EU-RISK MANAGEMENT PLAN FOR SUTIMLIMAB

Data Lock Point (DLP)	25-JAN-2022
RMP Version number	Version 1.2
Date of final sign-off	12-JUL-2022

[redacted]

Table 1 - RMP version to be assessed as part of this application

Rationale for submitting an updated RMP	Update of the RMP with data from all completed CAD studies. Request of CHMP/PRAC to submit an updated RMP along with responses to D180 list of outstanding issues.
Summary of significant changes in this RMP	Update of the DLP. Reclassification of the important risk of serious infections from potential to identified. Addition of a patient guide as an aRMM. Update of Cadence protocol. Update of the Physician's Guide survey protocol.

aRMM: Additional Risk Minimization Measure; CAD: Cold Agglutinin Disease; CHMP: Committee for Medicinal Products for Human Use; DLP: Data Lock Point; PRAC: Pharmacovigilance Risk Assessment Committee; RMP: Risk Management Plan.

Table 2 - Other RMP versions under evaluation

RMP Version number	Submitted on	Submitted within
Not applicable	-	-

RMP: Risk Management Plan.

Table 3 - Details of the currently approved RMP

Version number	Not applicable (initial submission)
Approved with procedure	Not applicable (initial submission)
Date of approval (opinion date)	Not applicable (initial submission)

RMP: Risk Management Plan.

Table 4 - QPPV name and signature

QPPV name	Hadj Benzerdjeb[a], MD
QPPV signature	Electronic signature on file

a Deputy QPPV by delegation from Heike Schoepper, QPPV for Sanofi.

QPPV: Qualified Person Responsible for Pharmacovigilance.

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ABBREVIATIONS

AE:	Adverse Event
aHR:	Adjusted Hazard Ratio
AIDS:	Acquired Immuno Deficiency Syndrome
AIHA:	Autoimmune Hemolytic Anemia
AMR:	Antibody-Mediated Rejection
anti-dsDNA:	Anti-Double Stranded DNA
anti-ENA:	Anti-Extractable Nuclear Antigen
AP:	Alternative Pathway
aRMM:	Additional Risk Minimization Measure
ATC:	Anatomical Therapeutic Chemical
AUC:	Area Under the Curve
BP:	Bullous Pemphigoid
C1q:	Complement component 1, q subcomponent
C1r:	Complement component 1, r subcomponent
C1s:	Complement component 1, s subcomponent
C2:	Complement component 2
C3:	Complement component 3
C3b:	Complement component 3, b subcomponent
C3d:	Complement component 3, d subcomponent
C4:	Complement component 4
C5:	Complement component 5
C5b:	Complement component 5, b subcomponent
C8:	Complement component 8
CA:	Cold Agglutinin
CAD:	Cold Agglutinin Disease
CAS:	Cold Agglutinin Syndrome
CHMP:	Committee for Medicinal Products for Human Use
CHO:	Chinese Hamster Ovary
CI:	Confidence Interval
CIC-C1q:	Circulating Immune Complexes-Complement component 1, q subcomponent
C_{max}:	Maximum Plasma Concentration
CMD:	Complement-Mediated Disorder
CNS:	Central Nervous System
CP:	Classical Complement Pathway
CSF:	Cerebrospinal Fluid
CSR:	Clinical Study Report
CVS:	Cardiovascular System
DAT:	Direct Antiglobulin Test
DLP:	Data Lock Point
DNA:	Deoxyribonucleic Acid
e-CTD:	Electronic Common Technical Document
EEA:	European Economic Area
EMA:	European Medicines Agency

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EPAR:	European Public Assessment Report
ePPND:	Enhanced Pre/Postnatal Development
EU:	European Union
FIC:	First-In-Class
FIH:	First In Human
GMP:	Good Manufacturing Practice
HCP:	Healthcare Professional
HCV:	Hepatitis C Virus
HIV:	Human Immunodeficiency Virus
IC50:	Half Maximal Inhibitory Concentration
IC90:	90% Inhibitory Concentration
ICH:	The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IgG:	Immunoglobulin G
IgG4:	Immunoglobulin G4
IgM:	Immunoglobulin M
INN:	International Nonproprietary Name
ITP:	Immune Thrombocytopenic Purpura
IV:	Intravenous
LP:	Lectin Pathway
mAb:	Monoclonal Antibody
MAD:	Multiple-Ascending Dose
MAH:	Marketing Authorization Holder
MCB:	Master Cell Bank
NHV:	Normal Healthy Volunteer
NOAEL:	No-Observed-Adverse-Effect Level
PIL:	Patient Information Leaflet
PK:	Pharmacokinetic
PK/ADA:	Pharmacokinetic/Anti-Drug Antibody
PRAC:	Pharmacovigilance Risk Assessment Committee
PSUR:	Periodic Safety Update Report
Q:	Quarter
QOL:	Quality of Life
QPPV:	Qualified Person Responsible for Pharmacovigilance
RBC:	Red Blood Cell
RMP:	Risk Management Plan
SAD:	Single-Ascending Dose
SAE:	Serious Adverse Event
SLE:	Systemic Lupus Erythematosus
SmPC:	Summary of Product Characteristics
TE:	Thromboembolic Event
TEAE:	Treatment-Emergent Adverse Event
UK:	United Kingdom
US:	United States
WAIHA:	Warm Auto-Immune Hemolytic Anemia
WFI:	Water for Injection

RISK MANAGEMENT PLAN - PART I: PRODUCT (S) OVERVIEW

Table 5 - Product Overview

Active substance (INN or common name)	Sutimlimab
Pharmacotherapeutic group (ATC Code)	L04AA55 sutimlimab
Marketing Authorization Applicant	Genzyme Europe B.V.
Medicinal products to which this RMP refers	1
Invented name in the EEA	ENJAYMO®
Marketing authorization procedure	Centralized
Brief description of the product	Chemical class: Anti-C1s Esterase Humanized IgG4 monoclonal antibody.
	Summary of mode action: Sutimlimab binds to and inhibits the CP specific serine protease, C1s, thus inhibiting CP activity.
	Important information about its composition: Sterile, non-pyrogenic, isotonic aqueous solution containing 50 mg/mL BIVV009 with 10 mM sodium phosphate buffer, 140 mM NaCl, 0.02% polysorbate 80 (Tween-80), and WFI; the pH is 6.1. The osmolarity is 268-312 mOsm/kg.
Hyperlink to the product information	Refer to e-CTD sequence 0003, Module 1.3.1 English proposed Product Information.
Indication in the EEA	Current: Treatment of hemolytic anemia in adult patients with CAD.
	Proposed: Not applicable
Dosage in the EEA	Current: The recommended dosage of ENJAYMO for patients with CAD is based on body weight. For patients weighing 39 kg to less than 75 kg, the recommended dose is 6500 mg and for patients weighing 75 kg or more, the recommended dose is 7500 mg. Administer ENJAYMO IV weekly for the first two weeks, with administration every two weeks thereafter.
	Proposed: Not applicable
Pharmaceutical form and strength	Current: Solution for infusion (IV), 50 mg/mL
	Proposed: Not applicable

Will the product be subject to additional monitoring in the EU?	Yes

ATC: Anatomical Therapeutic Chemical; C1s: Complement component 1, s subcomponent; CAD: Cold Agglutinin Disease; CP: Classical Complement Pathway; e-CTD: Electronic Common Technical Document; EEA: European Economic Area; EU: European Union; IgG4: Immunoglobulin G4; INN: International Nonproprietary Name; IV: Intravenous; RMP: Risk Management Plan; WFI: Water for Injection.

RISK MANAGEMENT PLAN - PART II MODULE SI: EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

Sutimlimab is a first-in-class (FIC), humanized IgG4 monoclonal antibody (mAb) that targets the CP by inhibiting the CP-specific serine protease, C1s. Upstream inhibition of the CP retains the important immune surveillance functional activities of lectin and alternative pathways (APs).

Sutimlimab has been developed for the treatment of hemolytic anemia in adult patients with CAD, a CP-mediated life-threatening orphan disease.

The epidemiology of the disease is summarized in the following table.

Table 6 - Epidemiology of the cold agglutinin disease

Indication	Cold Agglutinin Disease
Incidence and prevalence	Cold agglutinin disease is a sub-type of AIHA characterized by hemolysis driven by activation of the CP. (1)(2)(3)(4)(5)(6) Cold agglutinin disease accounts for approximately 15%-25% of all AIHA. (4)(7) The rarity of CAD has limited the ability to perform large population-based studies. In 2006, the first population-based study in CAD suggested an annual incidence of 10 cases per 100 000 people in Norway. (8) In 2013, the incidence of CAD was 0.18 per 100 000 inhabitants in Denmark. (9) In 2020, a published study reported a CAD incidence rate of 1.9 per million per year in cold European climates versus a rate of 0.5 per million per year in warmer European regions. (10) In Denmark, Hansen (2020) reported that the 2008-2016 CAD incidence was 0.18/100 000 person-years, and CAD prevalence was 1.04/100 000 persons in 2015. (11) This is similar to the previous estimate of a prevalence of CAD of 1.26 per 100 000 inhabitants in Denmark in 2013. (9) In 2020, a published study reported a CAD prevalence estimate of 20 per million in cold European climates versus a rate of 5 per million in warmer European regions. (10)
Demographics of the population in the authorized/proposed indication	The risk of CAD onset increases after age 55 years. In the Norwegian cohort (N = 86), the median age at onset of CAD was 67 years (range 30-92 years) and the male to female ratio was 0.55. (8) The slight preponderance in women in some studies is likely due to women living to an older age, where the onset of the disease is more common. In a retrospective analysis of 89 CAD patients in the US (Mayo Clinic, year 1970-2012) median age at diagnosis was 72 years (range 43-91 years). (4) In a retrospective longitudinal analysis of CAD patients seen at Stanford Health Care, US (N = 29, year 2000 to 2016), 45% of patients were male and the average age at disease onset was 59 years (range 19-74 years). (12) Based on the recently (13) published first international consensus recommendations for AIHA in Dec-2019; it particularly highlights the importance of distinguishing CAD from CAS. Cold agglutinin disease is a low-grade B-Cell lymphoproliferative disorder detectable in blood or marrow with no clinical or radiological evidence of malignancy. Cold agglutinin disease is mediated by CA which are IgM autoantibodies that are able to agglutinate red blood cells upon binding to the I surface antigen. Cold agglutinin disease is defined by chronic hemolysis, a significant CA titre (most often defined as >64) at 4˚C, Typical DAT pattern is a positive monospecific test for C3d only. In contrast to CAD, cold agglutinin syndrome is a secondary form and associated with underlying infections, overt malignancy, or autoimmune conditions. The same laboratory criteria apply to CAS complicating aggressive lymphoma or specific infections. (13) Therefore, the previous designation of “primary CAD” is aligned with “CAD” as defined in these guidelines.

Indication	Cold Agglutinin Disease
Main existing treatment options	In EU, there are currently no approved pharmacological therapies for CAD and no established standard-of-care treatment. This results in varied treatment protocols with inconsistent response. Immunomodulatory and chemotherapy options are utilized off-label with limited efficacy in controlling hemolysis with delay in onset, variable hemoglobin responses, and incomplete durability of treatment outcome in the setting of significant side-effects and safety concerns. Cold agglutinin disease is currently managed by supportive therapy (cold avoidance), blood transfusions, off-label B-cell directed immunologic therapies and/or chemotherapy (eg, rituximab with or without bendamustine or fludarabine). Corticosteroid (due to limited efficacy and requirement to use high doses) and splenectomy (as extravascular hemolysis occurs predominantly in the liver) are not recommended for treatment CAD; however, are utilized. Rituximab monotherapy produces approximately 50% partial response rates, with a delay in response of 1.5 months, and median response duration of 11 months. Whereas the combination of rituximab with chemotherapy has shown better results but is associated with more toxicity including severe neutropenia. (1)(3)(14)(15) Due to the temporary effectiveness of existing CAD treatments, patients often relapse and experience acute hemolytic crisis and require additional interventions (3.5 was the average number of therapies that patients with CAD received). (12) While RBC transfusion are utilized in CAD, it has limited efficacy due to the ubiquitous presence of the I antigen on all RBC, including the donor RBC, which are rapidly hemolyzed after a transfusion contributing to even higher hemolytic activity and thus has limited ability to alleviate anemia. Chronic transfusion support is typically not used in CAD for this reason, despite the ongoing presence of varying degrees of anemia. In population-based retrospective natural history studies, approximately 35% to 49% of CAD patients did not receive transfusion support despite being anemic. (8)(12) Despite its limitations, the majority of CAD patients experience at some point during their disease a clinical exacerbation that requires RBC transfusion support. (12)
Natural history of the indicated condition in the untreated population including mortality and morbidity	Classical complement pathway mediated hemolysis leads to a chronic anemia of varying severity, with the median hemoglobin level in a population-based CAD study of 8.9 g/dL. (8) Acute Hemolytic Crisis in CAD patients may be triggered by febrile illness, trauma, or surgery. Symptoms can range from slight acrocyanosis to disabling Raynaud phenomena, fatigue, dyspnea, hemoglobinuria, weakness, and weight loss, with a median overall survival of 12.5 years (range, 1-21 years) from disease onset. (4)(8)(16) The prognosis of CAD patients depends on the severity of the disease. Death may result from infection or severe anemia or sometimes from an underlying lymphoma. Most commonly reported causes of death are lymphohematopoietic diseases; other causes of death include severe anemia complications, ischemic stroke, and infection. (12) The most recent population-based study in CAD, published in 2019, used the Danish National Health Registries and found a median survival for CAD patients of 8.5 years. Cold agglutinin disease patients had increased mortality compared with a matched general population cohort from Denmark (aHR: 1.84; 95% CI: 1.10-3.06; P = 0.020), with the highest mortality observed during the first 5 years after diagnosis (aHR: 2.27; 95% CI: 1.32-3.89; P = 0.003). Mortality rates 1 and 5 years after diagnosis were 17% and 39% in the CAD group versus 3% and 18% in the comparison cohort, respectively. (9) For the 29 retrospectively identified CAD patients in the Stanford Translational Research Integrated Database Environment database who were treated from 2000 to 2016, (12) 7.1 severe anemia events per patient-year were observed over the follow-up time, with 2/3 of patients having a severe anemia event within the first year of diagnosis. Patients used a mean of 3.5 therapies and 67% had a severe anemia event within 6 months of their initial therapy. In reference to CAD-related health care use, in the first year after disease onset, 93% used outpatient services with a median of 26 outpatient visits per patient.

Indication	Cold Agglutinin Disease
	Recent studies have also shown that patients with CAD have an increased risk of TEs compared to matched controls. Similar to other hemolytic diseases, patients with CAD have an increased risk of thromboembolisms, including potentially life-threatening TEs such as pulmonary emboli and stroke, and early mortality. (17) In addition, the Danish population-level study also showed that the incidence rate of TEs was 30.4 (95% CI: 14.5-63.8) per 1000 person-years in CAD patients, compared with 18.6 (95% CI: 14.2-24.5) per 1000 person-years in the matched comparison group. (18) Further, a retrospective analysis of a Japanese claims database identified 344 Japanese patients with CAD and compared these to 3440 matched control patients, and found that the CAD cohort had higher TE rates than controls (34.8% versus 17.9%; P<0.0001). Both arterial and venous TEs were increased in the CAD group compared to the control group (25.0% versus 4.6% and 8.4% versus 4.0%, respectively; both P<0.0001). Most arterial TEs in the CAD cohort (87.2%) were myocardial infarctions. Overall odds ratio for TE development in CAD was 2.81 (95% CI: 2.18-3.61). (19)
Important co-morbidities	Cold agglutinin disease is considered a low-grade B-Cell lymphoproliferative disorder detectable in blood or marrow with no clinical or radiological evidence of malignancy. Cold agglutinin disease is characterized by immune hemolysis which is entirely complement-dependent, predominantly mediated by activation of the classical pathway. Cold agglutinin syndrome is transient and associated with underlying infections, overt malignancy, or autoimmune conditions. (1)(2)(3)(4)(5) Due to the fact that CAD is a rare disease, limited information is available. Lymphoproliferative Disorders or Haematological Malignancies: In a population-based retrospective follow-up study of 86 CAD patients in Norway, an abnormal kappa/lambda ratio in bone marrow was found in 90%, lymphoma in 76%, and lymphoplasmacytic lymphoma in 50%. Transformation to aggressive lymphoma occurred in 3.5% during 10 years. (8) Viral or Bacterial Infections: Postinfectious cold agglutinins are seen with viral and bacterial pathogens including mycoplasma (20), Epstein-barr virus (21)(22)(23), and legionella. There have been reports of cold agglutinin associated hemolysis associated with varicella (24)(25)(26), Citrobacter (27) and influenza. (4)(28)(29) Immune Diseases: Autoimmune diseases other than CAD were reported in 8% of patients in a population-based retrospective study of 86 CAD patients in Norway. (8) In addition, there have been other reports of association with SLE and rheumatoid arthritis. (30)(31)(32)

aHR: Adjusted Hazard Ratio; AIHA: Autoimmune Hemolytic Anemia; C3: Complement component 3; C3d: Complement component 3, d subcomponent; CA: Cold Agglutinin; CAD: Cold Agglutinin Disease; CAS: Cold Agglutinin Syndrome; CI: Confidence Interval; CP: Classical Complement Pathway; DAT: Direct Antiglobulin Test; EU: European Union; IgG: Immunoglobulin G; IgM: Immunoglobulin M; RBC: Red Blood Cell; SLE: Systemic Lupus Erythematosus; TE: Thromboembolic Event; US: United States.

