CLINICAL TRIAL PROTOCOL

Protocol title:	**An open-label study for sutimlimab in participants with cold agglutinin disease (CAD) who have completed the CARDINAL study (BIVV009-03/EFC16215, Part B) or CADENZA study (BIVV009-04/EFC16216, Part B) in Japan.**
Protocol number:	**LTS17352**
Amendment number:	**Not applicable**
Compound number (INN/Trademark):	**BIVV009 (sutimlimab)**
Brief title:	**Sutimlimab for the adult participants with cold agglutinin disease (CAD) who have completed Phase 3 studies (CARDINAL or CADENZA) in Japan.**
Study phase:	**Phase 3**
Sponsor name:	**Sanofi K.K.**
Legal registered address:	**3-20-2, Nishi Shinjuku, Shinjuku-ku, Tokyo 163-1488, Japan**
Monitoring team's representative name and contact information	

Regulatory agency identifier number(s):

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PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY

Document	Country/countries impacted by amendment	Date, version
Original Protocol		30 June 2021, version 1 (electronic 1.0)

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Not applicable.

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Protocol title:

An open-label study for sutimlimab in participants with cold agglutinin disease (CAD) who have completed the CARDINAL study (BIVV009-03/EFC16215, Part B) or CADENZA study (BIVV009-04/EFC16216, Part B) in Japan.

Brief title: Sutimlimab for the adult participants with cold agglutinin disease (CAD) who have completed Phase 3 studies (CARDINAL or CADENZA) in Japan.

Rationale:

Currently, no approved treatment is available for CAD. Clinical studies have been performed to demonstrate the efficacy and safety of sutimlimab. This study intends to fulfil an unmet need while Sanofi is seeking regulatory approval of sutimlimab by providing treatment for the participants in Japan with CAD who have completed CARDINAL or CADENZA studies.

Objectives and endpoints

Objectives	Endpoints
Primary	
• Evaluation of overall safety profile for sutimlimab	• Adverse event (AE) / serious adverse event (SAE) / adverse event of special interest (AESI)
Secondary	
• Not applicable	• Not applicable

Overall design:

Multi-center, single treatment-group study in Japan has an open label, repeated dose design.

Brief summary:

This is a multi-center, single treatment-group, open-label study to provide sutimlimab to the adult participants with CAD who have completed the CARDINAL or CADENZA studies, and benefitted from sutimlimab treatment in Japan.

- Study and treatment duration: the period between the participant's completion of the CARDINAL and CADENZA studies and sutimlimab or other appropriate CAD therapy still becoming commercially available to participants in Japan.

Number of participants:

Maximum 7 participants will be enrolled.

Intervention and duration:

Intervention: sutimlimab

Duration: The period between screening/baseline visit (upon the participant's completion* of the CARDINAL and CADENZA studies) and end of treatment with sutimlimab in this study. Determined by sutimlimab or other appropriate CAD therapy becoming commercially available to participants in Japan.

* "Completion" which means that participants completed the "End of Study" visit in Cardinal or Cadenza. Participants must complete the 9-week safety follow-up period as per protocol and then complete an "End of Study" visit.

Study intervention

Investigational medicinal product

- Formulation: sutimlimab will be supplied to the pharmacy in 25 mL glass vials containing 22 ml of 50 mg/mL sutimlimab with 10 mM sodium phosphate buffer, 140 mM NaCL, 0.02% polysorbate 80 (Tween80), and water for injection.
- Route of administration: Intravenous (IV) infusion
- Dose regimen: sutimlimab dose is 6.5 g for participants whose weight is ≥39 kg to <75 kg or 7.5 g for participants ≥75 kg. The dosing schedule consists of an initial dose (Day 0), followed by a dose one week later (Day 7), which is followed by a maintenance dose every other week beginning on Day 21.

Statistical considerations:

- **Primary endpoint: Evaluation of safety profile for sutimlimab**
  - Summarize all adverse event (AE), serious adverse event (SAE) and adverse event of special interest (AESI).
- **Main secondary endpoints:**
  - Not applicable.

Data Monitoring/Other committee:

Not applicable.

1.2 SCHEMA

Not applicable.

