

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761164Orig1s000

CLINICAL REVIEW(S)

BLA 761164
ENJAYMO (sutimlimab-jome)
Clinical Review Addendum
Feb 4, 2022

On Feb 4, 2022, the Division of Non-Malignant Hematology approved sutimlimab-jome to decrease the need for red blood cell (RBC) transfusion due to hemolysis in adults with cold agglutinin disease (CAD). The summary review uploaded in DARRTs in Feb 4, 2022 contained the wrong post marketing requirements (PMR) numbers (4216). The correct PMR numbers should be 3922 and are also the same numbers that were included in the action letter to the Applicant. There were no changes to the text of post marketing requirements.

PMR 3922-1:

Conduct a 5-year registry study to characterize the safety of sutimlimab in patients with primary Cold Agglutinin Disease. Yearly interim reports and the final study report should include a summary of the major safety findings and outcome of events. The summaries must discuss available information on autoimmune diseases, serious bacterial infections, sutimlimab dosing, vaccination status, serotype/serogroup of *Streptococcus pneumoniae* and *Neisseria meningitidis* isolates, and concomitant medications.

Draft Protocol Submission: 09/2022
Final Protocol Submission: 04/2023
Annual Interim Report #1: 08/2024
Annual Interim Report #2: 08/2025
Annual Interim Report #3: 08/2026
Annual Interim Report #4: 08/2027
Annual Interim Report #5: 08/2028
Annual Interim Report #6: 08/2029
Annual Interim Report #7: 08/2030
Final Report Submission: 10/2031

PMR 3922-2: Complete part B of study BIVV009-03, "A Phase 3, Pivotal, Open-Label, Multicenter Study to Assess the Efficacy and Safety of BIVV009 in Patients with Primary Cold Agglutinin Disease Who Have a Recent History of Blood Transfusion ". Include updated summary safety and efficacy analysis and submit datasets at the time of final clinical study report submission.
Final Report Submission: 08/2022

PMR: 3922-3 Complete part E of study BIVV009-01, "Safety, Tolerability and activity of TNT009 in Healthy Volunteers and Patient with Complement-Mediated Disorders. A Single/Multiple Ascending Dose Phase 1 Study". Include updated summary safety and efficacy analysis in the final clinical study report.
Final Report Submission: 08/2022

PMR: 3922-4 Complete Part B of Study BIVV009-04, "A Phase 3, randomized, double-blind,

placebo-controlled study to assess the efficacy and safety of BIVV009 in patients with primary Cold Agglutinin Disease without a recent history of blood transfusion". Include updated safety information and submit datasets at the time of final clinical study report submission.

Final Report Submission: 08/2022

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

TANYA M WROBLEWSKI
02/04/2022 04:32:18 PM

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CLINICAL REVIEW

Application Type	BLA resubmission
Application Number(s)	761164
Priority or Standard	Priority
Submit Date(s)	08/05/2021
Received Date(s)	08/05/2021
PDUFA Goal Date	02/04/2022
Division/Office	DNH/OCHEN
Reviewer Name(s)	Clinical: Carrie Diamond, M.D. (Clinical Reviewer, DNH) Tanya Wroblewski, M.D. (Clinical Team Leader, DNH)
Established/Proper Name	Sutimlimab-jome
(Proposed) Trade Name	ENJAYMO
Applicant	Bioverativ Therapeutics, Inc
Dosage Form(s)	Injection: 1100 mg/22 mL (50 mg/mL)
Applicant Proposed Dosing Regimen(s)	Sutimlimab 6500mg ^{(b) (4)} or 7500mg (for patients $\geq$ 75kg), administered as an intravenous infusion over 1-2 hours once per week for the first 2 doses followed by every other week dosing
Applicant Proposed Indication(s)/Population(s)	Treatment of hemolysis in adult patients with cold agglutinin disease
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	To decrease the need for red blood cell transfusions due to hemolysis in adults with Cold Agglutinin Disease (CAD).

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Glossary

AE	adverse event
AMR	antibody mediated reaction
AR	adverse reaction
BLA	biologics license application
BP	bullous pemphigoid
C1s	component 1, s subcomponent
CAD	cold agglutinin disease
CAS	cold agglutinin syndrome
CI	confidence interval
CMD	complement mediated disorder
CP	complement pathway
CR	Complete Response
CRF	case report form
CSR	clinical study report
FDA	Food and Drug Administration
FMQ	FDA Medical Query
Hgb	hemoglobin
IgG4	immunoglobulin G subclass 4
IgM	immunoglobulin M
ISS	integrated summary of safety
ITP	immune thrombocytopenia purpura
LDH	lactate dehydrogenase
MAD	multiple ascending dose
MedDRA	Medical Dictionary for Regulatory Activities
NHV	normal healthy volunteer
NME	new molecular entity
OPMA	Office of Pharmaceutical Manufacturing Assessment
OPQ	Office of Pharmaceutical Quality
ORA	Office of Regulatory Affairs
PMR	postmarketing requirement
PT	preferred term
RBC	red blood cell
REMS	risk evaluation and mitigation strategy
SAD	single ascending dose
SAE	serious adverse event
SAR	serious adverse reaction
SCS	Summary of clinical safety

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SLE systemic lupus erythematosus
TEAE treatment emergent adverse event
USPI United States Prescribing Information
WAIHA warm autoimmune hemolytic anemia

2. Introduction

Bioverativ Therapeutics Incorporated originally submitted their Biologic Licensing Application (BLA) for marketing approval of sutimlimab for the treatment of hemolysis in adult patients with Cold Agglutinin Disease (CAD) on March 13, 2020. During the initial review cycle of the Application, all disciplines recommended approval except for the Office of Pharmaceutical Manufacturing Assessment (OPMA), Office of Pharmaceutical Quality (OPQ), CDER due to deficiencies related to readiness for commercial manufacturing and data integrity that were observed at the FDA pre-license inspection of the [REDACTED] (b) (4) drug substance manufacturing facility. Deficiencies included lack of quality oversight, significant data integrity concerns, and failure to conduct a comprehensive assessment to ensure acute and reliable results submitted to the BLA. The Application received a Complete Response Letter (CRL) on November 13, 2020.

The Applicant submitted a response to the CRL on August 5, 2021. This review of the response to the CRL focuses only on the review of the deficiencies (OPQ), updated safety, labeling and postmarketing requirements.

3. Benefit-Risk Assessment

Benefit-risk considerations for sutimlimab to reduce the need for transfusions in adult patients with CAD were based on the results of a well-controlled (baseline control) and adequate trial, BIVV009-03 Part A, also referred to as CARDINAL. CARDINAL was an international, single-arm, open-label trial in 24 adult patients with CAD and at least one blood transfusion in the 6 months prior to enrollment, hemoglobin (Hgb) ≤ 10 g/dL, and symptomatic disease. The primary endpoint was the percent of patients who met criteria of the responder definition. Patients met the responder definition if they demonstrated an increase from baseline in hemoglobin (Hgb) level ≥ 2 g/dL or normalization of Hgb level to ≥ 12 g/dL at the treatment assessment time point (mean value from weeks 23, 25, and 26) and did not receive a blood transfusion from week 5 through week 26 or any treatment for CAD beyond what was permitted in the protocol. Results from the prospectively planned primary composite endpoint and analyses of the individual components demonstrated a response for patients with CAD. In total, 13 out of the 24 patients [54.2% (95% confidence interval (CI): 32.8%, 74.4%)] in full analyses set met the responder criteria the composite primary endpoint and the lower bound of the 95% CI of response was greater than the prespecified value of 30%. The results for each of the components of the composite endpoint were also persuasive: 15 (62.5%) patients met the Hgb endpoint, 17 (70.8%) were transfusion free from Week 5 to Week 26 and 22 (91.7%) patients did not receive protocol prohibited CAD mediations. To further support efficacy, biomarkers of hemolysis including lactate dehydrogenase (LDH) and bilirubin were measured. Among 14 patients with baseline and follow-up values, the mean bilirubin was 55 μ mol/L (2.7-fold the upper limit of

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normal (ULN)) at baseline and 15µmol/L (0.8-fold ULN) at the treatment assessment timepoint. Among 17 patients with baseline and follow-up values, the mean LDH decreased from 424 U/L (1.7-fold ULN) at baseline to 301 U/L (1.2 fold ULN) at the treatment assessment timepoint. The decrease in mean bilirubin and LDH values compared to baseline provide further evidence of decreased hemolysis.

Mechanistic evidence of improvement in hemolysis due to sutimlimab is further demonstrated in study BIVV009-01 Part C and E. This was a phase 1, open-label, dose finding study which included 6 patients with primary CAD. In Part C, the median hemoglobin increased from median baseline of 7.7g/dL to 10.7g/dL four weeks after the last dose of sutimlimab. After a sutimlimab washout, the hgb levels decreased to pre-treatment baseline levels. A total of 5 patients had evaluable LDH and bilirubin samples. Four out of 5 patients had an elevated LDH at baseline and all four patients had a decrease in LDH and 3 patients had normalization of LDH. All five patients had normalization of bilirubin levels 14 days after the first dose of sutimlimab. LDH and bilirubin levels increased following the sutimlimab washout period as hemolysis reoccurred. In Part E, four patients were administered sutimlimab, and demonstrated an increase in hemoglobin with a corresponding decrease in bilirubin and LDH levels. These results were sustained in these patients with the exception of one patient who discontinued therapy.

A single, baseline-controlled trial provides substantial evidence of effectiveness for this application, given the robust improvement in objective laboratory parameters that would be extremely unlikely to occur spontaneously in an untreated population with this disease. Thus, substantial evidence of effectiveness was established via one adequate and well controlled trial plus confirmatory evidence (mechanistic evidence of increase in hgb and decreases in LDH and bilirubin levels, showing a clear reduction in hemolytic markers and return to baseline values after sutimlimab washout from study BIVV009-01 Part C). Flexibility is appropriate in this setting of rare, serious and chronic disease, especially because there are no FDA-approved therapies at this time.

The size of the safety database is acceptable for the population and indication. The toxicity profile was determined to be manageable and safety issues could be addressed in labeling. For further details see the clinical review dated November 12th, 2020. The safety update provided with this resubmission did not alter the benefit-risk profile of sutimlimab. Post Marketing Requirements (PMRs) were issued to establish a registry to evaluate and to complete ongoing studies to further evaluate long term safety and the risks of autoimmune disease and serious infections.

The review team determined that sutimlimab confers substantial benefits of reduction in blood transfusion and increases in hemoglobin levels in symptomatic patients with CAD who recently received a blood transfusion and that these benefits outweigh the risks. (b) (4)

indicated to decrease the need for red blood cell transfusions due to hemolysis in adults with Cold

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Agglutinin Disease (CAD)’. Although the study population was limited to patients with a recent blood transfusion (within 6 months), there is no scientific concern that sutimlimab would not be effective to decrease RBC transfusion risk in patients with blood transfusions more than 6 months prior, or to patients who have not received transfusion.