[redacted]

RISK MANAGEMENT PLAN - PART II MODULE SII: NON-CLINICAL PART OF THE SAFETY SPECIFICATION

Key non-clinical findings

This section presents a summary of non-clinical safety data for sutimlimab. Because sutimlimab either does not bind to or have functional activity against C1s of the CP of any of the non-clinical species used, with the exception of the cynomolgus monkey, the non-clinical safety profile of sutimlimab was evaluated only in the monkey. The non-clinical safety profile of sutimlimab, was evaluated in the following in vivo and ex-vivo studies,

- Repeat-dose general toxicology studies with sutimlimab up to 26 weeks duration using the IV route in cynomolgus monkeys;
- An enhanced pre/postnatal development (ePPND) toxicology study with sutimlimab in cynomolgus monkeys using the IV route;
- An ex-vivo tissue cross-reactivity study in human tissues with biotinylated sutimlimab;
- An exploratory in vitro immunogenic potential study

The sutimlimab-related findings are described below in Table 7.

The doses administered in the toxicology studies provided substantially higher maximum plasma concentration (C_{max}) levels in vivo, relative to 90% inhibitory concentration (IC_{90}) values determined by an evaluation of CP activity, confirming target saturation.

Cynomolgus monkeys constitute a pharmacologically-relevant species for non-clinical evaluation of sutimlimab. The pharmacologic activity of sutimlimab is comparable to that for humans in vitro (half maximal inhibitory concentration [IC_{50}] values of 15.6 or 14.7 µg/mL for inhibition of 80% serum-mediated hemolysis in monkeys and humans, respectively) and in vivo (IC_{90} values of 22.3 or 20.1 µg/mL for inhibition of CP activity in monkeys or humans, respectively).

Safety pharmacology endpoints were assessed as part of the nonhuman primate repeat-dose toxicology studies, evaluating the cardiovascular system (CVS), central nervous system (CNS) and respiratory parameters. No sutimlimab-related effects were observed in any of the safety pharmacology assessments.

Sutimlimab was well tolerated in repeat-dose general toxicology studies in cynomolgus monkeys following the IV administration of 100 mg/kg/week for 5 weeks and 180 mg/kg/week for 26 weeks. The highest dose administered (180 mg/kg/week) was the no-observed-adverse-effect level (NOAEL). Sutimlimab displayed equivalent, maximal inhibition of serum CP activity at all doses, but a dose-dependent duration of inhibition was observed. Despite consistent exposure to sutimlimab and inhibition of CP activity for up to 31 weeks at 180 mg/kg/week, there were no sutimlimab-related alterations in autoimmune parameters, including circulating immune complexes-complement component 1, q subcomponent (CIC-C1q) concentrations, and anti-extractable nuclear antigen (anti-ENA) IgG and anti-double stranded DNA (anti-dsDNA) IgG antibody levels.

[redacted]

Sutimlimab was not evaluated in genetic toxicology studies, which were considered inappropriate for biotechnology-derived pharmaceuticals, consistent with recommendations in International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) S6. Based upon the large molecular weight (approximately 145 kDa), sutimlimab is not anticipated to cross cellular and nuclear membranes as an intact molecule or to directly interact with deoxyribonucleic acid (DNA).

Based on a carcinogenicity risk assessment, which evaluated the weight-of-evidence from the animal toxicology studies and the literature assessment of the CP and its inhibition, sutimlimab does not appear to increase the risk of cancer.

The potential effects of CP inhibition on embryo-fetal and postnatal development were studied in an ePPND study in monkeys. Sutimlimab was well tolerated in adult pregnant cynomolgus monkeys and in their offspring at doses of up to 180 mg/kg/week IV, which were monitored up to 3 months of age. There were no sutimlimab-related findings (maternal, fetal, or infant) in any assessed parameter. The maternal and developmental NOAEL was considered to be 180 mg/kg/week IV, the highest dose evaluated.

A tissue cross-reactivity study evaluating the binding of sutimlimab in normal human tissues, demonstrated specific immunostaining of C1s that was identified in most tissues evaluated, which is the expected staining pattern for C1s. Immunostaining in tissues is primarily within the vasculature (plasma) and extracellular spaces (matrix) and not on tissue or cellular surfaces.

The immunogenic potential of sutimlimab was assessed in an ex-vivo T-cell proliferation assay. Results indicated that sutimlimab has a very low potential (0% response rate) for immunogenicity. In conclusion, no positive T-cell proliferation responses to the fully humanized sutimlimab antibody were observed indicating that sutimlimab has a very low potential for immunogenicity.

There was no evidence in animal toxicology or pharmacology studies to suggest a dependence potential or abuse liability for sutimlimab. The rationale for not performing drug abuse and liability assessment studies was supported by the absence of behavioral and anatomic pathology effects in the CNS in any of the toxicology studies.

Overall, sutimlimab has a low potential for causing immune system-related adverse effects, either directly through inhibition of C1s or indirectly affecting general immune function.

The key non-clinical findings are presented in the following table.

Table 7 - Key safety findings from non-clinical studies and relevance to human usage

Key Safety Findings	Relevance to human usage
Toxicity <u>Repeat-Dose Toxicity</u> No test article-related changes were observed in repeat-dose toxicity studies in monkeys up to 26 weeks in duration. The highest dose evaluated (180 mg/kg/week IV) was considered the NOAEL.	The margin of safety is based on comparing the 26 weeks repeat-dose monkey AUC at the NOAEL dose to the projected human AUC (based on a Population PK analysis; Report POH0756) for the highest dose test in humans (7.5 g sutimlimab IV per week) is 3.6-fold.
<u>Reproductive and Developmental Toxicity</u> • Embryo-fetal and Developmental toxicity In an ePPND study in cynomolgus monkeys, sutimlimab was administered IV at doses up to	Since no fertility study was performed with sutimlimab, it is not possible to state whether or not sutimlimab would have an effect on pregnancy or early embryo development.

[redacted]

Key Safety Findings	Relevance to human usage
180 mg/kg/week to pregnant monkeys from Day-20 post coitum until delivery (approximately 21 doses). Maternal toxicity endpoints before and after delivery were assessed. Monitoring of offspring from approximately 3 months after delivery was performed. Administration of sutimlimab did not cause any embryo-fetal effects or effect on gestation length. No differences in maternal loss (abortions or still births) were observed. Therefore, it was concluded that sutimlimab did not affect either the maintenance of pregnancy or natural delivery. No sutimlimab-related effects in infants were noted up to 3 months after birth in the following parameters: clinical observations, body weight, neurobehavioral test battery, skeletal development, coagulation, serum chemistry, organ weights, macroscopic observations, and microscopic findings. The maternal and infant NOAEL was 180 mg/kg/week IV, the highest dose evaluated. The margin of safety is based on comparing the ePPND monkey AUC at the NOAEL dose (180 mg/kg/week) to the projected human AUC (based on a Population PK analysis; Report POH0756) for the highest dose tested in humans (7.5 g sutimlimab IV per week) is 2.9-fold.	Evidence from the ePPND study does suggest that sutimlimab had no effect on the maintenance of pregnancy, embryo-fetal development (eg, no teratogenicity), natural birth, and early infant development following birth. Furthermore, reproductive organs/tissues (male/female) were not targets following the chronic administration (26 weeks) of sutimlimab to cynomolgus monkeys. While there is no evidence in the literature suggesting that inhibition of C1s would have the potential of adversely impacting fertility and ability to get pregnant, this has not been evaluated for sutimlimab. Considering limited reproductive toxicity information and a lack of clinical experience with the use of sutimlimab in pregnant or breast-feeding women, appropriate recommendations are provided in the label. Of note, the risk of CAD onset increases after age of 55 years (refer to the Norwegian cohort (N = 86) where the median age at onset of CAD was 67 years (range 30-92 years) and the male to female ratio was 0.55. (8) Thus, the use of sutimlimab in womb or pregnant women is anticipated to be limited.
Carcinogenicity Based on the weight-of-evidence from the animal toxicology studies and the literature assessment of CP inhibition, the data supported the conclusion that chronic administration of sutimlimab does not pose an increased risk of cancer.	A preclinical evaluation that sutimlimab did not pose an increased risk of cancer is relevant to human use considering that some immunomodulating drugs in the market can be associated with higher risk of cancers.
Safety pharmacology No evidence of sutimlimab-related CVS, CNS, or respiratory changes in 5-week and 6-month repeat-dose study in cynomolgus monkeys.	Pre-clinical studies did not show evidence that treatment with sutimlimab increased injury to heart, lung, and CNS in human.
Other toxicity-related information or data	Not applicable

AUC: Area Under the Curve; C1s: Complement component 1, s subcomponent; CAD: Cold Agglutinin Disease; CNS: Central Nervous System; CP: Classical Complement Pathway; CVS: Cardiovascular System; ePPND: Enhanced Pre-/Post-natal Development; IV: Intravenous; NOAEL: No-Observed-Adverse-Effect Level; PK: Pharmacokinetic.

No additional non-clinical safety studies have been performed to evaluate the safety of sutimlimab in any special populations.

Conclusion:

No outstanding safety concern has been concluded based on the absence of key-safety findings from non-clinical studies.

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RISK MANAGEMENT PLAN - PART II MODULE SIII: CLINICAL TRIAL EXPOSURE

Sutimlimab (BIVV009) is a FIC, humanized IgG4 mAb that targets the CP by inhibiting the CP-specific serine protease, C1s. Sutimlimab has been developed for the treatment of hemolytic anemia in adult patients with CAD, a life-threatening orphan disease. The proposed dose regimen of sutimlimab is 6.5 g (for patients <75 kg) or 7.5 g (for patients ≥75 kg), depending on the patient's body weight at baseline, which is to be administered by IV infusion over 1-2 hours once per week for the first 2 doses followed by every other week dosing thereafter.

As of the data cut-off date for the RMP, the clinical development program for sutimlimab includes a total of 6 clinical studies. All the clinical studies have been completed. A tabular summary of the 6 studies (BIVV009-01, TNT009-02, BIVV009-03, BIVV009-04, BIVV009-05, and BIVV009-201) in the sutimlimab clinical development program is provided in Table 8.

Table 8 - List of studies evaluated in the Summary of Clinical Safety

Study	Study Design	Treatment and duration	Number of patients/subjects evaluated for safety[a]
BIVV009-01 Part A/B	**Part A**: FIH, Phase 1, double-blind, randomized, placebo-controlled, SAD study in NHVs treated with placebo or sutimlimab 0.3, 1, 3, 10, 30, 60, or 100 mg/kg.	**Part A**: **Treatment**: One day, single dose **Duration**: Single dose of study treatment on Day 1 and safety follow-up through Day 14.	**Part A**: 48 subjects; sutimlimab: 36 subjects; placebo: 12 subjects
	Part B: FIH, Phase 1, double-blind, randomized, placebo controlled, MAD study in NHVs treated with placebo or sutimlimab 30 or 60 mg/kg once weekly for 4 weeks. **Primary Objective (Part A/B)**: Evaluate the safety and tolerability of sutimlimab in humans.	**Part B**: **Treatment**: Four weeks (weekly dosing) **Duration**: Multiple doses of study treatment once weekly for 4 weeks and safety follow-up through Day 35.	**Part B:** 16 subjects; sutimlimab: 12 subjects; placebo: 4 subjects
TNT009-02	Phase 1, prospective, double-blind, randomized, placebo-controlled study to evaluate the safety and tolerability of multiple doses of sutimlimab 75 mg/kg in NHVs. **Primary Objective**: Evaluate the safety and tolerability of multiple doses of sutimlimab in humans.	**Treatment**: 75 mg/kg x 4 (60-minute infusions on days 1, 8, 22, and 36) **Duration**: Days 1, 8, 22, 36 with safety follow-up on Day 50. Additional PK/ADA sampling on Days 64 and 92.	Sutimlimab: 18 subjects placebo: 6 subjects
BIVV009-05 (Part A/B)	Phase 1, randomized, open-label PK study in healthy Japanese volunteers. **Part A**: Cohorts (6 subjects per/cohort) were randomized to receive a single	**Part A**: **Treatment:** Single dose of either: 30 mg/kg, 60 mg/kg, or 100 mg/kg.	**Part A**: Total: 18 subjects 30 mg/kg: 6 subjects 60 mg/kg: 6 subjects

Study	Study Design	Treatment and duration	Number of patients/subjects evaluated for safety[a]
	dose of sutimlimab 30, 60, or 100 mg/kg by IV infusion on Day 1.	**Duration**: Single dose with safety and tolerability assessed through Day 64.	100 mg/kg: 6 subjects
	Part B: Subjects stratified by body weight to receive sutimlimab by IV infusion on Days 1, 8, and 22. **Primary Objective**: Evaluate the PK of a single dose of sutimlimab (Part A) and multiple doses of sutimlimab (Part B).	**Part B**: **Treatment:** Multiple doses of sutimlimab 6.5 grams if <75 kg or 7.5 grams if ≥75 kg on Days 1, 8, and 22. **Duration**: Multiple doses of sutimlimab with safety and tolerability assessed through Day 85.	**Part B**: Total: 12 subjects 6.5 g: 9 subjects 7.5 g: 3 subjects
BIVV009-03	Pivotal, open-label, Phase 3, single-arm, multi-center study in CAD patients who are symptomatic, have a hemoglobin ≤10 g/dL during screening, and received at least 1 transfusion during the 6 months prior to study entry.	**Part A**: **Treatment:** 6.5 grams if <75 kg or 7.5 grams if ≥75 kg of sutimlimab (60-minute infusions on days 0, 7, 21, 35, 49, 63, 77, 91, 105, 119, 133, 147, 161, and 175) **Duration**: Treatment for 6 months (26 weeks).	**Part A**: 24 patients
	Objective: Evaluate efficacy (Part A), and the long-term safety and tolerability (Part B) of sutimlimab in patients with CAD.	**Part B**: **Treatment**: 6.5 grams if <75 kg or 7.5 grams if ≥75 kg of sutimlimab every 2 weeks. **Duration**: Treatment with biweekly sutimlimab administrations for 2 years after last patient out of Part A. Safety follow-up continues for 9 weeks after the last study drug administration.	**Part B**: 22 patients
BIVV009-01 Part C	Phase 1, open-label, multi-dose administration of sutimlimab 60 mg/kg in patients with other CMDs including BP, WAIHA, and AMR. **Primary Objective**: Evaluate the safety and tolerability of sutimlimab in humans with complement-mediated disorders.	**Treatment**: Single dose (10 mg/kg) and subsequent weekly doses x 4 (60 mg/kg). **Duration**: Patients were dosed on Days 0, 4, 11, 18, and 25 with safety follow-up for 4 weeks after the last dose until the end of study visit on Day 53.	**BP**: 10 patients **WAIHA**: 4 patients **AMR**: 10 patients **CAD**: 10 patients
BIVV009-01 Part E	Open-label, Phase 1, extension part in a subset of patients with CAD who were previously treated with sutimlimab in another clinical study or named patient use.	**Treatment**: Part E: Patients who weigh less than 75 kg receive fixed doses of 6.5 grams of sutimlimab and patients who weigh 75 kg or more receive fixed doses of 7.5 grams of sutimlimab.	4 patients