1.3 SCHEDULE OF ACTIVITIES (SOA)

Study visit	Screening/ Baseline	Treatment period				Safety Follow-up
	Day 0	Day 7	Day 21	Every 2 weeks after Day 21	Every 3 months after Day 21	9 weeks after Last Dose[h]
Visit windows			± 2 days	± 2 days	± 14 days	± 2 days
Written informed consent	X					
Demographic & baseline characteristics[a]	X					
Detailed medical history[b c]	X					
Inclusion/exclusion criteria	X					
Pregnancy test (if applicable)[d]	X		X	X Every 4 weeks after Day 21		X
Body weight and height	X				X Only weight	X Only weight
Physical examination, full	X					X
Physical examination, brief					X	
Vital signs (BP, PR, RR, oral temperature)	X				X	X
Hematology (local laboratory)	X				X	X
Clinical chemistry and urinalysis (local laboratory)	X				X	X
Auto immune disorder (including SLE) sign and symptom[e]	X				X	X
Study drug administration[f]	X	X	X	X		
Prior & concomitant medications including transfusions	X	X	X	X	X	X
Adverse events[g]	X	X	X	X	X	X

Abbreviation: BP = blood pressure, PR = pulse rate, RR = respiratory rate, SLE = systemic lupus erythematosus

a Age, Sex, Race, Height (cm), Weight (kg), BMI (kg/ m^2), presence or absence of CAD circulatory symptoms (Acrocyanosis or Raynaud's phenomenon, disabling circulatory symptoms), Hemoglobin, Total bilirubin and LDH (can be assayed by local lab. testing procedures)

b Ongoing and relevant AEs from CARDINAL study and CADENZA study should be recorded in medical history.

c New AEs that started between end of CARDINAL/CADENZA and start of this study should be recorded in medical history.

d Female of child-bearing potential only. Serum pregnancy test to be performed at Screening. Urine pregnancy test to be performed prior to study drug infusion on Day 0 and at Safety follow-up Visit. Repeat urine pregnancy test every 4 weeks during treatment period.

e Monitored for signs and symptoms of Auto immune disorder (including SLE) and evaluated appropriately.

f Sutimlimab doses of 6.5 g (if ≥39 kg to <75 kg) or 7.5 g (if ≥75 kg) based on participant's baseline body weight will be administered via IV infusion over ~60±5 minutes on Days 0, 7, and every other week thereafter during treatment period. Participants with underlying cardiopulmonary disease may receive a 2-hour infusion with Sponsor approval. If a participant misses a scheduled dose (outside of the 2-day window or >17 days since last dose), they must return to site (unscheduled visit) to receive another loading dose and then resume bi-weekly dosing schedule one week later.

g Adverse events will be recorded from the time the participant provides signed informed consent through the safety follow-up period.

h If participants switch to marketed drug, safety follow-up should be continued until the day of infusion of marketed drug or for 9 weeks, whichever comes first. In some cases, if the transition to marketed drug may occur without interruption in the every other week infusion schedule, this time period could be approximately 2 weeks.

2 INTRODUCTION

CAD is a type of autoimmune hemolytic anemia caused by IgM-induced complement classical pathway (CP) activation. The disease is characterized by the presence of autoantibodies called cold agglutinins that typically bind to the I antigen uniformly present on the surface of all red blood cells (RBCs). The autoantibodies bind in accordance to their thermal amplitude and results in agglutination of RBCs, resulting in symptoms such as acrocyanosis and Raynaud syndrome.

2.1 STUDY RATIONALE

Currently, no approved treatment is available for CAD. Clinical studies have been performed to demonstrate the efficacy and safety of sutimlimab. This study intends to fulfil an unmet need while Sanofi is seeking regulatory approval of sutimlimab by providing treatment for the participants with CAD who have completed CARDINAL and CADENZA studies and shown to benefit with sutimlimab treatment in Japan.

CARDINAL study

CARDINAL Part A was the pivotal 26-week, open-label, single-arm, Phase 3 study designed to evaluate the efficacy, safety, and tolerability of sutimlimab in participants with CAD with hemoglobin levels ≤10.0 g/dL and a recent history of blood transfusion (defined as at least 1 transfusion during the last 6 months prior to enrollment). CARDINAL Part B is running for 2 years following Last Participant Out (LPO) under Part A to provide supportive data on durability of response and long-term safety and tolerability.