Lastly, all deficiencies related to data integrity issues are now resolved and (b) (4) site as a quality control testing facility has acceptable CGMP compliance status.

Table 1. Benefit Risk Table

	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Cold Agglutinin Disease (CAD) is a type of autoimmune hemolytic anemia resulting from a clonal B-cell proliferative disorder of the bone marrow, which in turns activates the classical complement pathway. • The incidence is estimated at approximately 1 to 1.8 per million with a prevalence of approximately 13 to 16 per million, based on retrospective reviews from Scandinavian countries. • This rare disease primarily affects middle-aged to elderly adults. Cold Agglutinin Disease CAD is a form of Autoimmune Hemolytic Anemia (AIHA) that results from a clonal B-cell proliferative disorder of the bone marrow. This rare disease primarily affects middle aged adults and the elderly. The classical complement pathway is activated by cold agglutinins • Symptoms related to anemia such as fatigue, dyspnea, and weakness can substantially impair quality of life. In addition, patients often have symptoms such as acrocyanosis and may be at an increased risk for thromboembolic events.	• CAD is rare, serious disease with chronic morbidities with many patients experiencing flares of hemolysis and anemia that can be severe, and can require RBC transfusion and be associated with significant impairment in quality of life.
Current Treatment Options	• Treatment of CAD often consists of supportive therapies, including avoidance of cold, blood transfusions, and warming of blood during transfusions. • Other therapies used off-label include rituximab (off-label) as monotherapy or in combination with cytotoxic agents; however, these may not be effective or durable and can be associated with significant toxicities. • Corticosteroids generally have no role in the treatment of CAD. • There are no approved therapies for CAD	• There are no FDA-approved therapies for the treatment of CAD. • There is an unmet medical need for an effective treatment for patients with CAD in the United States. Treatments for CAD are needed because of high morbidity associated with this disease.

Benefit	- In a single-arm, open-label trial (BIVV009-03 Part A), 24 patients with symptomatic CAD and a recent blood transfusion received sutimlimab, administered on Days 0 and 7, followed by treatment every two weeks for 26 weeks. 54.2% (95% CI: 32.8, 74.4) of patients met the responder definition: Hgb level ≥ 12 g/dL or increased by ≥ 2 g/dL from baseline, transfusion independence, no use of prohibited therapies. - In total, 62.5% of patients met the predefined Hgb endpoint (Hgb level ≥ 12g/dL or Hgb level increased by ≥ 2 g/dL from baseline at the treatment assessment endpoint), 70.8% were transfusion-free from Week 5 to 26, and 91.7% of patients did not receive protocol-prohibited CAD medications. - Symptoms of hemolysis were assessed as secondary endpoints but could not be interpreted due to trial design. - In Study BIVV009-01 Part C and E, patients with CAD demonstrated objective improvement in markers of hemolysis, i.e., decreases in LDH and bilirubin as well as an increase in hemoglobin from baseline values. Overall, after sutimlimab washout period, hemolytic markers increased, and hemoglobin returned to near baseline values.	- The CARDINAL study demonstrates that sutimlimab confers substantial benefits in terms of reduction in blood transfusions and increase in hemoglobin levels in patients with CAD. - A benefit on symptoms, e.g. fatigue, was not established. - Improvements in hemoglobin, LDH and bilirubin levels provide important, objective, mechanistic support for the efficacy findings. - the single, baseline-controlled trial (plus confirmatory evidence) provides substantial evidence of effectiveness for this application, given the robust improvement in objective laboratory parameters that would be extremely unlikely to occur spontaneously in an untreated population with this disease. Flexibility is appropriate in the setting of this rare, serious, and chronic disease, especially because there are no FDA-approved therapies at this time.
Risk	- Primary safety results included 34 patients pooled from BIVV009-01 Part C&E and BIVV009-03 Part A and B. - The most common types (>10%) of TEAEs reported in the 24 patients in the pivotal study (BIVV009-03 Part A) were: respiratory tract infections, viral infections, diarrhea, dyspepsia, cough, arthralgia, arthritis, and peripheral edema. - In the primary safety population, the most common type of treatment-emergent SAEs were infections, reported in 7 of 34 patients (21%). Serious infections included; urinary tract infection, pneumonia, pulmonary sepsis, erysipelas, streptococcal sepsis, wound infection staphylococcal, escherichia sepsis, acute cholecystitis, respiratory tract infection, and viral infection. - Given the mechanism of action of the drug, patients may be at risk for infections caused by	- Overall, acceptable risk benefit profile. - Size of safety database acceptable given rarity of disease. - Risks of sutimlimab can be sufficiently addressed through Warnings and Precautions in the United States Prescribing Information (USPI). - Longer term safety will be assessed in post marketing requirements.

	encapsulated organisms, in particular <i>Neisseria meningitidis</i>, <i>Streptococcus pneumoniae</i>, and <i>Hemophilus influenzae</i>. Infections from encapsulated bacteria were reported. One patient had pneumococcal sepsis despite receiving a vaccination. • There is a theoretical risk of autoimmunity with inhibition of early components of the classical complement pathway. No clear trend was demonstrated in studies with sutimlimab to date.	

4. Background

4.1.1. Product Information

Sutimlimab-jome (proprietary name, ENJAYMO) is a humanized immunoglobulin G subclass 4 (IgG4) monoclonal antibody that inhibits the classical complement pathway (CP) and specifically binds to complement protein component 1 s subcomponent (C1s), a serine protease which cleaves C4.

4.1.2. Therapeutic Context

Cold Agglutinin Disease is a type of autoimmune hemolytic anemia caused by IgM induced complement activation. CAD is diagnosed by the presence of IgM antibodies that agglutinate red blood cells at temperatures below normal body temperature, chronic hemolytic anemia and its resultant symptoms. Chronic hemolysis is due the binding of the cold agglutinin IgM antibodies to the I antigen, a glycoprotein membrane antigen universally present on RBCs. Binding of IgM antibodies to the I antigen results in the recruitment of activated complement fragments on the RBC, which leads to uptake and lysis of the red blood cell by the reticuloendothelial system with intravascular hemolysis and anemia. The anemia can result in symptoms such as fatigue dizziness, dyspnea and acrocyanosis. Chest pain and Raynaud syndromes are also reported patients are predisposed to thrombotic events. LDH typically increases because of the hemolysis. As complement coated RBCs are usually cleared through extravascular hemolysis and phagocytosis by liver macrophages, elevated total bilirubin is also typical with the disease.

CAD is a rare disease that mostly affects middle-aged and elderly patients with median age of onset of 67 years. There is a female predominance, although this may be due to the longer lifespan than males. Patient with CAD can display varying levels of chronic hemolysis with

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episodes of hemolytic flares, exacerbating symptoms of fatigue, shortness of breath and general weakness.

There are currently no FDA-approved therapies for the treatment of CAD. Treatments are considered if the patient develops symptomatic anemia or disabling cold-induced circulatory symptoms. Supportive nonpharmacological therapies include keeping warm avoidance of cold infusions and blood transfusions and folic and erythropoietin may be used as supportive therapies. Corticosteroids are often not effective in CAD. Patients may be treated with rituximab monotherapy (off-label) or in combination with cytotoxic agents, however these therapies may not always be effective or durable and can be associated with significant toxicities.

4.1.3. Office of Product Quality

During the first review cycle the application was not approved due to deficiencies related to readiness for commercial manufacturing and data integrity that were observed at the FDA pre-license inspection of (b) (4) drug substance manufacturing facility.

In the BLA resubmission, the Applicant adequately addressed the (b) (4) facility deficiencies communicated in the CR Letter. The Applicant removed the (b) (4) site as the drug substance manufacturing facility but kept (b) (4) site for quality control testing for both drugs substance and drug product. The Office of Regulatory Affairs (ORA) led the PLI on (b) (4) site and concluded that data integrity issues identified at (b) (4) site related to the testing results submitted in BLA 761164 were resolved, and (b) (4) site as a quality control testing facility has acceptable CGMP compliance status. Therefore, this BLA resubmission is recommended for approval from a facility standpoint.

4.1.4. Nonclinical Pharmacology/Toxicology

The nonclinical pharmacology review was performed by Shaji Theodore and C. Lee Elmore on October 1st, 2020. There are no new updates to this assessment. The non-clinical reviewers concluded that there are no deficiencies in the nonclinical data that would preclude approval of BLA 761164, and they recommend approval.

4.1.5. Clinical Pharmacology

The Office Clinical Pharmacology (OCP) reviewers were Xiaolei Pan, Sudharshan Hariharan, Jihye Ahn, Justin Earp, Shirley Seo. They recommend approval of sutimlimab for the treatment of CAD. The resubmission includes additional immunogenicity data obtained from the CADENZA study. No revisions were made to the USPI as the new data did not alter risk associated with immunogenicity. Please refer to the initial review by Dr. Xiaolei Pan (Dated 11/06/2020) for

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other clinical pharmacology discussions. Please also refer to the review by Xiaolei Pan for review of the resubmission data.

4.1.6. Clinical Efficacy

Efficacy was previously established and there are no new updates to this assessment. Please refer to the combined Division Director and Cross Discipline Team leader review dated November 13, 2020, the combined clinical review and statistical review dated November 12, 2020 in DARRTs.

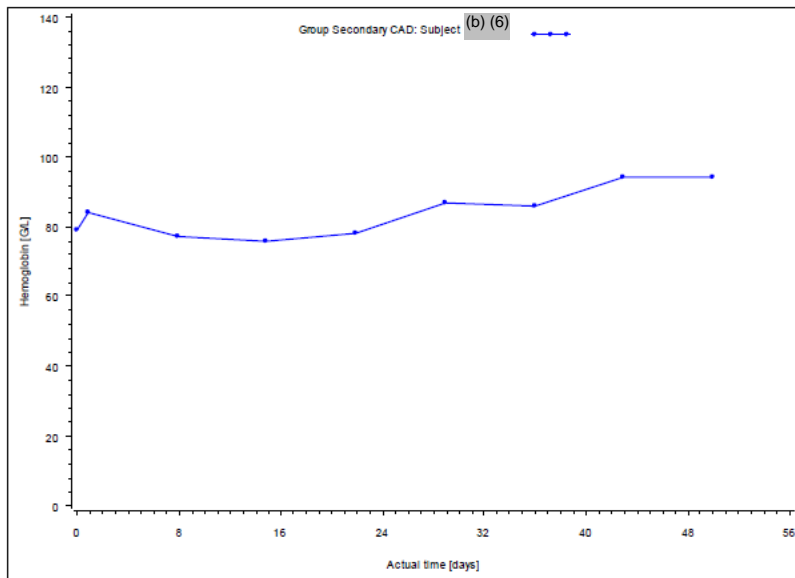
Mechanistic Support from Study BIVV009-01 Parts C and E

This section clarifies the original clinical review for this application, i.e., that evidence of mechanistic support (confirmatory evidence) was provided in the original Application submission from study BIVV009-01 Part C and E. BIVV009-01 Parts A-C and E, was a first-in-human, phase I study composed of a single ascending dose (SAD) part in healthy volunteers, multiple ascending dose (MAD) part in healthy volunteers, and multiple dose part in patients with complement mediated disorders (CMDs). Part C consisted of patient with CMDs including patients with CAD, bullous pemphigoid (BP), warm autoimmune hemolytic anemia (WAIHA) and antibody-mediated reaction (AMR) after renal transplant. All patients received a single IV test dose of sutimlimab at 10mg/kg IV followed by 4 weekly doses of 60mg/kg. In Part E, 4 patients with CAD who responded to sutimlimab in Part C restarted sutimlimab at fixed doses of 5.5 g for every 2 weeks. Doses were later increased and based on weight categories (6.5 g for patients <75 kg, 7.5 g for patients ≥75 kg) under a protocol amendment.