[redacted]

Study	Study Design	Treatment and duration	Number of patients/subjects evaluated for safety[a]
	Primary Objective: Evaluate the safety and tolerability of sutimlimab in humans with CAD.	**Duration**: Patients dosed on Day 0, Week 1, and every 2 weeks thereafter until the last visit. Safety follow-up continues for 9 weeks after the last dose of study drug administration.	
BIVV009-04 (Part A/B)	**Part A**: Phase 3, supportive, randomized, double-blind, placebo-controlled study designed to evaluate the efficacy, safety, and tolerability of sutimlimab in patients with symptomatic primary CAD who have a hemoglobin ≤10 g/dL and who have not received a recent transfusion. Up to 40 patients will be randomized 1:1 to receive an IV infusion of sutimlimab or placebo.	**Part A**: **Treatment**: 6.5 grams if <75 kg or 7.5 grams if ≥75 kg of sutimlimab on Day 0, 7 and ever 2 weeks for remainder of study.	**Part A**: 42 patients Sutimlimab: 22 patients Placebo: 20 patients
	Part B: Following completion of dosing in Part A, patients will roll into the long-term safety and durability of response extension phase and receive sutimlimab in an open-label manner. **Primary Objective (Part A)**: Determine whether sutimlimab administration results in a ≥1.5 g/dL increase in hemoglobin level and avoidance of transfusion in patients with primary CAD without a recent history of blood transfusion. **Primary Objective (Part B)**: Evaluate long-term safety and tolerability of sutimlimab in patients with CAD.	**Duration**: Treatment on Days 0, 7, 21, 35, 49, 63, 77, 91, 105, 119, 133, 147, 161, and 175. End-of-treatment visit on Day 182 (Week 26). **Part B**: **Treatment**: Biweekly dosing with 6.5 grams if <75 kg or 7.5 grams if ≥75 kg of sutimlimab. **Duration**: a minimum of 52 weeks of biweekly administration of sutimlimab after last patient out from Part A with 9-weeks follow-up after last dose of study drug.	**Part B**: 39 patients 19 patients from sutimlimab group 20 patients from placebo group
BIVV009-201 (Part A/B)	Phase 1, open-label, multicenter, study of multiple doses of sutimlimab in up to 16 patients who have chronic ITP. **Part A**: Open-label study with 21-week treatment period.	**Part A**: **Treatment:** 6.5 grams if <75 kg or 7.5 grams if ≥75 mg of sutimlimab on Day 0, 7 and then every 2 weeks for remainder of study.	**Part A**: 12 patients
	Part B: Open-label long-term treatment for patients who benefited from sutimlimab in Part A. Patients who experience an insufficient response to sutimlimab during Part B of the study may receive concomitant therapy for ITP if combination therapy provides benefit.	Duration: 11-dose treatment period, 9-week safety follow-up/washout period. **Part B**: **Treatment**: 6.5 grams if <75 kg or 7.5 grams if ≥75 kg of sutimlimab every 2 weeks.	**Part B**: 7 patients

[redacted]

Study	Study Design	Treatment and duration	Number of patients/subjects evaluated for safety[a]
	Primary Objective: Evaluate the safety and tolerability of multidose sutimlimab in adult patients with chronic ITP.	**Duration**: Sutimlimab administration continues biweekly for up to 52 weeks with 9-week safety follow-up after last dose of study drug.	

a Data from all completed studies is included in the table.
AMR: Antibody-Mediated Rejection; BP: Bullous Pemphigoid; CAD: Cold Agglutinin Disease; CMD: Complement-Mediated Disorder; CP: Classical Complement Pathway; CSR: Clinical Study Report; FIH: First In Human; ITP: Immune Thrombocytopenic Purpura; IV: Intravenous; MAD: Multiple-Ascending Dose; NHV: Normal Healthy Volunteer; PK/ADA: Pharmacokinetic/Anti-drug Antibody; SAD: Single-Ascending Dose; WAIHA: Warm Auto-Immune Hemolytic Anemia.

A total of 208 subjects (76 patients with CAD, 36 patients with other CMDs, and 96 NHVs) were enrolled in sutimlimab studies.

The CAD safety analysis set is the primary focus of the safety analysis in the RMP and includes CAD patients who received at least one dose of sutimlimab in the completed Phase 1 open-label study BIVV009-01 (Part C), the completed Phase 1 open-label extension phase of study BIVV009-01 (Part E), the completed Phase 3 open-label study BIVV009-03 (Part A), the completed extension phase of study BIVV009-03 (Part B), the completed double-blind placebo-controlled Phase 3 study BIVV009-04 (Part A) and the completed open-label extension phase of study BIVV009-04 (Part B). Overall, 76 patients with CAD were exposed to sutimlimab for a total of 146.94 patient-years. Exposure data from these studies are summarized in Table 9.

Safety data in patients with other CMD, BP, WAIHA, renal allograft AMR and ITP were considered supportive to the safety profile characterized in the CAD population with data included from one completed Phase 1 open-label study BIVV009-01 Part C and one completed Phase 1 open-label study BIVV009-201 Parts A and B. A total of 36 patients with other CMDs received at least one dose of sutimlimab for 16.16 patient-years. Exposure data from these studies are summarized in Table 10.

Safety data in NHVs treated with sutimlimab were also considered supportive to the safety profile characterized in the CAD population with data included from one completed Phase 1 double-blind randomized study BIVV009-01 Parts A and B, one completed Phase 1 double-blind study TNT009-02, and one completed Phase 1 open-label study BIVV009-05 Parts A and B. Among the 96 NHVs who were exposed to sutimlimab the total of subject years exposure is of 6.76. Of these, 39 were exposed for 5 weeks or more, representing 4.38 subject-years. Of these subjects, 54 received a single dose of sutimlimab and 42 received multiple doses of sutimlimab. No additional exposure information is provided in the RMP for NHVs.

Table 9 - Summary of number of subjects and subject-years by subgroups CAD Safety Analysis Set

	BIVV009	
Subgroup	**Number of subjects**	**Subject-years**
Total BIVV009 (CAD Safety Analysis Set)	76	146.94
Age (years)		
<18	0	0

[redacted]

		BIVV009	
	Subgroup	**Number of subjects**	**Subject-years**
	Male	0	0
	Female	0	0
18 to <40		0	0
	Male	0	0
	Female	0	0
40 to <65		25	45.66
	Male	4	4.93
	Female	21	40.73
≥65		51	101.55
	Male	16	28.93
	Female	35	72.62
Gender			
Male		20	33.86
Female		56	113.35
Race			
White		16	25.86
Black or African American		0	0
Asian		11	23.98
American Indian or Alaska Native		0	0
Native Hawaiian or other Pacific Islander		0	0
Other		0	0
Not Collected		48	95.79
Not Reported		1	1.58
Ethnicity			
Hispanic/Latino		1	0.60
Not Hispanic/Latino		16	37.97
Not Collected		58	107.07
Not Reported		1	1.58
Duration of exposure (Weeks)[a]			
≥5 weeks		75	147.15
≥15 weeks		65	145.87
≥25 weeks		64	145.45
≥35 weeks		63	144.85
≥45 weeks		62	144.00
≥55 weeks		60	142.04

[redacted]

Subgroup	BIVV009	
	Number of subjects	Subject-years
≥65 weeks	55	136.42
≥75 weeks	54	135.13
≥85 weeks	51	130.41
≥95 weeks	45	120.16
≥105 weeks	42	114.43
BIVV009 dose level[b]		
60mg/kg	10	1.03
5.5g	4	10.25
6.5g	51	103.08
7.5g	15	32.85

NOTE: 1. The CAD Safety Analysis Set is defined as all subjects who received at least one dose (full or partial) of BIVV009 in BIVV009-03 (Part A and/or B), all subjects who received at least one dose (full or partial) of BIVV009 or placebo in study BIVV009-04 (Part A and/or B), and all CAD subjects who received at least one dose (full or partial) of BIVV009 in BIVV009-01 Part C and/or E. Cold agglutinin disease group includes primary, secondary, and mixed AIHA and CAD.

a Subject-years exposed to study treatment is calculated as the sum of duration of exposure in days/365.25. Duration of exposure in days is defined as (date of last dose of study drug - date of first dose of study drug + 15) for subjects who completed or early terminated from a given study. The gap between BIVV009-01 Part C (CAD) and E is excluded.

b Subjects may appear in more than one dose level. The subject-years is the sum of duration of exposure at that dose level. 10 mg/kg is the 1st test dose for BIVV009-01C, which is included in the 60 mg/kg regimen.

PGM=PRODOPS/BIVV009/RMP/RMP_2022/REPORT/PGM/t_exp_subgrp_cad.sas OUT=REPORT/OUTPUT/t_exp_subgrp_cad_x.rtf (07JUL2022 19:02)

AIHA: Autoimmune Hemolytic Anemia; CAD: Cold Agglutinin Disease.

Table 10 - Summary of number of subjects and subject years by subgroups Other CMD Safety Analysis Set

Subgroup		BIVV009	
		Number of subjects	Subject-years
Total BIVV009 (Other CMD Safety Analysis Set)		36	16.16
Age (years)			
<18		0	0
	Male	0	0
	Female	0	0
18 to <40		5	0.42
	Male	2	0.12
	Female	3	0.30
40 to <65		17	11.90
	Male	7	1.05
	Female	10	10.85
≥65		14	3.84
	Male	7	0.65

Subgroup	BIVV009	
	Number of subjects	Subject-years
Female	7	3.19
Gender		
Male	16	1.83
Female	20	14.33
Race		
White	31	7.78
Black or African American	3	8.14
Asian	1	0.14
American Indian or Alaska Native	0	0
Native Hawaiian or other Pacific Islander	0	0
Other	1	0.10
Not collected	0	0
Ethnicity		
Hispanic/Latino	1	0.06
Not Hispanic/Latino	11	13.84
Not Collected	24	2.26
Duration of exposure (Weeks)[a]		
≥5 weeks	30	15.85
≥15 weeks	7	13.45
≥25 weeks	6	11.73
≥35 weeks	6	11.73
≥45 weeks	5	10.89
≥55 weeks	5	10.89
≥65 weeks	4	9.76
≥75 weeks	4	9.76
≥85 weeks	4	9.76
≥95 weeks	4	9.76
≥105 weeks	4	9.76
BIVV009 dose level[b]		
5.5 g	5	1.46
6.5 g	3	3.33
7.5 g	7	9.11
60 mg/kg	24	2.26

[redacted]

Subgroup	BIVV009	
	Number of subjects	Subject-years

NOTE 1: The Other CMD Safety Analysis Set is defined as all subjects who received at least one dose of BIVV009 (full or partial) in study BIVV009-201 (ITP) (Part A and/or B) and BIVV009-01 Part C, whose disease group is BP, WAIHA, or AMR.

a Subject-years exposed to study treatment is calculated as the sum of duration of exposure in days/365.25. Duration of exposure in days is defined as (date of last dose of study drug - date of first dose of study drug + 15) for subjects who completed or early terminated from a given study, or (date of data cutoff - date of first dose of study drug + 1) for subjects ongoing in BIVV009-201. The gap between BIVV009-201 Part A and B is excluded.

b Subjects may appear in more than one dose level. The subject-years is the sum of duration of exposure at that dose level.

PGM=PRODOPS/BIVV009/RMP/RMP_2022/REPORT/PGM/t_exp_subgrp_oth_cmd.sas
OUT=REPORT/OUTPUT/t_exp_subgrp_oth_cmd_x.rtf (07JUL2022 19:02)

AMR: Antibody-Mediated Rejection; BP: Bullous Pemphigoid; CMD: Complement-Medicated Disorder; WAIHA: Warm Autoimmune Hemolytic Anemia.

RISK MANAGEMENT PLAN - PART II MODULE SIV: POPULATIONS NOT STUDIED IN CLINICAL TRIALS

SIV.1 EXCLUSION CRITERIA IN PIVOTAL CLINICAL STUDIES WITHIN THE DEVELOPMENT PROGRAMME

Table 11 - Important exclusion criteria in pivotal studies in the development program

Exclusion criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
Patients with specific past or current medical history			
Clinical diagnosis of SLE or other autoimmune disorders with anti-nuclear antibodies at screening.	Subjects with the clinical diagnosis of SLE or other autoimmune disorders identified at study screening were excluded to minimize confounding of sutimlimab safety and efficacy evaluation from the mechanism-based potential risk of SLE development and the association between autoimmune diseases and CAS or anemia of chronic inflammation. (33)(34)(35)(36)(37)(38)	No	Development of Systemic Lupus Erythematosus. is considered an important potential risk with sutimlimab.
Clinically significant medical history or ongoing chronic illness that would jeopardize the safety of the patient or compromise the quality of the data derived from his/her participation in this study (as determined by the Investigator [or designee]) at Screening.	The presence of clinically significant medical illnesses could confound the efficacy and safety assessment of sutimlimab.	No	This exclusion criterion does not meet the level of importance to be retained in missing information and was included because it is a typical exclusion in clinical studies.
History of hypersensitivity to sutimlimab or any of its components.	This is a standard exclusion criterion in clinical studies due to safety concerns. Severe hypersensitivity reactions and anaphylaxis may occur with IV infusion of exogenous proteins, such as mAbs, and may involve immediate or delayed hypersensitivity reactions.(39)(40) Patients with a history of hypersensitivity reactions to	No	Serious hypersensitivity reactions and/or anaphylaxis with sutimlimab is considered an important potential risk. Hypersensitivity reactions to sutimlimab or its components will remain a contraindication for sutimlimab use.

Exclusion criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
	sutimlimab or any of its components are excluded to avoid confounding the safety assessment of sutimlimab.		
Subjects without documented vaccinations against encapsulated bacterial pathogens (*Neisseria meningitis*, including serogroup B meningococcus where available, *Haemophilus influenzae*, and *Streptococcus pneumoniae*) within 5 years of enrollment or as specified per protocol.	Subjects without vaccinations treated with sutimlimab may be at increased risk for infections with certain encapsulated bacteria.	No	Serious infections is an important identified risk and meningococcal infections is an important potential risk with sutimlimab. Vaccinations will be required in patients prior to receiving sutimlimab.
Infections and infestations: • Clinically relevant infection of any kind within the month preceding enrollment (eg, active hepatitis C, pneumonia). • Positive hepatitis panel (including hepatitis B surface antigen and/or hepatitis C virus antibody). • Positive HIV antibody at Screening.	Patients with the presence of these conditions were excluded to avoid confounding the efficacy and safety evaluation of sutimlimab. Febrile illnesses or other infections may trigger exacerbations of anemia in patients with CAD. (41) Cold agglutinins have been reported in small numbers of subjects with HIV and HCV (42)(43) and autoimmune hemolytic anemias have been reported among HCV infected persons. (44) Like other causes of CAS, treatment of these underlying conditions may lead to resolution of the cold agglutinins.	No	Serious infections is an important identified risk and meningococcal infections is an important potential risk with sutimlimab. Sutimlimab should be used with caution in patients with serious or systemic infections.
Cold agglutinin syndrome secondary to infection, rheumatologic disease, or active hematologic malignancy.	The presence of CAS may confound the assessment of the efficacy profile of sutimlimab. Cold agglutinin disease is due to a low-grade lymphoproliferative bone marrow disorder characterized by generation of IgM autoantibodies, cold agglutinins, from an often monoclonal expansion of B-cells. (8)(45) Cold agglutinin syndrome is often associated with polyclonal cold agglutinins, which may resolve	No	This exclusion criteria for secondary CAD/CAS was not due to specific safety concern with the use of sutimlimab. Sutimlimab should be used with caution in patients with serious or systemic infections.

