																
Isatuximab		X				X[e]	X	X	X	X						
Pre-medication[q]		X				X										
Safety assessments																
HIV, hepatitis B and C, and SARS-CoV-2 testing[f]	X															
Clinical chemistry and urinalysis[g]	X	X[j]			X		X[j]		X[j]		X			X	X	
Ferritin	X															
PT/INR and PTT	X					X[j]	X[j]		X[j]		X		X		X	

Procedure	Screening (up to 28 days before Day 1)	Intervention period										Follow-up period			ED	Notes
		D1	D3[a]	D5[a]	D8[a]	D15	D29	D43	D57	D71	D85	D113	D141	D169		ED = Early Discontinuation
					W1	W2	W4	W6	W8	W10	W12	W16	W20	W24		
12-lead ECG	X															
Blood type[h]	X						X[j]					X		X		
Adverse events		←==========→														
Concomitant medications		←==========→														
Serum pregnancy test (WOCBP only)	X	X[o]														WOCBP = Women of childbearing potential
Urine pregnancy test (WOCBP only)							X[j]		X[j]		X	X	X	X	X	
Serum immunoglobulin levels	X	X[j]				X[j]	X[j]		X[j]		X	X		X	X	
Efficacy and biomarkers																
Complete blood count[p]	X	X[j]			X	X[j]	X[j]	X[j]	X[j]	X[j]	X	X	X	X	X	
LDH, haptoglobin, total bilirubin, and reticulocytes[p]	X[u]	X[j]	X		X	X[j]	X[j]	X[j]	X[j]	X[j]	X	X	X	X	X	
PGIC, CGI-I, CGI-E[t]					X	X[j]	X[j]		X[j]		X	X	X	X	X	
PGIS, CGI-S[t]		X[j]			X	X[j]	X[j]		X[j]		X	X	X	X	X	
FACIT-fatigue scale		X[j]						X[j]			X			X		

Procedure	Screening (up to 28 days before Day 1)	Intervention period										Follow-up period			ED	Notes
		D1	D3[a]	D5[a]	D8[a]	D15	D29	D43	D57	D71	D85	D113	D141	D169		ED = Early Discontinuation
					W1	W2	W4	W6	W8	W10	W12	W16	W20	W24		
Genetic sample		X[j]														
Vaccine serologies[i]		X[j]									X			X	X	
Direct antiglobulin test		X[j]					X[j]		X[j]		X			X	X	
T, B, NK cell panel[k]		X[j]	X		X	X[j]	X[j]				X	X	X	X	X	
Plasmablast panel[n]		X[j]				X[j]					X			X		
Bone marrow biopsy/aspirate[l]	X											X				
Sample for RNAseq[r]		X[j]	X[s]			X[j]			X[j]		X			X		
Pharmacokinetics																
PK (isatuximab)		P00[j]	P01	P02	P03	P04[j]	P05[j]	P06[j]	P07[j]	P08[j]	P09	P10	P11	P12		
Antidrug antibodies		AB00[j]					AB01[j]				AB02			AB03[m]	X	

a Visits on Days 3, 5, and 8 may be performed with a home nursing service.

b Includes details regarding DAT positivity, anti-RBC antibodies (if known), and treatment history including current therapy.

c Includes at minimum an assessment of the skin, lungs, cardiovascular system, and abdomen, as well as weight and height (height only measured at screening). Physical exams may be performed on an ad hoc basis at other visits as per the discretion of the investigator based on the assessment of AEs.

d On Day 1, vital signs will be assessed prior to isatuximab administration and 1 hour, 2 hours, and 4 hours after administration. On Day 15, vital signs will be assessed prior to isatuximab administration and 1 hour and 2 hours after administration. On other days of isatuximab administration, vital signs will assessed prior to isatuximab administration and 1 hour after administration.

e The first 3 participants in the study (Part A, Cohort 1) will receive the D1 and D15 doses only. Retreatment of these participants may occur as per Section 6.6.1. In that case, participants will follow the SoA as above except for visits at Days 3 and 5. All safety assessments as well as complete blood count, LDH, haptoglobin, total bilirubin, reticulocytes, and ADA will be performed as per the SoA. The other efficacy, biomarker, and pharmacokinetic assessments will not be performed.

f Hepatitis B and C testing includes: HBsAg, anti-HBs, anti-HBc (total and IgM, followed by HBV DNA in case of anti-HBc positivity), anti-HCV Ab, and HCV RNA (if anti-HCV Ab is positive). Need for SARS-CoV-2 testing to be determined for each site, and should be a molecular test. If HBV vaccination will be started before the first study administration, anti-HBs should be monitored at 1, 2, and 3 months after the end of vaccination.

g See Section 10.2 for the list of tests to be performed. An FSH should be performed at screening to confirm menopausal status if applicable.

h Blood type and phenotype if not obtained within the past 1 month. The blood bank needs to be informed that the participant is receiving treatment with an anti-CD38 antibody and a potential interference with the Coombs test is possible.
i Titers for measles, mumps, tetanus, and diphtheria.
j To be performed prior to isatuximab administration.
k Includes TBNK, T Cell 3, and isatuximab NK/NKT panels for flow cytometry.
l Optional and for participants in Part B only; the screening bone marrow biopsy/aspirate may be performed any time during the screening period before the first isatuximab dose. The post-treatment bone marrow biopsy/aspirate may be performed after Week 12 and throughout the follow-up period.
m Participants with positive ADA at the EOS visit or upon early discontinuation, who during the study experienced an AE potentially related to ADA, will continue to be followed for up to 6 months after the last isatuximab dose. Follow-up may include additional ADA measurements
n If plasmablasts are not detectable at baseline on Day 1, no further plasmablast panels will be performed.
o Performed prior to drug administration. If the result of a serum test will not be available in a reasonable timeframe prior to drug administration, a urine pregnancy test is acceptable.
p Samples for CBC, haptoglobin. LDH, total bilirubin and reticulocytes should be sent to local laboratories.
q Pre-medication for infusion reactions is to be given prior to the first two isatuximab administrations, as described in Section 6.1.
r The decision to collect samples for RNAseq will be determined by the Sponsor prior to the start of Part B. If collected, it will be collected for participants in Part B only.
s If the Day 3 visit is performed at home, an RNAseq sample will not be collected.
t PGIC, CGI-I, CGI-E, PGIS, and CGI-S to be collected in Part B only.
u Indirect bilirubin can be used instead of total bilirubin for screening as per inclusion criteria I02b.

2 INTRODUCTION

Isatuximab is an IgG1 monoclonal antibody directed against CD38, a signal-transducing receptor and multifunctional ectoenzyme expressed on hematopoietic cells. Plasma cells, the primary antibody-producing cells of the body, express the highest density of CD38. Isatuximab is currently approved for the treatment of relapsed refractory multiple myeloma (RRMM; multiple myeloma is a cancer of plasma cells) in combination with pomalidomide and dexamethasone, and is also being developed for the treatment of other advanced malignancies, including solid tumors and lymphomas. Plasma cells, which produce approximately 1000 antibodies per second per cell (1), are believed to play a central role in autoimmune diseases in which autoantibodies directly contribute to pathogenesis (2). By targeting the plasma cell, isatuximab may have a role in the treatment of autoimmune diseases.

Warm autoimmune hemolytic anemia (wAIHA) is the most common type of autoimmune hemolytic anemia. It is mediated by autoantibodies that target antigens on red blood cells (RBC). These antibodies optimally react with their antigens at 37°C, thus the designation “warm”. Approximately half of wAIHA cases are primary, without an apparent underlying disorder, and approximately half are secondary, typically associated with systemic lupus erythematosus or lymphomas. wAIHA can be quite severe, requiring frequent blood transfusion, and has a reported mortality rate of 11% (3). There are currently no approved therapies for wAIHA. First-line therapy typically consists of glucocorticoids, followed by rituximab then splenectomy and other immunosuppressive agents (such as azathioprine, mycophenolate mofetil, cyclosporine, and cyclophosphamide). Limited options exist for those who do not have an adequate response to these interventions.

2.1 STUDY RATIONALE

The anti-CD38 antibody isatuximab targets antibody-producing plasma cells, which express a high density of CD38. Isatuximab treatment may decrease anti-RBC autoantibody levels in individuals with wAIHA, thereby decreasing RBC destruction and increasing hemoglobin levels. The first part of this study will assess safety and determine the isatuximab dose for this patient population. The second part of the study will assess efficacy.

2.2 BACKGROUND

Among antibody-producing cells, plasma cells are unique in that they are long-lived (lifespan of months to years), reside primarily in the spleen, bone marrow, and inflamed tissue, and do not express CD20, the target of rituximab (2). Neither conventional immunosuppressive therapies nor rituximab deplete plasma cells. As a result, there has been significant interest in the use of anti-CD38 therapies in diseases in which antibodies play a significant role in pathogenesis. Currently there are 5 ongoing trials investigating anti-CD38 monoclonal antibodies for the treatment of autoimmune or antibody-mediated diseases. These diseases include: antibody-mediated rejection in the setting of kidney (NCT04294459) and heart (NCT04088903) transplantation, myasthenia gravis (NCT04159805), systemic lupus erythematosus (NCT03724916), and persistent primary immune thrombocytopenia (NCT04278924).

wAIHA is characterized by anti-RBC autoantibodies, which directly result in RBC destruction through Fc-related mechanisms such as antibody-dependent cell-mediated cytotoxicity (ADCC) or complement fixation. The diagnostic test for wAIHA is the direct Coombs test (also called the direct antiglobulin test (DAT)), which detects antibodies on the surface of RBCs. This test is positive in over 99% of wAIHA patients, as compared to less than 1% of the general population (4). The depletion of autoantibodies in wAIHA should therefore directly impact disease pathogenesis and result in improvement of anemia. In a Phase 3 clinical trial comparing the combination of rituximab and steroids to steroids alone, all participants who no longer harbored anti-RBC antibodies at Week 52 (as demonstrated by a negative DAT) also achieved a complete response (5).

First-line treatment for wAIHA is corticosteroids, which results in long-term remission in approximately 30% of patients (6). Rituximab is often introduced as second-line therapy. While approximately 85% of individuals with wAIHA respond to rituximab, with over 50% maintaining disease-free survival at 2 years (7), options are limited for those who do not. These patients typically undergo splenectomy or are treated with other immunosuppressive or cytotoxic agents such as cyclophosphamide, many of which have significant adverse effects. There has been accumulating evidence that patients with autoimmune hemolytic anemia who do not respond to rituximab have continued autoantibody production mediated by plasma cells. In wAIHA patients who failed to respond to rituximab and subsequently underwent splenectomy, plasma cells secreting anti-RBC autoantibodies were present in the spleen (8). The hypothesis that plasma cells are responsible for continued RBC destruction in patients who fail rituximab has been tested through the use of bortezomib, a proteasome inhibitor that causes apoptosis of plasma cells. In two case series, a total of 12 wAIHA patients who failed numerous therapies including rituximab were treated with bortezomib (9, 10). Overall, 9 of the 12 patients had a response to bortezomib (5 partial responses and 4 complete responses). Additionally, case reports describe the use of daratumumab, another anti-CD38 monoclonal antibody, in 4 patients with rituximab-refractory hemolytic anemia following hematopoietic stem cell transplantation (HSCT) (11, 12). These patients were treated with multiple therapies, including rituximab and bortezomib, but a sustained response was observed in 3 of the 4 patients only following daratumumab therapy. A case report also describes a wAIHA patient who responded to daratumumab after being refractory to azathioprine and rituximab (13). Thus, isatuximab represents a promising approach for the treatment of wAIHA, particularly for those patients who have previously failed prior therapies.

A detailed description of the chemistry and pharmacology of isatuximab, and its efficacy in the setting of RRMM and other hematological malignancies, is provided in the Investigator's Brochure and package insert.

2.3 BENEFIT/RISK ASSESSMENT

As of the cut-off date of 05 January 2020, it was estimated that approximately 1652 individuals have been treated with intravenous isatuximab in the setting of multiple myeloma and other malignancies, including various solid tumors. In general, isatuximab is well-tolerated. The most common adverse reactions for isatuximab are infusion reactions (IRs), which are clinically manageable.

Isatuximab has been investigated either as monotherapy or in combination with other anticancer agents in patients with hematological malignancies and other advanced malignancies. When isatuximab is given in combination with other anticancer agents, the overall safety profile of the combination appears consistent with the safety profile of each drug individually. The safety profile of isatuximab monotherapy has been assessed by a pooled analysis of monotherapy studies in 212 participants with multiple myeloma (TED10893 and TED14154). In these studies, the most common treatment emergent adverse events (TEAE), excluding the AEs corresponding to laboratory abnormalities, included IRs, fatigue, nausea, anemia, cough, upper respiratory infection, diarrhea, headache, and dyspnea. No safety data is available from healthy volunteers or non-oncology patient populations.

2.3.1 Infusion reactions

Infusion reactions occurred in 53.8% of the 212 participants assessed in studies TED10893 and TED14154. Almost all participants received pre-medication for infusion reactions. Approximately 98% of infusion reactions were Grade 1 or 2, with 2 Grade 3 and 6 Grade 4 reactions. There were no deaths. There was not a clear dose-response relationship for the incidence of IRs, but the incidence was higher at doses ≥10 mg/kg (56.8% of participants experienced an IR) than at doses <10 mg/kg (35.4% of participants experienced an IR). The majority of IRs occurred with the first infusion and all IRs were reported on the day of infusion. Among participants who received doses <10 mg/kg, no infusion reactions occurred after the second infusion.