In total, 6 patients with CAD and a hemoglobin <11g/dL were enrolled and completed Part C. The median baseline hemoglobin was 7.7g/dL (range: 6.8-8.3g/dL) and all patients were transfusion dependent. There was an increase in the baseline median hemoglobin from 7.7g/dL to 10g/dL at 4 weeks after the last sutimlimab infusion. Following completion of a sutimlimab washout, the hemoglobin values declined to pretreatment levels in 5 patients with a median hemoglobin level of 7.3g/dL (range 7.1-8.8g/dL). The 6th patient's course was complicated by gynecological malignancy and erythropoietin-deficiency. Figure 1 below provides the hemoglobin response over time for the 6 patients in Part C.

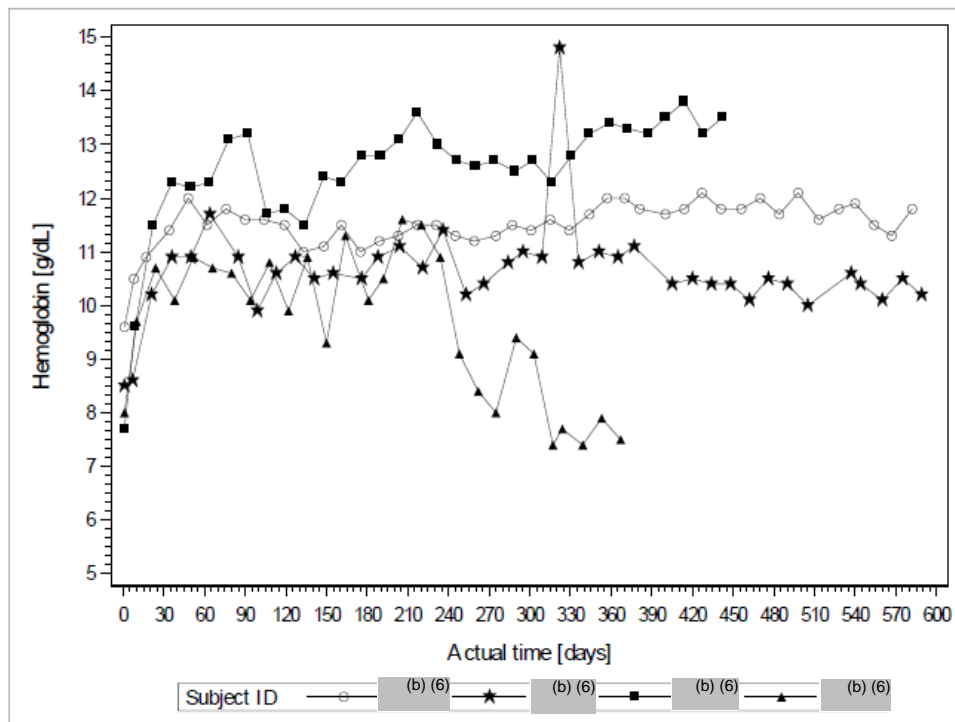
In Part E, after restarting sutimlimab, the median increase in hemoglobin was 2.65g/dL (range; 2.4 to 4.5g/dL) by week 7. Of the four patients who enrolled in Part E, 3 patients (75%) had an increase in hemoglobin which was sustained after 5 weeks of treatment (Figure 2). The one patient that did not have a sustained increase from hemoglobin discontinued from study due to adverse reactions.

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 Figure 1. Hemoglobin Response in CAD Population, BIVV009-01 Part C



Source: Applicant's CSR, Section 14

Figure 2. Hemoglobin Response by Patient, Study BIVV009-01 Part E



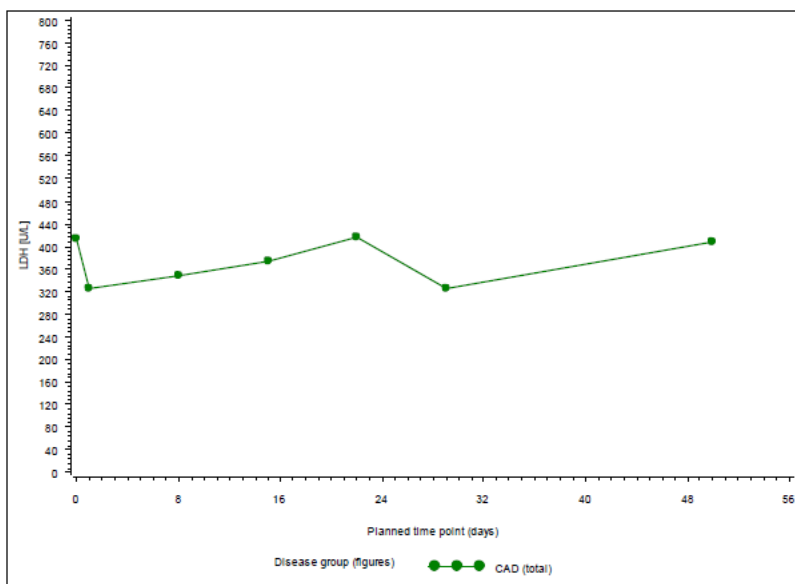
Source: Applicant's CSR

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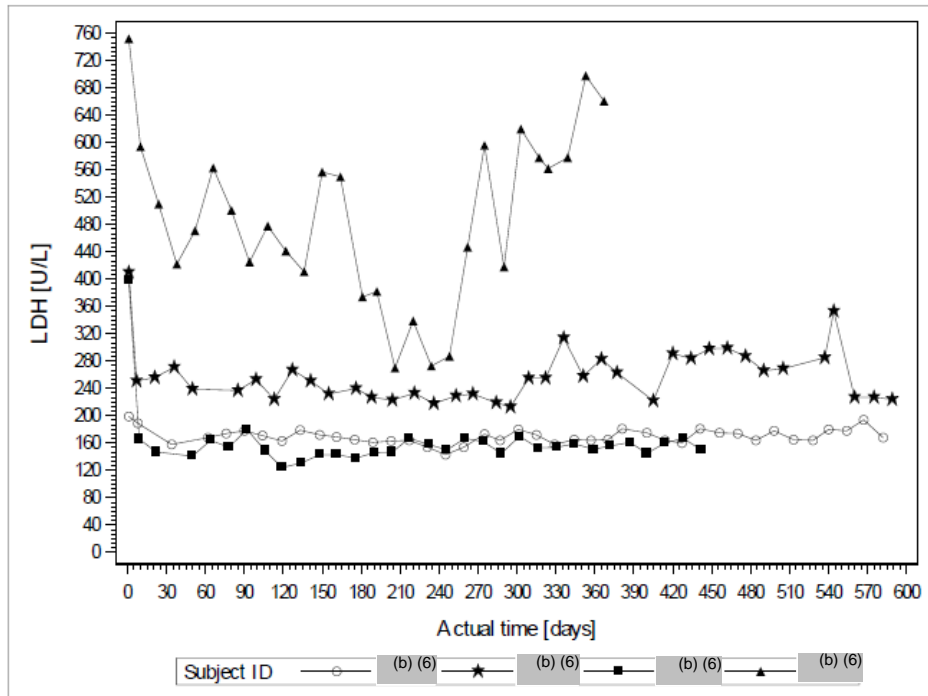
Of the 5 patients with evaluable LDH responses, 4 out of 5 patients had an elevated LDH at baseline. All four patients with elevated LDH at baseline had a decline in LDH response and 3 had normalization of LDH. During the washout period there was a slight increase in the LDH in 3 out of the 4 patients. The one patient that did not have an increase in LDH had persistent sutimlimab levels. See LDH response over time in Figure 3 below. In Part E, after resumption of sutimlimab after the washout, all four patients had decreases in LDH by week 3 with a mean decrease in LDH of -215.7U/L (range, -251 to -154U/L). The one patient who did not have a sustained response discontinued from study. See LDH response in Figure 4.

Figure 3 LDH Response in CAD Population, Study BIVV009-01 Part C



Source: Applicant's CSR, Section 14

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 Figure 4. LDH Response by Patient, Study BIVV009-01 Part E



Source: Applicant's CSR

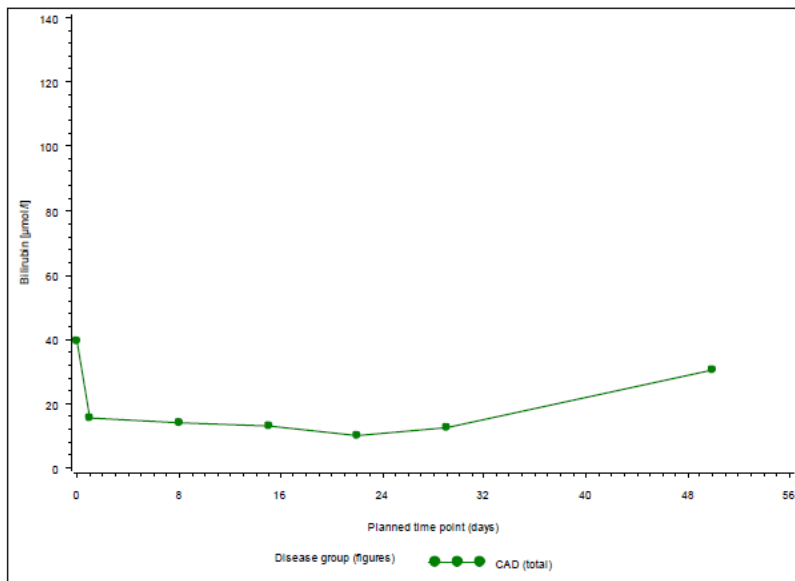
Bilirubin was elevated in at baseline in all 5 patients with an evaluable bilirubin level. Bilirubin levels normalized in all 5 patients within 14 days of the first dose of sutimlimab at 60mg/kg IV. Bilirubin levels subsequently increased in 4 out of 5 patients during the washout period. The one patient that did not have an increase in bilirubin had persistent sutimlimab levels. See Figure 5 for bilirubin change over time. In Part E, all four patients had a rapid decline in bilirubin levels by 2 weeks of treatment, this was sustained in all but one patient (Figure 6).