Exclusion criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
	spontaneously or with appropriate treatment of the associated underlying condition. (4)(46) Subjects with CAS due to active hematologic malignancy were excluded due to potential drug-drug interaction with sutimlimab and chemotherapeutic agents and that the receipt of additional chemotherapeutic agents might impact the safety evaluation of sutimlimab.		
Females who are pregnant, lactating, or, if having reproductive potential, are considered potentially unreliable with respect to contraceptive practice.	This exclusion criterion is commonly applied to clinical trials for drugs or biologics in development before the safety profile is established in non-pregnant patients.	No	This exclusion criteria is considered as a common exclusion criterion in clinical trials and not due to specific safety concern. Human IgG antibodies are known to cross the placental barrier and to pass into human milk, however, there is no available data evidence in the literature suggesting that C1s inhibitors would have a potential of adversely impacting fertility and ability to get pregnant. Moreover, pregnant and breast-feeding women may not be a target population since risks of CAD onsets increase after the age of 55 years. Use in females who are pregnant or lactating is properly addressed in the label.
• Concurrent treatment with corticosteroids other than a stable daily dose equivalent to ≤10 mg/day prednisone for previous 3 months. • Treatment with rituximab monotherapy within 3 months or rituximab combination therapies (eg, with bendamustine, fludarabine, ibrutinib, or cytotoxic drugs)	Corticosteroids and rituximab may be used as treatment for CAD. The use of these pharmacologic therapies may confound the evaluation of the efficacy and safety profile of sutimlimab.	No	Although there is limited Company sponsored clinical trial experience with subjects who received rituximab or rituximab combination therapies or an equivalent daily dose of ≥10 mg/day prednisone or have had changes in the steroid dose during the conduct of the study, corticosteroids, rituximab and rituximab combination therapies are immunosuppressive agents that may increase the risk for infections. Therefore, exposure to other immunomodulatory agents is considered as a risk factor and addressed as such in [Part II SVII]. The label recommends to use caution when treating patients who may be immunocompromised.

[redacted]

Exclusion criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
within 6 months prior to enrollment.			
• Erythropoietin deficiency. Concurrent treatment with erythropoietin is permitted if the patient has been on a stable dose for the previous 3 months. • Concurrent usage of iron supplementation unless the patient has been on a stable dose for at least 4 weeks.	Iron and erythropoietin may be used to treat non-CAD causes of anemia. The introduction of these pharmacologic therapies may confound the evaluation of the efficacy profile of sutimlimab.	No	The exclusion of subjects receiving erythropoietin or iron was not due to a specific safety concern with sutimlimab but to avoid confusion in the evaluation of the efficacy profile of Sutimlimab.
Exclusion criteria related to study methodology			
Patients <18 years of age.	Exclusion of pediatric patients is typical in early development and the target indication does not typically affect pediatric patients.	No	Cold agglutinin disease is an adult-onset disorder. Pediatric subjects are not part of the target patient population for this indication.
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.	Effects of these treatments may confound the safety and efficacy evaluation of sutimlimab.	No	The exclusion was not due to a specific safety concern with the use of sutimlimab but to avoid confusion in the evaluation of the efficacy profile of sutimlimab.
Weight less than 39 kg.	Subjects with weight less than 39 kg were excluded per calculated endotoxin limits for exposure based on the 18 mg/mL sutimlimab formulations.	No	The exclusion was due to be compliant with endotoxin limits calculated using the precise formulation of the drug used in clinical studies.

C1s: Complement component 1, s subcomponent; CAD: Cold Agglutinin Disease; CAS: Cold Agglutinin Syndrome; HCV: Hepatitis C Virus; HIV: Human Immunodeficiency Virus; IgG: Immunoglobulin G; IgM: Immunoglobulin M; IV: Intravenous; mAb: Monoclonal Antibody; SLE: Systemic Lupus Erythematosus.

[redacted]

SIV.2 LIMITATIONS TO DETECT ADVERSE REACTIONS IN CLINICAL TRIAL DEVELOPMENT PROGRAMMES

The clinical development program is unlikely to detect certain types of adverse reactions such as rare or very rare adverse reactions and adverse reactions with a long latency that is beyond study period.

Cumulative effects are not anticipated due to the short half-life of sutimlimab, extensive metabolism and lack of tissue accumulation.

SIV.3 LIMITATIONS IN RESPECT TO POPULATIONS TYPICALLY UNDER-REPRESENTED IN CLINICAL TRIAL DEVELOPMENT PROGRAMMES

Table 12 - Exposure of special populations included or not in clinical trial development programs

Type of special population	Exposure
Pregnant women	Not included in the clinical development program. As of DLP for this RMP, no pregnancies were reported in the clinical development program.
Breast-feeding women	
Patients with relevant co-morbidities • Patients with hepatic impairment • Patients with renal impairment • Patients with cardiovascular impairment • Patients with a disease severity different from inclusion criteria in clinical trials	• Number of CAD subjects (and subject-years) with history of: - Hepatic impairment: 9 (17.2 subject-years) - Renal impairment: 6 (12.84 subject-years) - Cardiovascular impairment: 15 (32.10 subject-years) Not relevant
Populations with relevant different ethnic origin	Not relevant
Subpopulations carrying known and relevant genetic polymorphisms	Not relevant
Other: • Elderly (≥65 years of age) • Pediatric patients (<18 years of age)	Number of CAD subjects (and subject-years): 51 (99.51 subject-years). Pediatric population not included in the clinical development program

CAD: Cold Agglutinin Disease; DLP: Data Lock Point; RMP: Risk Management Plan.

No data are available concerning the use of sutimlimab in pregnant or breast-feeding women. To date, there is no evidence from non-clinical studies that sutimlimab is teratogenic or embryotoxic based on a 26-week ePPND study in cynomolgus monkeys. Most subjects with CAD are elderly subjects, however, women of child-bearing potential may be included in the target population.

Use of sutimlimab in pregnant or breastfeeding women is properly addressed in the label.

To date, there is no information to suggest that patients of specific racial or ethnic origins are adversely affected by sutimlimab.

To date, there is no information suggesting the existence of polymorphism relevant to the efficacy or safety of sutimlimab in the currently proposed indication.

[redacted]

To date, there is no information to suggest that the patients of specific ages are adversely affected by the use of sutimlimab.

Subjects with hepatic, renal and cardiovascular impairment were not specifically excluded from the clinical development program. While subjects with cardiovascular impairment might require slower infusion due to drug volume, there are no specific safety concerns in these patient populations.

[redacted]

RISK MANAGEMENT PLAN - PART II MODULE SV: POST-AUTHORIZATION EXPERIENCE

As of the DLP of the RMP, the drug is not yet registered in any market. This module is therefore “not applicable”.

[redacted]

RISK MANAGEMENT PLAN - PART II MODULE SVI: ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

SVI.1 POTENTIAL FOR MISUSE FOR ILLEGAL PURPOSES

Overall, there was no evidence in animal toxicology or pharmacology studies to suggest a dependence potential or abuse liability for sutimlimab and thus, no dedicated drug abuse liability assessment studies of sutimlimab were conducted. The reasons for this are detailed below.

Sutimlimab is a humanized IgG4 mAb that binds to and inhibits the CP specific serine protease, C1s. With a molecular weight of approximately 145 kDa, sutimlimab is unlikely to cross the blood-brain barrier to any significant extent. In general, brain penetration is limited unless a therapeutic molecule is lipid soluble with a molecular weight of less than 400 to 600 Da. (47) Thus, considering the literature data on similar monoclonal antibodies, very low concentrations of sutimlimab would be expected in the cerebrospinal fluid and any potential for abuse liability is considered very limited. (48)

Monoclonal antibodies do not have any active metabolites and are not precursors of identified controlled drug substances. It is generally recognized that monoclonal antibodies are metabolized by degradation into small peptides and individual amino acids and follow endogenous catabolism, and these small peptides and amino acids lack any other significant biological activity. Therefore, the potential for drug dependence and abuse liability from a degradation product of sutimlimab is very low.

In non-clinical, repeat-dose toxicology studies with sutimlimab, no functional or anatomic pathology effects in the CNS were evident in cynomolgus monkeys at doses up to 180 mg/kg/week IV for 26 weeks. No sutimlimab-related abnormal behavioral clinical signs or anatomic pathology findings in CNS tissues were observed. In the ePPND study in which sutimlimab was administered up to 180 mg/kg/week IV, no test article-related functional effects or anatomic pathology findings were observed in the CNS of pregnant monkeys or their offspring which were evaluated up to three months after birth. Functional developmental assessments in the offspring from sutimlimab-treated pregnant monkeys (including grasp support, eye reflexes, elicited postural tones (hip abduction, knee flexed, toes flexed, shoulder abducted, elbow flexed, finder glexed, head extended), elicited dorsiflexion (wrist; ankle), moro reflex, build-up, righting reflex, prone progression, clasp/grasp reflex, visual following, sucking, rooting, snout reflex, pupil response, glabellar tap, lipsmack orient) were comparable to the control group and no sutimlimab related effects were observed. For the 26-week repeat-dose toxicology study, the NOAEL C_{max} of 11 700 µg/mL was above the ex-vivo IC_{90} for sutimlimab-mediated inhibition of CP activity (22.3 µg/mL).

[redacted]

RISK MANAGEMENT PLAN - PART II MODULE SVII: IDENTIFIED AND POTENTIAL RISKS

SVII.1 IDENTIFICATION OF SAFETY CONCERNS IN THE INITIAL RMP SUBMISSION

The following safety topics are discussed and presented in Section SVII.1.1 (Risks not considered important for inclusion in the list of safety concerns in the RMP):

- Potential harm from overdose
- Risks related to the administration procedure
- Effect on fertility
- Risk in pregnant and lactating women
- Hypertension
- Acrocyanosis and Raynaud's phenomenon
- Pediatric safety issues
- Potential for off-label use
- Potential for transmission of infectious agents

The following safety topics are discussed and presented in Section SVII.1.2 (Risks considered important for inclusion in the list of safety concerns in the RMP):

- Serious infections
- Meningococcal infections
- Development of Systemic Lupus Erythematosus
- Serious hypersensitivity reactions and/or anaphylaxis

SVII.1.1 Risks not considered important for inclusion in the list of safety concerns in the RMP

Reason(s) for not including an identified or potential risk in the list of safety concerns in the RMP

- Risks related to administration:

Sutimlimab will have a single formulation, single IV route of administration and be packaged as single use vials of 1.1 g each. The final dose will be prepared and dispensed by a healthcare professional (HCP) based on the subject's weight (either 6 vials for a 6.5 g dose or 7 vials for a 7.5 g dose) in an inpatient hospital or infusion center or at home in case of home infusion at the time of each dose.

- Potential harm from overdose: Pharmacodynamically, sutimlimab exhibits a binary "all or none" complete or nearly complete inhibition of CP deficiency, with increased dose levels leading to increased duration of inhibition. The human safety risk from off target effects of mAbs therapeutics is generally considered to be low. Based on the data from

[redacted]

non-clinical and clinical studies conducted to date, there is no evidence of overdose or increased risk of intentional overdose. In toxicologic studies, no adverse effects were observed from sutimlimab administration up to the highest dose evaluated (180 mg/kg/week). Sutimlimab will be prepared by an HCP and administrated within an inpatient hospital or infusion center or at home in case of home infusion. Therefore, the potential risk of overdose is considered low for which no specific pharmacovigilance or risk minimization activities are necessary.

- Risks related to the administration procedure: Sutimlimab is administered via IV infusion pump without an associated medical device. The risks related to the administration procedure are similar to other products administered intravenously and are unrelated to sutimlimab. Thus, there are no risks related to the administration procedure specific to sutimlimab and no specific pharmacovigilance or risk minimization activities are required.

- Risk with minimal clinical impact on patients:
  - Effect on fertility: Dedicated animal fertility studies have not been conducted for sutimlimab to assess the impact on fertility or sperm, so it is not known whether sutimlimab can affect fertility or sperm development in humans. No adverse effects on reproductive organs have been observed in cynomolgus monkeys of either sex, up to the highest dose evaluated (180 mg/kg/week) following 26 weeks of administration. The target patient population with CAD is generally over 55 years old, so the impact on fertility would not be considered applicable for that patient population. A specific labeling statement is proposed, and no additional pharmacovigilance or risk minimization activities are necessary.
  - Risk in pregnant and lactating women: As previously mentioned, the target patient population with CAD is generally over 55 years old. A specific labeling statement is proposed, and no additional pharmacovigilance or risk minimization activities are deemed necessary.
- Known risks that do not impact the risk-benefit profile
  - Hypertension: As of the DLP of the RMP, of the 66 patients who participated in two phase 3 CAD clinical studies (BIVV009-03 Part A and B and BIVV009-04 Part A and B) 16 patients (21.1%), experienced an event of hypertension and 3 patients (4.5%) experienced an event of increased blood pressure. Of the 10 patients who participated in the BIVV009-01 C and E studies, none of them experienced an event of hypertension or blood pressure increased. Overall the increase of systolic blood pressure and diastolic blood pressure during treatment with sutimlimab have been minimal with values remaining close to normal range, resulting in the initiation of an antihypertensive drug or adaptation of underlying antihypertensive treatment in a limited number of patients. This is an adverse drug reaction listed in the labeling.
  - Acrocyanosis/Raynaud's phenomenon: As of the DLP of the RMP, of the 66 patients who participated in two phase 3 CAD clinical studies (BIVV009-03 Part A and B and BIVV009-04 Part A and B) 13 patients (19.7%) experienced acrocyanosis and 7 patients (10.6%) experienced Raynaud's phenomenon. Of the 10 patients who participated in the BIVV009-01 C and E study, 2 (20%) patients experienced Raynaud's phenomenon and none of the patients experienced acrocyanosis. Acrocyanosis and Raynaud's phenomenon are symptoms of the underlying disease (CAD). Substantial

reductions in their incidence at Week 26 versus baseline were observed in the sutimlimab group compared with minimal changes in the placebo group, however in a limited subset of patients a new onset or a worsening of these symptoms occurred during treatment with sutimlimab. Acrocyanosis and Raynaud's phenomenon are considered as a potential risk of sutimlimab and are addressed in the labeling.

- Not applicable due to the target patient population for this indication
  - Pediatric safety issues: Cold agglutinin disease is an adult-onset disorder. Pediatric subjects are not part of the target patient population for this indication.
- Other reasons for considering the risks not important
  - Potential for off-label use: The potential for off-label use of sutimlimab is expected to be low given the specific mode of action of sutimlimab.
  - Potential for transmission of infectious agents: Sutimlimab is produced from the master cell bank (MCB) [redacted] derived from the Chinese hamster ovary (CHO)-M cell line [redacted]. Sutimlimab is expressed in CHO cells and is produced using standard mammalian cell cultivation methods followed by chromatographic purification. Drug product is manufactured from drug substance by sterile filtration and aseptic filling into Type I glass vials with bromobutyl rubber caps and aluminum crimp seals. The aseptic manufacture of sutimlimab is validated and carried out in accordance with the "EU Guidelines to Good Manufacturing Practice (GMP) for Medicinal Products for Human Use, Annex 1". The risk of transmission of infectious agents is therefore considered to be low.

SVII.1.2 Risks considered important for inclusion in the list of safety concerns in the RMP

Table 13 - Important identified risks considered for inclusion in the list of safety concerns: Serious infections

Serious infections	
Scientific evidence that has led to the inclusion	Mechanism of action, class effect seen with terminal complement inhibitors and literature findings in subjects with acquired or inherited classical complement deficiency. The CP has multiples roles in both innate and adaptive immunity. Pharmacologic inhibition or inherited deficiency of the CP may lead to impaired opsonization of antigen-antibody complexes, phagocytosis and pathogen neutralization or killing. (49)(50) While the CP plays an essential role for bacterial killing, particularly gram-negative or encapsulated organisms, complement activation also occurs with other pathogens, such as viruses. (51)
Risk-benefit impact	Serious infections such as pneumoniae, sepsis, or meningitis may result in death, be life-threatening, or result in significant disability if not prevented or managed appropriately. As of the DLP of the RMP, of the 66 patients who participated in two phase 3 CAD clinical studies (BIVV009-03 Part A and B and BIVV009-04 Part A and B) 10 patients (15.2%) experienced at least one serious TEAE of infection. Of the 10 patients who participated in the BIVV009-01 C and E studies, 2 (20.0%) patients experienced serious infections. Serious infections due to encapsulated bacteria have been reported. This remains a mechanism related risk and CAD patients have limited therapy choices. Thus, the risk-benefit profile of sutimlimab remains favorable.

CAD: Cold Agglutinin Disease; CP: Classical Complement Pathway; DLP: Data Lock Point; RMP: Risk Management Plan; TEAE: Treatment-Emergent Adverse Event.