The underlying mechanism of infusion reactions due to immune-cell directed monoclonal antibodies remains unclear, but these reactions appear to be reduced with subcutaneous administration (14). Approximately 50% of RRMM patients who receive intravenous daratumumab experience an IR, even in the setting of pre- and post-medication. In a study of daratumumab SC (also administered with pre- and post-medication), patients who received 1200 mg or 1800 mg of daratumumab SC had an IR incidence of 12.5% and 24.4%, respectively, significantly lower than the incidence seen with IV administration (15). In a healthy volunteer study of the anti-CD38 monoclonal antibody TAK-079, in which participants received maximum doses of 0.06 mg/kg IV and 0.6 mg/kg SC, no infusion reactions were reported (16). Two of 6 participants who received 0.6 mg/kg SC did have mild cytokine release syndrome, as demonstrated by minimal cytokine increases and the presence of mild clinical symptoms (headache, dizziness, and chills). Of note, no pre-medication or post-medication to prevent or reduce the incidence of infusion reactions was administered in that study.

Preliminary data for the incidence of infusion reactions for isatuximab SC is available from protocol TCD15484. As of March 2020, 11 participants with RRMM have completed the first cycle of isatuximab 1000 mg SC in combination with pomalidomide (1 cycle consists of 4 weekly isatuximab injections). Among these patients, there was only a single recorded infusion reaction (graded as mild), which occurred with the first infusion.

Overall, the available data for anti-CD38 antibodies suggest that infusion reactions occur less frequently when the antibody is administered subcutaneously and at low doses. In this study, participants will receive pre-medication before the first two administrations of isatuximab. Participants may also receive these medications prior to subsequent doses if deemed necessary by the Investigator, in consultation with the Sponsor.

2.3.2 Infections, COVID-19, and other risks

While plasma cells can produce pathogenic autoantibodies, they also produce protective antibodies, such as those that emerge following infection or vaccination. By depleting plasma cells, isatuximab has the potential to increase the risk of infection, although conclusions in this regard from RRMM studies are difficult as RRMM patients have an inherently increased risk of infection. Data collected from the use of the anti-CD38 monoclonal antibody daratumumab in the setting of RRMM has been conflicting. In one study with 30 RRMM patients, 4 weeks of daratumumab therapy did not significantly alter the levels of polyclonal IgG, although levels of IgA, IgM, and IgE did significantly decline (17). Additionally, 17 RRMM patients were vaccinated against *S. pneumoniae* and *H. influenzae* Type B during daratumumab therapy and had response rates similar to that of RRMM patients not treated with daratumumb (17). In another study, significant rates of hypogammaglobulinemia, a known risk factor for infection, were seen, and occurred as early as 4 weeks after the start of daratumumab in some patients (18 and communication with author). Internal data with isatuximab in RRMM patients has shown that patients with non-IgG myelomas treated with isatuximab for 6 months did not have significant declines in overall IgG levels, although IgA levels declined in patients with IgG myelomas. The effect of isatuximab on the production of anti-infective antibodies therefore remains uncertain.

If isatuximab does in fact decrease levels of antiviral antibodies, participants infected with SARS-CoV-2 during isatuximab treatment may experience a longer or more severe infection, or may not generate protective antibodies as a result of infection. Testing for SARS-CoV-2 infection during screening will be determined by the Investigators and Sponsor based on local guidelines and COVID-19 prevalence at each site. Participants known to have had COVID-19 prior to study entry must be fully recovered in order to be eligible for participation. Participants enrolled in the study will be counseled to avoid situations that may place them at increased risk for COVID-19. If a patient is diagnosed with COVID-19 during the study, isatuximab will be discontinued. If the participant is asymptomatic but has a positive SARS-CoV-2 test, the decision regarding discontinuation will be made by the Investigator in consultation with the Sponsor. Once the patient is fully recovered, the decision to restart treatment will be made by the Investigator and Sponsor.

The effect of isatuximab on vaccination responses is unknown. By targeting plasma cells, isatuximab may interfere with vaccine-elicited immune responses. However, a series of RRMM patients who received vaccinations against *S. pneumoniae*, *H. influenzae* type B, and seasonal influenza during daratumumab treatment produced protective IgG antibody titers (17). Thus, vaccination during isatuximab treatment may indeed elicit protective titers. Antibody titers for common vaccines will be measured before, during, and after isatuximab therapy. While SARS-CoV-2 vaccination may be administered at any time during the study, it is recommended that the final vaccine dose be administered at least 2 weeks prior to the first dose of isatuximab, or that the vaccine be administered 30 days or more after the final dose of isatuximab.

CD38 is expressed on other lymphoid and myeloid cells, but at densities lower than plasma cells. Isatuximab could affect these cell populations as well. Modulation of such cells could increase the risk of infection and the risk of malignancies. A higher rate of secondary primary malignancies was observed in multiple myeloma patients who received isatuximab, pomalidomide, and dexamethasone as compared to those who received pomalidomide and dexamethasone alone.

However, the rate of secondary malignancies among patients who received isatuximab was not higher than the background rate in multiple myeloma patients.

Based on its mechanism of action, isatuximab can cause fetal harm when administered to a pregnant woman by causing fetal immune cell depletion and decreased bone density.

Isatuximab may cause neutropenia. Higher rates of neutropenia and febrile neutropenia were observed in multiple myeloma patients treated with isatuximab, pomalidomide, and dexamethasone as compared to those who received pomalidomide and dexamethasone alone.

RBCs express CD38, but at significantly lower density than plasma cells. Worsening of anemia is not expected, and anemia was not reported in healthy volunteers who received the anti-CD38 monoclonal antibody TAK-079 (16). Because isatuximab binds to CD38 found on red blood cells, it may interfere with routine blood bank compatibility testing and cross-matching, resulting in a false-positive indirect Coombs test. This interference is limited to the minor blood groups. Isatuximab may also interfere with serum protein electrophoresis and immunofixation tests.

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

2.3.3 Risk assessment

Table 1 - Risk assessment

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
Infusion reactions	Infusion reactions are a common side effect of anti-CD38 monoclonal antibodies. However, these reactions appear to occur less frequently with subcutaneous administration and at lower doses.	Pre-medication for infusion reactions with diphenhydramine, famotidine, acetaminophen/paracetamol, and montelukast will be given prior to the first two administrations of isatuximab. Steroids (in addition to what the participant is already taking for wAIHA) will not be administered as such administration could confound the efficacy analysis. If an investigator wishes to continue pre-medication after the second isatuximab dose, this may be performed in consultation with the Sponsor.
Infection	Isatuximab may increase the risk of infection by depleting immune cells, particularly plasma cells, which produce antibodies. Data for the risk of infection with isatuximab derives primarily from multiple myeloma patients, who are at increased risk of infection as a result of their disease.	Serum immunoglobulin levels will be checked at screening and monitored throughout the study to detect instances of hypogammaglobulinemia. Participants with hypogammaglobulinemia may be treated with IVIg as per the investigator's discretion.

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
COVID-19	Isatuximab may decrease levels of antiviral antibodies and result in more severe infection, or prevent the development of immunity following infection.	The need for SARS-CoV-2 testing during screening will be determined by the Sponsor and the Investigators at each site. Participants will be counseled to avoid situations that may place them at increased risk for COVID-19. If a patient is diagnosed with SARS-CoV-2 during the study, isatuximab will be at least temporarily discontinued. If the participant is asymptomatic but has a positive SARS-CoV-2 test, the decision regarding discontinuation will be made by the Investigator in consultation with the Sponsor.
Embryo-fetal toxicity	Isatuximab can cause fetal harm when administered to a pregnant woman by causing fetal immune cell depletion and decreased bone density.	WOCBP are required to use contraception during the study and for 5 months after the last isatuximab dose. Pregnancy testing will be performed every 4 weeks during the study.
Neutropenia	Isatuximab may cause neutropenia	Complete blood counts will be monitored throughout the study.
Malignancy	Secondary malignancies were observed following isatuximab treatment in multiple myeloma patients	Patients will undergo clinical assessments for 14 weeks after the last isatuximab dose. Of note, patients with multiple myeloma have an increased rate of secondary malignancies, and isatuximab does not appear to increase this rate above background levels. Additionally, there is no evidence of an elevated risk of malignancies among wAIHA patients.
Interference with laboratory tests	Isatuximab may cause a false-positive indirect Coombs test and may interfere with serum protein electrophoresis and immunofixation tests	Blood typing will be performed prior to isatuximab dosing if not previously obtained within the past 1 month.

2.3.4 Benefit assessment

Individuals with wAIHA who are refractory to current therapies have substantial morbidity associated with their disease, including fatigue, exertional dyspnea, thromboembolism, and the need for frequent blood transfusions. Severe cases can be life-threatening. Treatment with isatuximab may improve hemoglobin levels and possibly resolve anemia in these individuals, resulting in sustained improvements in quality of life and potential long-term treatment-free remission.

2.3.5 Overall benefit: risk conclusion

Considering the measures taken to minimize risk to participants participating in this study, the potential risks identified in association with isatuximab are justified by the anticipated benefits that may be afforded to participants with wAIHA.

3 OBJECTIVES AND ENDPOINTS

Table 2 - Objectives and endpoints

Objectives	Endpoints
Primary	
• Part A: To evaluate the safety and tolerability of subcutaneous injections of isatuximab in adults with wAIHA.	• Standard clinical and laboratory parameters and adverse events.
• Part B: To evaluate the efficacy of the selected dose in adults with wAIHA.	• Overall response rate (response (R) or complete response (CR)) at Day 85. R is defined as an increase in hemoglobin by ≥2 g/dL from baseline and an absence of transfusion in the last 7 days and absence of rescue medications in the past 4 weeks. Biochemical evidence of hemolysis may still be present. CR is defined as hemoglobin ≥11 g/dL (women) or ≥12 g/dL (men), no evidence of hemolysis (normal bilirubin, LDH, haptoglobin, and reticulocytes), and absence of transfusion in the last 7 days and absence of rescue medication in the past 4 weeks.
Secondary	
Part A (Cohorts 2 and 3 only)	
• To evaluate the efficacy of isatuximab in adults with wAIHA.	• Overall response rate (response (R) or complete response (CR)) at Day 85. R is defined as an increase in hemoglobin by ≥2 g/dL from baseline and an absence of transfusion in the last 7 days and absence of rescue medications in the past 4 weeks. Biochemical evidence of hemolysis may still be present. CR is defined as hemoglobin ≥11 g/dL (women) or ≥12 g/dL (men), no evidence of hemolysis (normal bilirubin, LDH, haptoglobin, and reticulocytes), and absence of transfusion in the last 7 days and absence of rescue medication in the past 4 weeks.
• To evaluate the durability of response to isatuximab and time to response.	• Proportion of participants with durable hemoglobin response by Day 169. Durable response is defined as Hb level ≥10 g/dL with an increase from baseline of ≥2 g/dL on three consecutive evaluable visits during the study period; with absence of transfusion and no rescue medication during the period of 3 consecutive visits and for at least 7 days (transfusions) and 4 weeks (rescue medication) prior to the first consecutive visit. • Overall response rate at Day 169, median time to R or CR, median time to loss of R or CR (loss of R defined as hemoglobin <10 g/dL at two consecutive visits at least 7 days apart and initiation of new treatment for anemia or increase in steroid dose; loss of CR is defined as hemoglobin <11 g/dL (women) or <12 g/dL (men) at two consecutive visits at least 7 days apart), proportion of participants requiring rescue therapy (any wAIHA-directed therapy other than prednisone or transfusion) or splenectomy.

Objectives	Endpoints
• To evaluate the impact of isatuximab treatment on fatigue.	• FACIT-fatigue scale score at Day 85 and Day 169.
Part B	
• To evaluate the safety and tolerability of isatuximab in adults with wAIHA.	• Standard clinical and laboratory parameters and adverse events.
• To evaluate the durability of response to isatuximab and time to response.	• Proportion of participants with durable hemoglobin response by Day 169. Durable response is defined as Hb level ≥10 g/dL with an increase from baseline of ≥2 g/dL on three consecutive evaluable visits during the study period; with absence of transfusion and no rescue medication during the period of 3 consecutive visits and for at least 7 days (transfusions) and 4 weeks (rescue medication) prior to the first consecutive visit. • Overall response rate at Day 169, median time to R or CR, median time to loss of R or CR (loss of R defined as hemoglobin <10 g/dL at two consecutive visits at least 7 days apart and initiation of new treatment for anemia or increase in steroid dose; loss of CR is defined as hemoglobin <11 g/dL (women) or <12 g/dL (men) at two consecutive visits at least 7 days apart), proportion of participants requiring rescue therapy (any wAIHA-directed therapy other than prednisone or transfusion) or splenectomy.
• To evaluate the impact of isatuximab treatment on fatigue.	• FACIT-fatigue scale score at Day 85 and Day 169.
Parts A (all Cohorts) and B	
• To evaluate the effect of isatuximab on markers of hemolysis.	• Change from baseline in LDH, haptoglobin, reticulocytes, and total bilirubin at 1, 2, 4, 8, 12, and 24 weeks.
• To characterize the pharmacokinetic profile of isatuximab in adults with wAIHA.	• PK parameters after subcutaneous administrations (including C_{max} and $AUC_{0\text{-}2\ week}$).
• To evaluate the immunogenicity of isatuximab.	• Incidence and titer (if relevant) of anti-isatuximab antibodies.
Tertiary/Exploratory	
Parts A (all Cohorts) and B	
• To describe the effect of isatuximab on levels of circulating immune cells with high CD38 expression.	• Levels of plasmablasts and NK cells.
• To describe the effect of isatuximab on levels of circulating immune cells with moderate to low CD38 expression.	• Levels of B cells and T cell subsets and other cells types.
• To evaluate the PK/PD relationship.	• Relationship of PK parameters to hemoglobin levels and levels of plasmablasts and NK cells.
• To evaluate the effect of isatuximab on immunoglobulin levels.	• Total IgG, IgM, and IgA levels.
• To evaluate the effect of isatuximab on vaccine antibody titers.	• Measles, mumps, tetanus, and diphtheria titers.
• To evaluate genetic determinants of isatuximab response.	• Relationship between FcgrIII polymorphisms and other genes and isatuximab response. • Immune cell gene expression using RNAseq and/or scRNAseq.