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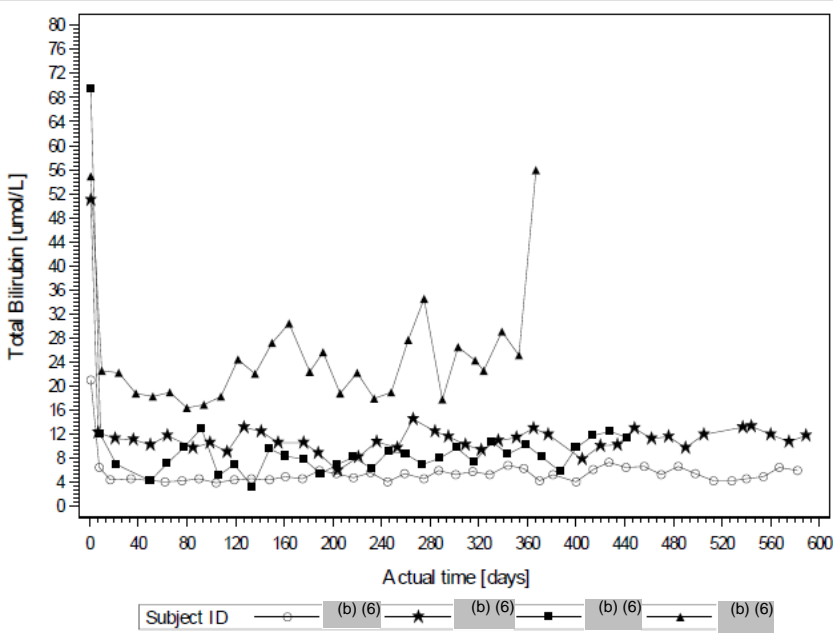
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Figure 5. Bilirubin Response in CAD Population, Study BIVV009-01 Part C



Source: Applicant's CSR, Section 14



Source: Applicant's CSR

4.1.7. Safety Update in CRL

In the original BLA, the primary safety database included a total of 34 patients with CAD from pooled studies (BIVV009-01 Parts C&E (CAD patients only) and BIVV009-03 Part A&B)). Please refer to Table 2 for a summary of clinical trials included in the Application. The safety analysis focused on the pivotal study BIVV009-03 Part A, a single-arm, open-label study which consisted of 24 patients with CAD and a recent blood transfusion who received sutimlimab for 25 weeks. The data cut-off for the primary database was July 11th, 2019. A secondary safety database was also assessed in patients with other complement mediated disorders (N=32) and normal healthy volunteers (N=96).

The safety update in the BLA resubmission includes 42 additional patients (for a total N=76 patients) from ongoing studies in patients with CAD (BIVV009-01 Part E and BIVV009-03 Part B) and also study BIVV009-04 Parts A&B (CADENZA). CADENZA Part A is a randomized, double-blind, placebo-controlled trial in patients with CAD who had not received a recent blood transfusion. This part of the trial is now completed and included 22 patients in the sutimlimab arm and 20 in the placebo arm. CADENZA Part B is the open-label, extension portion and is ongoing. The data cut-off for the primary database was September 29, 2020. (b) (4)

Table 2. Listing of Clinical Trials Relevant to this BLA Resubmission

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Trial Identity	NCT number	Population	Design	Treatment Dosing	Primary Objectives	Sample Size ¹	Status
Pivotal Study to Support Safety and Efficacy							
BIVV00 9-03 (Part A and Part B) ²	NCT033 47396	CAD (recent blood transfusion)	Phase 3, open label, single arm, multicenter study <u>Part B:</u> Extension of Part A with assessment of long term safety	<u>Part A:</u> Sutimlimab fixed 6.5g (<75kg) or 7.5g (≥75kg), dosing at week 0, 7, and every other week to week 25 <u>Part B:</u> Following completion of part A, every 2 weeks (same dosing as Part A) for up to 2 years following the last patient out of Part A	<u>Part A:</u> To determine whether sutimlimab administration results in a ≥ 2 g/dL increase in hemoglobin (Hgb) levels or increases Hgb to ≥ 12 g/dL and obviates the need for blood transfusion during treatment in patients with primary CAD who had a recent history of blood transfusion. <u>Part B:</u> Evaluate the long-term safety and tolerability	<u>Part A:</u> 24 <u>Part B:</u> 22	<u>Part A:</u> Completed <u>Part B:</u> Ongoing
22 sites screened at least one patient, 16 study sites enrolled at least 1 patient: United States, Australia, Germany, France, Italy, Japan, Norway, United Kingdom, Austria, Belgium							
Additional Studies to Support Safety, Efficacy, or PK							
BIVV00 9-01 (Part A,B,C,E)	NCT025 02903	<u>Part A,B:</u> NHV <u>Part C:</u> CMD (BP, AMR, WAIHA, CAD) <u>Part E:</u> CAD and previously treated with sutimlimab	<u>Part A:</u> Phase 1, double-blind, randomized, placebo controlled, single dose <u>Part B:</u> Phase 1, double-blind, randomized, placebo controlled, multiple ascending dose	<u>Part A:</u> Single dose Sutimlimab (0.3-100mg/kg) <u>Part B:</u> Weekly dosing x 4 Sutimlimab (30 or 60 mg/kg) <u>Part C:</u> Single dose Sutimlimab of 10mg/kg followed by 4 weekly doses of 60mg/kg <u>Part E:</u> Initially Sutimlimab 5.5g, modified to 6.5g (<75kg) or 7.5g	<u>Part A,B,C,E:</u> Safety and tolerability of Sutimlimab	<u>Part A:</u> 48 (36 sutimlimab, 12 placebo) <u>Part B:</u> 16 (12 sutimlimab, 4 placebo) <u>Part C:</u> 34 (10 with CAD or CAS, 4 with	<u>Part A,B,C:</u> Completed <u>Part E:</u> Ongoing

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Trial Identity	NCT number	Population	Design	Treatment Dosing	Primary Objectives	Sample Size ¹	Status
			<u>Part C,E:</u> Phase 1, open label	(≥75kg) weekly for the first two doses followed by every other week		WAIHA, 10 with AMR, 10 with BP) <u>Part E:</u> 4 with CAD	
BIVV00 9-04 (Part A and B)	NCT033 47422	CAD (no recent blood transfusion)	<u>Part A:</u> Phase 3, double-blind, randomized, placebo-controlled <u>Part B:</u> Phase 3, open label, extension, long term safety	<u>Part A:</u> Sutimlimab 6.5g (<75kg) or 7.5g (≥75kg), dosing at week 0, 1, and every other week to week 25 <u>Part B:</u> Following completion of Part A, Sutimlimab 6.5g(<75kg) or 7.5g (≥75kg) every 2 weeks for up to 1 year after the last patient out of part A	<u>Part A:</u> To determine whether sutimlimab administration results in a ≥1.5g/dL increase in hemoglobin level and avoidance of transfusion and CAD prohibited medications between week 5 and 26 <u>Part B:</u> Long-term safety and tolerability	<u>Part A:</u> 42 (22 sutimlimab, 20 placebo) <u>Part B:</u> 37 (17 from sutimlimab arm, 20 from placebo arm)	<u>Part A:</u> Completed <u>Part B:</u> Ongoing
BIVV00 9-201 (Part A and B)	NCT032 75454	Chronic ITP	<u>Part A:</u> Phase 1, open label, single-arm <u>Part B:</u> Phase 1, open label, extension with long term safety	<u>Part A:</u> Sutimlimab fixed 6.5g (<75kg) or 7.5g (≥75kg), dosing at week 0, 7, and every other week for approximately 21 weeks <u>Part B:</u> Sutimlimab 6.5g (<75kg) or 7.5g (≥75kg) biweekly for up to 2 years following completion of last patient included in part B	Safety and tolerability in patients with chronic ITP	<u>Part A:</u> 12 <u>Part B:</u> 7	Ongoing

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Trial Identity	NCT number	Population	Design	Treatment Dosing	Primary Objectives	Sample Size ¹	Status
TNT009-02	--	NHV	Phase 1, randomized, double-blind, controlled parallel group	Sutimlimab 75mg/kg x 4 (days 1, 8, 22, 36)	To assess safety and tolerability of multi-dose sutimlimab in NHVs	18 sutimlimab, 6 placebo	Completed
BIVV009-05	--	NHV	Phase 1, randomized, open label	<u>Part A:</u> Sutimlimab single dose of either 30mg/kg, 60mg/kg, or 100mg/kg <u>Part B:</u> Sutimlimab 6.5 (<75kg) or 7.5g (≥75kg) on day 1, 8, 22	Evaluate the PK of a single-dose and multi-dose sutimlimab in healthy Japanese subjects	<u>Part A:</u> 18 <u>Part B:</u> 12	Completed

¹sample size is based on number of treated patients at the initial data cut-off

²Pivotal study includes Part A of BIVV009-03. Part B of BIVV009-03 is supportive.

5. Safety

5.1. Safety Review Approach

The Applicant submitted a safety update as required per the CRL; which included safety updates of the ongoing clinical studies: BIVV009-01 (Part E), BIVV009-03 (Part B), BIVV009-04 (Part A and Part B) and BIVV009-201.

Studies completed prior to the original BLA submission (BIVV009-01 Part A, BIVV009-01 Part B, TNT009-02, BIVV009-05, BIVV009-01 Part C and BIVV009-03 Part A) were reviewed previously and no update to these studies was included as part of this resubmission. A summary of these studies are described in the table above (Table 2). Refer to review of this safety update data in DARRTs, dated November 12, 2020.

Review of safety update was based upon:

- Integrated summary of safety (ISS) data set and BIVV009-03 Part B data set
- Summary of clinical safety (SCS)
- Clinical Study Reports (CSR) for BIVV009-04 Part A and BIVV009-03 Part B

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- Protocol for BIVV009-04 Part A
- Patient narratives and case report forms (CRFs) from BIVV009-04 Part A

The ISS ADAE.xpt data file was reviewed for accuracy of translation of the verbatim to preferred term by manual review. Similar preferred terms were grouped by standardized groupings of related preferred terms through FDA Medical Queries (FMQs).

The review team concluded that the Applicant provided the safety update information that was required per the CR letter. In addition, the safety update provides reassurance that the safety findings in the original review are reliable. A detailed review regarding the safety update can be found in DARRTs on February 3rd, 2022.

The safety data in the safety update was generally consistent with the original safety findings. In addition, safety data reported in the USPI from the original submission consisted primarily of patients with CAD who received a recent blood transfusion. Additional data provided in the safety update was primarily based on 42 patients with CAD who had not received a recent blood transfusion. As the safety update does not alter the benefit risk profile of sutimlimab no additional data from ongoing studies were included in the USPI.

Revisions were made to the UPSI based on the safety analysis from the original Application submission.

During this resubmission, the clinical review team reviewed the Applicant's rationale for revising the Adverse Reaction table in Section 6, this document was submitted on October 23, 2020 during the first review cycle. The Applicant recommended removal of (b) (4) and fatigue from the USPI. After review of the Applicant's rationale the clinical review team agreed with removal of (b) (4). Fatigue will continued to be listed as an ADR. See discussion below.