CADENZA study

CADENZA Part A was the pivotal 26-week randomized, double-blind, placebo-controlled, Phase 3 study designed to evaluate the efficacy and safety of sutimlimab in symptomatic participants with CAD who have hemoglobin levels ≤10.0 g/dL and who do not have a recent history of blood transfusion. CADENZA Part B is running for 1 year following LPO under Part A to provides supportive data on durability of response and long-term safety and tolerability.

It is anticipated that participants could enter this study (LTS17352) immediately upon completion of the End of Study visit of CARDINAL and CADENZA studies Part B.

2.2 BACKGROUND

Sutimlimab is an investigational humanized monoclonal IgG 4 serotype antibody (mAb) directed against human complement factor complement component 1 s subcomponent factor (C1s), a key subcomponent complex that along with complement component 1 r subcomponent (C1r) and complement component 1 q subcomponent (C1q) sits at the apex of the CP. By inhibiting C1s, BIVV009 prevents activation of the CP, thereby hypothesized to stop the mechanism by which hemolysis occurs in CAD.

A review of clinical experience with sutimlimab is in the Investigator's Brochure (IB).

2.3 BENEFIT/RISK ASSESSMENT

Considering the measures taken to minimize risk to the participant entering this study, the potential risks associated with treatment with sutimlimab are justified by the anticipated benefits that may be afforded to this participant. Therefore, only participants who demonstrated benefit and without major safety concern during treatment in Cardinal/Cadenza will be considered for participation.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of sutimlimab may be found in the IB and informed consent form (ICF).

3 OBJECTIVES AND ENDPOINTS

Table 1 - Objectives and endpoints

Objectives	Endpoints
Primary	
• Evaluation of overall safety profile for sutimlimab	• Adverse event (AE) /serious adverse event (SAE) / Adverse event of special interest (AESI)
Secondary	
• Not applicable	• Not applicable

3.1 APPROPRIATENESS OF MEASUREMENTS

Clinical studies have been performed to demonstrate the efficacy and safety of sutimlimab. This study intends to fulfil an unmet critical need while Sanofi is seeking regulatory approval of sutimlimab by providing treatment for the participants with CAD who have completed CARDINAL and CADENZA studies in Japan and demonstrated benefit from treatment with sutimlimab.

4 STUDY DESIGN

4.1 OVERALL DESIGN

This Japanese single treatment-group, multi-center study has an open label, repeated dose design.

This study is intended to be in place until sutimlimab becomes commercially available in Japan, but Sanofi reserves the right to end this study at any time.

The participants can withdraw from this study at any time for any reason. Participants who were withdrawn from the study for whatever reason may not re-enter this study.

The participants may continue to receive sutimlimab until the earliest of: the participant's own voluntary withdrawal; this study ending; commercial treatment with sutimlimab becoming available to participants in Japan, or other appropriate therapy for CAD becomes available; or determination by the participant's physician that this treatment is no longer appropriate, or meeting any of the early termination criteria defined in Section 7.2.

The Sponsor reserves the right to end the study at any time.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

Parts A of the CARDINAL and CADENZA studies have been performed to assess the efficacy and safety of sutimlimab, Parts B of the CARDINAL and CADENZA studies are ongoing. This study is open-label extension study following completion of CARDINAL or CADENZA.

The objective of this study is to provide access to sutimlimab for the participants and to characterize the safety of sutimlimab. Sponsor will only enroll Japanese participants with CAD who have completed CARDINAL and CADENZA studies and shown to benefit with sutimlimab treatment. Therefore, the Sponsor will focus evaluation on safety outcomes (AE/SAE/AESI). Efficacy, pharmacodynamic, pharmacokinetic, and patient reported outcome assessments are not required/included.

4.3 JUSTIFICATION FOR DOSE

The same dose as used in CARDINAL and CADENZA studies was chosen. CARDINAL study has already confirmed safety and efficacy at below (1).

6.5 g for participants whose weight at baseline is ≥39 kg to <75 kg or 7.5 g for participants ≥75 kg at baseline.

The dosing schedule consists of an initial dose (Day 0), followed by a dose one week later (Day 7), which is followed by a maintenance dose every other week beginning on Day 21.

Participants who miss a dose (ie, outside the dosing window or >17 days since last dose) should return to the study site for an unscheduled visit 1 as soon as possible in order to receive an additional loading dose and then resume bi-weekly dosing schedule 1 week after the loading dose.