Objectives	Endpoints
• To describe the effect of isatuximab on bone marrow plasma cells, particularly those producing anti-RBC antibodies.	• Levels of plasma cells from bone marrow biopsy in participants who have a biopsy/aspirate performed.
Part B only	
• To investigate the effect of isatuximab on quality of life	• Change in the following assessments: Patient Global Impression of Change (PGIC), Patient Global Impression of Severity (PGIS), Clinical Global Impression of Efficacy (CGI-E), Clinical Global Impression of Improvement (CGI-I), Clinical Global Impression of Severity (CGI-S)

3.1 APPROPRIATENESS OF MEASUREMENTS

The efficacy endpoints for this study are based on international consensus guidelines for the diagnosis and treatment of autoimmune hemolytic anemia (19). Similar endpoints have been used in randomized Phase 3 trials of rituximab in individuals with wAIHA (5, 6). Considering that the current study is a Phase 1b/2 study, the primary endpoint will be evaluated at 12 weeks (Day 85), as opposed to 1 year, as was done in the Phase 3 studies above. The durability of the response will be evaluated as a secondary endpoint at 24 weeks (Day 169).

4 STUDY DESIGN

4.1 OVERALL DESIGN

This is a Phase 1b/2 open-label, non-randomized, multicenter study to evaluate the safety, pharmacokinetics, and efficacy of subcutaneous isatuximab in adults with wAIHA. The study will be conducted in 2 parts: Part A for safety and dose-finding, and Part B for assessment of the efficacy of the selected dose regimen. Approximately 17 to 23 participants are expected to be enrolled, depending on the number of participants in Part A who receive the regimen chosen for Part B.

Part A will have 2 to 3 cohorts. Cohort 1 consists of 3 participants who will receive 2 doses of isatuximab 140 mg (1 mL) SC administered 2 weeks apart. Cohort 2 can open following a review of available safety, pharmacokinetic (PK), and pharmacodynamic (PD) data after the 3 participants in Cohort 1 complete the Day 43 visit. Cohort 2 will consist of 3 participants who will receive isatuximab SC given every 2 weeks through Day 71 (total of 6 doses). The dose for Cohort 2 may be 70 mg (0.5 mL), 140 mg (1 mL), or 280 mg (2 mL), determined based on the safety profile, PK, and PD observed in Cohort 1.

Once the 3 participants in Cohort 2 have completed the Day 85 visit, an analysis of the available safety, PK, and PD data will be performed, and a decision will be made to either enroll 3 participants as an additional optional dose-finding cohort (Cohort 3) in which a dose up to 560 mg (4 mL) can be investigated, or to open Part B. If Cohort 3 is enrolled, Part B will open once available safety, PK, and PD data through the Day 85 visit from those participants have been reviewed.

Participants in Cohort 1 who experience no response by the end of the treatment period, or a response that subsequently wanes while still in follow up, can be retreated, after completing the Day 43 visit, with 6 administrations of the dose selected for the Cohort 2, Cohort 3, or Part B. Such participants will continue to be followed for at least 24 weeks from the first retreatment dose, but their response to the additional doses will not be included for efficacy analyses.

For the review of data between each cohort, the safety data will consist of clinical and laboratory parameters and adverse events. Unacceptable toxicity is defined as any verified Grade 4 AE or laboratory abnormality (except infusion reactions [IRs]) occurring during the treatment period, unless due to the underlying disease or due to a cause unrelated to the IMP, if confirmed by the Sponsor and Investigators. PK data will include standard PK parameters, with a focus on isatuximab exposure (C_{max} and $AUC_{0\text{-}2\ week}$). PD data will include hemoglobin levels, markers of hemolysis, and immune cell profiling.

A decision to de-escalate the dose between cohorts will primarily be based on safety signals, while a decision to dose escalate will primarily be based on an insufficient hemoglobin response. Additional PD and PK data will be used to help guide these decisions. While it is anticipated that dose selection for each cohort will occur after all participants in the previous cohort have completed the Day 43 (Part A, Cohort 1) or Day 85 (Part A, Cohorts 2 and 3) visits, in certain circumstances such decisions may be made earlier if clear safety or efficacy signals emerge. All

decisions regarding dose levels and the opening of new cohorts will be made by Sponsor representatives and the Principal Investigator at dose selection meetings. See Section 10.1.5 for the composition of the dose selection committee.

Part B will consist of 8 to 14 participants who will receive isatuximab SC every 2 weeks for a total of 6 doses, at a dose to be determined by the totality of safety, PK, an PD data available from all participants in Part A. The maximum allowable dose in Part B is 560 mg. Approximately 14 participants in the study will receive the isatuximab regimen selected for Part B. Thus, the number of participants in Part B may range from 8 to 14, depending on the number of participants in Part A who received that same regimen in the second or third cohort.

All participants will receive isatuximab subcutaneously. The screening period is 28 days, followed by a treatment period of 42 days (6 weeks) for Cohort 1 or 84 days (12 weeks) for the other participants in the trial. All participants will be followed for at least 24 weeks from the first isatuximab dose. The total length of the study, including screening, is 28 weeks.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

This study was designed to select and evaluate a dose of isatuximab that may offer substantial benefit for individuals with wAIHA who have failed prior therapies. Considering that the study population is rare and often without alternative treatment options, the starting dose for the study was selected with the goal that it would deplete at least 70%-80% of plasma cells (see Section 4.3).

While isatuximab is generally well-tolerated in RRMM patients, the first 3 participants in this study (Cohort 1) will receive only 2 doses as an initial evaluation of safety. The maximum allowable dose in this study, 560 mg, represents approximately 50% of the dose utilized in RRMM, as individuals with wAIHA have considerably less CD38 target abundancy than RRMM patients.

Participants in Part A who received the regimen selected for Part B will be included in the efficacy analysis. Thus, the number of participants in Part B may range from 8 to 14 to obtain approximately 14 participants overall who receive the regimen selected for Part B. The study was designed in this manner to maximize the contribution of each participant for this rare population.

Hemoglobin levels, which constitute the primary endpoint of the study, are a direct measure of disease activity.

4.2.1 Participant input into design

Participants were not directly involved in the design of the trial, but input was received from physicians who care for patients with wAIHA who are refractory to available therapies.

4.3 JUSTIFICATION FOR DOSE

The starting dose for this study (140 mg) was determined by simulations that incorporated in vitro data and data derived from RRMM patients treated with isatuximab, and through a comparison of doses utilized in different populations with the anti-CD38 antibody TAK-079.

In in vitro depletion experiments, different doses of isatuximab were added to plasmablasts isolated from healthy volunteers and individuals with autoimmune disease. Based on these experiments, the target plasma isatuximab concentration required to result in a 70%-80% reduction in plasmablasts was conservatively set to 1 μg/mL (internal data).

Simulations were then performed utilizing this target isatuximab concentration. These simulations were based on a population PK model developed in RRMM patients treated with isatuximab monotherapy at doses ranging from 1 to 20 mg/kg IV. Additional parameters included rates of subcutaneous absorption for monoclonal antibodies in general and preliminary data from isatuximab administered subcutaneously, and the interindividual variability of isatuximab observed in RRMM patients. The assumption was made that wAIHA patients will have significantly less target abundancy than RRMM patients, and therefore significantly less target-mediated drug disposition (TMDD). The simulation considered scenarios of no TMDD as well as 10%, 25%, and 50% of the maximum elimination rate (Vmax, which corresponds to the degree of TMDD) seen in RRMM patients.

These simulations demonstrated that a dose of 140 mg (2 mg/kg) administered every 2 weeks would achieve levels consistently above the target threshold in most patients even in the setting of moderate TMDD (25% Vmax of RRMM).

The isatuximab dose selected for this trial is also consistent with available data from studies conducted with the anti-CD38 monoclonal antibody TAK-079, which has been tested in healthy volunteers and RRMM patients. The doses of TAK-079 tested in healthy volunteers ranged from 0.0003-0.06 mg/kg IV and from 0.03-0.6 mg/kg SC. The dose of 0.6 mg/kg SC demonstrated the greatest PD effect, with a >90% reduction in plasmablasts (16). In a Phase 1b study in RRMM patients, fixed doses of 45-600 mg SC (0.6-8.6 mg/kg) were tested. The maximum PD effect was observed at 300 mg SC (4.3 mg/kg) (20). A comparison of these studies reveals that the dose that resulted in the maximum PD effect in healthy volunteers was approximately 14% of the dose at which a maximum PD effect was observed in RRMM patients. The amount of CD38+ cells in wAIHA patients treated with steroids is similar to that of healthy volunteers (8). Thus, a dose of an anti-CD38 antibody shown to have a significant PD effect in healthy volunteers would also be expected have a significant PD effect in wAIHA patients. The isatuximab monotherapy dose shown to have the maximum PD effect is 20 mg/kg (21). The starting dose for the current trial, 140 mg (2 mg/kg) is 10% of that dose, similar to the ratio of the TAK-079 healthy volunteer and RRMM doses.

In an ongoing study evaluating isatuximab SC in combination with pomalidomide and dexamethasone in RRMM patients (TCD15484), doses of 1000 mg and 1400 mg SC are being tested. Thus, the starting dose in this study (140 mg SC) represents 10%-14% of the dose currently being tested in RRMM patients receiving isatuximab subcutaneously.

The number of doses of an anti-CD38 antibody required for a sustained response in autoimmune diseases in general and wAIHA in particular is unknown. In the case reports cited above in which daratumumab was administered for hemolytic anemia as a result of HSCT, it was administered weekly at the oncology dose (16 mg/kg) for a total of 4-11 doses (11, 12). In current studies of TAK-079 for myasthenia gravis and primary immune thrombocytopenia, TAK-079 is being administered weekly for a total of 8 weeks.

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 Day 169 visit.

The end of the study is defined as the date of the last visit of the last participant in the study.

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 years of age, inclusive, at the time of signing the informed consent.

Type of participant and disease characteristics

I 02. Males and females with a confirmed diagnosis of primary wAIHA or systemic lupus erythematosus (SLE)-associated wAIHA (without other SLE-related manifestations apart from cutaneous and musculoskeletal manifestations) who meet the following criteria:

a) Hemoglobin level <10 g/dL at Screening.

b) Hemolysis (haptoglobin ≤40 mg/dL and total or indirect/unconjugated bilirubin above the upper limit of normal).

c) Positive direct antiglobulin test (DAT) (IgG or IgG + complement C_{3d} pattern or IgM warm autoantibodies [positive dual DAT]).

I 03. Participants who have previously failed to maintain a sustained response after treatment with corticosteroids (corticosteroid-refractory or corticosteroid-dependent primary wAIHA).

I 04. Part A only: Participants who have previously failed to maintain a sustained response after treatment with rituximab (or other anti-CD20 monoclonal antibodies). The last dose of the anti-CD20 antibody must have been administered at least 12 weeks before enrollment.

Part B: Participants who have had an insufficient response to at least 1 prior therapy in addition to corticosteroids (splenectomy is regarded as a prior therapy).

Note: For criteria specific to participants enrolled in France, see Appendix 7 (Section 10.7)

I 05. Eastern Cooperative Oncology Group (ECOG) performance status Grade 2 or lower.

I 06. Up-to-date vaccination status as per local guidelines.

Contraception

I 07. Contraceptive use by men or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. Additionally:

a) Male participants must be surgically sterile for at least 90 days or agree when sexually active with female partners of childbearing potential to use a male condom for 5 months after the last dose of isatuximab.

b) Female participants must be post-menopausal, surgically sterile, or be established on (≥3 months prior to screening) and agree to continue to use the same highly effective method of birth control for 5 months after the last dose of isatuximab. Highly effective methods of contraception include intrauterine device (IUD; Mirena®), established use of oral, implanted, or transdermal hormonal method of contraception associated with inhibition of ovulation, bilateral tubal ligation, or permanent birth control via the Essure procedure. Participants who practice true abstinence, because of the participant's lifestyle choice (eg, the participant should not become abstinent just for the purpose of study participation) are exempt from contraceptive requirements. Periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods) and withdrawal are NOT acceptable methods of contraception.

Informed Consent

I 08. Capable of giving signed informed consent as described in Appendix 1 (Section 10.1) of the protocol 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. Clinically significant medical history or ongoing chronic illness that would jeopardize the safety of the participant or compromise the quality of the data derived from his or her participation in the study as determined by the Investigator.