1. (b) (4) - For all events of (b) (4) the clinical reviewer agrees this should not be included as an ADR.

2. (b) (4) These events do not appear related to sutimlimab.

3. (b) (4), this adverse event will no longer be included in the ADR table.

4. Fatigue – Three patients had a TEAE of fatigue (preferred terms included: asthenia, fatigue, and mental fatigue). One patient had a TEAE of asthenia and the verbatim term was weakness

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due to diarrhea. One patient had fatigue which the Applicant states that it may have been due to anemia in a nonresponder. One patient had mental fatigue which the Applicant proposed a medical history of hypothyroidism as an alternate etiology. The clinical reviewer does not agree with the Applicant's assessment of relatedness and while possible alternate etiologies were proposed there is not a clear correlation. Sutimlimab could have also contributed to these TEAEs. Therefore, fatigue will remain an ADR as this was a single-arm, open-label study with no comparator arm to further assess this risk.

Serious adverse reactions (SARs) and adverse reactions leading to drug interruption were also revised in the USPI based on data presented in the original submission. See a brief discussion below.

Serious adverse events (SAEs) were reported in 7 out of 24 patients (29%). After reviewing the narratives it was determined that 3 out of 24 patients (12.5%) had an SAR. SARs were reported in one patient each (4.2%), including streptococcal sepsis, staphylococcal wound infection, arthralgia and respiratory tract infection. The SARs of streptococcal sepsis and staphylococcal wound infection occurred in the same patient. The following patients were determined to have SAEs unrelated to sutimlimab:

1. Patient (b) (6) had SAEs of gastrointestinal hemorrhage and hepatocellular carcinoma. As stated in the original review, the TEAE of hepatocellular occurred after receiving two doses of sutimlimab and was at a late stage at the time of diagnosis, this patient died shortly after diagnosis. The event of gastrointestinal bleeding was related to the hepatic cancer.
2. Patient (b) (6) had SAEs of anemia, coronary artery stenosis and parkinsonism. The SAE of anemia was related to the underlying CAD. The SAEs of coronary artery stenosis and parkinsonism were related to pre-existing conditions.
3. Patient (b) (6) had an SAE of renal cell carcinoma, this was diagnosed prior to receiving sutimlimab.
4. Patient (b) (6) had SAEs of vitreous hemorrhage and acute cholecystitis. The patient had a history of vitreous hemorrhage and was taking aspirin. The SAE of acute cholecystitis was likely related to gallstones which were visualized on imaging.

Drug interruptions due to TEAEs occurred in 6 out of 24 patients (25%). Upon reviewing narratives it was determined that 4 out of 24 patients (17%) had adverse reactions which led to interruption in the dosing of sutimlimab. This included adverse reactions of infection, streptococcal sepsis, staphylococcal wound infection, and infusion related reaction. There were two patients with drug interruptions with unrelated TEAEs, including acute cholecystitis and air embolism.

6. Labeling Recommendations

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 6.1. Prescription Drug Labeling

Summary of Significant Labeling Changes (High level changes and not direct quotations)		
Section	Proposed Labeling	Approved Labeling
Highlights of Prescribing Information		Revised to be consistent with FPI.
1 Indications and Usage	(b) (4)	"to decrease the need for RBC transfusion due to hemolysis in adults with CAD"
2 Dosage and Administration	No changes made from submitted labeling.	No changes made from submitted labeling.
3 Dosage Forms and Strengths	No changes made from submitted labeling.	No changes made from submitted labeling.
4 Contraindications	No changes made from submitted labeling.	No changes made from submitted labeling.
5 Warnings and Precautions	5.2 Rate of IRRs (b) (4) 5.4 (b) (4)	Rate (b) (4) to 8% based upon change of population to n=24. 5.4 Recurrent Hemolysis After ENJAYMO Discontinuation (change made to describe the risk, rather than mitigating strategy.
6 Adverse Reactions	Included (b) (4) CARDINAL trials.	(b) (4)
7 Drug Interactions	Section not in USPI	
8 Use in Specific Populations	No significant changes.	No significant changes.
10 Overdosage	Section not in USPI	
11 Description	No significant changes.	No significant changes.
12 Clinical Pharmacology	No significant changes.	No significant changes.
13 Non-Clinical Toxicology	No significant changes.	No significant changes.
14 Clinical Studies	Table 3, included (b) (4)	Table 3: Added Standard Deviations to Hgb, Bilirubin, and LDH results.

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	Included (b) (4)	Deleted (b) (4)
15 References	Section not in USPI	
16 How Supplied/Storage and Handling	No significant changes.	No significant changes.
17 Patient Counseling Information	No significant changes.	No significant changes.
Patient Labeling Medication Guide		Updated to be consistent with USPI

7. Risk Evaluation and Mitigation Strategies (REMS)

No safety issues were identified during the review of the application that warranted a REMS.

8. Postmarketing Requirements and Commitments

PMR 4216-1 Conduct a 5-year registry study to characterize the safety of sutimlimab in patients with primary Cold Agglutinin Disease. Yearly interim reports and the final study report should include a summary of the major safety findings and outcome of events. The summaries must discuss available information on autoimmune diseases, serious bacterial infections, sutimlimab dosing, vaccination status, serotype/serogroup of *Streptococcus pneumoniae* and *Neisseria meningitidis* isolates, and concomitant medications.

Draft Protocol Submission: 09/2022
 Final Protocol Submission: 04/2023
 Annual Interim Report #1: 08/2024
 Annual Interim Report #2: 08/2025
 Annual Interim Report #3: 08/2026

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Annual Interim Report #4: 08/2027

Annual Interim Report #5: 08/2028

Annual Interim Report #6: 08/2029

Annual Interim Report #7: 08/2030

Final Report Submission: 10/2031

PMR 4216-2 Complete part B of study BIVV009-03, "A Phase 3, Pivotal, Open-Label, Multicenter Study to Assess the Efficacy and Safety of BIVV009 in Patients with Primary Cold Agglutinin Disease Who Have a Recent History of Blood Transfusion ". Include updated summary safety and efficacy analysis and submit datasets at the time of final clinical study report submission.

Final Report Submission: 08/2022

PMR 4216-3 Complete part E of study BIVV009-01, "Safety, Tolerability and activity of TNT009 in Healthy Volunteers and Patient with Complement-Mediated Disorders. A Single/Multiple Ascending Dose Phase 1 Study". Include updated summary safety and efficacy analysis in the final clinical study report.

Final Report Submission: 08/2022

PMR 4216-4 Complete Part B of Study BIVV009-04, "A Phase 3, randomized, double-blind, placebo-controlled study to assess the efficacy and safety of BIVV009 in patients with primary Cold Agglutinin Disease without a recent history of blood transfusion". Include updated safety information and submit datasets at the time of final clinical study report submission.

Final Report Submission: 08/2022

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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 ENJAYMO (sutimlimab-jome)

CLINICAL REVIEW OF SAFETY

Application Type	BLA
Application Number(s)	761164
Priority or Standard	Priority
Submit Date(s)	08/05/2021
Received Date(s)	08/05/2021
PDUFA Goal Date	02/04/2022
Division/Office	DNH/OCHEN
Reviewer Name(s)	Clinical: Carrie Diamond, M.D. (Clinical Reviewer, DNH) Tanya Wroblewski, M.D. (Clinical Team Leader, DNH)
Review Completion Date	02/03/2022
Established/Proper Name	Sutimlimab-jome
(Proposed) Trade Name	ENJAYMO
Applicant	Bioverativ Therapeutics, Inc
Dosage Form(s)	Injection: 1100 mg/22 mL (50 mg/mL)
Applicant Proposed Dosing Regimen(s)	Sutimlimab 6500mg (b) (4) or 7500mg (for patients $\geq$ 75kg), administered as an intravenous infusion over 1-2 hours once per week for the first 2 doses followed by every other week dosing
Applicant Proposed Indication(s)/Population(s)	Treatment of hemolysis in adult patients with cold agglutinin disease

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Glossary

AC	advisory committee
AE	adverse event
AESI	adverse event of special interest
AR	adverse reaction
BLA	biologics license application
C1s	component 1, s subcomponent
CAD	cold agglutinin disease
CAS	cold
CMD	complement mediated disorder
CP	complement pathway
CR	Complete Response
CRF	case report form
CSR	clinical study report
DVT	deep vein thrombosis
ECG	electrocardiogram
FDA	Food and Drug Administration
FMQ	FDA Medical Query
Hgb	hemoglobin
IgG4	immunoglobulin G subclass 4
IgM	immunoglobulin M
ISS	integrated summary of safety
ITP	immune thrombocytopenia purpura
LDH	lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
MOA	mechanism of action
NHV	normal healthy volunteer
NME	new molecular entity
OPQ	Office of Pharmaceutical Quality
PMR	postmarketing requirement
PT	preferred term
RBC	red blood cell
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAR	serious adverse reaction
SCS	Summary of clinical safety
SLE	systemic lupus erythematosus
SOC	system organ class

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TE thromboembolic events

TEAE treatment emergent adverse event

TIA transient ischemic attack

USPI United States Prescribing Information

UTI urinary tract infection

1. Introduction

Sutimlimab-jome (proprietary name, ENJAYMO) is a humanized immunoglobulin G subclass 4 (IgG4) monoclonal antibody that inhibits the classical complement pathway (CP) and specifically binds to complement protein component 1, s subcomponent (C1s), a serine protease which cleaves C4.

Bioerativ Therapeutics Incorporated originally submitted their Biologic Licensing Application (BLA) for marketing approval of sutimlimab for the treatment of hemolysis in adult patients with Cold Agglutinin Disease (CAD) on March 13, 2020. The Application received a Complete Resposne (CR) on November 13, 2020 due to deficiencies related to readiness for commercial manufacturing and data integrity that were observed at the FDA pre-license inspection of the (b) (4) drug substance manufacturing facility.

The Applicant submitted a response to the CRL on August 5, 2021. This review of the response to the Complete Response focuses only on the review of the updated safety information which was required.

2. Safety Update Summary

This resubmission includes the required safety update. In the original BLA, the primary safety database included a total of 34 patients with CAD from pooled studies (BIVV009-01 Parts C&E (CAD patients only) and BIVV009-03 Part A&B)). The safety analysis focused on the pivotal study BIVV009-03 Part A, a single-arm, open-label which consisted of 24 patients who received sutimlimab for 25 weeks. The data cut-off for the primary database was July 11th, 2019. A secondary safety database was also assessed in patients with other complement mediated disorders (N=32) and normal healthy volunteers (N=96).

The safety update included in the BLA resubmission includes 42 additional patients (for a total N=76 patients) from ongoing studies in patients with CAD (BIVV009-01 Part E and BIVV009-03 Part B) and also study BIVV009-04 Parts A&B (CADENZA). All 42 additional patients were from CADENZA. CADENZA Part A is a randomized, double-blind, placebo-controlled trial in patients with CAD who had not received a recent blood transfusion. This part of the trial is now completed and included 22 patients in the sutimlimab arm and 20 in the placebo arm. CADENZA Part B is the open-label, extension portion and is ongoing. The data cut-off for the primary database was September 29, 2020. In addition, upon the Division's request, the Applicant submitted datasets for CADENZA Part A.