4.4 END OF STUDY DEFINITION

1. The study will continue until sutimlimab becomes commercially available to participants in Japan.
2. Other appropriate therapy for CAD becomes available, whichever comes first; or
3. The Sponsor ends the study.

The Sponsor reserves the right to end the study at any time.

The end of the study is defined as the date of the last visit in the study shown in the Schedule of Activities (SoA) for the last participant in the trial.

A participant is considered to have completed the study if he/she has completed all phases of the study including the last visit.

5 STUDY POPULATION

When the participant enters this clinical study, participant information should be recorded on the case report form (CRF).

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

Up to 7 participants are expected to be enrolled in this program.

5.1 INCLUSION CRITERIA

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

Age

I 01. Participant must be adults.

Type of participant and disease characteristics

I 02. Participants who have been enrolled in, and has completed Part B of CARDINAL or CADENZA study with demonstration of efficacy while on study considered by the investigator to be clinically meaningful

I 03. Participants who are ongoing diagnosis of CAD (previously also referred to as primary CAD)

I 04. Participants who continue to require treatment for CAD upon completion of participation in the previous study evidenced by return of CAD-related symptoms of anemia and/or deterioration on markers of hemolysis after the end of study visit following the 9-week safety follow up period. (9-week follow up period).

I 05. Participants who have acceptable benefit/risk profile:

a) No ongoing treatment emergent serious adverse events (TESAEs) related to sutimlimab.

b) No events rendering benefit/risk unfavorable if sutimlimab is continued, based on the treating physician's judgement.

I 06. Participant who has acceptable infection risk, including:

a) No active serious infection and/or active systemic encapsulated bacterial infection. Participants who have experienced a serious infection with encapsulated bacteria within the past 3 months are excluded.

b) Received vaccination for Neisseria meningitidis and Streptococcus pneumoniae within the prior 5 years.

I 07. Participants who have no available appropriate alternative therapy for CAD and not eligible for any recruiting clinical trial with open-label treatment of CAD

Weight

I 08. Body weight of ≥39 kg at Screening/baseline.

Sex, contraceptive/barrier method and pregnancy testing requirements

I 09. If female and of childbearing potential or male and sexually active, participant who is willing to abstain from heterosexual intercourse in accordance with her or his preferred and usual life style, or to use 2 acceptable, effective contraceptive methods, while participating in this study and for 4 weeks after the last infusion of sutimlimab.

Informed Consent

I 10. Capable of giving signed informed consent as described in Appendix 1 of the protocol which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

5.2 EXCLUSION CRITERIA

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

Medical conditions

E 01. Clinical diagnosis of systemic lupus erythematosus (SLE); or immune complex mediated autoimmune disorders

E 02. Participants who meet recent Rituximab and/or immunosuppressive therapy

a) Has received Rituximab monotherapy or similar immunosuppressive monotherapy therapies within the prior 3 months.

b) Has received Rituximab combination therapies (e.g., with bendamustine, fludarabine, ibrutinib, or cytotoxic drugs) within prior 6 months.

E 03. Any of the following medical conditions:

a) Active, serious intercurrent illness which will preclude enrolment until recovery is complete.

b) Pregnancy or breast-feeding

Other exclusions

E 04. End of Study visit in CARDINAL or CADENZA took place more than 3 months before baseline visit in this study.

E 05. Individuals accommodated in an institution because of regulatory or legal order; prisoners or participants who are legally institutionalized

E 06. 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 07. Participants 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)

E 08. Any specific situation during study implementation/course that may raise ethics considerations

E 09. Hypersensitivity reactions to sutimlimab or components thereof, or other allergy that, in the opinion of the Investigator, contraindicates participation in the study

5.3 LIFESTYLE CONSIDERATIONS

Not applicable.

5.4 SCREEN FAILURES

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

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. Rescreened participants should be assigned a new participant number for every screening event.

5.5 CRITERIA FOR TEMPORARILY DELAYING

Not applicable.