E 02. Serious infection that required hospitalization within 3 months prior to enrollment.

E 03. Secondary wAIHA from any cause including drugs, lymphoproliferative disorders, infectious or autoimmune disease (SLE without other SLE-related manifestations apart from cutaneous and musculoskeletal manifestations is allowed), or active hematologic malignancies. Participants with positive antinuclear antibodies but without a definitive diagnosis of an autoimmune disease are allowed.

E 04. History of coagulation or bleeding disorders (Evans Syndrome is allowed).

E 05. Uncontrolled or active HBV infection: Participants with positive HBsAg and/or HBV DNA. Of note:

- Patient can be eligible if anti-HBc IgG positive (with or without positive anti-HBs) and HBsAg and HBV DNA are negative.
  - If anti-HBV therapy in relation with prior infection was started before initiation of IMP, the anti-HBV therapy and monitoring should continue throughout the study treatment period.
- Participants with negative HBsAg and positive HBV DNA observed during screening period will be evaluated by a specialist for start of anti-viral treatment; study treatment could be proposed if HBV DNA becomes negative and all the other study criteria are still met.

Active HCV infection: positive HCV RNA and positive anti-HCV. Of note:

- 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 RNA without antiviral therapy for HCV are eligible.

E 06. HIV infection.

E 07. Positive SARS-CoV-2 molecular test (if COVID-19 testing required).

E 08. Serum gammaglobulin levels <3 g/L.

E 09. Ferritin levels below the lower limit of normal.

E 10. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) >3 x ULN.

E 11. Prothrombin time (PT/INR) or activated partial thromboplastin time (aPTT) above the ULN and deemed to be clinically significant by the Investigator.

E 12. WBC count < 3.0 x 10^9/L or neutrophil count < 1.5 x 10^9/L

E 13. Females who are pregnant, lactating, or considered unreliable with respect to contraceptive practice.

E 14. Recent history of substance abuse or mental illness.

E 15. Treatment for malignant disease within 3 years prior to enrollment.

Prior/concomitant therapy

E 16. Receipt of live vaccine(s) within 3 months prior to enrollment.

E 17. Concurrent treatment with corticosteroids, unless the participant has been on a stable daily dose for ≥15 days prior to enrollment.

E 18. Concurrent treatment with erythropoietin, unless the patient has been on a stable dose for 3 months prior to enrollment.

E 19. Concurrent use of iron supplementation, unless the patient has been on a stable dose for ≥30 days prior to enrollment.

E 20. Treatment with cyclophosphamide within 4 weeks prior to enrollment.

E 21. Treatment with cytotoxic drugs (other than cyclophosphamide) within 12 weeks prior to enrollment.

E 22. Treatment with non-cytotoxic, immunomodulatory drugs (including but not limited to Cyclosporine, Sirolimus, Tacrolimus, Idelalisib, Ibrutinib), excluding biologic agents, within 4 weeks prior to enrollment.

E 23. Treatment with any biologic agent within 12 weeks prior to enrollment.

E 24. Use of prescribed or over-the-counter medications, supplements, vitamins, and/or herbal remedies within 2 weeks before enrollment which, in the judgment of the Investigator, may adversely affect the participant's welfare or the integrity of the study results.

Prior/concurrent clinical study experience

E 25. Concurrent treatment with other experimental drugs or participation in another clinical trial with any investigational drug within 30 days or 5 half-lives, whichever is greater, prior to treatment start.

E 26. Known allergy to any of the study medications, their analogues, or excipients in the various formulations of any agent.

Other exclusions

E 27. Participant not suitable for participation, whatever the reason, as judged by the Investigator, including medical or clinical conditions, or participants potentially at risk of noncompliance to study procedures.

E 28. Participants who are employees of the clinical study site or other individuals directly involved in the conduct of the study, or immediate family members of such individuals (in conjunction with Section 1.61 of the ICH-GCP Ordinance E6).

5.3 LIFESTYLE CONSIDERATIONS

No lifestyle restrictions are required for this study in addition to any restrictions that may be in place as a result of the participant's disease.

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered in the study. 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 serious adverse event (SAE).

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

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

All details of preparation and administration of isatuximab are provided in the Pharmacy Manual. Details of the IMP and diluted solution storage conditions are provided in the Pharmacy Manual.

Table 3 - Overview of IMP administered

Type	Drug
Dose formulation	Solution for subcutaneous administration
Unit dose strength(s)	140 mg/mL isatuximab, 9 mM histidine, 110 mM L-Arginine monohydrochloride, 0.4% (w/v) Poloxamer 188 and 2% (w/v) sucrose, pH 6.2. Each vial contains a nominal content of 1960 mg of isatuximab C1P3F3.
Dosage level(s)	Part A, Cohort 1: 140 mg every 2 weeks x 2 Part A, Cohort 2: 70 mg, 140 mg, or 280 mg every 2 weeks x 6, based on results from Cohort 1 Part A, Cohort 3, and Part B: Dose administered every 2 weeks x 6; dose level to be determined based on results from prior Cohorts; the dose will not exceed 560 mg
Route of administration	Subcutaneous route
Use	Experimental
IMP and NIMP	IMP
Packaging and labeling	Study Intervention will be provided in one glass vial per box. Each vial and box will be labeled according regulatory country requirement.
Current/Former name(s) or alias(es)	Isatuximab SAR650984

Non-investigational medicinal products

Pre-medication for prevention of infusion reactions will be administered prior to the first two (2) administrations of isatuximab for all participants. Premedication will consist of the following regimen:

Diphenhydramine, famotidine, acetaminophen/paracetamol, montelukast

- Route of administration: Oral
- Dose regimen: To be administered approximately 15 to 30 minutes (and never >60 minutes) prior to isatuximab
  - Montelukast 10 mg orally

- Acetaminophen/paracetamol 650 to 1000 mg orally
- Famotidine 40 mg orally (or equivalent)
- Diphenhydramine 25-50 mg orally (or equivalent)

The above medications may be used post-treatment for any infusion reactions that occur. If an investigator wishes to continue pre-medication after the second isatuximab dose, this may be performed in consultation with the Sponsor.

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 (deficiency in condition, appearance, pertaining documentation, labeling, expiration date, etc) must be promptly notified to the Sponsor. Some deficiencies may be recorded through a complaint procedure (see Section 8.3.7).

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 DTP 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

This is an open-label and non-randomized study; participants who meet all the inclusion criteria and none of the exclusion criteria will be eligible for inclusion in the study. Each participant will be registered and receive an incremental identification number per site corresponding to his/her order of enrollment in the study.

6.4 STUDY INTERVENTION COMPLIANCE

6.4.1 Treatment accountability and compliance

Administration of the study treatment 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 for patient and destroyed or returned to the Sponsor. The packaging batch number (IP00xxxxx) must be recorded on the drug accountability form.

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

6.4.2 Return and/or destruction of treatments

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

The Investigator must not destroy the unused IMP unless Sanofi provides written authorization. Further guidance and information for the accountability purpose of use and unused study interventions are provided in the pharmacy manual.

6.5 CONCOMITANT THERAPY

Any medication 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

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

Participants who experience an infusion reaction may be treated post-injection with the medications listed in Section 6.1, as well as additional medications, if deemed necessary by the investigator.

The SARS-CoV-2 vaccine is permitted during the study, as per local standard of care, investigator discretion, and local labels. If feasible, it is preferable that the last dose of the SARS-CoV-2 vaccine be administered at least 2 weeks prior to the first dose of isatuximab, or for the vaccine to be administered 30 days or more after the final dose of isatuximab.

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

If antiviral therapy for HBV or HCV was started before initiation of IMP and the patient was eligible for the trial, the antiviral therapy for HBV or HCV should continue throughout the treatment period as recommended by a specialist.

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 participants with resolved infection*), study treatment will be held and a specialist consulted for initiation of anti-viral treatment and monitoring of the patient. Restart of study treatment should be agreed between sponsor, investigator and specialist (hepatologist) if infection is controlled. Close monitoring of ALT and AST should continue up to study treatment discontinuation. HBV DNA to be monitored as per 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.*

6.5.1 Rescue therapy

The use of rescue medications is allowable during the study. The date and time of rescue medicine as well as the name and dosage regimen of the rescue medication/intervention must be recorded.

6.6 DOSE MODIFICATION

Dose modification is not allowed within a cohort, with the exception of participants in Cohort 1, who may be re-dosed with the dose selected for Cohort 2, Cohort 3, or Part B if they experience no response or a response that subsequently wanes.

6.6.1 Retreatment criteria

Participants in Cohort 1 may receive additional study interventions if they meet retreatment criteria and agree to be retreated. The retreatment criteria are as follows:

- No response in hemoglobin (R) by end of the treatment period (Day 43).
- A hemoglobin response (R) that subsequently wanes prior to the end of study, with hemoglobin falling below 10 g/dL on 2 occasions at least 7 days apart

These participants will be followed for a total of 24 weeks from the first retreatment dose, but the retreatment period will not be included in PK, PD, or efficacy analyses.

6.7 INTERVENTION AFTER THE END OF THE STUDY

There will be no further interventions following the end of the study.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

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 (definitive discontinuation). If study intervention is definitively discontinued, the participant will remain in the study to be evaluated for safety.

Pregnancy will lead to definitive treatment discontinuation in all cases.

Discontinuation of study intervention for abnormal liver function should be considered by the Investigator when a participant meets one of the conditions outlined in Section 10.6 or if the Investigator believes that it is in best interest of the participant.

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.

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 that could result in treatment discontinuation will be immediately rechecked for confirmation (within 24 hours) before making a decision regarding definitive discontinuation of the IMP for the concerned participant.

Handling of participants after definitive intervention discontinuation

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

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

All cases of definitive intervention discontinuation must be recorded by the Investigator in the appropriate pages of the electronic-case report form (e-CRF) when considered as confirmed.

7.1.2 Temporary discontinuation

Temporary intervention discontinuation may be considered by the Investigator because of suspected AEs or disruption of the clinical trial due to a regional or national emergency declared by a governmental agency (described in Section 8). For all temporary intervention discontinuations, duration should be recorded by the Investigator in the appropriate pages of the case report form (CRF) or eCRF.

Temporary discontinuation will occur for participants diagnosed with COVID-19. Once the patient is fully recovered, the decision to restart treatment will be determined by the Investigator and Sponsor.

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. 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 both from the study intervention and 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.

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 e-CRF 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 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 maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will be within a safe limit for human clinical trials as recommended by the local Institutional Review Boards and Ethics Committees. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

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

- A regional or national emergency declared by a governmental agency (eg, public health emergency, natural disaster, pandemic, terrorist attack) may prevent access to the clinical trial site.
- Contingency procedures are suggested below and in Section 7.1.2, Section 9.4, and Section 10.1.3 for an emergency that prevents access to the study site, to ensure the safety of the participants, to consider continuity of the clinical study conduct, protect trial integrity, and assist in maintaining compliance with Good Clinical Practice in Conduct of Clinical Trials Guidance. Sponsor agreement MUST be obtained prior to the implementation of these procedures for the duration of the emergency.
- During the emergency, if the site will be unable to adequately follow protocol mandated procedures, alternative treatment outside the clinical trial should be proposed, and screening/enrollment/randomization/administration of study intervention may be delayed.
- Attempts should be made to perform all assessments in accordance with the approved protocol to the extent possible. In case this is not possible due to a temporary disruption caused by an emergency, focus should be given to assessments necessary to ensure the safety of participants and those important to preserving the main scientific value of the study.

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

- If onsite visits are not possible, remote visits (eg, with home nurses, home health vendor, etc) may be planned for the collection of possible safety and/or efficacy data.
- If onsite visits are not possible visit windows may be extended for assessment of safety and/or efficacy data that cannot be obtained remotely.
- Use of local clinic or laboratory locations may be allowed.
- Contingencies implemented due to emergency will be documented.

8.1 EFFICACY ASSESSMENTS

The primary efficacy endpoint, overall response rate, is determined by hemoglobin levels and markers of hemolysis, which will be assessed by the central lab.

The FACIT-fatigue scale will be administered by investigators at each site as per the SoA.

8.2 SAFETY ASSESSMENTS

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

8.2.1 Physical examinations

- A physical examination will include, at a minimum, assessment of the skin, lungs, cardiovascular system, and abdomen. Height (at screening only) 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 adverse event.

8.2.2 Vital signs

- Temperature, pulse rate, respiratory rate, and blood pressure will be assessed.
- On Day 1, vital signs will be assessed prior to isatuximab administration and 1, 2, and 4 hours after administration. On Day 15, vital signs will be assessed prior to isatuximab administration and 1 and 2 hours after administration. On other days of isatuximab administration, vital signs will assessed prior to isatuximab administration and 1 hour after administration.
- If a participant has an IR, at the subsequent isatuximab administration vital signs will be assessed prior to administration and at 1, 2, and 4 hours after administration; for the following administration, vital signs will be assessed prior to administration and at 1 and 2 hours after administration; for the remaining administrations vital signs will be assessed prior to administration and at 1 hour after administration.

- 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 performed with the participant sitting and preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (eg, television, cell phones).

8.2.3 Electrocardiograms

- A 12-lead ECG will be obtained as part of the screening procedures (see Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals.

8.2.4 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 CRF. 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 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 CRF.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

Adverse events 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, particularly those that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study intervention or study (see Section 7).