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The safety update did not alter the benefit-risk profile of sutimlimab. The proposed USPI was not updated based on this safety update. For further discussion see clinical review submitted to DARRTs.

3. Safety Update

3.1. Safety Review Approach

The focus of the review will be the studies with patients with a diagnosis of CAD (BIVV009-03, BIVV009-04, and BIVV009-01) also referred to as the primary safety population. Study BIVV009-201 will be reviewed as part of the supportive safety population. Studies completed prior to the original BLA submission (BIVV009-01 Part A, BIVV009-01 Part B, TNT009-02, BIVV009-05, BIVV009-01 Part C and BIVV009-03 Part A) were reviewed previously and no update to these studies was included as part of this resubmission. For details on the previously reviewed studies, refer to the review in DARRTs on November 12th, 2020 by Carrie Diamond.

Ongoing studies with updates included with the resubmission:

BIVV009-01 (Part E): A Phase 1, open-label, multiple dose study in patients with CAD who were previously treated with sutimlimab. Data cut-off for the original submission was July 11, 2019 and the data cut-off for 90-day safety update was November 29, 2019. Study is ongoing.

BIVV009-03 (Part B) or CARDINAL: A Phase 3, open-label, single-arm study in patients with CAD with a recent blood transfusion in the previous 6 months prior to enrollment who completed Part A of study BIVV009-03. Data cut-off for the original submission was July 11, 2019 and the data cut-off for 90-day safety update was November 29, 2019. Study is ongoing

BIVV009-04 (Part A and Part B) or CADENZA: A Phase 3, randomized, double-blind, placebo-controlled study in patients with CAD who have not received a recent blood transfusion (≤ 1 blood transfusion during the previous year and no transfusion during the 6 months prior to enrollment). Part A was the randomized, placebo-controlled part for 6 months. Part B was the extension open-label part. Data cut-off for the original submission was July 11, 2019 and the data cut-off for 90-day safety update was November 29, 2019. Part A is completed, and the clinical study report has been submitted. Part B is ongoing.

BIVV009-201 (Parts A and B): A Phase 1, open-label study of multiple-dose sutimlimab in patients with chronic immune thrombocytopenia purpura (ITP). Data cut-off for the original submission was April 11, 2019 and the data cut-off for 90-day safety update was January 16, 2020. Study is ongoing

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Review of safety was based upon:

- Safety update
- Integrated summary of safety (ISS) data set and BIVV009-03 Part B data set
- Summary of clinical safety (SCS)
- Clinical Study Reports (CSR) for BIVV009-04 Part A and BIVV009-03 Part B
- Protocol for BIVV009-04 Part A
- Patient narratives and case report forms (CRFs) from BIVV009-04 Part A

The following treatment-emergent adverse events (TEAEs) of special interest were described by the Applicant and included: thromboembolic events, hypersensitivity reactions, infections, and development of systemic lupus erythematosus (SLE). These events of special interest were previously agreed upon and reviewed by the clinical review team.

The ISS ADAE.xpt data file was reviewed for accuracy of translation of the verbatim to preferred term by manual review. Similar preferred terms were grouped by standardized groupings of related preferred terms through FDA Medical Queries (FMQs).

Clinical comment: With the safety update, BIVV009-04 Part A (CADENZA) was completed and the CSR was submitted. CADENZA is a randomized, double-blind, placebo-controlled trial in which patients with CAD (without a recent blood transfusion) received sutimlimab or placebo for 6 months, with the option of continuing treatment in the open-label extension part (Part B). In total 42 patients were included in the study (22 randomized to sutimlimab and 20 patients received placebo).

(b) (4)

3.2. Review of the Safety Database

3.2.1. Overall Exposure

In the original BLA submission, a total of 162 patients or subjects (34 patients with CAD or cold agglutinin syndrome (CAS), 32 patients with other complement mediated disorders (CMDs), and 96 normal healthy volunteers (NHVs)) were treated with sutimlimab. Patients in CADENZA were not included as the study was ongoing and blinded. In the 34 patients with CAD the median number of administration was 20 and the median duration of treatment was 38.4 weeks.

The data cut-off for the resubmission was September 29, 2020. There were an additional 42 patients with CAD and 4 additional patients with CMD included in the safety update. In total, 208 patients (76 patients with cold agglutinin disease (CAD), 36 patients with other CMDs, and 96 NHVs) were exposed to at least 1 dose of sutimlimab. Exposure to the sutimlimab in patients with CAD is summarized in Table 1.

	BIVV009-01 (Part C and E) N=10	BIVV009-03 (Part A and B) CARDINAL N=24	BIVV009-04 (Part A and B) CADENZA		Total N=76
			Sutimlimab N=22	Placebo N=20	
Total number of administrations Median, (range)	5 (5-79)	52 (2-68)	28 (4-64)	22.5 (2-44)	33 (2-79)
Duration of study treatment (weeks) Median, (range)	5.5 (5.3-154)	103 (3.1-134.3)	55.5 (7.1-123.1)	43.7 (3-86)	63.9 (3-154)
Total Dose (grams) Median, (range)	19.08 (13.9-476.2)	364.8 (15-510)	191.75 (26-416)	146.3 (13-330)	222.5 (13-510)

Source: Derived from the Applicant's SCS

Study BIVV009-201 included 12 patients with ITP. The median duration of study treatment was 43.4 (range: 3.1-130.1) weeks. The median number of sutimlimab administrations was 17.5 (range: 2-64). The median total dose of sutimlimab was 119.8 (range: 11- 462.5) grams.

Clinical reviewer comment: The safety update included more patients with CAD compared to the original BLA submission (76 patients with updated safety vs 34 patients in the original BLA submission. In addition, patients with CAD were treated for a longer period of time (median) compared to the original BLA submission (38.4 weeks vs 63.9 weeks, respectively). This enhances the clinical review team safety assessment for sutimlimab and provides insight into long-term safety.

3.2.2. Relevant characteristics of the safety population:

Primary Safety Population

In the original BLA submission, the median age was 70.5 (range 55-85) years. Overall, there were more females (23/34; 67.6%). Most patients were from Europe (27/34; 79.4%). The majority of data on ethnicity and race were not collected.

In the BLA resubmission, the median age was 69.5 (range 46-88) years. Overall, there were more females (56/76; 73.7%). Most patients were from Europe (55/76; 72.4%). The majority of data on ethnicity and race were not collected.

Table 2. Summary of Demographic Characteristics in the Primary CAD Safety Population

	BIVV009-01 C&E N=10 n(%)	BIVV009-03 A&B N=24 n(%)	BIVV009-04 A&B		Total N=76 n(%)
			Sutimlimab N=22 n(%)	Placebo N=20 n(%)	
Age (years)					
Median	69.5	71.5	64	69	69.5
Mean	68.7	71.3	65.3	68.2	68.4
Range	55, 76	55, 85	46, 88	51, 83	46, 88
Gender					
Male, n (%)	2 (20%)	9 (37.5%)	5 (22.7%)	4 (20%)	20 (26.3%)
Female, n (%)	8 (80%)	15 (62.5%)	17 (77.3%)	16 (80%)	56 (73.7%)
Race					
White, n (%)	9 (90%)	3 (12.5%)	0	4 (20%)	16 (21.1%)
Asian, n (%)	1 (10%)	3 (12.5%)	5 (22.7%)	2 (10%)	11 (14.5%)
Not reported, n (%)	0	0	1 (4.5%)	0	1 (1.3%)
Not collected, n (%)	0	18 (75%)	16 (72.7%)	14 (70%)	48 (63.2%)
Ethnicity					
Hispanic or Latino, n (%)	0	0	0	1 (5%)	1 (1.3%)
Not Hispanic or latino, n (%)	0	6 (25%)	5 (22.7%)	5 (25%)	16 (21.1%)
Not reported, n (%)	0	0	1 (4.5%)	0	1 (1.3%)
Not collected, n (%)	10 (100%)	18 (75%)	16 (72.7%)	14 (70%)	58 (76.3%)
Geographic location					
Europe, n (%)	10 (100%)	17 (70.8%)	15 (68.2%)	13 (65%)	55 (72.4%)
North America, n (%)	0	3 (12.5%)	3 (13.6%)	3 (15%)	9 (11.8%)
Asia, n (%)	0	3 (12.5%)	3 (13.6%)	3 (15%)	9 (11.8%)
Other, n (%)	0	1 (4.2%)	1 (4.5%)	1 (5%)	3 (3.9%)

Source: Derived from Applicant's SCS

Supportive safety population (non-CAD conditions)

In the original BLA application, in patients with ITP the mean age was 42.6 (27-65) years. The majority of patients were female 6/8 (75%). Most patients were enrolled in North America 7/8 (87.5%).

In the resubmission of the BLA, for patients with ITP the mean age was 44.4 (Range: 27-65) years. The majority of patients were female 9/12 (75%). Most patients were enrolled in North America 9/12 (75%).

Clinical reviewer comment: The patient demographics of the resubmission safety data are

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similar to the original BLA submission.

3.2.3. Adequacy of the safety database:

It appears that the Applicant appropriately submitted all available safety data according to the CRL.

3.3. Adequacy of Applicant's Clinical Safety Assessments

3.3.1. Issues Regarding Data Integrity and Submission Quality

For the resubmission, the ISS was well organized and relevant data was easily identified. The Applicant did not submit safety datasets for CADENZA Part A. These datasets were requested by the clinical team and subsequently provided by the Applicant. (b) (4)



3.3.2. Categorization of Adverse Events

For the safety update adverse events were classified using MedDRA, SOC, and PT. MedDRA version 23.0 was used for the integrated analyses in the resubmission compared to version 21.0 in the original submission. There were no further updates to the categorization of adverse events.

3.4. Safety Results

3.4.1. Deaths

In the original BLA submission, there were two deaths in the entire clinical development program, neither were related to sutimlimab. There was 1 death out of 34 patients (2.9%) in the primary safety population due to progressive hepatic cancer. In addition, there was 1 death in the supportive patient population in a patient with bullous pemphigoid who died due to cardiac failure.

No additional deaths were reported in the resubmission.

3.4.2. Serious Adverse Events

Primary safety population

In the original BLA submission, 12 out of 34 patients (35%) in the primary safety population experienced a treatment-emergent SAE (serious adverse event). The most common type of treatment-emergent SAEs were infections in 7 out of 34 patients (20.6%), including sepsis in 3 out of 34 patients (8.8%). Other treatment-emergent SAEs that occurred in more than 1 patient

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included; bacterial infection, bleeding, anemia, cholecystitis/cholelithiasis, and malignancy.

In the resubmission safety update, a total of 21 out of 76 patients (27.6%) with CAD had a treatment-emergent SAE. The most common type of treatment-emergent SAEs were infections in 10 out of 76 patients (13.2%). An updated table of treatment-emergent SAEs are described in below (Table 3).