[redacted]

Table 14 - Important potential risks considered for inclusion in the list of safety concerns: Meningococcal infections

Meningococcal infections	
Scientific evidence that has led to the inclusion	Mechanism of action, class effect seen with terminal complement inhibitors and literature findings in subjects with acquired or inherited classical and terminal complement deficiency. The complement system is part of our innate immunity and consists of three pathways (classical, lectin and alternative). The complement system has multiples roles in both innate and adaptive immunity. Pharmacologic inhibition or inherited deficiency of the components of the complement pathway may lead to impaired opsonization of antigen-antibody complexes, phagocytosis and pathogen neutralization or killing. Terminal complement inhibition may prevent the formation of the membrane-attack complex which is integral to the killing of *N. meningitidis*. (49)(50)
Risk-benefit impact	Meningococcal infections such as sepsis or meningitis may result in death, be life-threatening, or result in significant disability if not prevented or managed appropriately. As of the DLP of the RMP, there have been no report of meningococcal infections or meningitis identified. This remains a potential mechanism related risk and CAD patients have limited therapy choices. Thus, the risk-benefit profile of sutimlimab remains favorable.

CAD: Cold Agglutinin Disease; DLP: Data Lock Point; RMP: Risk Management Plan.

Table 15 - Important potential risks considered for inclusion in the list of safety concerns: Development of Systemic Lupus Erythematosus

Development of Systemic Lupus Erythematosus	
Scientific evidence that has led to the inclusion	Mechanism of action and literature findings in subjects with acquired or inherited classical complement deficiency. Long-term CP inhibition could theoretically increase the risk of SLE due to the role of the C1 complex in immune complex clearance, as seen in patients with congenital deficiencies of C1 complex components (C1q, C1s, and C1r). C4 and C1q deficiency identified as the strongest genetic risk factors for SLE. (52)(53)
Risk-benefit impact	Development of SLE is a serious chronic condition that may be life-threatening or result in persistent or significant disability if not managed appropriately. As of the DLP of the RMP, there have not been any SAE reports of SLE development in subjects receiving sutimlimab. As of now this remains a potential mechanism related risk and CAD patients have limited therapy choices. Thus, the risk-benefit profile of sutimlimab remains favorable.

CAD: Cold Agglutinin Disease; C1: Complement component 1; C1q: Complement component 1, q subcomponent; C1r: Complement component 1, r subcomponent; C1s: Complement component 1, s subcomponent; C4: Complement component 4; CP: Classical Complement Pathway; DLP: Data Lock Point; RMP: Risk Management Plan; SAE: Serious Adverse Event; SLE: Systemic Lupus Erythematosus.

Table 16 - Important potential risks considered for inclusion in the list of safety concerns: Serious hypersensitivity reactions and/or anaphylaxis

Serious hypersensitivity reactions and/or anaphylaxis	
Scientific evidence that has led to the inclusion	Mechanism of action, Class effect seen with mAbs. Large protein molecules, despite humanization, can be immunogenic. Sutimlimab is biologic therapeutic protein and hypersensitivity risk is considered a class effect with mAbs. Inhibition of CP doesn't prevent LP or AP activation, which may produce potent anaphylatoxins.
Risk-benefit impact	Symptoms may range from local injection site reactions to anaphylactic shock, which can be life-threatening.

[redacted]

Serious hypersensitivity reactions and/or anaphylaxis	
	As of the DLP of the RMP, there have been no SAEs reported suggestive of hypersensitivity reactions or anaphylaxis associated with sutimlimab administration. While the possibility of hypersensitivity or allergic reactions cannot be excluded, CAD patients have limited therapy choices and the risk-benefit profile of BIVV009 remains favorable.

AP: Alternative Pathway; CAD: Cold Agglutinin Disease; CP: Classical Complement Pathway; DLP: Data Lock Point; LP: Lectin Pathway; mAb: Monoclonal Antibody; RMP: Risk Management Plan; SAE: Serious Adverse Event.

SVII.2 NEW SAFETY CONCERNS AND RECLASSIFICATION WITH A SUBMISSION OF AN UPDATED RMP

Not applicable

SVII.3 DETAILS OF IMPORTANT IDENTIFIED RISKS, IMPORTANT POTENTIAL RISKS, AND MISSING INFORMATION

The following risks have been identified for sutimlimab:

- Important identified risk:
  - Serious infections
- Important potential risks:
  - Meningococcal infections
  - Development of Systemic Lupus Erythematosus
  - Serious hypersensitivity reactions and/or anaphylaxis
- Missing information:
  - None

SVII.3.1 Presentation of important identified risks and important potential risks

Table 17 - Important identified risk: Serious infections

Important identified risk	Serious infections
Potential mechanism	Based on the functions of the CP in the innate and adaptive immune system and experience in subjects receiving terminal complement inhibitors, CP inhibition could lead to impaired opsonization of antigen-antibody complexes and reduced pathogen killing, particularly with encapsulated bacterial organisms (eg, *S. pneumoniae* and *H. influenzae*). (49) Sutimlimab is an inhibitor of the CP and therefore long-term complement inhibition may increase the risk of serious infections, especially with encapsulated bacteria, such as pneumoniae, sepsis and meningitis.
Evidence source(s) and strength of evidence	Mechanism of action; literature reports in patients with inherited classical complement deficiencies, class effect in patients receiving terminal complement pathway inhibitors. The CP functions as part of the innate and adaptive immune response to foreign pathogens. Subjects with inherited CP component deficiencies have an increased risk of infections with a variety of encapsulated bacterial organisms, similar to patients with hypogammaglobulinemia. (49)(50)(52)(54) Unlike with terminal complement deficiencies where meningococcal infections

Important identified risk	Serious infections
	predominate, the types of infections seen in subjects with congenital CP deficiencies include a variety of encapsulated bacteria. (49)(54)(55)(56) Sutimlimab only targets the CP and leaves both the AP and LP intact for immune surveillance.
Characterization of the risk	As sutimlimab leaves the lectin and alternative pathways intact for immune surveillance as well as the terminal complement pathway intact for formation of the membrane attack complex, the risk of infection, particularly with encapsulated bacteria, may be lower than with other complement inhibitors. Unlike with terminal complement deficiencies, the type of infections in subjects with congenital CP deficiencies mimic those with hypogammaglobulinemia and include other organisms besides meningococcus. Cold agglutinin disease patients have an increased risk of serious infections at baseline due to impaired immune function as it affects an elderly, often medically complex patient population. Cold agglutinin disease subjects may receive other immunomodulatory agents, which depending on the gap before sutimlimab treatment may have a lingering impact on immune functions. Cold agglutinin disease is most often associated with an underlying B-cell lymphoproliferative disorder, which may separately impair immune response. Frequency: As of the DLP of the RMP, of the 66 patients who participated in two phase 3 CAD clinical studies (BIVV009 03 Part A and B and BIVV009 04 Part A and B) 10 patients (15.2%) have experienced at least one serious TEAE of infection, including infections with Escherichia coli, Staphylococcus aureus and Staphylococcus epidermidis, which are encapsulated bacteria. Of the 10 patients who participated in the BIVV009-01 C and E studies, 2 (20.0%) patients experienced serious infections. While serious infections have been reported in CAD patients receiving sutimlimab, these patients are elderly, medically complex, and the majority have other underlying risk factors for infection including prior/concomitant immunomodulatory therapies. Treatment with sutimlimab was discontinued in one patient due to serious TEAE of *Klebsiella pneumonia*. Severity and nature of risk: As of the DLP of the RMP, the pattern of infections in patients with CAD was consistent with an older, often medically complex patient population, including some patients who received chronic immunomodulatory therapies. While serious infections were reported, including with encapsulated bacteria (eg, E. coli, Streptococcus pyogenes, S. aureus, and S. epidermidis), often the causative organism was not identified. Most patients with serious infections had underlying risk factors for infection. Seriousness/outcomes: Serious infections may result in death or be life threatening. As of the DLP of the RMP, of the 66 patients who participated in two phase 3 CAD clinical studies (BIVV009-03 Part A and B and BIVV009-04 Part A and B), one patient died due to serious TEAE of *K. pneumonia*. There were no fatal events of infections reported from the BIVV009-01 C and E study. Background incidence/prevalence: The annual incidence of hospitalized pneumonia has been described in five hospitals in Chicago and Nashville, from Jan-2010 to Jun-2012, estimated at 248/100 000 adults (235 to 261), with the highest rates in adults aged 65-79 years (630/100 000), and 80+ years (1643/100 000). (57) In Europe, the annual incidence of community-acquired hospitalized pneumonia has been reported to range from 0.5 to 15.1 cases per 1000 people in adults, and up to 242/1000 in adults >85 years old (Sweden). (58) In US database studies, the cumulative 24-years incidence of sepsis rose exponentially across age groups, from 29.6/100 000 in 18-29 age group, to 2422.3/100 000 in 90-99 age group. The incidence of severe sepsis in older patients was 2620/100 000 population. The mean age of patients with severe sepsis was 63.8 years in the first study, which increased to 68.2 years in the latter study. (59) In a retrospective database study in Norway (Patient Registry and Statistics Norway), (60) on the occurrence, patient characteristics and outcomes of sepsis hospitalizations in 2011-2012, the annual population incidence of hospitalized sepsis was 140/100 000

Important identified risk	Serious infections
	inhabitants; ranging from 10 to 2270/100 000 across age groups, with a significant male predominance. No quantitative epidemiologic data were identified regarding the frequency of serious infections in CAD patients.
Risk factors and risk groups	Risk factors for serious infections may include: patients that are unvaccinated or incompletely vaccinated; exposure to other immunomodulatory agents; concurrent hematologic and/or solid organ malignancies; other inherited or acquired immunodeficiency; asplenia; HIV/AIDS; CSF leak; cochlear implants; poorly controlled diabetes; chronic liver, kidney, heart, lung disease; elderly.
Preventability	This risk can be reduced or prevented with an appropriate program of prophylactic vaccinations. Informing HCPs and patients of signs and symptoms may facilitate early diagnosis and treatment. Immediate treatment and management could prevent serious outcomes.
Impact on the benefit-risk balance of the product	Based on review of currently available preclinical and clinical data, the demographics of the CAD patient population, and the mechanism of action of sutimlimab, serious infections remains a mechanism related risk and the benefit-risk remains positive.
Public health impact	Depending on the pathogen, other infectious agents can be spread by skin-to-skin contact, respiratory secretions, oral-fecal transmission, sexual contact, or blood-borne transmission. The individual health risk could be serious if not managed appropriately. However, the impact on public health has not been evaluated.

AIDS: Acquired Immuno Deficiency Syndrome; AP: Alternative Pathway; CAD: Cold Agglutinin Disease; CP: Classical Complement Pathway; CSF: Cerebrospinal Fluid; DLP: Data Lock Point; HCP: Healthcare Professional; HIV: Human Immunodeficiency Virus; LP: Lecithin Pathway; RMP: Risk Management Plan; TEAE: Treatment-Emergent Adverse Event; US: United States.

Table 18 - Important potential risk: Meningococcal infections

Important potential risk	Meningococcal infections
Potential mechanism	Based on the functions of the CP in the innate and adaptive immune system and experience in subjects receiving terminal complement inhibitors, CP inhibition with sutimlimab could theoretically lead to impaired opsonization of antigen-antibody complexes and reduced killing of *N. meningitidis*. (49)
Evidence source(s) and strength of evidence	Mechanism of action; literature; class effect seen with terminal complement inhibitors. Terminal complement component deficiency, particularly of C5b-C8 components, is associated with a 7000 to 10 000-fold higher risk of developing meningococcal disease. This is due to apparent critical role of the membrane attack complex for cell lysis and bacterial killing of Neisserial species. (61) Up to 20-30% of patients with recurrent disseminated Neisserial infections have complement deficiency. (50) Use of Eculizumab (SOLIRIS®), a marketed C5 terminal complement pathway inhibitor, is associated with a 1000 to 2000-fold increased risk of meningococcal infection, even in vaccinated patients. (55) Fifty to sixty percent of patients with congenital terminal complement deficiencies have systemic bacterial infections reported, which are almost exclusively with *N. meningitidis* and may recur in 50% of patients. In comparison, 20% of patients with early CP deficiencies report systemic infections, over half of which are due to *S. pneumoniae*. These infections in patients with congenital CP component deficiencies are rarely recurrent with the same organism and are less likely to be overwhelming severe if innate immunity is intact. (53) The CP functions as part of the innate and adaptive immune response to foreign pathogens. Subjects with inherited CP component deficiencies have an increased risk of infections with a variety of encapsulated bacterial organisms, similar to patients with hypogammaglobulinemia.(49)(50)(52)(54) Unlike with terminal complement deficiencies where

Important potential risk	Meningococcal infections
	meningococcal infections predominate, the types of infections seen in subjects with congenital CP deficiencies include a variety of encapsulated bacteria. (49)(54)(55)(56) Sutimlimab selectively inhibits the CP and leaves the immune surveillance functions of the AP and LP intact. Activation of the AP and LP can still lead to downstream activation of the terminal complement pathway. Antibody-coated *N. meningitidis* can activate both the CP and AP. However, simultaneous inhibition of the CP and AP prevented killing of antibody-coated *N. meningitidis.* (62)
Characterization of the risk	As BIVV009 leaves the lectin and alternative pathways intact for immune surveillance as well as the terminal complement pathway intact for formation of the membrane attack complex following activation of the LP and AP, the risk of meningococcal infection may be lower than with other complement inhibitors. Unlike with terminal complement deficiencies, the type of infections in subjects with congenital CP deficiencies mimic those with hypogammaglobulinemia and include other organisms besides meningococcus. Frequency: As of the DLP of this RMP, there have been no AEs reported of meningococcal infections or meningitis in patients receiving sutimlimab. Severity and nature of risk: As of the DLP of this RMP, no cases of meningococcal infections or meningitis have been reported in patients receiving sutimlimab. Seriousness/outcomes: Meningococcal infections, such as sepsis or meningitis, may result in death or be life-threatening. Background incidence/prevalence: In Western countries (Finland, Netherlands, and the US), the incidence of bacterial meningitis in the general population was 0.7-0.9 per 100 000 per year in the past 10-20 years. In African countries (Burkina Faso and Malawi), incidence rates of bacterial meningitis in the general population are still substantially higher at 10-40 per 100 000 persons per year. (63) The incidence of meningitis in elderly patients (>65 old) has been described in a hospital in Barcelona, estimated at 7.4 per 100 000 inhabitants per year in the years 1982-2010 (64) and in a larger US study, where it was estimated at 1.73/100 000 1.44 to 2.06) in the years 2006-2007. (65) The US study showed a decline in the incidence over calendar years from 1998 to 2007. These studies also mentioned the negative impact of co-morbidities or conditions that may impair the immune system. No epidemiologic data is available regarding the frequency of meningitis in CAD patients.
Risk factors and risk groups	Risk factors for meningococcal infections may include patients that are unvaccinated or incompletely vaccinated against meningococcus, including serogroup B; exposure to terminal complement inhibitor therapies; other inherited or acquired immunodeficiency; asplenia; elderly.
Preventability	This risk can be reduced or prevented with an appropriate program of prophylactic vaccinations. Informing HCPs and patients of signs and symptoms may facilitate early diagnosis and treatment. Immediate treatment and management could prevent serious outcomes.
Impact on the benefit-risk balance of the product	Based on review of currently available preclinical and clinical data, the phenotype in patients with congenital CP deficiencies, and the different mechanism of action of sutimlimab versus terminal complement inhibitors, meningococcal infections remains a potential mechanism related risk and the benefit-risk remains positive.

[redacted]

Important potential risk	Meningococcal infections
Public health impact	Meningococcal infections can be spread by sharing respiratory or oral secretions through close and prolonged contacts. This risk can be reduced by use of prophylactic antibiotics in exposed contacts. (66) The individual health risk could be serious if not managed appropriately. However, the impact on public health has not been evaluated.

AE: Adverse Event; AP: Alternative Pathway; C5: Complement component 5; C5b: Complement component 5, b subcomponent; C8: Complement component 8; CAD: Cold Agglutinin Disease; CP: Classical Complement Pathway; DLP: Data Lock Point; HCP: Healthcare Professional; LP: Lecithin Pathway; RMP: Risk Management Plan; US: United States.