8.3.1 Time period and frequency for collecting AE and SAE information

All SAEs will be collected from the signing of the informed consent form (ICF) and throughout the study.

All AEs will be collected from the time of first IMP administration and throughout the study, as specified in the SoA (Section 1.3).

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 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. All SAEs and AEs of special interest (as defined in Section 8.3.6), will be followed 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 provided 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 (IRB)/Independent Ethics Committees (IEC), and Investigators.
- Adverse events that are considered expected will be specified in the Investigator's Brochure.

- Suspected unexpected serious adverse reactions (SUSARs) are reported to regulatory authorities, Investigators, and IRBs/IECs as follows:
  - For SUSARs that are life-threatening or result in death, reporting is immediately to regulatory authorities, from the moment the Sponsor has the minimum criteria for reporting a suspected SAE/SUSAR and at the latest within 7 days in Eudravigilance.
  - For SUSARs, other than those that are life-threatening or result in death, reporting is no later than 15 days after first knowledge by the Sponsor.
- An Investigator who receives an Investigator safety report describing a SAE, SUSAR or any other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it and will notify the IRB/IEC, if appropriate according to local requirements. It is the responsibility of the Sponsor to assess whether an event meets the criteria for a SUSAR, and therefore, is expedited to regulatory authorities.

8.3.5 Pregnancy

- Details of all pregnancies in female participants and female partners of male participants will be collected after the start of study intervention and until the end of the study.
- 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 Adverse event of special interest

Adverse event of special interest

An adverse event of special interest (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
  - 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
  - An overdose (accidental or intentional) with the IMP is an event suspected by the Investigator or spontaneously notified by the participant and defined as at least twice the intended dose within the intended therapeutic interval.
- Increase in alanine transaminase (ALT) >3 x ULN

8.3.7 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

The Sponsor does not recommend specific treatment for an overdose.

In the event of an overdose, the Investigator/treating physician should:

1. Contact the Medical Monitor immediately.
2. Closely monitor the participant for any AE/SAE and laboratory abnormalities.
3. Document appropriately in the CRF.

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

8.5 PHARMACOKINETICS

8.5.1 Pharmacokinetic and immunogenicity sampling times and handling procedures

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

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

- The sampling times for isatuximab PK and ADA may be reduced during the course of the study based on updated knowledge of isatuximab behavior, upon notification from the Sponsor.

Refer to the separate Laboratory Manual for details concerning handling procedures.

8.5.2 Pharmacokinetic and immunogenicity bioanalytical method

A brief outline of the bioanalytical assay is provided in Table 4.

Table 4 - Summary of bioanalytical method for PK and immunogenicity assessment

Sample type	PK + anti-isatuximab antibody
Analyte	Isatuximab and anti-isatuximab antibody
Matrix	Plasma
Analytical technique	Immunoassay
Blood sample volume	3 mL per sample (1 sample for PK and 1 sample for ADA)
Site of bioanalysis	Labcorp Early Development Laboratories

Abbreviations: ADA = Anti-drug antibody; PK = Pharmacokinetic; UK = United Kingdom.

8.5.3 Pharmacokinetic parameters

The following PK parameters will be calculated with PKDMS software (Pharsight), using non-compartmental methods from plasma concentrations of isatuximab. The parameters will include, but may not be limited to the following:

Table 5 - List of pharmacokinetic parameters and definitions

Parameters	Isatuximab	Definition
C_{max}	X	Maximum concentration observed after the first infusion
t_{max}	X	Time to reach C_{max}
C_{last}	X	Last concentration observed above the lower limit of quantification after the first infusion
t_{last}	X	Time of C_{last}
C_{trough}	X	Concentration observed just before treatment administration during repeated dosing
AUC_{last}	X	Area under the plasma concentration versus time curve calculated using the trapezoidal method from time zero to time of the last concentration observed above the lower limit of quantification (ie, C_{last})
AUC_{0-T}	X	Area under the plasma concentration versus time curve calculated using the trapezoidal method over the dosing interval T (336 h)

8.6 PHARMACODYNAMICS

8.6.1 Immunophenotyping

Levels of immune cells with high CD38 expression (ie, plasmablasts and NK cells) and low CD38 expression (B and T cells, including TREG cells) will be assessed by flow cytometry at the time points listed in the SoA (Section 1.3). Additionally, optional bone marrow biopsies/aspirates may allow for the assessment of plasma cells within the bone marrow. Details on processes for collection and shipment of these samples can be found in the laboratory manual.

8.7 GENETICS

Peripheral blood will be collected for DNA isolation on Day 1 for an analysis of immune genetic determinants to isatuximab response, such as FcγRIII polymorphisms.

In the event of DNA extraction failure, a replacement genetic blood sample may be requested from the participant. Signed informed consent will be required to obtain a replacement sample unless it was included in the original consent.

See Appendix 5 (Section 10.5) for information regarding genetic research. Details on processes for collection and shipment and destruction of these samples can be found in the laboratory manual.

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 using RNAseq and/or single-cell RNAseq to evaluate the association of gene expression with the observed clinical response to isatuximab.

8.9 IMMUNOGENICITY ASSESSMENTS

Antibodies to isatuximab will be evaluated in plasma samples collected from all participants according to the SoA. Additionally, plasma samples should also be collected at the final visit from participants who discontinued study intervention or were withdrawn from the study. These samples will be tested by the Sponsor or Sponsor's designee.

Plasma samples will be screened for antibodies binding to isatuximab and the titer of confirmed positive samples will be reported. Other analyses may be performed to verify the stability of antibodies to isatuximab and/or further characterize the immunogenicity of isatuximab.

The detection and characterization of antibodies to isatuximab will be performed using a validated assay method by or under the supervision of the Sponsor. All samples collected for detection of antibodies to isatuximab will also be evaluated for isatuximab serum concentration to enable interpretation of the antibody data. Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of the study intervention(s). Samples may be stored for a

maximum of 5 years (or according to local regulations) following the last participant's last visit for the study at a facility selected by the Sponsor to enable further analysis of immune responses.

8.10 MEDICAL RESOURCE UTILIZATION AND HEALTH ECONOMICS

Not applicable.

8.11 USE OF BIOLOGICAL SAMPLES AND DATA FOR FUTURE RESEARCH

Future research may help further the understanding of disease subtypes, disease biology, related conditions, drug response and toxicity, and can help identify new drug targets or biomarkers that predict participant response to treatment. Therefore, data and biological samples will be stored and used for future research when consented to by participants unless prohibited by local laws or IRBs/IECs (in such case, consent for future use of sample will not be included in the local ICF).

For participants who consent to the storage and use of their data and remaining and/or extra clinical samples, data and samples may be used after the study ends for future research related either to the drug, the mechanism of action, and the disease or its associated conditions. Such research may include, but is not limited to, performing assessments on DNA, RNA, proteins or metabolites. If future research on genetic material is performed, this will also be limited to the purpose of addressing research questions related to the drug, the mechanism of action, the disease or its associated conditions.

In the event future research is conducted for other purposes, the study participants will be informed of those purposes and will be given means to object to those research projects. Data and samples will be used in compliance with the information provided to participants in the ICF Part 2 (future research).

All study participant data and samples will be coded such that no participant direct identifiers will be linked to them. Coded data and samples may be transferred to a Sponsor site (or a subcontractor site), which may be located outside of the country where the study is conducted. The Sponsor adopts safeguards for protecting participant confidentiality and personal data (see Section 10.1.4).

The samples will be stored for a maximum of 15 years after the end of the study. Any samples remaining at the end of retention period will be destroyed. If a participant requests destruction of his/her samples before the end of the retention period, the Investigator must notify the Sponsor (or its contract organization) in writing. In such case, samples will be destroyed and related coded data will be anonymized unless otherwise required by applicable laws.

Study participant coded data will be stored for future research for up to 25 years after the end of the study. If data are still considered of important scientific value after this period, coded data already available will be anonymized unless otherwise required by applicable laws (the same will apply to the data of a study participant who has requested the destruction of his/her samples). A participant's coded data sets provided to researchers for a specific research project will be available to the researchers for a maximum of 2 years after the end of their specific project (end of project is defined by publication of the results or finalization of the future research project report).

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

No formal statistical test will be performed.

9.2 SAMPLE SIZE DETERMINATION

9.2.1 Part A

The primary objective of Part A is to evaluate the safety and tolerability of isatuximab in adults with wAIHA based on standard clinical and laboratory parameters and adverse events. A maximum of 9 participants will be assigned to the IMP in up to three successive cohorts. No sample size computation was done; sample size is based upon empirical considerations.

9.2.2 Part B

The primary objective of Part B is to evaluate the efficacy of isatuximab in adults with wAIHA based on the Overall response rate (response (R) or complete response (CR)) at Day 85. Sample size calculations were performed to ensure reasonable accuracy for the estimation of the response rate. The maximal half-width (when a 50% response rate is observed) of the exact two-sided 95% confidence interval using Clopper-Pearson method is displayed for various sample sizes in Table 6.

Table 6 - Accuracy of the 95% confidence interval

N	Response rate	Lower limit	Upper limit	Half-width
10	0.5	0.187	0.813	0.313
12	0.5	0.211	0.789	0.289
14	0.5	0.230	0.770	0.270
16	0.5	0.247	0.753	0.253

A sample size of 14 participants will provide a half-width for the 95% confidence interval of less than 0.275 which is deemed reasonable.

In addition to participants assigned to the IMP in Part B, the assessment of the proof of concept will include participants from Part A who received the same dose and number of administrations as selected for participants in Part B. Overall, approximately 14 participants assigned to the IMP at the selected dose will be included in the primary analysis, comprised of 0 to 6 participants from Part A and 8 to 14 participants from Part B.

9.3 POPULATIONS FOR ANALYSES

The populations for analyses are defined in Table 7.

Table 7 - Populations for analyses

Population	Description
Screened	All participants who sign the ICF.
Efficacy	All participants exposed to the IMP (regardless of the amount of treatment administered).
Safety	All participants exposed to the IMP (regardless of the amount of treatment administered).
Pharmacokinetic	All participants exposed to the IMP (regardless of the amount of treatment administered), without any major or critical deviations related to IMP administration and for whom the PK data are considered sufficient and interpretable.
Pharmacodynamic	All participants exposed to the IMP (regardless of the amount of treatment administered), without any major or critical deviations impacting PD measurements, and for whom the PD data are considered sufficient and interpretable.
PK/PD population	All participants included in both the PK and the PD populations.

ICF: informed consent form, IMP: investigational medicinal product, PD: pharmacodynamic, PK: pharmacokinetic

9.4 STATISTICAL ANALYSES

The statistical analysis plan will be finalized prior to the database lock and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and secondary endpoints.

The impact of a regional or national emergency declared by a governmental agency (see Section 8) on study conduct will be summarized (eg, study discontinuation or discontinuation, delay, or 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.

9.4.1 General considerations

Unless otherwise stated, all statistical analyses of Part B will include participants from Part A assigned to six administrations of the IMP at the selected dose for Part B, in addition to participants from Part B, and they will be described under Part B in what follows. All data from Part A will also be analyzed by dose level group separately.

Descriptive analyses will include summary statistics (using n, mean, standard deviation, inter quartile range, median, minimum, and maximum) for quantitative variables or number and percentage of participants in each category for qualitative data.

Participants from Cohort 1 in Part A may be retreated after Day 43 under specific conditions. If any, these participants will be followed for a total of 24 weeks from the first retreatment dose for safety, but the retreatment period will not be included in PK, PD, or efficacy analyses other than listings. Safety data post retreatment will be described or listed separately.

9.4.2 Primary endpoint(s)

9.4.2.1 Part A

Table 8 - Primary endpoint analysis for Part A

Primary endpoint	Statistical analysis methods
Standard clinical and laboratory parameters and adverse events.	Descriptive summaries of Treatment-Emergent Adverse Events and Potentially clinically significant abnormalities.

All the safety analyses will be performed using the safety population from Part A, by dose level group.

The safety evaluation will be based upon the review of the individual values (clinically significant abnormalities), descriptive statistics (summary tables, figures) and, if needed, on statistical analysis (appropriate estimations, confidence intervals).

Potentially clinically significant abnormality (PCSA) values are defined as abnormal values considered medically important by the Sponsor, according to predefined criteria/thresholds based on literature reviews and defined by the Sponsor for clinical laboratory tests and vital signs (from sponsor's document BTD-009536 "Analysis and reporting of safety data from Clinical Trials through the Clinical Study Report", Appendix 3).

Adverse events will be graded according to the NCI-CTCAE v5.0 and related analyses will be provided by grades. For clinical laboratory evaluation, vital signs, and physical examination, analyses will be provided according to PCSA.

For all safety data, the following observation periods are defined and used for classification of AEs and determination of on-treatment PCSA values:

- The **pre-treatment period** is defined as the time between informed consent signature and the first IMP administration.
- The **treatment emergent (TE) period** is defined as the period from the first IMP administration up to 30 days after the last IMP administration.
- The **post-treatment period** is defined as the time starting after the TE period.

9.4.2.1.1 Adverse events

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA; version in use by the Sponsor at the time of database lock).

Adverse events will be classified into predefined standard categories according to chronological criteria:

- Pre-treatment AEs: AEs that occurred, worsened, or became serious during the pre-treatment period.

- Treatment-emergent AEs: AEs that occurred, worsened, or became serious during the treatment emergent period.
- Post-treatment: AEs that occurred, worsened, or became serious during the post-treatment period.