Table 3. Serious Treatment-Emergent Adverse Events in the Primary CAD Safety Population in ≥ 2 Patients

FMQ	BIVV009-01 C&E N=10 n(%)	BIVV009-03 A&B N=24 n(%)	BIVV009-04 A&B		Total N=76 n(%)
			Sutimlimab (a) N=22 n(%)	Placebo(b) N=20 n(%)	
Infection, all*	2 (20%)	7 (29.2%)	1 (4.5%)	0	10 (13.2%)
Sepsis*	2 (20%)	3 (12.5%)	0	0	5 (6.6%)
Bacterial infection*	0	2 (8.3%)	0	0	2 (2.6%)
Viral infection*	0	2 (8.3%)	0	0	2 (2.6%)
Urosepsis	1 (10%)	1 (4.2%)	0	0	2 (2.6%)
Bleeding*	0	3 (12.5%)	0	0	3 (3.9%)
Hemolysis	0	2 (8.3%)	0	0	2 (2.6%)
Cholecystitis, cholelithiasis	0	2 (8.3%)	0	0	2 (2.6%)
Anemia*	0	2 (8.3%)	0	0	2 (2.6%)
Malignancy*	0	2 (8.3%)	0	0	2 (2.5%)
Fracture*	1 (10%)	0	1 (4.5%)	0	2 (2.6%)

Source: Clinical Reviewer, ISS

a) Including TEAEs which occurred during or after the first dose of BIVV009 in Part A to the data cutoff date of Part B based on BIVV009-treated patients in Part A.

(b) Including TEAEs which occurred during or after the first dose of BIVV009 in Part B to the data cutoff date of Part B based on placebo-treated patients in Part A (not including TEAEs which occurred during or after the first dose of placebo and up until the first infusion of BIVV009)

*The following preferred terms were combined:

Anemia: hemolytic anemia, cold type hemolytic anemia, anemia

Bacterial infection: Escherichia sepsis, pneumococcal sepsis, streptococcal sepsis, wound infection staphylococcal

Bleeding: gastrointestinal hemorrhage, occult blood positive, vitreous hemorrhage

Fracture: spinal fracture, hip fracture

Infection: Escherichia sepsis, pneumococcal sepsis, pulmonary sepsis, streptococcal sepsis, urosepsis

Malignancy: renal cell carcinoma, hepatic cancer

Sepsis: Escherichia sepsis, pneumococcal sepsis, pulmonary sepsis, streptococcal sepsis, urosepsis

Viral infection: viral infection, herpes zoster

In the additional updated dataset from Study BIVV009-04 Part A (CADENZA), 4 out of 42 patients (9.5%) experienced a serious TEAE. The rate of serious TEAEs was (3/22) 13.6% in the group that received sutimlimab compared to (1/20) 5% in the placebo group. Serious TEAEs in the sutimlimab group included cerebral venous thrombosis, blood immunoglobulin M increased, febrile infection, and Raynaud's phenomenon. The serious TEAE in the placebo group was

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anemia and vascular device infection in one patient. Patient narratives are described below for patients who received sutimlimab.

1. Patient (b) (6) had a serious TEAE of cerebral venous thrombosis. The patient was an elderly female, with history of steroid induced diabetes, who developed a grade 3 cerebral venous thrombosis (left lateral sinus) on day 86 of the study. The patient last received sutimlimab on day 78. The patient was admitted with headache and fever, in the setting of hypertension. MRI of the head showed empyema of the left cranial base. CT of the head showed flat meningioma spreading to the lateral, sigmoid and left cavernous sinus. Study drug was interrupted. The patient received anticoagulation. It was reported the patient had no history of thrombosis.
2. Patient (b) (6) had a serious TEAE of febrile infection and blood immunoglobulin M (IgM) increased. On day 2 of the study the patient developed a febrile infection within 24 hours of receiving sutimlimab. The patient was hospitalized and received intravenous antibiotics. They were also anemic and received 2 units of packed red blood cells. No action was taken with the study drug and the patient defervesced.
3. The patient had an elevated IgM increased at baseline. This included a level of 5.33g/dL (normal range: 0.4-2.3g/dL) on day -429 and a level of 22.98g/dL on day -44. On day 36 of the study the patient developed grade 3 IgM level increased (serum IgM = 76.97g/dL). Day 36 was the last dose of sutimlimab. On day 42 the event of IgM increased became serious and worsened to severe (serum IgM= 86.57g/dL with a normal range of 0.4-2.3g/dL). The patient received rituximab for treatment. Subsequent bone marrow biopsy was significant for low-grade B-cell lymphoma (degree of infiltration 15%) with associated kappa-restricted plasma cell population. The immunohistochemical test with CD20 antibodies revealed evidence of abundant B-lymphocytes. The IgM expression was also noted in most of the visualized plasma cells. The lambda light chain was barely expressed. Morphology was suggestive of lymphoplasmacytic lymphoma (Waldenstrom's disease). The serum IgM was 74.77 g/L (on Day 50), 66.38 g/L (on Day 57), 57.68 g/L (on Day 64), 52.77 g/L (on Day 71), 35.27 g/L (on Day 92), 20.36 g/L (on Day 120), and 10.66 g/L (on Day 169). Sutimlimab was discontinued due to this event.
4. Patient (b) (6) had a serious adverse event of Raynaud's phenomenon. Two months before the study the patient complained of Raynaud's phenomenon and pain in bilateral extremities. Less than 1 month before the study, the symptoms of acrocyanosis and Raynaud's phenomenon were worsening. After starting sutimlimab, on day 5, the patient visited the emergency room with more intense pain and aggravated symptoms of Raynaud's phenomenon. On day 49, the patient experienced right foot pain and received pain medication. On Day 53, the tip of the fingers changed color from purple to black due to Raynaud's phenomenon. On Day 58 of the study, the patient experienced Grade 3 non-serious adverse event of 'extremity necrosis' (necrosis of 10 fingers and

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lower legs due to Raynaud's phenomenon aggravated) and Grade 3 serious adverse event of Raynaud's phenomenon. The patient also developed staphylococcal skin infection and received antibiotics. The most recent sutimlimab administration was on day 51. On day 58, the patient visited the hospital urgently due to intense leg pain, general malaise, necrosis in bilateral fingers, edema in bilateral legs, and bullae on skin. The patient was hospitalized for pain control and red blood cells (RBC) transfusion. On Day 118, the patient had necrosis of fingers and necrosis along with pyoderma of toes. The necrosis of 4 limbs progressed and the study participant had difficulty in walking independently. The patient was scheduled to undergo below-knee amputation for wearing artificial legs, on day 174 and 178. A blood transfusion was required post-operatively. The patient underwent digital amputation of the fingers of both the hands on day 203. The last dose of study drug was on day 178.

Clinical reviewer comment: The proportion of patients who experienced an SAE was lower after the resubmission compared to the original application (27.6% vs 35%, respectively). Overall, the types of SAEs reported were similar, with infection and specifically sepsis continued to be the most common.

In CADENZA Part A, the frequency of SAEs was higher in the sutimlimab arm compared to the placebo arm (13.6% vs 5%, respectively). There were three patients with SAEs in the sutimlimab arm, this included cerebral venous thrombosis, Raynaud's phenomenon, febrile infection, and blood IgM increased. Causality is difficult to determine given the complexity of the patient population (i.e. elderly, multiple comorbidities, and several concomitant medications). After review of the patient narratives it is unlikely the blood IgM increase was due to sutimlimab. This patient had a rising IgM level prior to sutimlimab administration and subsequently was diagnosed with a low-grade B cell lymphoma, which was diagnosed after receiving only 4 doses of sutimlimab. While IgM level decreased after stopping sutimlimab, this was more likely due to treatment with rituximab. In addition, it is unlikely that the cerebral venous thrombosis was related to sutimlimab. This was an elderly patient with diabetes, infection meningioma, and CAD, these are risk factors for thrombosis and are most likely the etiology of the cerebral venous thrombosis. It is in the clinical reviewer's opinion that the proportion of patients with a serious adverse reaction (SAR) was 9.1%, including Raynaud's phenomenon and febrile infection.

Supportive Safety Population

In the original BLA submission, two out of 8 (25%) patients with ITP experienced serious TEAEs including; thrombocytopenia, migraine, and dural arteriovenous fistula.

In the safety update, 4 out of 12 patients (33.3%) experienced serious TEAEs including thrombocytopenia, diverticulitis, petechiae, migraine, and dural arteriovenous fistula.

3.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

Primary Safety Population

In the original BLA submission, three out of 34 patients (8.8%) from the primary safety population discontinued the study early due to TEAEs. This included one patient from study BIVV009-01 Part E who experienced worsening Waldenström's macroglobulinemia, one patient from study BIVV009-03 Part A who experienced polymyalgia rheumatica and one patient from study BIVV009-03 Part A who experienced hepatic cancer. All the described TEAEs leading to drug discontinuation were unlikely related to sutimlimab.

In the safety update, 6 out of 76 patients (7.9%) discontinued early due to a TEAE (Table 4). Of note, in the original submission one patient withdrew from polymyalgia rheumatica that was a pretreatment SAE. This patient is not included in the table below. In total, 3 out of 22 patients (13.6%) who received sutimlimab in CADENZA Part A discontinued therapy due to a TEAE, compared to none in the placebo arm. This included TEAEs of infusion related reaction, blood IgM increased, acrocyanosis and Raynaud's phenomenon.

Table 4. Dropouts and Discontinuations in the Primary CAD Safety Population

	BIVV009-01 C&E	BIVV009-03 A&B	BIVV009-04 A&B		Total N=76 n(%)
	N=10 n(%)	N=24 n(%)	Sutimlimab N=22 n(%)	Placebo N=20 n(%)	
Discontinued prematurely due to TEAE	1 (10%)	2 (8.3%)	3 (13.6%)	0 (0%)	6 (7.9%)

Source: Clinical reviewer, ISS dataset

Narratives of patients who discontinued but were not included in the original BLA submission are described below.

1. Patient (b) (6) from BIVV009-03 Part B discontinued therapy on day 364 for multiple TEAEs including cyanosis, dyspepsia, dysphagia, and gastritis erosive. The patient experienced acrocyanosis on day 37 of the study, the same day as sutimlimab administration. Sutimlimab was temporarily interrupted for cyanosis. The patient experienced dyspepsia on day 378, dysphagia and cyanosis on day 385, and gastritis erosive on day 389. The patient received multiple transfusions for symptomatic anemia.

2. Patient (b) (6) from BIVV009-04 discontinued due to a serious TEAE blood immunoglobulin M (IgM) increased. Narrative for this TEAE is located in Section 8.4.2 Serious Adverse Events.

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3. Patient (b) (6) from BIVV009-04 discontinued due to TEAEs of cyanosis and Raynaud's phenomenon on day 47 of the study. The patient experienced multiple events of acrocyanosis involving the nose, fingertips, feet and cheeks. On day 47 of the study the patient experienced the seventh episode of acrocyanosis and second episode of Raynaud's phenomenon. The most recent sutimlimab administration was on day 42. It was stated in the narrative that the TEAEs were related to elevated IgM that continued to increase after study treatment discontinuation and symptoms that continued after study drug discontinuation. The patient was subsequently diagnosed with progression of lymphoproliferative disease.