Table 19 - Important potential risk: Development of Systemic Lupus Erythematosus

Important potential risk	Development of Systemic Lupus Erythematosus
Potential mechanism	Long-term CP inhibition could theoretically increase the risk of SLE due to the role of the C1 complex in immune complex clearance, as seen in patients with congenital deficiencies of C1 complex components (C1q, C1s, and C1r). The proposed mechanism for SLE development with congenital CP deficiency is due to impaired immune complex processing, clearance of apoptotic cellular debris and regulation of B-cell mediated immune tolerance to self-antigens which may all contribute to auto-antibody formation. (67)(68)
Evidence source(s) and strength of evidence	Mechanism of action; literature finding in patients with congenital CP deficiencies. Inhibition of the CP may lead to impaired identification, opsonization, and clearance of immune complexes and apoptotic cellular debris leading to autoantibody formation and/or tissue deposits and inflammation. (67)(69) Extrapolating from rare human cases of congenital deficiency of complement factors C1, C2, or C4, which are amongst the strongest genetic risk factors for SLE, it is theoretically possible that chronic inhibition of any of these factors could result in an increased risk of SLE. (50)(70)(71)(72)(73)(74)(75)(76)(77)(78) Homozygous and heterogenous hereditary deficiency of an individual CP components (C1q, C1r, C1s, C4, and C2) is strongly associated with an increased susceptibility to SLE. Systemic lupus erythematosus incidence in C1q, C4 or C1r/C1s deficiency is 90%, 75% and 50-57% respectively. (63)(69) However, pharmacologic inhibition of C1s does not necessarily equate to congenital deficiency of the C1 complex. Sutimlimab inhibits the C1s enzymatic function in the C1 complex but leaves the non-enzymatic function of C1q intact, which is important for the opsonization and phagocytic removal of apoptotic cells, which may help protect against autoimmunity. The AP, which remains intact with sutimlimab administration, provides some redundancy for clearance of immune complexes and cellular debris via C3b binding and ultimately clearance via liver and splenic macrophages. (54) It is uncertain what level and duration of CP inhibition might be required to increase the risk for SLE development. Thus, SLE remains a theoretical, mechanism-related risk from C1s inhibition.
Characterization of the risk	Frequency: As of the DLP of the RMP, there have not been any reports of SLE development in patients receiving sutimlimab in CAD. Estimates of incidence and prevalence of SLE in the general population in North America are 23.2/100 000 person-years (95% CI: 23.4, 24.0) and 241/100 000 people (95% CI: 130, 352), respectively. The lowest incidences of SLE in the general population were reported in Africa and Ukraine (0.3/100 000 person-years), and the lowest prevalence of SLE in the general population was in Northern Australia (zero case in a sample of 847 people). Women were more frequently affected than men for every age and ethnic group. Incidence peaked in middle adulthood and occurred later for men. People of Black ethnicity had the highest incidence and prevalence of SLE, whereas those with White ethnicity had the lowest incidence and prevalence. (79)(80)

[redacted]

Important potential risk	Development of Systemic Lupus Erythematosus
	A matched cohort comparison study conducted in 2020 showed that the incidence of SLE in the CAD patients was 4.44 per 1000 person-year compared to a 0.45 per 1000 person-year in the matching comparison group. (81)(82) Severity and nature of risk: As of the DLP of the RMP, there have not been any reports of SLE development in patients receiving sutimlimab in CAD. Systemic lupus erythematosus is a rare, serious, chronic, autoinflammatory autoimmune disease that affects many organ systems and has no curative therapy. (83) In patients with congenital complement deficiencies, SLE has characteristic features including earlier age of onset, prominent photosensitivity, lower frequency of renal disease, and variable antinuclear antibody titers (anti-Ro present in approximately two-thirds). (54) Seriousness/outcomes: Systemic lupus erythematosus may be a life-threatening illness with deaths due to infection, chronic vascular disease or kidney-related complications. 15-year survival after diagnosis has been approximated at 76%. Subjects with more prolonged survival after SLE diagnosis often have considerable morbidity with impaired QOL and reduced functional abilities. (84)
Risk factors and risk groups	Patients that have concurrent autoimmune disease, pre-existing autoantibodies.
Preventability	Changes from positive to negative and negative to positive in SLE panel results were observed in both healthy volunteers and CAD patients receiving sutimlimab with no clear clinical correlate. Thus, SLE panel monitoring is unlikely to be useful for clinical management in the absence of clinical signs and symptoms. Close surveillance for the signs and symptoms of SLE may aid in early detection and treatment. It is unknown how to prevent development of SLE.
Impact on the benefit-risk balance of the product	Based on limited therapy choices for CAD patient and available data, benefit-risk remains positive.
Public health impact	Healthcare resource utilization may be high in patients with severe disease. (85)(86)(87)(88)(89)(90)(91) The individual health risk could be serious if not managed appropriately. However, the impact on public health has not been evaluated.

AP: Alternative Pathway; CAD: Cold Agglutinin Disease; C1: Complement component 1; C1q: Complement component 1, q subcomponent; C1r: Complement component 1, r subcomponent; C1s: Complement component 1, s subcomponent; C2: Complement component 2; C3b: Complement component 3, b subcomponent; C4: Complement component 4; CI: Confidence Interval; CP: Classical Complement Pathway; DLP: Data Lock Point; QOL: Quality of Life; RMP: Risk Management Plan; SLE: Systemic Lupus Erythematosus.

Table 20 - Important potential risk: Serious hypersensitivity reactions and/or anaphylaxis

Important potential risk	Serious hypersensitivity reactions and/or anaphylaxis
Potential mechanism	Large protein molecules, despite humanization, can be immunogenic. Hypersensitivity risk with sutimlimab theoretically could be either IgE mediated (acute reactions) or IgG mediated (or other isotype) with generalized and acute symptoms due to Fc-IgG mediated activation of immune cells. Inhibition of CP doesn't prevent LP or AP activation, which may produce potent anaphylatoxins.
Evidence source(s) and strength of evidence	Class effect with mAbs (literature); mechanism of action Large protein molecules, despite humanization, can be immunogenic. Sutimlimab is biologic therapeutic protein and hypersensitivity risk, including anaphylaxis, is considered a class effect with mAbs. Serious hypersensitivity reactions, including anaphylaxis, have been observed with other mAbs.

[redacted]

Important potential risk	Serious hypersensitivity reactions and/or anaphylaxis
Characterization of the risk	Frequency: As of the DLP of the RMP, there have been no SAEs reported of serious hypersensitivity reactions or anaphylaxis. As of the DLP of the RMP, non-serious reports suggestive of potential hypersensitivity reactions have been reported in patients receiving sutimlimab in the two phase 3 CAD clinical trials. AEs suggestive of potential hypersensitivity reactions associated with sutimlimab included infusion-related reactions, experienced by 4 (6.1%) patients, injection site erythema 2 (3.0%), injection site pruritis 1 (1.5%), Of the 10 patients who participated in the BIVV009-01 C and E studies, 1 (10.0%) patient experienced nonserious TEAE of rash that was suggestive of potential hypersensitivity reaction. Severity and nature of risk: Symptoms may range from local injection site reactions to anaphylactic shock which may be life-threatening. Onset of symptoms may be immediate upon initiation of infusion or occur up to 14 days after administration or with subsequent exposures. The severity and mechanism of hypersensitivity reactions may depend on amount of foreign antigen and rate of infusion. Seriousness/outcomes: As of the DLP of the RMP, of the 66 patients who participated in the two phase 3 CAD studies (BIVV009-03 Part A and B and BIVV009-04 Part A and B), one patient discontinued sutimlimab due to non-serious event of infusion-related reaction. Of the 10 patients who participated in the BIVV009-01 C and E studies, none of them discontinued sutimlimab due to an event suggestive of potential hypersensitivity reaction.
Risk factors and risk groups	History of prior allergic reaction to sutimlimab and/or its excipients; Atopic individuals.
Preventability	Exclusion of subjects with history of prior allergic reaction to sutimlimab or its excipients, close monitoring during infusions and slowing the infusion time as needed may help prevent hypersensitivity reactions in subjects receiving sutimlimab. Patients and HCPs should be informed of the signs and symptoms of hypersensitivity reactions to facilitate early diagnosis, and potentially mitigate the potential risk and serious outcomes.
Impact on the benefit-risk balance of the product	Serious hypersensitivity reactions and anaphylaxis are established potential complications of mAb therapy. Appropriate measures are in place as part of routine clinical practice: Hypersensitivity to sutimlimab or its components will be a contraindication to sutimlimab use. Based on limited therapy choices for CAD patients and available data, the benefit-risk remains positive.
Public health impact	There is no public health impact.

AE: Adverse Event; AP: Alternative Pathway; CAD: Cold Agglutinin Disease; CP: Classical Complement Pathway; DLP: Data Lock Point; HCP: Healthcare Professional; IgE: Immunoglobulin E; IgG: Immunoglobulin G; LP: Lecithin Pathway; mAb: Monoclonal Antibody; RMP: Risk Management Plan; SAE: Serious Adverse Event; TEAE: Treatment-Emergent Adverse Event.

SVII.3.2 Presentation of the missing information

Not applicable

[redacted]

RISK MANAGEMENT PLAN - PART II MODULE SVIII: SUMMARY OF THE SAFETY CONCERNS

Summary of the safety concerns

Important identified risk	Serious infections
Important potential risks	Meningococcal infections Development of Systemic Lupus Erythematosus Serious hypersensitivity reactions and/or anaphylaxis
Missing information	None

RISK MANAGEMENT PLAN - PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORIZATION SAFETY STUDIES)

III.1 ROUTINE PHARMACOVIGILANCE ACTIVITIES

The following routine pharmacovigilance activities beyond adverse reactions reporting and signal detection will be/are in place, including:

- Specific adverse reaction follow-up questionnaires for:
  - Infections (including serious infections and meningococcal infections)
  - Autoimmune disorders (including SLE)
  - Serious hypersensitivity reactions and/or anaphylaxis

III.2 ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

An ongoing cold-agglutinin disease-specific registry (Cadence) has been implemented by the marketing authorization holder (MAH) as the Sponsor to collect longitudinal data in patients with cold agglutinin disease in order to better understand patient and clinical characteristics, disease progression, complications, treatment impact, and patient-reported outcomes. While not a product-specific registry for sutimlimab, this registry will be used to conduct a post-approval non-interventional safety and effectiveness study of sutimlimab in patients with CAD (cohort study). Due to the limitations inherent to the rarity of CAD, the future uptake of sutimlimab within the registry population, and therefore the size of this cohort study, the approach will remain descriptive on the safety endpoints and effectiveness endpoints. The registry will also capture data on the vaccination status and dates of vaccination for all patients, including the patients who will get exposed to sutimlimab.

In addition, to describe the distribution, understanding and impact on action of the educational tool (Physician’s Guide), which is an aRMM proposed to address the potential risks of meningococcal infections and serious infections in relation to sutimlimab treatment, a survey will be carried. It will target the population of physicians who treat patients with CAD and may intend to prescribe sutimlimab in the European countries included in this survey. This survey may involve approximately 50 physicians with possibly arround 10 HCPs having actually prescribed sutimlimab (depending on future uptake of sutimlimab), in a self-administered way, and start between 6 and 18 months after distribution of Physician’s Guide. For the physicians who will have already prescribed sutimlimab, the survey will describe the implementation of vaccination (if vaccination status of patients has been checked, if vaccinations have been performed), and if patients have been counselled regarding course of action should early signs and symptoms of serious infections or meningococcal infections occur. The survey may be conducted in up to two waves. In the event that the survey has been open for 6 months in all countries and 30 completed surveys have not been achieved, with a minimum of 10 of those having been completed by HCP prescribers, a second wave of the survey will be conducted 6 to 12 months later.

[redacted]

Table 21 - Additional pharmacovigilance activities (category 1 to 3) summary

Cold Agglutinin Disease Real World Evidence Registry (Cadence) (Category 3)

Study short name and title:

Cold Agglutinin Disease Real World Evidence Registry (Cadence)

Rationale and study objectives:

Rationale:

The aim of this disease registry is to develop an international database of patients with CAD and CAS to prospectively collect longitudinal data and better understand patient and clinical characteristics, disease progression, complications (including TE events), treatment impact, and patient-reported outcomes.

All patients with CAD and CAS will be eligible, regardless of the type of CAD-specific therapy they are receiving.

In addition, the registry will be used to conduct a post-approval safety and effectiveness study of sutimlimab in patients with CAD and CAS (as off-label use of sutimlimab) as a drug cohort study.

Objectives of the drug cohort study:

The safety objective of the post-approval safety and effectiveness cohort study of sutimlimab is:

- To describe the long-term safety of sutimlimab in the treatment of patients with CAD in a real-world setting (including CAS patients with off-label use of sutimlimab).

Study design:

Multinational, multi-center, observational, prospective, longitudinal registry study designed to collect data on patients with CAD and CAS.

This registry study will be conducted in Austria, France, Germany, Italy, Japan, Spain, UK and the US, at sites known to treat and follow-up patients with CAD and CAS.

Patients will be followed up throughout the registry duration, for up to 3 years after the last patient is enrolled in the disease registry. In total, patients will be followed up for up to 6 years (3-year enrollment period + at least 3 years of follow-up for all patients).

Study populations:

Patient aged >18 years, with a diagnosis of CAD and willing and able to provide written informed consent to participate in the registry.

The disease registry study plans to enroll approximately 400 patients with CAD or CAS. Among them, at least 30 patients with CAD treated with sutimlimab are expected to be enrolled in the drug cohort study (with safety data collection including also off-label CAS patients).

The registry size is constrained by feasibility aspects, and for the patients exposed to sutimlimab, the estimate is based on projections about the potential future uptake of sutimlimab in the CAD population.

Milestones:

Synopsis submission (along with the initial RMP)	Oct-2021
Protocol Submission	Apr-2022
Start of data collection	Q2 2022
End of data collection	Q3 2028
Interim reports	Annually throughout the cohort study
Final report of study results	Q4 2031

Q: Quarter; RMP: Risk Management Plan.

A Survey of Healthcare Professionals in Europe to Evaluate the Effectiveness of the ENJAYMO™ Physician's Guide (Category 3)

Study short name and title:

A Survey of Healthcare Professionals in Europe to Evaluate the Effectiveness of the ENJAYMO™ Physician's Guide

[redacted]

Rationale and study objectives:

The overall goal of this study is to perform an effectiveness evaluation of the sutimlimab Physician's Guide among physicians who treat patients with CAD.
Main objectives are to describe physician's reported levels of receipt and reading of the Physician's Guide and assess the physicians' knowledge levels of key information included in the ENJAYMO™ Physician's Guide.

In addition, among the physicians who will have already prescribed sutimlimab, the survey will describe impact of the Physician's Guide on the clinical actions associated with vaccination (if vaccination status of patients has been checked, if vaccinations have been performed), and if patients have been counselled regarding course of action should early signs and symptoms of serious infections or meningococcal infections occur.

Study design:

Non-interventional, cross-sectional survey study to evaluate the effectiveness of the Physician's Guide among physicians who treat patients with CAD and may prescribe sutimlimab. Countries may include: Austria, Germany, Italy and the Netherlands.

The survey is planned to be conducted in one wave between 6 and 18 months, after the distribution of the sutimlimab Physician's Guide.

The survey may be conducted in up to two waves. In the event that the survey has been open for 6 months in all countries and 30 completed surveys have not been achieved, with a minimum of 10 of those having been completed by HCP prescribers, a second wave of the same survey will be conducted 6 to 12 months later.

Study population and study size:

Study population:

This survey will be conducted amongst HCPs from included countries who treat CAD (potential prescribers) and were sent the Physician's Guide.

Study size:

The sample size was determined based on both feasibility and statistical considerations, giving the rarity of CAD and therefore anticipated low number of actual sutimlimab prescribers. A sample of 50 completed surveys is targeted for this study, with possibly around 10 HCPs having actually prescribed sutimlimab (this number depends on uptake of sutimlimab and is difficult to predict).

Milestones:

Synopsis submission (along with the initial RMP)	Oct-2021
Protocol Submission	Apr-2022
Start of data collection	Q2 2023/Q2 2024[a]
End of data collection	Q2 2025/Q2 2026[a]
Final report of study results	Q4 2026[b]

a Estimate depending on the future dates of launch and reimbursement of Sutimlimab in the participating countries.
b Estimate depending on the date of end of data collection.
Q: Quarter; RMP: Risk Management Plan.

CAD: Cold Agglutinin Disease; CAS: Cold Agglutinin Syndrome; HCP: Healthcare Professional; RMP: Risk Management Plan; Q: Quarter; TE: Thromboembolic Event; UK: United Kingdom; US: United States.