Treatment-emergent AEs will be assigned to the dose level group actually received.

The following AEs summaries will be generated with number (%) of participants experiencing at least one event by dose level group for the safety population. Multiple occurrences of the same event in the same participant will be counted only once in the tables, using the maximum (worst) grade by treatment phase. Summaries will be provided for all grades combined and for Grade ≥3 (including Grade 5):

- Overview of TEAEs: number and percentage of participants with any TEAE, any Grade ≥3 TEAEs, any serious TEAE, any TEAE leading to death, any TEAE leading to permanent intervention discontinuation, any TEAE of special interest (AESI).
- Summary of TEAEs by primary SOC, high level group term, high level term, and preferred term: number and percentage of participants with at least one TEAE.
- Summary of TEAEs by primary SOC and PT: number and percentage of participants with at least one TEAE.
- TEAEs will also be described according to seriousness, maximum intensity (ie, grade), relation to the IMP and action taken.
- Number and percentage of participants experiencing treatment emergent AESI will be presented by AESI category and PT.
- Post-treatment AEs: overview, summary of AEs and serious AEs by primary SOC and PT.

All AEs reported in the study will be listed, sorted by participant and onset date. Participants presenting TEAEs will be listed sorted by primary SOC and PT. Any deaths, serious adverse events of special interest and other significant AEs, any AEs leading to permanent intervention discontinuation, will be listed.

9.4.2.1.2 Laboratory data

For parameters with laboratory ranges and/or abnormality criteria (PCSA), analysis will be performed using all post-baseline assessments done during the TE period, including all unplanned and rechecked values. Counts of participants with PCSAs according to baseline status will be presented by dose level group. The same type of summary tables will be provided for out-of-normal laboratory range values.

Descriptive statistics of values and changes from baseline at each scheduled visit and graphs over time of key laboratory parameters will be provided for the intervention period and the follow-up period overall.

9.4.2.1.3 Vital signs and physical examinations

For all parameters with PCSA definition, counts of participants with PCSAs will be presented by dose level group, regardless of the baseline status. All post-baseline assessments done during the TE period, including all unplanned and rechecked values, will be taken into account.

Descriptive statistics of vital signs, ie, heart rate (HR), systolic and diastolic blood pressures (SBP and DBP), will be provided by dose level group on the value and change from baseline at each scheduled visit for the intervention period and the follow-up period overall.

In addition, graphs over time may be provided for heart rate and blood pressures.

9.4.2.2 Part B

Table 9 - Primary endpoint analysis for Part B

Primary endpoint	Statistical analysis methods
Overall response rate (response (R) or complete response (CR)) at Day 85: • R is defined as an increase in hemoglobin by ≥2 g/dL from baseline and an absence of transfusion in the last 7 days and absence of rescue medications in the past 4 weeks, without biochemical resolution of hemolysis. • CR is defined as hemoglobin ≥11 g/dL (women) or ≥12 g/dL (men), no evidence of hemolysis (normal bilirubin, LDH, haptoglobin, and reticulocytes), and absence of transfusion in the last 7 days and absence of rescue medication in the past 4 weeks	The proportion of overall response will be computed at Day 85 together with its exact 95% confidence interval using Clopper-Pearson method. Participants whose response at Day 85 is not evaluable, whatever the reason (eg, early discontinuation), will be considered as non-responders.

The primary analysis will be conducted in the efficacy population, which will be used as the denominator for computation of the response rate.

Sensitivity analysis

The overall response rate (including the breakdown for complete response and response) will be described at each scheduled visit of the intervention period.

The estimation of the response rate at D85 and its exact 95% confidence interval using Clopper-Pearson method will also be computed in participants who had an evaluable response at this visit.

Additional sensitivity analyses and subgroup analyses (eg, for primary wAIHA and SLE-associated wAIHA) may be performed and will be detailed in the SAP.

9.4.3 Secondary endpoint(s)

9.4.3.1 Part A (Cohorts 2 and 3 only)

9.4.3.1.1 Analysis of efficacy

The following analysis of clinical response and fatigue will be conducted in the efficacy population of Part A for Cohorts 2 and 3 only. Response data will be listed for participants from all cohorts.

Overall response rate at Day 85

The overall response rate (including the breakdown for complete response and response) will be described by dose level group at each visit of the intervention period including Day 85 and using the same approach for participants with a non-evaluable response as in Section 9.4.2.2.

Time to response and durability of response

The proportion of participants with durable hemoglobin response by Day 169 will be computed together with its exact 95% confidence interval.

The proportion of overall response will be computed at Day 169. Participants whose response at Day 169 is not evaluable, whatever the reason (eg, early discontinuation), will be considered as non-responders.

The overall response rate (including the breakdown for complete response and response) will be described by dose level group at each visit of the follow-up period.

The time to response (CR or R) will be computed as the time between the start of treatment until the first documented response (in days) and described by summary statistics (using n, mean, standard deviation, interquartile range, median, minimum, and maximum)

The time to loss of response (in days) will be computed as the time between the first documented response (CR or R) and the first documented loss of response (ie, neither R nor CR as detailed in Section 3) and described by summary statistics (using n, mean, standard deviation, interquartile range, median, minimum, and maximum). For participants still showing a response at the end of the follow-up period, the end date will be the last date where the response is assessed.

Depending on the number of responses, the time to response and the time to loss of response will be listed or described by dose level group in the subset of participants who achieved a response during the intervention period as well as in the subset of participants who achieved a response during the study including the follow-up period (if different).

The time to loss of CR (in days) will be computed as the time between the first documented CR and the first documented loss of CR (as detailed in Section 3) and described by summary statistics (using n, mean, standard deviation, interquartile range, median, minimum, and maximum). For participants still showing a CR at the end of the follow-up period, the end date will be the last date where the response is assessed.

Depending on the number of CRs, the time to loss of CR will be listed or described by dose level group in the subset of participants who achieved a CR during the intervention period as well as in the subset of participants who achieved a CR during the study including the follow-up period (if different).

The proportion of participants requiring rescue therapy (any wAIHA-directed therapy other than prednisone or transfusion) or splenectomy will also be described by dose level group.

Fatigue

Descriptive statistics of the FACIT-fatigue scale score will be provided for the value at each scheduled visit of the intervention and follow-up periods (including Day 85 and Day 169) and on the change from baseline by dose level group.

9.4.3.2 Part B

9.4.3.2.1 Analysis of safety

All the safety analyses will be performed using the safety population. Statistical analysis of safety data will be conducted following the same approach as described in Section 9.4.2.1.

9.4.3.2.2 Secondary efficacy endpoints

Analysis of secondary efficacy endpoints will be conducted in the efficacy population. Subgroup analyses (eg, for primary wAIHA and SLE-associated wAIHA) may be performed and will be detailed in the SAP.

Time to response and durability of response

The proportion of overall response at Day 169 and its exact 95% confidence interval using Clopper-Pearson method, the time to response and durability of response, and the proportion of participants requiring rescue therapy or splenectomy will be summarized, using the same approach and definitions as in Section 9.4.3.1.1.

Fatigue

Descriptive statistics of the FACIT-fatigue scale score will be provided for the value at each scheduled visit of the intervention and follow-up periods (including Day 85 and Day 169) and on the change from baseline.

In addition, a mixed-effect model for repeated measures will be implemented providing estimates and 95% confidence intervals at Day 85 and Day 169 for the change from baseline: the full model specifications will be provided in the SAP.

9.4.3.3 Parts A and B

9.4.3.3.1 Other secondary efficacy endpoints

Markers of hemolysis

To evaluate the effect of isatuximab on markers of hemolysis, the values and change from baseline at each scheduled visit in LDH, haptoglobin, reticulocytes, and total bilirubin will be described.

Hemoglobin

Descriptive statistics and graphs of hemoglobin values and change from baseline over time for each scheduled visit will be provided.

9.4.3.3.2 Analysis of pharmacokinetic parameters

Descriptive statistics (eg, mean, geometric mean, median, SD, SEM, CV, minimum, and maximum) for the pharmacokinetic parameters of isatuximab will be provided by dose level, under the responsibility of the Sanofi Pharmacokinetics, Dynamics and Metabolism (PKDM) department.

9.4.3.3.3 Immunogenicity

Anti-Drug Antibodies (ADA) incidence will be described. Individual ADA sample status (positive, negative or inconclusive) will be listed.

9.4.4 Tertiary/exploratory endpoint(s)

The analysis described below will be performed for Parts A and B.

9.4.4.1 Pharmacodynamic analysis

PD biomarkers (eg, levels of circulating immune cells, immunoglobulin levels, vaccine antibody titers, bone marrow plasma cells) will be described or plotted in the Pharmacodynamic population. Additional details will be provided in the SAP.

9.4.4.2 Pharmacokinetic/pharmacodynamic analysis

The analysis of PK/PD relationship (eg, relationship of PK parameters to hemoglobin levels and levels of plasmablasts and NK cells) will be described and reported separately.

9.4.5 Other safety analyse(s)

Any other safety analyses will be detailed in the SAP.

9.4.6 Other analyse(s)

Not applicable.

9.5 INTERIM ANALYSES

No formal interim analysis is planned. For Part A, a descriptive summary may be provided on key parameters of interest after each cohort for decision making on the dose.

The study analysis will be conducted in two steps. The first step analysis will be conducted when all participants in Part B have completed Day 85 (and including 30 days after the last IMP administration) or withdrawn from the intervention period. The final analysis will be conducted at the end of the study.

9.6 COMMITTEES OR OTHER REVIEW BOARDS

For details on Dose Selection Committee refer to Appendix 1 (Section 10.1.5).

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 Good Clinical Practice (GCP) Guidelines.
  - Applicable laws and regulations (eg, data protection law as General Data Protection Regulation - GDPR).
- 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. Determining whether an incidental finding should be returned to a participant and, if it meets the appropriate criteria, to ensure the finding is returned (an incidental finding is a previously undiagnosed medical condition that is discovered unintentionally and is unrelated to the aims of the study for which the tests are being performed). The following should be considered when determining the return of an incidental finding:
    - The return of such information to the study participant (and/or his/her designated healthcare professional, if so designated by the participant) is consistent with all applicable national, state, or regional laws and regulations in the country where the study is being conducted, and
    - The finding reveals a substantial risk of a serious health condition or has reproductive importance, AND has analytical validity, AND has clinical validity.
    - The participant in a clinical study has the right to opt out of being notified by the Investigator of such incidental findings. In the event that the participant has opted out of being notified and the finding has consequences for other individuals, eg, the finding relates to a communicable disease, Investigators should seek independent ethical advice before determining next steps.

  - In case the participant has decided to opt out, the Investigator must record in the site medical files that she/he does not want to know about such findings.
- 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.

As applicable, according to Directive 2001/20/EC, the Sponsor will be responsible for obtaining approval from the Competent Authorities of the EU Member States and/or Ethics Committees, as appropriate, for any amendments to the clinical trial that are deemed as "substantial" (ie, changes which are likely to have a significant impact on the safety or physical or mental integrity of the clinical trial participants or on the scientific value of the trial) prior to their implementation.

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 are required to sign a new ICF.

The ICF will contain a separate section that addresses the use of remaining mandatory samples or new extra 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 consent 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 consent.

For a regional or national emergency declared by a governmental agency, contingency procedures many implemented for the duration of the emergency (See Section 8).

The participant or their legally authorized representative may 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).

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 (General Data Protection Regulation). The study Sponsor is the Sanofi company responsible for ensuring compliance with this matter, when processing data from any individual who may be included in the Sanofi databases, including Investigators, nurses, experts, service providers, Ethics Committee members, etc.

When archiving or processing personal data pertaining to the Investigator and/or to the participants, the Sponsor takes all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

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 African American population for the 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 to the Sponsor.
- 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 as described in the informed consent.
- 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.

- 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.
- Participants must be informed that their study-related data will be used for the whole "drug development program", ie, for this trial as well as for the following steps necessary for the development of the investigational product, including to support negotiations with payers and publication of results.

Protection of data related to professionals involved in the study

- Personal data (eg, contact details, affiliation(s) details, job title and related professional information, role in the study, professional resume, training records) are necessary to allow Sanofi to manage involvement in the study and/or the related contractual or pre-contractual relationship. They may be communicated to any company of the Sanofi group ("Sanofi") or to Sanofi service providers, where needed.
- Personal data can be processed for other studies and projects. At any time, objection to processing can be made by contacting the Sanofi Data Protection Officer (link available at Sanofi.com).
- In case of refusal to the processing of personal data by or on behalf of Sanofi, it will be impossible to involve the professionals in any Sanofi study. In case the professionals have already been involved in a Sanofi study, they will not be able to object to the processing of their personal data as long as they are required to be processed by applicable regulations. The same rule applies in case the professionals are listed on a regulatory agencies disqualification list.
- Personal data can be communicated to the following recipients:
  - Personnel within Sanofi or partners or service providers involved in the study
  - Judicial, administrative and regulatory authorities, in order to comply with legal or regulatory requirements and/or to respond to specific requests or orders in the framework of judicial or administrative procedures. Contact details and identity may also be published on public websites in the interest of scientific research transparency
- Personal data may be transferred towards entities located outside the Economic European Area, in countries where the legislation does not necessarily offer the same level of data protection or in countries not recognized by the European Commission as offering an adequate level of protection. Those transfers are safeguarded by Sanofi in accordance with the requirement of European law including, notably:
  - The standard contractual clauses of the European Commission for transfers towards our partners and service providers,
  - Sanofi's Binding Corporate Rules for intra-group transfers.
- Professionals have the possibility to lodge a complaint with Sanofi leading Supervisory Authority, the "Commission Nationale de l'Informatique et des Libertés" (CNIL) or with any competent local regulatory authority.