6 STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

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

6.1 STUDY INTERVENTION(S) ADMINISTERED

Table 2 - Overview of study interventions administered

Intervention label	sutimlimab
Intervention name	sutimlimab
Type	Biologic
Dose formulation	Liquid
Unit dose strength(s)	6.5 g or 7.5 g
Dosage level(s)	6.5 g for participants whose weight is ≥39 kg to < 75 kg or 7.5 g for participants ≥75 kg. The dosing schedule consists of an initial dose (Day 0), followed by a dose one week later (Day 7), which is followed by a maintenance dose every other week beginning on Day 21.
Route of administration	IV infusion
Use	experimental
IMP or NIMP	IMP
Packaging and labeling	Study Intervention will be provided in a kit carton box. Each sutimlimab vial is labeled with a vial label and there will be two types of kits: 6-vial kit and 1-vial kit labeled with a carton booklet label. These will be labeled as per country requirement.
Current/Former name(s) or alias(es)	Not applicable

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

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 sutimlimab (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 sutimlimab 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 sutimlimab and eliminate potential hazards.

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

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

Not applicable.

6.4 STUDY INTERVENTION COMPLIANCE

When participants are dosed at the study site, they will receive study intervention directly from the Investigator or designee, under medical supervision. The date and time of each dose (including start time, stop time, and time of interruption, in any) administered in the study site will be recorded in the source documents and recorded. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

6.5 DOSE MODIFICATION

Not applicable.

6.6 CONTINUED ACCESS TO INTERVENTION AFTER THE END OF THE STUDY

Post-study access to study medication will not be provided.

6.7 TREATMENT OF OVERDOSE

In the event of an overdose, the Investigator should:

- Contact the Sponsor immediately.
- Evaluate the participant to determine, in consultation with the Sponsor, whether study intervention should be interrupted or whether the dose should be reduced.
- Closely monitor the participant for any AE/SAE and laboratory abnormalities

- Document appropriately in the CRF.
- Report and submit as AESI.

6.8 CONCOMITANT THERAPY

Participants will refrain from participation in any other investigational study drug trial in which receipt of any investigational drug occurred within 5 half-lives or 30 days, whichever is longer, prior to Day 0 and during the entire study.

Any medication or vaccine (including over-the-counter or prescription medicines, recreational drugs, vitamins, and/or herbal supplements) or other specific categories of interest) 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 Sponsor should be contacted if there are any questions regarding concomitant or prior therapy.

Treatment with rituximab monotherapy or rituximab combination therapies (eg, with bendamustine, fludarabine, ibrutinib, or cytotoxic drugs) is prohibited.

Topical therapies without risk of systemic absorption may be allowed, and non-prescription medications for treatment of minor intercurrent illnesses (headache, viral upper respiratory tract infections, etc.) are permitted at the discretion of the Investigator. Hormonal contraception in female participants are allowed provided participants are receiving stable treatment ≥3 months prior to Screening. Any medication taken by the participant during the study, along with its strength, frequency of dosing, and reason for its use, will be documented in the paripant’s source data and the CRF.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

Treatment may be discontinued temporarily or permanently. Any treatment discontinuation should be documented.

7.1.1 Permanent discontinuation

In rare instances, it may be necessary for a participant to permanently discontinue study intervention. If study intervention is permanently discontinued, the participant will be evaluated for safety. Such participants will not be eligible to re-enter the study. See the SoA for data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed.

Handling of participants after permanent intervention discontinuation

Participants will be followed-up over the 9-week follow up period, 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 permanent discontinuation of intervention, the participants will be assessed using the procedure normally planned for the last dosing day with the sutimlimab.

All cases of permanent intervention discontinuation must be recorded by the Investigator in the appropriate pages of the 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. For all temporary intervention discontinuations, duration should be recorded by the Investigator in the appropriate pages of the CRF.

Temporary intervention discontinuation decided by the Investigator corresponds to more than 1 dose not administered to the participant.

In case of temporary discontinuation with dosing gap >17 days since last dose, participants must return to site (unscheduled visit) to receive another loading dose and then resume bi-weekly dosing schedule 1 week after the loading dose.

7.1.3 Rechallenge

Not applicable.

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, or compliance 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.
- 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.
- Not demonstration of efficacy while on study considered by the investigator to be clinically meaningful.
- Occurrence of AEs that, in the opinion of the Investigator, may jeopardize participant safety or data integrity.
- Occurrence of pregnancy in participant while receiving sutimlimab.
- Intake of non-permitted concomitant medication or enrollment in another clinical study.
- Diagnosis of SLE or immune complex mediated autoimmune disorders.
- Once sutimlimab is available to participants commercially, or appropriate alternative therapy for CAD becomes available.