III.3 SUMMARY TABLE OF ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Table 22 - Ongoing and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1- Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
Not applicable				

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 2- Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
Not applicable				
Category 3- Required additional pharmacovigilance activities				
Cold Agglutinin Disease Real World Evidence Registry (Cadence) **Planned**	The safety objective of the post-approval safety and effectiveness drug cohort study is to: • Describe the long-term safety of sutimlimab in the treatment of patients with CAD in a real-world setting (including CAS patients with off-label use of sutimlimab).	• Serious infections • Meningococcal infections • Development of Systemic Lupus Erythematosus • Serious hypersensitivity reactions and/or anaphylaxis	Synopsis submission (along with the initial RMP) Protocol submission Start of data collection End of data collection Interim reports Final report of study results	Oct-2021 Apr-2022 Q2 2022[a] Q3 2028 Annually throughout the cohort study Q4 2031
A Survey of Healthcare Professionals in Europe to Evaluate the Effectiveness of the ENJAYMO™ Physician's Guide **Planned**	• Describe physician's reported levels of receipt and reading of the Physician's Guide. • Assess physician's knowledge levels of key information included in the sutimlimab Physician's Guide. • Assess impact of the Physician's Guide on clinical action.	• Serious infections • Meningococcal infections	Synopsis submission (along with the initial RMP) Protocol submission Start of data collection End of data collection Final study report	Oct-2021 Apr-2022 Q2 2023/Q2 2024[a] Q2 2025/Q2 2026[a] Q4 2026[b]

a Estimate depending on the future dates of launch and reimbursement of Sutimlimab in the participating countries.
b Estimate depending on the date of end of data collection.
CAD: Cold Agglutinin Disease; CAS: Cold Agglutinin Syndrome; Q: Quarter; RMP: Risk Management Plan.

[redacted]

RISK MANAGEMENT PLAN PART IV: PLANS FOR POST-AUTHORIZATION EFFICACY STUDIES

No imposed post-authorization efficacy studies as a condition of the marketing authorization or which are specific obligations in the context of conditional marketing authorization or marketing authorization under exceptional circumstances are planned or ongoing for sutimlimab.

RISK MANAGEMENT PLAN - PART V: RISK MINIMIZATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMIZATION ACTIVITIES)

V.1 ROUTINE RISK MINIMIZATION MEASURES

Table 23 - Description of routine risk minimization measures by safety concern

Safety concern	Routine risk minimization activities
Serious infections	**Routine risk communication:** SmPC sections 4.2, 4.4 and 4.8 PIL sections 2 and 4 **Routine risk minimization activities recommending specific clinical measures to address the risk:** • SmPC sections 4.2 and 4.4: Patients should be vaccinated according to the most current local recommendations for patients with persistent complement deficiencies. • SmPC section 4.4: Patients should be monitored for early signs and symptoms of infections. **Other routine risk minimization measures beyond the Product Information:** • Legal status: Medicinal product subject to medical prescription.
Meningococcal infections	**Routine risk communication:** SmPC sections 4.2 and 4.4 PIL sections 2 and 4 **Routine risk minimization activities recommending specific clinical measures to address the risk:** • SmPC sections 4.2 and 4.4: Patients should be vaccinated according to the most current local recommendations for patients with persistent complement deficiencies. • SmPC section 4.4: Patients should be monitored for early signs and symptoms of infections. **Other Routine risk minimization measures beyond the Product Information:** • Legal status: Medicinal product subject to medical prescription.
Development of Systemic Lupus Erythematosus	**Routine risk communication:** SmPC section 4.4 PIL section 2 **Routine risk minimization activities recommending specific clinical measures to address the risk:** • SmPC section 4.4: Patients being treated with sutimlimab should be monitored for signs and symptoms of SLE and evaluated appropriately. **Other routine risk minimization measures beyond the Product Information:** • Legal status: Medicinal product subject to medical prescription.

Safety concern	Routine risk minimization activities
Serious hypersensitivity reactions and/or anaphylaxis	**Routine risk communication:** SmPC sections 4.2, 4.3 and 4.4 PIL sections 2, 3 and 4 **Routine risk minimization activities recommending specific clinical measures to address the risk:** • SmPC section 4.2: - If an adverse reaction occurs during the administration of sutimlimab, the infusion may be slowed or stopped at the discretion of the physician. - Monitor the patient for at least two hours following completion of the initial infusion for signs or symptoms of an infusion and/or hypersensitivity reaction. - Monitor the patient for one hour following completion of subsequent infusions for signs or symptoms of an infusion reaction. • SmPC section 4.4: - If hypersensitivity reactions occur, discontinue sutimlimab and initiate appropriate treatment. **Other routine risk minimization measures beyond the Product Information:** • Legal status: Medicinal product subject to medical prescription.

PIL: Patient Information Leaflet; SmPC: Summary of Product Characteristics; SLE: Systemic Lupus Erythematosus.

V.2 ADDITIONAL RISK MINIMIZATION MEASURES

In addition to routine risk minimization measures, an educational tool for physicians, a "Physician's Guide" and an educational tool for patients, a "Patient's Guide" are proposed to further support the safe use of sutimlimab with regards to the important identified risk of serious infections and the important potential risk of meningococcal infections.

These tools will be distributed to potential prescribers of sutimlimab at the product's launch and will be made available thereafter through appropriate channels.

Details about the Physician's Guide and the Patient's Guide are provided in Table 24. Proposed key messages to be conveyed by the tools are provided in [Annex 6].

Table 24 - Additional risk minimization measures

Physician's Guide	
Objectives	Educate physicians that patients should be vaccinated (according to most current local vaccination guidelines for vaccine use in patients with persistent complement deficiencies) prior to initiating sutimlimab. Recommend on-treatment monitoring for early signs and symptoms of infection. Recommend individualized patient counselling. Risks addressed: Serious infection and meningococcal infections.
Rationale for the additional risk minimization activity	Serious infection, which may result in death or be life-threatening, can be reduced or prevented with an appropriate program of prophylactic vaccination. Informing HCPs (and patients via HCPs) of signs and symptoms may facilitate early diagnosis and treatment. Immediate treatment and management could prevent serious outcomes.

[redacted]

Physician's Guide	
Target audience and planned distribution path	Target audience: physicians expected to manage patients with CAD (mainly hematologists). Distribution rate: The Physician's Guide should be distribution at the product launch and made available through appropriate channels thereafter. Distribution path: face to face, mail, e-mail, web-posting.
Plans to evaluate the effectiveness of the interventions and criteria for success	Routine pharmacovigilance surveillance will provide an indirect assessment of the overall effectiveness of risk minimization measures. A survey will be conducted to assess distribution and understanding of the Physician's Guide, as well as its impact on clinical action. A minimum knowledge level of 80% will be considered as a criterion for success.
Patient's Guide	
Objectives	Enhance awareness of increased risk of infection and the need for vaccination. Enhance awareness of early signs and symptoms of infections and the need to seek immediate medical attention should they occur.
Rationale for the additional risk minimization activity	Serious infection, which may result in death or be life-threatening, can be reduced or prevented with an appropriate program of prophylactic vaccination. Informing patients of signs and symptoms may facilitate early diagnosis and treatment. Immediate treatment and management could prevent serious outcomes.
Target audience and planned distribution path	Target audience: Patients through physicians expected to manage patients with CAD (mainly hematologists). Distribution rate: The Patient's Guide should be distribution at the product launch and made available through appropriate channels thereafter. Distribution path: face to face, mail complemented by e-mail, web-posting.
Plans to evaluate the effectiveness of the interventions and criteria for success	Routine pharmacovigilance surveillance will provide an indirect assessment of the overall effectiveness of risk minimization measures. The survey which will be conducted to assess the effectiveness of the Physician's Guide will also describe HCP's reported level of dissemination of the Patient's Guide.

CAD: Cold Agglutinin Disease; HCP: Healthcare Professional.

V.3 SUMMARY OF RISK MINIMIZATION MEASURES

Table 25 - Summary table of pharmacovigilance activities and risk minimization activities by safety concern

Safety concern	Risk minimization measures	Pharmacovigilance activities
Serious infections	**Routine risk minimization measures:** SmPC sections 4.2, 4.4 and 4.8 PIL sections 2 and 4 Legal status: Medicinal product subject to medical prescription	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Adverse Event follow-up form **Additional pharmacovigilance activities:** • Cold Agglutinin Disease Real World Evidence Registry (Cadence)

[redacted]

Safety concern	Risk minimization measures	Pharmacovigilance activities
	Additional risk minimization measures: • Physician's Guide • Patient's Guide	• A Survey of Healthcare Professionals in Europe to Evaluate the Effectiveness of the ENJAYMO™ Physician's Guide
Meningococcal infections	**Routine risk minimization measures:** SmPC sections 4.2 and 4.4 PIL sections 2 and 4 Legal status: Medicinal product subject to medical prescription **Additional risk minimization measures:** • Physician's Guide • Patient's Guide	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Adverse Event follow-up form **Additional pharmacovigilance activities:** • Cold Agglutinin Disease Real World Evidence Registry (Cadence) • A Survey of Healthcare Professionals in Europe to Evaluate the Effectiveness of the ENJAYMO™ Physician's Guide
Development of Systemic Lupus Erythematosus	**Routine risk minimization measures:** SmPC section 4.4 PIL section 2 Legal status: Medicinal product subject to medical prescription **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Adverse Event follow-up form **Additional pharmacovigilance activities:** Cold Agglutinin Disease Real World Evidence Registry (Cadence)
Serious hypersensitivity reactions and/or anaphylaxis	**Routine risk minimization measures:** SmPC sections 4.2, 4.3 and 4.4 PIL sections 2, 3 and 4 Legal status: Medicinal product subject to medical prescription **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Adverse Event follow-up form **Additional pharmacovigilance activities:** Cold Agglutinin Disease Real World Evidence Registry (Cadence)

PIL: Patient Information Leaflet; SmPC: Summary of Product Characteristics.

[redacted]

RISK MANAGEMENT PLAN - PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for ENJAYMO (Sutimlimab)

This is a summary of the RMP for ENJAYMO. The RMP details important risks of ENJAYMO how these risks can be minimized, and how more information will be obtained about ENJAYMO's risks.

ENJAYMO's SmPC and its PIL give essential information directed to HCPs and patients on how ENJAYMO should be used.

This summary of the RMP for ENJAYMO should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European public assessment report (EPAR).

Important new concerns or changes to the current ones will be included in updates of ENJAYMO's RMP.

I. THE MEDICINE AND WHAT IT IS USED FOR

ENJAYMO is authorized for treatment of hemolytic anemia in adult patients with CAD (see SmPC for the full indication). It contains sutimlimab as the active substance and it is given by intravenous (IV) route.

Further information about the evaluation of ENJAYMO's benefits can be found in ENJAYMO's EPAR, including in its plain-language summary, available on the European medicines agency (EMA) website, under the medicine's webpage:

https://www.ema.europa.eu/en/medicines/human/EPAR/enjaymo

II. RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMIZE OR FURTHER CHARACTERIZE THE RISKS

Important risks of ENJAYMO, together with measures to minimize such risks and the proposed studies for learning more about ENJAYMO's risks, are outlined in the next sections.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the PL and SmPC addressed to patients and HCPs;
- Important advice on the medicine's packaging;

- The authorized pack size - the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;

- The medicine's legal status - the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.

In the case of ENJAYMO, routine risk minimization measures are supplemented with aRMMs mentioned under relevant important risks, outlined in the next sections.

In addition to the risk minimization measures, information about adverse reactions is collected continuously and regularly analyzed, including periodic safety update report (PSUR) assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

II.A List of important risks and missing information

Important risks of ENJAYMO are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of ENJAYMO. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine);

Table 26 - List of important risks and missing information

Important identified risk	Serious infections
Important potential risks	Meningococcal infections Development of Systemic Lupus Erythematosus Serious hypersensitivity reactions and/or anaphylaxis
Missing information	None

II.B Summary of important risks

Table 27 - Important identified risk with corresponding risk minimization activities and additional pharmacovigilance activities: Serious infections

Important identified risk: Serious infections	
Evidence for linking the risk to the medicine	Mechanism of action, class effect seen with terminal complement inhibitors and literature findings in subjects with acquired or inherited classical complement deficiency. The CP has multiple roles in both innate and adaptive immunity. Pharmacologic inhibition or inherited deficiency of the CP may lead to impaired opsonization of antigen

Important identified risk: Serious infections	
	antibody complexes, phagocytosis and pathogen neutralization or killing. (49)(50) While the CP plays an essential role for bacterial killing, particularly gram negative or encapsulated organisms, complement activation also occurs with other pathogens, such as viruses. (51)
Risk factors and risk groups	Risk factors for serious infections may include: patients that are unvaccinated or incompletely vaccinated; exposure to other immunomodulatory agents; concurrent hematologic and/or solid organ malignancies; other inherited or acquired immunodeficiency; asplenia; HIV/AIDS; CSF leak; cochlear implants; poorly controlled diabetes; chronic liver, kidney, heart, lung disease; elderly.
Risk minimization measures	**Routine risk minimization measures:** SmPC sections: 4.2, 4.4 and 4.8 PIL sections: 2 and 4 Legal status: Medicinal product subject to medical prescription **Additional risk minimization measures:** • Physician's Guide • Patient's Guide
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** • Cold Agglutinin Disease Real World Evidence Registry (Cadence) • A Survey of Healthcare Professionals in Europe to Evaluate the Effectiveness of the ENJAYMO™ Physician's Guide

AIDS: Acquired Immuno Deficiency Syndrome; CSF: Cerebrospinal Fluid; CP: Classical Complement Pathway; HIV: Human Immunodeficiency Virus; PIL: Patient Information Leaflet; SmPC: Summary of Product Characteristics.

Table 28 - Important potential risk with corresponding risk minimization activities and additional pharmacovigilance activities: Meningococcal infections

Important potential risk: Meningococcal infections	
Evidence for linking the risk to the medicine	Mechanism of action, class effect seen with terminal complement inhibitors and literature findings in subjects with acquired or inherited classical and terminal complement deficiency. The complement system is part of our innate immunity and consists of three pathways (classical, lectin and alternative). The complement system has multiples roles in both innate and adaptive immunity. Pharmacologic inhibition or inherited deficiency of the components of the complement pathway may lead to impaired opsonization of antigen antibody complexes, phagocytosis and pathogen neutralization or killing. Terminal complement inhibition may prevent the formation of the membrane attack complex which is integral to the killing of *N. meningitidis*. (49)(50)
Risk factors and risk groups	Risk factors for meningococcal infections may include: patients that are unvaccinated or incompletely vaccinated against meningococcus, including serogroup B; exposure to terminal complement inhibitor therapies; other inherited or acquired immunodeficiency; asplenia; elderly.
Risk minimization measures	**Routine risk minimization measures:** SmPC sections: 4.2 and 4.4 PIL sections: 2 and 4 Legal status: Medicinal product subject to medical prescription

Important potential risk: Meningococcal infections	
	Additional risk minimization measures: • Physician's Guide • Patient's Guide
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** • Cold Agglutinin Disease Real World Evidence Registry (Cadence) • A Survey of Healthcare Professionals in Europe to Evaluate the Effectiveness of the ENJAYMO™ Physician's Guide

PIL: Patient Information Leaflet; SmPC: Summary of Product Characteristics.

Table 29 - Important potential risk with corresponding risk minimization activities and additional pharmacovigilance activities: Development of Systemic Lupus Erythematosus

Important potential risk: Development of Systemic Lupus Erythematosus	
Evidence for linking the risk to the medicine	Mechanism of action and literature findings in subjects with acquired or inherited classical complement deficiency. Long-term CP inhibition could theoretically increase the risk of SLE due to the role of the C1 complex in immune complex clearance, as seen in patients with congenital deficiencies of C1 complex components (C1q, C1s, and C1r). C4 and C1q deficiency identified as the strongest genetic risk factors for SLE. (52)(61)
Risk factors and risk groups	Patients that have concurrent autoimmune disease, pre-existing autoantibodies.
Risk minimization measures	**Routine risk minimization measures:** SmPC section: 4.4 PIL section: 2 Legal status: Medicinal product subject to medical prescription **Additional risk minimization measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Cold Agglutinin Disease Real World Evidence Registry (Cadence)

C1: Complement component 1; C1q: Complement component 1, q subcomponent; C1r: Complement component 1, r subcomponent; C1s: Complement component 1, s subcomponent; C4: Complement component 4; CP: Classical Complement Pathway; PIL: Patient Information Leaflet; SLE: Systemic Lupus Erythematosus; SmPC: Summary of Product Characteristics.