- Personal data of professionals will be retained by Sanofi for up to thirty (30) years, unless further retention is required by applicable regulations.
- In order to facilitate the maintenance of Investigators personal data, especially if they contribute to studies sponsored by several pharmaceuticals companies, Sanofi participates in the Shared Investigator Platform (SIP) and in the TransCelerate Investigator Registry (IR) project (https://transceleratebiopharmainc.com/initiatives/investigator-registry/). Therefore, personal data will be securely shared by Sanofi with other pharmaceutical company members of the TransCelerate project. This sharing allows Investigators to keep their data up-to-date once for all across pharmaceutical companies participating in the project, with the right to object to the transfer of the data to the TransCelerate project.
- Professionals have the right to request the access to and the rectification of their personal data, as well as their erasure (where applicable) by contacting the Sanofi Data Protection Officer: Sanofi DPO - 54 rue La Boétie - 75008 PARIS - France (to contact Sanofi by email, visit https://www.sanofi.com/en/our-responsibility/sanofi-global-privacy-policy/contact).

10.1.5 Committee structure

Dose Selection Committee

The dose selection committee will determine the dose for Part A, Cohorts 2 and 3, and Part B. The committee will also determine whether to open Cohort 3. The committee will be comprised of (at a minimum) the Study Medical Manager, Clinical Research Director, Pharmacokineticist, Statistician, Global Safety Officer, and overall study Principal Investigator.

10.1.6 Dissemination of clinical study data

Sanofi shares information about clinical trials and results on publically 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.

Professionals involved in the study or in the drug development program

Sanofi may publicly disclose, and communicate to relevant authorities/institutions, the funding, including payments and transfers of value, direct or indirect, made to healthcare organizations and professionals and/or any direct or indirect advantages and/or any related information or document if required by applicable law, by regulation or by a code of conduct such as the "EFPIA Code on Disclosure of Transfers of Value from Pharmaceutical Companies to Healthcare Professionals and Healthcare Organisations".

10.1.7 Data quality assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- 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 CRF 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 reported on the CRF or 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 start and closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The Sponsor or designee reserves the right to close a 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

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the subject and should assure appropriate subject therapy and/or follow-up.

Dose limiting toxicity (DLT) and study stopping rules

DLT rules for Part A

- A DLT in Part A is defined as a Grade 3 or higher AE, unless clearly attributable to wAIHA or clearly unrelated to the study drug
- If 1 DLT occurs in any cohort, the dose for the next cohort cannot be increased
- If >1 DLT occurs in any cohort, the dose for the next cohort must be reduced

DLT rules for Part B

- A DLT in Part B is defined as a Grade 4 or higher AE, unless clearly attributable to wAIHA or clearly unrelated to the study drug
- If >1 DLT occurs in Part B, a dosing and enrollment hold will occur. The hold may be lifted if the benefit/risk ration of the study is still deemed to be favorable by applicable competent authorities

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

- Required laboratory tests are detailed in Table 10.
- Because of the likelihood of hemolysis in samples obtained from patients with wAIHA, hematology and hemolysis parameters (CBC, haptoglobin, LDH, total bilirubin, and reticulocyte count) which are critical to study endpoints should be performed in local laboratories. The remaining parameters should be performed at the central laboratory (Labcorp). It is important that samples for central and local analysis are obtained at the same time. Local laboratory results for the hematology and hemolysis parameters above must be entered into the eCRF. Additionally, local laboratory results performed in cases where the parameter could not be processed centrally or when used to make a study intervention decision or response evaluation must also 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 local regulations.
- Pregnancy testing, blood typing, and the Direct Antiglobulin Test (DAT) will be performed locally.

Table 10 - Protocol-required laboratory assessments

Laboratory assessments	Parameters
Hematology (local lab)	
	Platelet count
	Red blood cell (RBC) count
	Hemoglobin
	Hematocrit
	RBC indices:
	MCV
	MCH
	Reticulocytes
	White blood cell (WBC) count with differential:
	Neutrophils
	Lymphocytes
	Monocytes
	Eosinophils
	Basophils
	Markers of hemolysis:
	LDH
	Haptoglobin
	Total bilirubin
	Direct Antiglobulin Test
Clinical chemistry	
	Blood urea nitrogen (BUN)
	Creatinine
	Glucose (non-fasting)
	Potassium
	Sodium
	Calcium
	Aspartate aminotransferase (AST)/Serum glutamic-oxaloacetic transaminase (SGOT)
	Alanine aminotransferase (ALT)/Serum glutamic-pyruvic transaminase (SGPT)
	Alkaline phosphatase
	Total and direct bilirubin
	Total protein
Coagulation	
	PT/INR
	PTT
Other tests	
	Ferritin (Screening only)
	FSH (screening only, when applicable)
	Serology (screening only): HIV antibody, hepatitis B surface antigen (HBsAg), anti-HBs, anti-HBc (total and IgM, followed by HBV DNA in case of anti-HBc positivity), and hepatitis C virus antibody, hepatitis C virus RNA (if positive anti-HCV Ab)
	SARS-CoV-2 molecular test

Laboratory assessments	Parameters
	Quantitative immunoglobulins (IgA, IgG, IgM) Measles, mumps, tetanus, diphtheria titers
Routine urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick • Microscopic examination (if blood or protein is abnormal)

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

10.3.1 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:
  - Symptomatic and/or
  - Requiring either corrective treatment or consultation, and/or
  - 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.

- "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE.

Events NOT meeting the AE definition

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

10.3.2 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

b) Is life-threatening

- The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c) Requires inpatient hospitalization or prolongation of existing hospitalization

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

d) Results in persistent disability/incapacity

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

e) Is a congenital anomaly/birth defect

f) Other situations

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

10.3.3 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 CRF.
- It is **not** acceptable for the Investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by the 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 the 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 (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report to the 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 the 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 the Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the Investigator will provide the Sponsor with a copy of any post-mortem findings including histopathology.
- 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.

10.3.4 Reporting of SAEs

SAE reporting to the Sponsor via an electronic data collection tool

- The primary mechanism for reporting an SAE to the 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 the 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 in 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 post-menopausal 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:

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 below.

Table 11 - 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 - (oral, intravaginal, or transdermal) • Progestogen-only hormone contraception associated with inhibition of ovulation - (oral or injectable)
Highly effective methods that are user independent[a]
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation - Intrauterine device (IUD) - Intrauterine hormone-releasing system (IUS) • Bilateral tubal occlusion

Vasectomized partner
Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not and less than 1 year after vasectomy, additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.
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 treatment. 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.

COLLECTION OF PREGNANCY INFORMATION:

Male participants with partners who become pregnant

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

Female participants who become pregnant

- The Investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. The initial information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of a participant's pregnancy.
- The participant will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the Sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- Any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- A spontaneous abortion (occurring at <22 weeks gestational age) or still birth (occurring at >22 weeks gestational age) 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.

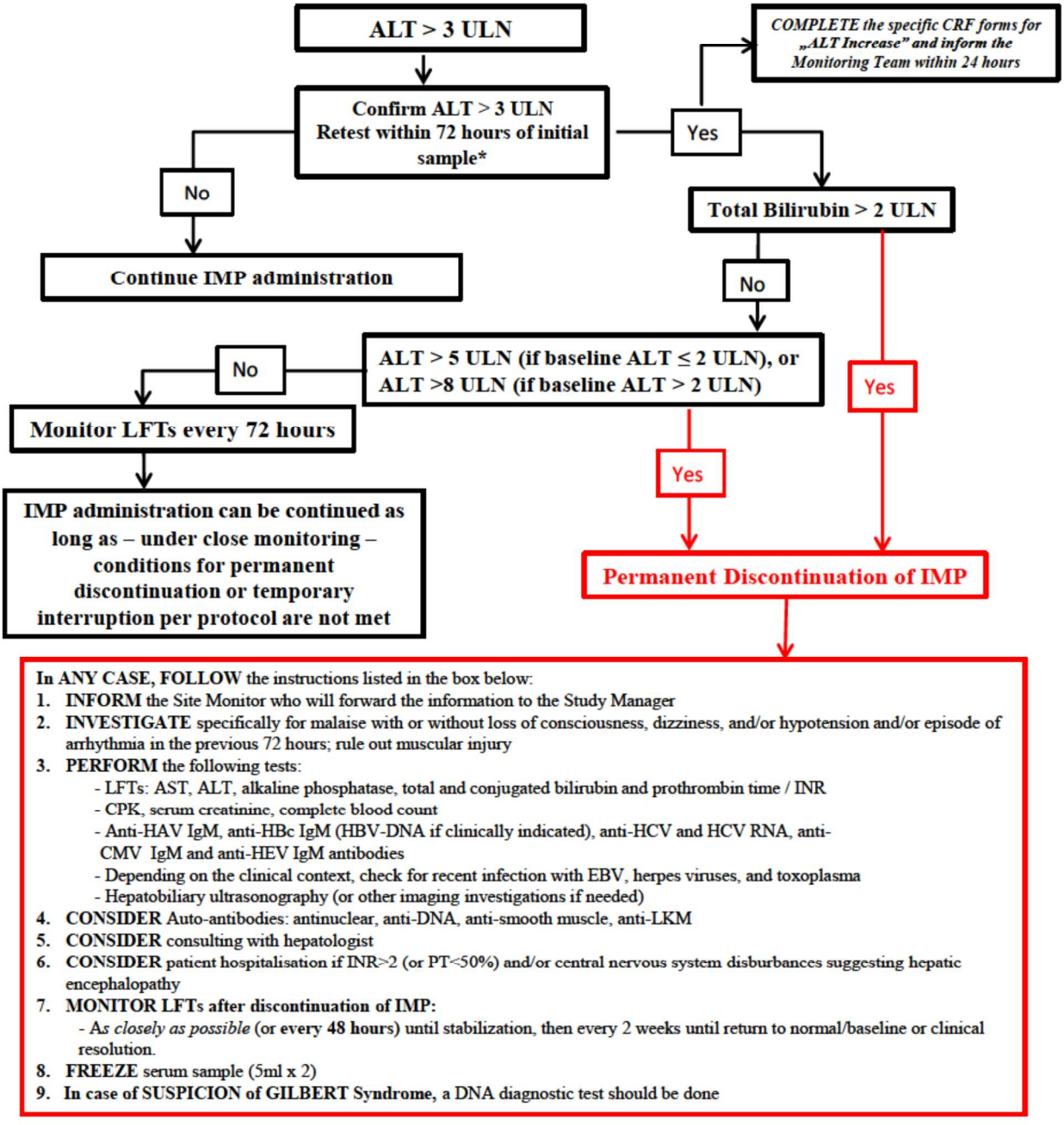
10.5 APPENDIX 5: GENETICS

Use/Analysis of DNA

- Genetic variation may impact a participant's response to study intervention, susceptibility to, and severity and progression of disease. Variable response to study intervention may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis from consenting participants.
- DNA samples will be used for research related to anti-CD38 antibodies or wAIHA and related diseases. They may also be used to develop tests/assays including diagnostic tests related to anti-CD38 antibodies or wAIHA. Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome (as appropriate).
- DNA samples will be analyzed for FcγRIII polymorphisms. Additional analyses may be conducted if it is hypothesized that this may help further understand the clinical data.
- The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to isatuximab or study interventions of this class to understand study disease or related conditions.
- The results of genetic analyses may be reported in the clinical study report (CSR) or in a separate study summary.
- The Sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on isatuximab or other anti-CD38 antibodies continues but no longer than 5 years or other period as per local requirements.

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

INCREASE IN ALT



In ANY CASE, FOLLOW the instructions listed in the box below:

1. **INFORM** the Site Monitor who will forward the information to the Study Manager
2. **INVESTIGATE** specifically for malaise with or without loss of consciousness, dizziness, and/or hypotension and/or episode of arrhythmia in the previous 72 hours; rule out muscular injury
3. **PERFORM** the following tests:
   - LFTs: AST, ALT, alkaline phosphatase, total and conjugated bilirubin and prothrombin time / INR
   - CPK, serum creatinine, complete blood count
   - Anti-HAV IgM, anti-HBc IgM (HBV-DNA if clinically indicated), anti-HCV and HCV RNA, anti-CMV IgM and anti-HEV IgM antibodies
   - Depending on the clinical context, check for recent infection with EBV, herpes viruses, and toxoplasma
   - Hepatobiliary ultrasonography (or other imaging investigations if needed)
4. **CONSIDER** Auto-antibodies: antinuclear, anti-DNA, anti-smooth muscle, anti-LKM
5. **CONSIDER** consulting with hepatologist
6. **CONSIDER** patient hospitalisation if INR>2 (or PT<50%) and/or central nervous system disburbances suggesting hepatic encephalopathy
7. **MONITOR LFTs after discontinuation of IMP:**
   - A*s closely as possible* (or **every 48 hours**) until stabilization, then every 2 weeks until return to normal/baseline or clinical resolution.
8. **FREEZE** serum sample (5ml x 2)
9. **In case of SUSPICION of GILBERT Syndrome,** a DNA diagnostic test should be done

*If unable to retest in 72 hours, use original lab results to decide on further reporting/monitoring/discontinuation.