If participants no longer wish to take the sutimlimab, they will be encouraged to complete the 9-week post-treatment follow up period.

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 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 this study cannot be treated in this study again. 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 study site 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, telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

8 STUDY ASSESSMENTS AND PROCEDURES

- 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, urine tests) 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.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 EFFICACY ASSESSMENTS

Not applicable.

8.2 SAFETY ASSESSMENTS

This section presents safety assessments other than AEs which are presented in Section 8.3.

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

8.2.1 Physical examinations

- A complete physical examination will include, at a minimum, assessments of the general appearance, head and neck, eyes and ears, nose and throat, chest, lungs, heart, abdomen, extremities and joints, lymph nodes, skin, and neurology systems. Height and weight will also be measured and recorded.
- A brief physical examination will include, at a minimum, assessments of the general appearance, chest, lungs, heart, abdomen, and skin.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.2.2 Vital signs

Oral temperature, respiratory rate, supine blood pressure, and pulse rate will be assessed. Vital signs will be measured after the participant has been supine for at least 5 minutes.

8.2.3 Electrocardiograms

Not applicable.

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 (Section 1.3) for the timing and frequency.
- Safety laboratory tests will be performed at a local laboratory. A serum pregnancy test is required if any urine pregnancy test is positive.
- The clinical laboratory data consist of analysis results, including hematology, clinical chemistry, and urinalysis.
- Only clinically significant laboratory test abnormalities will be recorded as AEs in the CRF.

8.2.5 Pregnancy testing

If the participant is a woman of childbearing potential, a urine pregnancy test will be performed every 4 weeks from Day 21, up to 24 hours before the sutimlimab infusion. A serum pregnancy test is required if any urine pregnancy test is positive.

8.3 ADVERSE EVENTS (AES), SERIOUS ADVERSE EVENTS (SAES) AND OTHER SAFETY REPORTING

The definitions of AEs and SAEs can be found in Appendix 3 (Section 10.3). The definition of AESI is provided in Section 8.3.6.

AE will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up all AEs OR AEs that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study intervention (see Section 7).

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

8.3.1 Time period and frequency for collecting AE and SAE information

All AEs (serious or nonserious) will be collected from the signing of the ICF until the follow-up visit at the time points 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 information on AEs or SAEs after conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the Investigator must promptly notify the Sponsor.

8.3.2 Method of detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and 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. At the pre-specified study end-date, all SAEs, and AEs of special interest, 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 an 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.
- Serious adverse events that are considered expected will be specified in the reference safety information in the IB.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.
- An Investigator who receives an Investigator safety report describing an SAE, SUSAR or any other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements. It is the responsibility of the Sponsor to assess whether an event meets the criteria for a SUSAR, and therefore, is expedited to regulatory authorities.

8.3.5 Pregnancy

- Details of all pregnancies in female participants and, if indicated, female partners of male participants will be collected after the start of study intervention and until time period for reporting pregnancies should align with the time period for post-intervention.
- If a pregnancy is reported, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the female participant or female partner of male participant (after obtaining the necessary signed informed consent from the female partner pregnancy).
- While pregnancy as such is considered as an AESI, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.
- 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.
- Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the Investigator will be reported to the Sponsor as described in Section 8.3.4. While the Investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study intervention or be withdrawn from the study.

8.3.6 Adverse event of special interest

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

- Pregnancy of a female participant entered in a study as well as pregnancy occurring in a female partner of a male participant entered in a study with sutimlimab
  - 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, sutimlimab 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.
- Symptomatic overdose (serious or nonserious) with sutimlimab
  - A symptomatic overdose (accidental or intentional) with the sutimlimab is an event suspected by the Investigator or spontaneously notified by the participant (not based on

systematic drug accountability/verification of consumption of solution for infusion) defined as intake of the study drug at dose significantly greater than scheduled, or administered in less than half the recommended duration of administration (i.e. <30 min), and resulting in clinical signs or symptoms attributable to the overdose.

8.3.7 Guidelines for reporting product complaints

Any defect in the sutimlimab 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 PHARMACOKINETICS

Not applicable.

8.5 GENETICS AND/OR PHARMACOGENOMICS

Not applicable.

8.6 BIOMARKERS

Not applicable.