Table 30 - Important potential risk with corresponding risk minimization activities and additional pharmacovigilance activities: Serious hypersensitivity reactions and/or anaphylaxis

Important potential risk: Serious hypersensitivity reactions and/or anaphylaxis	
Evidence for linking the risk to the medicine	Class effect with mAbs (literature); mechanism of action. Large protein molecules, despite humanization, can be immunogenic. Sutimlimab is biologic therapeutic protein and hypersensitivity risk, including anaphylaxis, is considered a class effect with mAbs. Serious hypersensitivity reactions, including anaphylaxis, have been observed with other mAbs. Inhibition of CP doesn't prevent LP or AP activation, which may produce potent anaphylatoxins.
Risk factors and risk groups	History of prior allergic reaction to sutimlimab and/or its excipients; Atopic individuals.
Risk minimization measures	**Routine risk minimization measures:** SmPC sections: 4.2, 4.3 and 4.4

Important potential risk: Serious hypersensitivity reactions and/or anaphylaxis	
	PIL sections: 2, 3 and 4 Legal status: Medicinal product subject to medical prescription **Additional risk minimization measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Cold Agglutinin Disease Real World Evidence Registry (Cadence)

AP: Alternative Pathway; CP: Classical Complement Pathway; LP: Lectin Pathway; mAb: Monoclonal Antibody; PIL: Patient Information Leaflet; SmPC: Summary of Product Characteristics.

II.C Post-authorization development plan

II.C. I *Studies which are conditions of the marketing authorization*

There are no studies which are conditions of the marketing authorization or specific obligation of ENJAYMO.

II.C. II *Other studies in post-authorization development plan*

Table 31 - Other studies in post-authorization development plan

Cold Agglutinin Disease Real World Evidence Registry (Cadence)
Purpose of the study: A disease registry that will be used to conduct a post-authorization safety study to describe the long-term safety and effectiveness of sutimlimab in patients with CAD in a real-word setting (including CAS patients in case of off-label use).
A Survey of Healthcare Professionals in Europe to Evaluate the Effectiveness of the ENJAYMO™ Physician's Guide
Purpose of the study: The overall goal of this study is to perform an effectiveness evaluation of the sutimlimab Physician's Guide among physicians who treat patients with CAD.

CAD: Cold Agglutinin Disease; CAS: Cold Agglutinin Syndrome.

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RISK MANAGEMENT PLAN - PART VII: ANNEXES

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ANNEX 4 SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

TABLE OF CONTENTS

SPECIFIC ADVERSE REACTION FOLLOW-UP QUESTIONNAIRE FOR:

- Infections (including serious infections and meningococcal infections)
- Autoimmune disorders (including SLE)
- Serious hypersensitivity reactions and/or anaphylaxis

[redacted]

ANNEX 4.1 Infections (including serious infections and meningococcal infections)

Sutimlimab - Infection

Targeted Follow-up Form (coversheet)

- **In the 'Suspect Product(s) Information' section of Individual Safety Information (ISI) Documentation Form and in the 'Suspect Medication/Medical Device (MD)/Vaccine (V)' section of Unsolicited Individual Safety Information (ISI) Report Form, ensure to collect:**

  - Start/stop dates of sutimlimab
  - Last dose of sutimlimab prior to event onset including time of administration if known
  - A causality assessment (i.e. related, unrelated, unknown) between the event and Sutimlimab

- **In the 'Adverse Event Information (Describe Event)' section of ISI Documentation Form and in the 'Description of the Case' section of Unsolicited ISI Report Form, ensure to collect:**

  - Final unifying diagnosis for infection which should include body location and type of infection (i.e. bacterial, viral, fungal, etc.)
  - Causative organism if identified or state organism unknown
  - Presenting signs and symptoms
  - Site / anatomical location of infection
  - Source of infection if identified
  - Type of infection - bacterial, viral, fungal
  - If the patient has history of a similar infection in the past, specify what and when
  - Briefly list the management/treatment (e.g., drugs, procedures, including dates) of the infection
  - Was the patient hospitalized or required an ER visit? If yes, provide the hospitalization diagnosis, date(s) of hospitalization, and a copy of discharge report if available.
  - If patient required blood pressure and respiratory support, specify type and dates of additional support
  - If patient required intensive care unit (ICU) admission and dates of care in ICU
  - Was sutimlimab temporarily or permanently discontinued because of the event? If yes, specify the date, reason, and whether the event improved, resolved, or abated after discontinuation.
    - Was sutimlimab later resumed? If so, specify the date, dosing regimen, and whether the event recurred or worsened after restarting.

- **In the 'Concomitant Medicines (e.g. drugs, devices, vaccines)' section of ISI Documentation Form and in the 'Concomitant Medication/Medical Device/Vaccine' section of Unsolicited ISI Report Form, ensure to collect:**

  - List of any immunosuppressant drugs used concurrently or within the past 6-12 months as relevant based on half-life of product (specify name, indication, dose, dates of administration)
  - Vaccination status including brand name and dates of administration, particularly vaccinations against encapsulated bacterial organisms:
    - Meningococcus
    - Pneumococcus
    - Haemophilus influenzae B
    - Influenza virus
    - Any other immunizations relevant to reported infection
  - Any booster vaccinations administered

- Blood pressor support medications including name and dates of administration

- **In the 'Medical History/Risk Factors' section of ISI Documentation Form and in the 'Ongoing Illness/Medical History/Risk Factors' section of Unsolicited ISI Report Form, ensure to collect:**

  - Risk factors for infections including:
    - Previous/chronic infection history (HIV, hepatitis, recurrent urinary tract infections, etc.)
    - Indwelling lines/catheters
    - Recent surgical operations
    - Comorbidities associated with increased risk of infections (eg: hematologic and/or solid organ malignancies, inherited or acquired immunodeficiencies, asplenia, cerebrospinal fluid leak, cochlear implants, elderly age, diabetes, chronic kidney/liver/heart disease, solid organ transplant recipient)

- **In the 'Adverse Event Information (Describe Event)' section of ISI Documentation Form and in the 'Complementary Investigations' section of Unsolicited ISI Report Form, ensure to collect:**

  - Microbiologic test results (eg: blood/urine/cerebrospinal fluid/abscess cultures, viral PCR or serologies, etc.)
  - White blood cell counts, differential and inflammatory markers if obtained
  - Imaging findings relevant to infection

ANNEX 4.2 Autoimmune disorders (including SLE)

Sutimlimab - Autoimmune Disorder

Targeted Follow-up Form (coversheet)

- **In the 'Suspect Product(s) Information' section of Individual Safety Information (ISI) Documentation Form and in the 'Suspect Medication/Medical Device (MD)/Vaccine (V)' section of Unsolicited Individual Safety Information (ISI) Report Form, ensure to collect:**

  - Start/stop dates of sutimlimab
  - Last dose of sutimlimab prior to event onset including time of administration if known
  - A causality assessment (i.e. related, unrelated, unknown) between the event and Sutimlimab

- **In the 'Adverse Event Information (Describe Event)' section of ISI Documentation Form and in the 'Description of the Case' section of Unsolicited ISI Report Form ensure to collect:**

  - If newly diagnosed autoimmune disease, provide:
    - Definitive diagnosis provided by health care professional and date diagnosis made
    - Presenting signs and symptoms and date of initial symptom onset
  - If previous history of other autoimmune disorders, describe:
    - Date of onset of each other autoimmune disease
    - Symptoms and management prior to initiation of sutimlimab
    - If worsening of previous symptoms or development of new symptoms after starting sutimlimab:
      - Treatment/management of disease at time of initiation of sutimlimab
      - Any changes in treatment/management after initiation of sutimlimab
  - If adverse event is a worsening of a pre-existing autoimmune disease after initiation of sutimlimab, please describe:
    - Signs/symptoms/management at time of initial diagnosis
    - Clinical course after initial diagnosis
    - Recent worsening of condition
  - Relevant physical examination findings
  - List the management/treatment (e.g., drugs, procedures, specify dates) of the event
  - Was sutimlimab temporarily or permanently discontinued because of the event? If yes, specify the date, reason, and whether the event improved, resolved, or abated after discontinuation.
    - Was sutimlimab later resumed? If so, specify the date, dosing regimen, and whether the event recurred or worsened after restarting.

- **In the 'Concomitant Medicines (e.g. drugs, devices, vaccines)' section of ISI Documentation Form and in the 'Concomitant Medication/Medical Device/Vaccine' section of Unsolicited ISI Report Form, ensure to collect:**

  - List of any immunosuppressant drugs used within the past 6-12 months (specify name, indication, dose, dates of administration)

- **In the 'Medical History/Risk Factors' section of ISI Documentation Form and in the 'Ongoing Illness/Medical History/Risk Factors' section of Unsolicited ISI Report Form, ensure to collect:**

  - Medical history of any autoimmune disorder (provide specific diagnosis and date of diagnosis)
  - Family history of any autoimmune disorder (provide specific diagnosis)

- **In the 'Adverse Event Information (Describe Event)' section of ISI Documentation Form and in the 'Complementary Investigations' section of Unsolicited ISI Report Form, ensure to collect:**

  - Dates, type and results of any imaging studies or procedures
  - Dates and results of relevant laboratory tests including but not limited to:
    - Inflammatory markers
    - Complete blood count with differential
    - Antinuclear antibodies (ANA) multiplex with double stranded DNA
    - Other autoantibody titers such as Anti-La/SSB antibody (SS-B), Anti-ribonucleoprotein antibody (RNP), Anti-Smith antibody (Sm), Anti-Ro/SSA antibody (SS-A)

ANNEX 4.3 Serious hypersensitivity reactions and/or anaphylaxis

Sutimlimab

Hypersensitivity and Anaphylaxis

Targeted Follow-up Form (coversheet)

- **In the 'Suspect Product(s) Information' section of Individual Safety Information (ISI) Documentation Form and in the 'Suspect Medication/Medical Device (MD)/Vaccine (V)' section of Unsolicited Individual Safety Information (ISI) Report Form, ensure to collect:**

  - Start/stop dates of sutimlimab
  - Last dose of sutimlimab prior to event onset including time of administration if known
  - A causality assessment (i.e. related, unrelated, unknown) between the event and Sutimlimab

- **In the 'Adverse Event Information (Describe Event)' section of ISI Documentation Form and in the 'Description of the Case' section of Unsolicited ISI Report Form, ensure to collect:**

  - The diagnosis for the symptoms experienced (anaphylaxis, hypersensitivity/allergic reaction, other).
  - What was the cause of the event or state if unknown?
  - Was the reaction witnessed by a healthcare professional?
  - Date/time of event onset
  - All signs and symptoms, including any systemic symptoms including cutaneous, cardiovascular, respiratory and gastrointestinal symptoms e.g. hives, generalized urticarial, rash, angioedema, paresthesia, nausea/vomiting, restlessness, faintness, hypotension, tachycardia, lethargy, dyspnea, wheezing, chest tightness.
  - Briefly list details on the management/treatment (e.g., drugs, procedures, specify dates) of the event
  - Was the patient hospitalized or required an ER visit? If yes, provide the hospitalization diagnosis, date(s) of hospitalization, and a copy of discharge report if available.
  - Was sutimlimab temporarily or permanently discontinued because of the event? If yes, specify the date, reason, and whether the event improved, resolved, or abated after discontinuation.
    - Was sutimlimab later resumed? If so, specify the date, dosing regimen, and whether the event recurred or worsened after restarting.

- **In the 'Medical History/Risk Factors' section of ISI Documentation Form and in the 'Ongoing Illness/Medical History/Risk Factors' section of Unsolicited ISI Report Form, ensure to collect:**

  - Medical history of similar event(s)
  - Medical history of allergic reactions or related risk factors (asthma, medication reactions, food allergies, drug hypersensitivity, environmental allergies, hives and/or eczema)
  - History of exposure to any potential allergens (such as new foods or seafood eaten recently, medications, herbs or supplements, or environmental exposures) prior to the onset of the event?

- **In the 'Adverse Event Information (Describe Event)' section of ISI Documentation Form and in the 'Complementary Investigations' section of Unsolicited ISI Report Form, ensure to collect:**

  - Attach or provide details of any relevant laboratory investigations and tests (such as eosinophilia, RAST testing, urinalysis, renal function tests, serological/immunological studies, imaging studies, tryptase, complement levels), units, and reference ranges for the event. Include testing dates, name of testing laboratory, and if applicable units of measurement and reference ranges.

ANNEX 6 DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION ACTIVITIES

Draft key messages of the additional risk minimization measures

1. Physician educational material:

- The Summary of Product Characteristics
- The Physician's Guide

1.1 The Physician's Guide:

Relevant information on the safety concerns addressed by the additional risk minimization measure (aRMM)

Sutimlimab targets the classical complement pathway specifically binding to complement component 1, s subcomponent (C1s) preventing the cleavage of complement component 4 (C4); although the lectin and alternate pathways remain unaffected, patients may have an increased susceptibility to serious infections, especially infections caused by encapsulated bacteria such as *Neisseria meningitidis, Streptococcus pneumoniae* and *Haemophilus influenza*.

In clinical studies, serious infections have been reported in patients receiving treatment with sutimlimab *(see Product Monograph).*

This risk can be reduced or prevented with an appropriate program of prophylactic vaccinations. Informing HCPs and patients of signs and symptoms may facilitate early diagnosis and treatment. Immediate treatment and management could prevent serious outcomes.

Details on how to minimize the safety concerns addressed by the aRMM

- Immunization

Immunize patients without a prior history of completed vaccination (or if the interval from the prior vaccination requires revaccination based on local guidelines) against encapsulated bacteria at least 2 weeks prior to receiving the first dose of sutimlimab. This should include meningococcal conjugate vaccine(s) and meningococcal serogroup B vaccine(s) when recommended and available, as well as the recommended pneumococcal vaccine(s).

If urgent sutimlimab therapy is indicated in a patient without a history of completed vaccination, administer vaccine(s) as soon as possible. Comply with the current local vaccination guidelines for vaccine use in patients with persistent complement deficiencies. Revaccinate patients in accordance with these guidelines, considering the duration of sutimlimab therapy.

The benefits and risks of antibiotic prophylaxis for prevention of infections in patients receiving sutimlimab have not been established.

- Monitoring patients

Monitor patients closely for early signs and symptoms of infections such as meningitis, sepsis and pneumonia, evaluate immediately if infection is suspected and treat as appropriate.

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If sutimlimab treatment is administered to patients with active systemic infections, monitor closely for signs and symptoms of worsening infection. Use caution when treating patients with serious infections, chronic systemic infections (such as Hepatitis B or C or human immuno-deficiency virus [HIV]) or those who may be immunocompromised.

- Key safety messages to convey in patients counselling

Patients treated with sutimlimab may have an increased susceptibility to serious infections caused by certain bacteria. Patients need to receive vaccinations against infections caused by certain bacteria before their first dose of sutimlimab. They may need to have additional vaccinations during treatment with sutimlimab. Vaccinations may reduce the risk of these infections but do not prevent all infections.

Patients should seek immediate medical attention if they suspect they may have an infection or develop any of the following symptoms: headache with nausea or vomiting, headache with a stiff neck or stiff back, headache and a fever, fever, chills, fever and rash, muscle aches with flu-like symptoms, confusion, eyes sensitive to light, cough/difficulty breathing.

Remarks on the importance of reporting on specific adverse reactions:

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions especially infections.

2. Patient educational material:

- Package leaflet
- The Patient's Guide

2.1 The Patient's Guide:

- Key safety messages conveyed by the Patient's Guide:
  - Patients treated with sutimlimab may have an increased susceptibility to serious infections caused by certain bacteria. Patients need to receive vaccinations against infections caused by certain bacteria before their first dose of sutimlimab. Vaccinations may reduce the risk of these infections but do not prevent all infections.
  - Patients should seek immediate medical attention if they suspect they may have an infection or develop any of the following symptoms: headache with nausea or vomiting, headache with a stiff neck or stiff back, headache and a fever, fever, chills, fever and rash, muscle aches with flu-like symptoms, confusion, eyes sensitive to light, cough/difficulty breathing.

[redacted]