Notes:

"Baseline" refers to ALT sampled at baseline visit; or if baseline value unavailable, to the latest ALT sampled before the baseline visit. The algorithm does not apply to the instances of increase in ALT during screening.

See Section 10.3 for guidance on safety reporting.

Normalization is defined as ≤ULN or baseline value, if baseline value is >ULN.

The workup for elevated liver tests may be performed either centrally or locally, depending on the clinical situation and the availability of each test.

10.7 APPENDIX 7: COUNTRY-SPECIFIC REQUIREMENTS

For participants enrolled in France:

I 04. Applicable for both Part A and Part B: Participants who have previously failed to maintain a sustained response after treatment with rituximab (or other anti-CD20 monoclonal antibodies). The last dose of the anti-CD20 antibody must have been administered at least 12 weeks before enrollment.

10.8 APPENDIX 8: ABBREVIATIONS

ADCC:	antibody-dependent cell-mediated cytotoxicity
AE:	adverse event
AESI:	adverse event of special interest
CR:	complete response
HSCT:	hematopoietic stem cell transplantation
IR:	infusion reaction
MedDRA:	medical dictionary for regulatory activities
NIMP:	noninvestigational medicinal product
PCSA:	potentially clinically significant abnormality
PD:	pharmacodynamics
PK:	pharmacokinetics
R:	response
RRMM:	relapsed refractory multiple myeloma
SLE:	systemic lupus erythematosus
TEAE:	treatment-emergent adverse event
TMDD:	target-mediated drug disposition
Vmax:	maximum elimination rate

10.9 APPENDIX 9: PROTOCOL AMENDMENT HISTORY

AMENDED PROTOCOL 05 (02 Dec 2021)

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

OVERALL RATIONALE FOR THE AMENDMENT

Changes in retreatment criteria for Cohort 1 and clarification of clinical laboratory testing.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis; 4.1 Overall Design; 6.6 Dose Modification; 6.6.1 Retreatment Criteria	Retreatment criteria for cohort 1 participants	Cohort 1 retreatment criteria too restrictive.
1.3 Schedule of activities, footnote p; 10.2 Appendix 2: Clinical Laboratory Tests	Clarification regarding use of local laboratories	Clarification

AMENDED PROTOCOL 04 (31 August 2021)

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

OVERALL RATIONALE FOR THE AMENDMENT

Changes in response to ANSM (French National Agency for Medicines and Health Products Safety) feedback and alignment with other wAIHA studies

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis; 3 Objectives and Endpoints; 9.4.2.2 Part 2	Absence of rescue medication for the past 4 weeks added as part of the definition of the endpoint for response and complete response	Alignment with other wAIHA studies
1.1 Synopsis; 3 Objectives and Endpoints	“Median” added to the definition of time to event endpoints	Clarification
1.1 Synopsis; 3 Objectives and Endpoints	Additional durability of response endpoint added	Alignment with other wAIHA studies
1.3 Schedule of Activities	Baseline chemistry and urinalysis on Day 1 added	Correction

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities; 3 Objectives and Endpoints	Quality of life questionnaires (PGIS, PGIC, CGI-E, CGI-I, CGI-S) added for Part B participants	Alignment with other wAIHA studies
5.1 Inclusion criteria I04; 10.7 Country-specific requirements	For both Parts A and B, participants enrolled in France must have previously failed to maintain a sustained response to rituximab or other anti-CD20 monoclonal antibodies	ANSM request
5.1 Inclusion criteria I07	Male contraception use extended to 5 months after the last isatuximab dose	ANSM request
5.2 Exclusion criteria E12	WBC and neutrophil cutoffs added instead of utilizing investigator judgement	ANSM request
8.3.4 Regulatory reporting requirements for SAEs	Updated reporting guidelines for SUSARs	ANSM request
8.5.2 Pharmacokinetic and immunogenicity bioanalytical method; 10.2 Appendix 2: Clinical laboratory tests	Covance acquired by Labcorp, name changed accordingly	Correction
9.4.3 Secondary endpoints	Clarifications as to the statistical methods and definitions of endpoints	Clarification
10.1.4 Data protection	Additional language regarding protection of data related to professionals involved in the study	Updated standard language
10.1.6 Dissemination of clinical study data	Additional language regarding professionals involved in the study or in the drug development program	Updated standard language
10.1.9 Study and site start and closure	Updated dose limiting toxicity and study stopping rules	ANSM request
10.10 Appendix 10: Questionnaires	Appendix containing the questionnaires to be used in this study added	Addition

AMENDED PROTOCOL 03 (05 May 2021)

This amended protocol (amendment 03) is considered to be not 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

Correction of inclusion criteria value.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
5.1 Inclusion criteria, criterion I02, b	Haptoglobin value corrected from ≤4 mg/dL to ≤40 mg/dL	The original value of ≤4 mg/dL was an error; the lower limit of

Section # and Name	Description of Change	Brief Rationale
		quantification for the assay is typically 10 mg/dL

AMENDED PROTOCOL 02 (01 March 2021)

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

OVERALL RATIONALE FOR THE AMENDMENT

Health authority feedback as well as clarifications and corrections

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of activities	LDH, haptoglobin, total bilirubin, and reticulocytes will be collected during screening	Correction
1.3 Schedule of activities, footnote l	Bone marrow biopsies/aspirates may only be performed for participants in Part B; clarification as to when the procedure can be performed	To limit performance of bone marrow biopsies/aspirates to when the final dose is established
1.3 Schedule of activities, footnote m	Antidrug antibody titers will be collected after the end of study only for participants who have positive ADA at the end of the study and experienced an AE during the study potentially related to ADA	Alignment with other internal studies
1.3 Schedule of activities, footnote r	The decision to collect samples for RNAseq will be determined by the Sponsor prior to the start of Part B. If collected, it will be collected for participants in Part B only	Feasibility constraints may not allow for the collection of these samples
1.3 Schedule of activities, footnote s	If the Day 3 visit is performed at home, a sample for RNAseq will not be collected	Operational complexity in processing and shipping this sample if collected at the participant's home
2.3.2 Infections, COVID-19, and other risks	Additional information on the impact of isatuximab on vaccine titers and SARS-CoV-2 vaccination	MHRA guidance on COVID-19 vaccination for clinical trials
5.1 Inclusion criteria, criterion I07	Mention of the use of a male condom plus spermicide removed	To align with the Clinical Trial Facilitation Group contraception guidelines
5.2 Exclusion criteria, criterion E05	Active HCV infection defined as positive HCV RNA and positive anti-HCV	Prior definition included "negative anti-HCV" which was incorrect
5.2 Exclusion criteria	E15 and E16 added	Hungarian health authority request
6.5 Concomitant therapy	Guidance on SARS-CoV-2 vaccination added	Clarification

Section # and Name	Description of Change	Brief Rationale
8.11 Use of biological samples and data for future research	Section added	Correction
10.1.9 Study and site start and closure	Additional criteria for study hold/termination	Paul Ehrlich Institute request
10.2 Appendix 2: Clinical laboratory tests	Clarification that blood typing is to be performed locally	Clarification
10.4 Appendix 4: Contraceptive guidance and collection of pregnancy information, Table 11	Double barrier method removed as an acceptable contraception method	To align with the Clinical Trial Facilitation Group contraception guidelines
10.6 Appendix 6: Liver safety	Clarification that the workup for elevated liver tests may be performed centrally or locally	Clarification
Throughout	Clarification that the bone marrow biopsy may be a biopsy or aspirate	Clarification
Throughout	Additional corrections to typography and formatting	

AMENDED PROTOCOL 01 (19 October 2020)

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

OVERALL RATIONALE FOR THE AMENDMENT

This amendment is in response to feedback from the U.S. FDA.

Protocol amendment summary of changes table

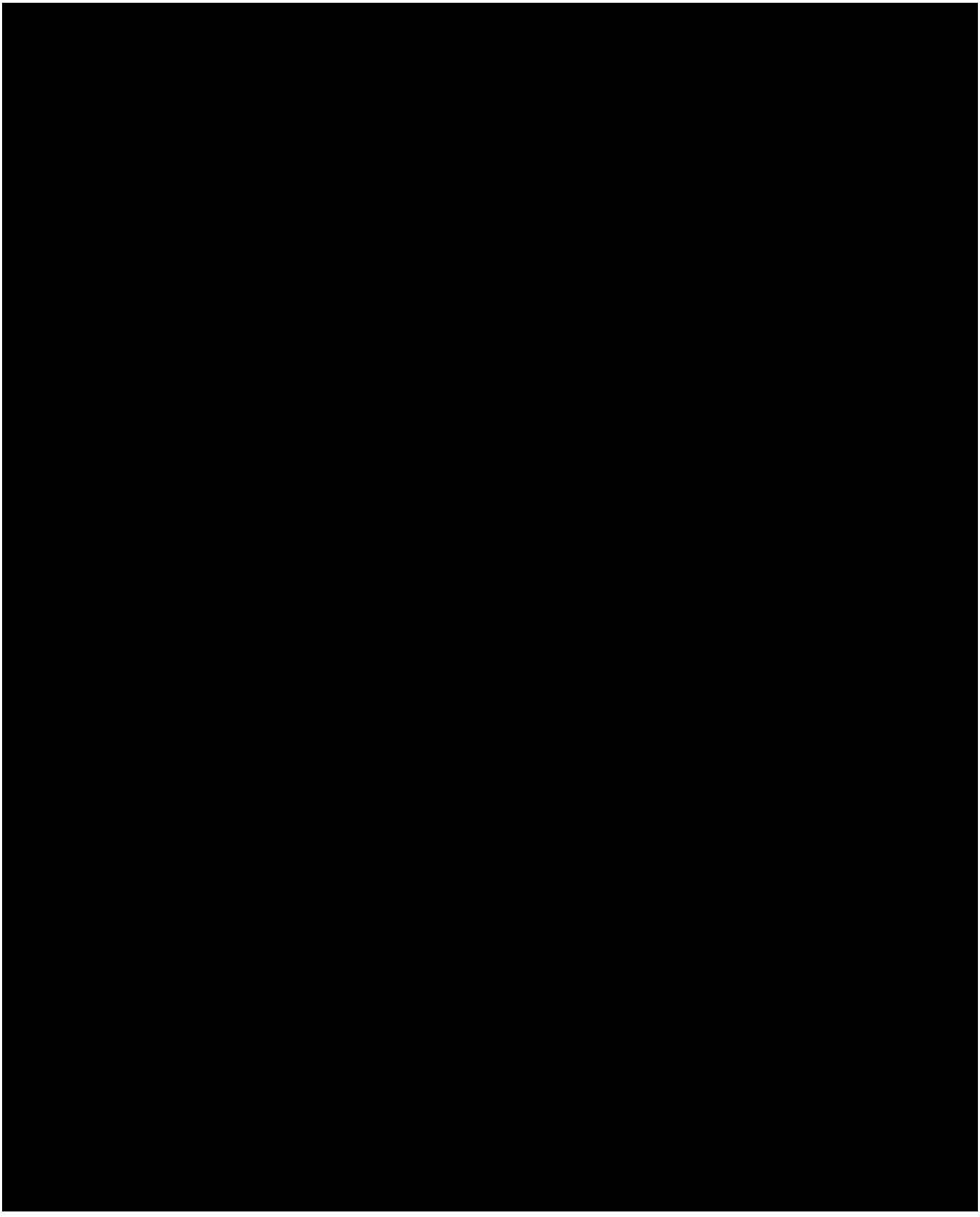
Section # and Name	Description of Change	Brief Rationale
Section 6.1 Study Intervention(s) Administered; Section 2.3 Benefit/Risk Assessment	In the prior version of the protocol, pre-medication for infusion reactions would only be instituted if deemed necessary by the Investigator/Sponsor. Pre-medications for infusion reactions will now be given prior to the first two doses of isatuximab for all participants.	Additional safety measure
Section 5.1 Inclusion Criteria	Length of contraception extended to 5 months after the last isatuximab dose for women of childbearing potential	Alignment with SARCLISA U.S. Package Insert
Section 2.3 Benefit/Risk Assessment	Potential risk of neutropenia clarified; language regarding potential risk of tumorigenicity, embryo-fetal toxicity, and interference with serum protein electrophoresis and immunofixation tests added	Alignment with SARCLISA U.S. Package Insert

10.10 APPENDIX 10: QUESTIONNAIRES

FACIT Fatigue Scale (Version 4)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

		Not at all	A little bit	Some-what	Quite a bit	Very much
H17	I feel fatigued	0	1	2	3	4
H12	I feel weak all over	0	1	2	3	4
An1	I feel listless ("washed out")	0	1	2	3	4
An2	I feel tired	0	1	2	3	4
An3	I have trouble starting things because I am tired	0	1	2	3	4
An4	I have trouble finishing things because I am tired	0	1	2	3	4
An5	I have energy	0	1	2	3	4
An7	I am able to do my usual activities	0	1	2	3	4
An8	I need to sleep during the day	0	1	2	3	4
An12	I am too tired to eat	0	1	2	3	4
An14	I need help doing my usual activities	0	1	2	3	4
An15	I am frustrated by being too tired to do the things I want to do	0	1	2	3	4
An16	I have to limit my social activity because I am tired	0	1	2	3	4



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