8.7 IMMUNOGENICITY ASSESSMENTS

Not applicable.

9 STATISTICAL CONSIDERATIONS

The material in this section constitutes the statistical analysis plan for the study.

9.1 SAMPLE SIZE DETERMINATION

Up to 7 participants will be enrolled to this study.

Up to 7 participants are expected to complete CARDINAL study or CADENZA study, and to be enrolled to this study.

9.2 POPULATIONS FOR ANALYSES

All the statistical analyses will be conducted on Safety population. Safety population is defined as all enrolled participants who take at least 1 dose of study intervention.

Table 3 - Populations for analyses

Population	Description
Safety	All enrolled participants who take at least 1 dose of study intervention.

9.3 STATISTICAL ANALYSES

The statistical analysis plan to be developed separately will include a more technical and detailed description of the statistical analyses described in this section. This section defines statistical analyses of the most important endpoints including primary endpoints only.

9.3.1 DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Parameters identified in the schedule of activities (Section 1.3) will be summarized and listed.

9.3.2 CONCOMITANT MEDICATIONS

Medications will be coded according to the World Health Organization Drug Dictionary. All concomitant medications will be listed.

9.3.3 Primary endpoint (Analysis of safety data)

Summary tables of AEs defined in Section 9.3.3.1 will be provided. Each AE will be coded to a preferred term, high level group term, high level term, and system organ class, using the Medical Dictionary for Regulatory Activities (MedDRA). All AEs and safety parameters described in Section 1.3 and Section 8.2 will be listed (when corresponding CRF data are available).

9.3.3.1 Adverse events

General common rules for adverse events

The primary focus of adverse event reporting will be on treatment-emergent adverse events (TEAEs). Ongoing AE from CARDINAL study and CADENZA study will be recorded in medical history. New AE that started between end of CARDINAL/CADENZA and start of this study will be recorded in medical history.

TEAEs are defined as AEs that developed, worsened or became serious during the treatment-emergent period (from the time from the first dose of study treatment in this study to the last contact on study).

Analysis of all adverse events

Summary table will be provided for the following types of TEAEs: all TEAEs, all treatment emergent AESI (defined with a PT or a prespecified grouping), all treatment emergent SAEs and all TEAEs leading to permanent treatment discontinuation.

The AE summaries will be generated with number (%) of participants experiencing at least one event.

All deaths will be listed.

9.4 INTERIM ANALYSES

Not applicable.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1 Regulatory and ethical considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and the applicable amendments and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations (eg, data protection law as General Data Protection Regulation - GDPR)
- The protocol, protocol amendments, ICF, IB and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation 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 (as per Sanofi policy) 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 study site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, 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 participants or their legally authorized representative, and answer all questions regarding the study, including what happens to the participant when his/her participation ends (post-trial access strategy for 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, Privacy and Data Protection requirements including those of the General Data Protection Regulation (GDPR) and of the French law, 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.
- In case of ICF amendment while the participants are still included in the study, they must be re-consented to the most current version of the ICF(s).Where participants are not in the

study anymore, teams in charge of the amendment must define if those participants must or not re-consent or be informed of the amendment (eg, if the processing of personal data is modified, if the Sponsor changes, etc.).

- A copy of the ICF(s) must be provided to the participant or their legally authorized representative, where applicable.

Participants who are rescreened are required to sign a new ICF.

10.1.4 Data protection

All personal data collected and/or processed in relation to this study will be handled in compliance with all applicable Privacy & Data Protection 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, IRB/IEC 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.

Protection of participant data

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 they are expected to modify the drug response/because they 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)". They will not be collected in the countries where this is prohibited by local regulation.

- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor or its service providers will be identifiable only by the unique identifier; 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 applicable data protection laws. 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.
- 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 phamaceutical 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 Dissemination of clinical study data

Study participants

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

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

Individual participant data and supporting clinical documents are available for request at clinicalstudydatarequest.com. While making information available we continue to protect the privacy of participants in our clinical 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”.

10.1.6 Data quality assurance

- All participant data relating to the study will be recorded on printed 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 signing 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.
- 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).
- 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.

10.1.7 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 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.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- 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.

10.1.8 Study closure

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

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

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

- For study termination:
  - Information on the product leads to doubt as to the benefit/risk ratio
  - Discontinuation of further study intervention development
- For site termination:
  - Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines

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 participant and should assure appropriate participant therapy and/or follow-up.

10.1.9 Publication policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.
- The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2 APPENDIX 2: CLINICAL LABORATORY TESTS

The following determinations will be performed by the local laboratory.

Hematology

- Hematocrit
- Hemoglobin
- Red blood cell count
- White blood cell count with differential
- Platelet count

Clinical chemistry

- Sodium
- Potassium

- Calcium
- Magnesium
- Chloride
- Total protein
- Albumin
- Glucose
- Creatinine
- Blood urea nitrogen
- Lactate dehydrogenase
- Creatine kinase
- ALT
- AST
- ALP
- Gamma glutamyl transferase
- Total and direct bilirubin

Urinalysis

- Specific gravity
- pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick
- Microscopic examination (if blood or protein is abnormal)

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

10.3 APPENDIX 3: AES AND SAES: 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 participant or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.

- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events meeting the AE definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, 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),
  - Symptomatic and/or
  - Requiring either corrective treatment or consultation, and/or
  - Leading to sutimlimab discontinuation and/or
  - Fulfilling a seriousness criterion, and/or
  - Defined as an AESI
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.

Events NOT meeting the AE definition

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

10.3.2 Definition of SAE

An SAE is defined as any adverse event 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 admitted (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 or significant 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) Is a suspected transmission of any infectious agent via an authorized medicinal product

g) Other situations:

- Medical or scientific judgment should be exercised by the Investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that 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.
- Note: The following list of medically important events is intended to serve as a guideline for determining which condition has to be considered as a medically important event. The list is not intended to be exhaustive:
    - Intensive treatment in an emergency room or at home for:
        - Allergic bronchospasm
        - Blood dyscrasias (ie, agranulocytosis, aplastic anemia, bone marrow aplasia, myelodysplasia, pancytopenia, etc)
        - Convulsions (seizures, epilepsy, epileptic fit, absence, etc).

- Development of drug dependence or drug abuse
- ALT >3 × ULN + total bilirubin >2 × ULN or asymptomatic ALT increase >10 × ULN
- Suicide attempt or any event suggestive of suicidality
- Syncope, loss of consciousness (except if documented as a consequence of blood sampling)
- Bullous cutaneous eruptions

10.3.3 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.
- It is not acceptable for the Investigator to send photocopies of the participant's medical records to the Sponsor's representative in lieu of completion of the required form.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor's representative. 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's representative.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of intensity

The Investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort to interfere with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. "Severe" is a category used for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

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

Assessment of causality

- The Investigator is obligated to assess the 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 that 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 Sanofi. 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** Sanofi**.**
- The Investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor's representative 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 sponsor with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally submitted documents.
- 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 paper data collection tool

- Facsimile transmission of the SAE paper data collection tool is the preferred method to transmit this information to the Sponsor's representative.

- Contacts for SAE reporting will be provided.

10.4 APPENDIX 8: COUNTRY-SPECIFIC REQUIREMENTS

Not applicable.

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

Not applicable.

10.6 APPENDIX 11: ABBREVIATIONS AND DEFINITIONS

Abbreviations	Definitions
AE	adverse event
AESI	adverse event of special interest
CAD	cold agglutinin disease
CIOMS	Council for International Organizations of Medical Sciences
CONSORT	Consolidated Standards of Reporting Trials
CP	complement classical pathway
CRF	case report form
C1q	complement component 1 q subcomponent
C1r	complement component 1 r subcomponent
C1s	complement component 1 s subcomponent
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICF	informed consent form
IEC	Independent Ethics Committees
IR	Investigator Registry
IRB	Institutional Review Boards
IV	intravenous
mAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
RBC	red blood cell
SAE	serious adverse event
SIP	Shared Investigator Platform

Abbreviations	Definitions
SLE	systemic lupus erythematosus
SoA	Schedule of Activities
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event

10.7 APPENDIX 12: PROTOCOL AMENDMENT HISTORY

Not applicable.

11 REFERENCES

1. Röth A, Barcellini W, D'Sa S, Miyakawa Y, Broome CM, Michel M, et al. Sutimlimab in Cold Agglutinin Disease. N Engl J Med. 2021 Apr 8;384(14):1323-1334. doi: 10.1056/NEJMoa2027760.