4. Patient (b) (6) from BIVV009-04 discontinued due to a TEAE of infusion related reaction on day 22 and 36. The infusions reactions both took place on the same day as sutimlimab administration and included pain in lumbar spine and both legs. The patient received steroids and the infusion was interrupted and slowed down the first time. The second time sutimlimab was permanently discontinued.

Supportive safety population

In the original BLA submission, one (12.5%) out of 8 patients with ITP discontinued prematurely due to withdrawal of consent, the patient also required rescue therapy for thrombocytopenia.

In the safety update no further patients discontinued due to TEAEs.

Clinical reviewer comment: A similar proportion of patients discontinued sutimlimab due to TEAEs in the safety update compared to the original submission (7.9% vs 8.8%, respectively). No patient discontinued sutimlimab due to the same TEAE. In CADENZA Part A, 13.6% of patients in the sutimlimab arm discontinued therapy due to a TEAE, compared to none in the placebo arm. Reasons for drug discontinuation included blood IgM increased, Raynaud's phenomenon, cyanosis (acrocyanosis) and infusion related reaction. After reviewing the patient narratives it is in the clinical reviewer's opinion that blood IgM increased was not due to sutimlimab (please see section 3.4.2 for further discussion). Therefore, the proportion of patient who discontinued sutimlimab due to an adverse reaction was 2 out of 22 patients (9.1%).

3.4.4. Significant Adverse Events

Adverse Events Leading to Dose Interruption

Primary Safety Population

In the original BLA submission, dose interruption due to TEAEs occurred in 9 out of 34 (26.5%) patients. The most common (occurring in 2 or more patients) reason was dose interruption due to infection occurring in 11.8% of patients and infusion related reaction occurring in 5.9% of patients.

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In the safety update provided in the BLA resubmission, 15 out of 76 patients (19.7%) had a dose interruption due to a TEAE. The only TEAE leading to dose interruption that occurred in more than one patient was infusion related reactions, which occurred in 4 out of 76 patients (5.3%).

In CADENZA part A, a higher proportion of patients in the sutimlimab group experienced a TEAE that led to drug interruption compared to placebo group (18.2% vs 5%, respectively). TEAEs that led to drug interruption in the sutimlimab group included nasopharyngitis, cerebral venous thrombosis, pruritis, chest discomfort, and infusion related reactions. The TEAE leading to drug interruption in the placebo group was febrile infection.

Supportive Safety Population

In the original BLA submission, in the CMD population, 3 out of 32 (9.4%) patients had dose interruptions. Reasons for dose interruptions included infusion reaction, antinuclear antibody positive and thrombocytosis.

In the BLA resubmission, in the ITP population, 3 out of 12 patients (25%) had dose interruptions due to TEAEs. Reasons for dose interruptions which occurred in more than one patient was infusion related reaction (N=2). Other reasons for dose interruption which occurred in one patient each included antinuclear antibody positive, thrombocytosis, infusion site pain, lower abdominal pain and diverticulitis.

Clinical reviewer comment: The proportion of patients who had a dose interruption was lower in the resubmission compared to the original submission (19.7% vs 26.5%, respectively). Similar to the original submission, the only TEAE leading to drug interruption that occurred in more than one patient was infusion related reaction. In CADENZA Part A, 4 patients (18.2%) had drug interruption, including nasopharyngitis, cerebral venous thrombosis, pruritis, chest discomfort, and infusion related reaction..

Severity of Adverse Events

Primary Safety Population

In the original BLA submission, 13 out of 34 (38.2%) of patients in the primary safety population experienced at least 1 Grade 3 (severe) TEAE. The most common (occurring $\geq 5\%$ of the total population) TEAEs Grade ≥ 3 were infections including sepsis and bacterial infection, bleeding and anemia.

In the resubmission of the BLA, 26 out of the 76 patients (34.2%) in the primary safety population experienced at least 1 grade 3 (severe according CTCAE) TEAE. The most common TEAEs Grade ≥ 3 were infections including sepsis, bacterial infection and urinary tract infection, anemia and bleeding (Table 5).

Table 5. Most common (>2%) TEAEs Grade ≥ 3 in the Primary Safety Population

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Medical Query	BIVV009-01 C&E N=10 n(%)	BIVV009-03 A&B N=24 n(%)	BIVV009-04 A&B		Total N=76 n(%)
			Sutimlimab (a) N=22 n(%)	Placebo (b) N=20 n(%)	
Infection	2 (20%)	8 (33.3%)	2 (9.1%)	0	12 (15.8%)
Sepsis*	2 (20%)	3 (12.5%)	0	0	5 (6.6%)
Infection, bacterial*	0	2 (8.3%)	1 (4.5%)	0	3 (3.9%)
Urinary tract infection	1 (10%)	2 (8.3%)	0	0	3 (3.9%)
Infection, viral*	0	2 (8.3%)	0	0	2 (2.6%)
Anemia*	0	4 (16.7%)	0	0	4 (5.3%)
Bleeding*	0	3 (12.5%)	0	0	3 (3.9%)
Systemic hypertension	0	0	1 (4.5%)	1 (5%)	2 (2.6%)
Arthralgia, arthritis*	0	1 (4.2%)	0	1 (5%)	2 (2.6%)
Malignancy*	0	2 (8.3%)	0	0	2 (2.6%)

Source: Clinical reviewer, ISS dataset

a) Including TEAEs which occurred during or after the first dose of BIVV009 in Part A to the data cutoff date of Part B based on BIVV009-treated patients in Part A.

(b) Including TEAEs which occurred during or after the first dose of BIVV009 in Part B to the data cutoff date of Part B based on placebo-treated patients in Part A (not including TEAEs which occurred during or after the first dose of placebo and up until the first infusion of BIVV009)

*The following preferred terms were combined:

Anemia: anemia, cold type hemolytic anemia

Arthralgia, arthritis: arthralgia, osteoarthritis

Bleeding: gastrointestinal hemorrhage, occult blood positive, vitreous hemorrhage

Infection, bacterial: Escherichia sepsis, pneumococcal sepsis, staphylococcal skin infection, streptococcal sepsis

Infection, viral: herpes zoster, viral infection

Malignancy: hepatic cancer, renal cell carcinoma

Sepsis: Escherichia sepsis, pneumococcal sepsis, pulmonary sepsis, streptococcal sepsis, urosepsis

In CADENZA Part A, a higher proportion of patients in the sutimlimab group experienced Grade 3 TEAE compared to the placebo group (22.7% vs 15%, respectively). All Grade 3 TEAEs are listed in Table 6.

Table 6. TEAEs Grade $\geq$ 3 in CADENZA Part A

Preferred term	Sutimlimab N=22 n(%)	Placebo N=20 n(%)
Blood immunoglobulin M increased	1 (4.5%)	0
Cerebral venous thrombosis	1 (4.5%)	0
Dyspnea	1 (4.5%)	0
Extremity necrosis	1 (4.5%)	0
Febrile infection	1 (4.5%)	0
Hypertension	1 (4.5%)	0
Poor venous access	1 (4.5%)	0
Raynaud's phenomenon	1 (4.5%)	0

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Preferred term	Sutimlimab N=22 n(%)	Placebo N=20 n(%)
Staphylococcal skin infection	1 (4.5%)	0
Anemia	0	2 (10%)
Hemolysis	0	1 (5%)
Osteoarthritis	0	1 (5%)
Vascular device infection	0	1 (5%)

Source: Clinical reviewer, BIVV009-04 Part A ADAE.xpt dataset

a) Including TEAEs which occurred during or after the first dose of BIVV009 in Part A to the data cutoff date of Part B based on BIVV009-treated patients in Part A.

(b) Including TEAEs which occurred during or after the first dose of BIVV009 in Part B to the data cutoff date of Part B based on placebo-treated patients in Part A (not including TEAEs which occurred during or after the first dose of placebo and up until the first infusion of BIVV009)

Supportive Safety Population

In the original BLA submission in the ITP population, 3 out of 8 (37.5%) patients experienced a total of 5 grade 3 TEAEs.

In the resubmission, 5 out of 12 patients (41.7%) experienced grade 3 or greater TEAEs including diverticulitis, colitis, petechiae, migraine, dural arteriovenous fistula and thrombocytopenia.

Clinical reviewer comment: In the primary safety population, a similar proportion of patients experienced $\geq$ grade 3 TEAEs in the resubmission compared to the original submission (34.2% vs 38.2%, respectively). The most common grade 3 TEAEs in the resubmission safety data were consistent with what was observed in initial safety data which included infections, sepsis, and anemia. Anemia was likely due to the underlying CAD and not due to sutimlimab.

3.4.5. Treatment Emergent Adverse Events and Adverse Reactions

In the original BLA submission, 32 out of 34 patients (94%) in the primary safety population had a TEAE. The most common type of TEAEs (>20%) were respiratory tract infection, urinary tract infections (UTI) and fatigue.

In the resubmission, 72 out of 76 patients with (94.7%) in the primary safety population had a TEAE. TEAEs (including grouping of closely related adverse events) are shown in Table 7. The most common TEAEs (>15%) were respiratory tract infection, nasopharyngitis, arthralgia, arthritis, diarrhea, headache, and hypertension.

Table 7. Most Common (>10%) Treatment Emergent Adverse Events in the Primary CAD Safety Population

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Medical Query	BIVV009-01 C&E	BIVV009-03 A&B	BIVV009-04 A&B		Total
	N=10 n(%)	N=24 n(%)	Sutimlimab(a) N=22 n(%)	Placebo(b) N=20 n(%)	
Infection	4 (40%)	19 (79.2%)	13 (59.1%)	10 (50%)	46 (60.5%)
Respiratory tract infection*	4 (40%)	9 (37.5%)	9 (40.9%)	6 (30%)	28 (36.8%)
Nasopharyngitis*	4 (40%)	5 (20.8%)	8 (36.4%)	3 (15%)	20 (26.3%)
Infection, viral*	3 (30%)	5 (20.8%)	4 (18.2%)	2 (10%)	14 (18.4%)
UTI*	2	8 (33.3%)	0	1 (10%)	11 (14.5%)
Herpes virus*	3 (30%)	2 (8.3%)	2 (9.1%)	2 (10%)	9 (11.8%)
Musculoskeletal and connective tissue disorders					
Arthralgia, arthritis*	3 (30%)	7 (29.2%)	4 (18.2%)	3 (15%)	17 (22.4%)
Gastrointestinal disorders					
Diarrhea	2 (20%)	5 (20.8%)	3 (13.6%)	6 (30%)	16 (21.1%)
Nausea	3 (30%)	5 (20.8%)	1 (4.5%)	3 (15%)	12 (15.8%)
Dyspepsia*	1 (10%)	5 (20.8%)	4 (18.2%)	1 (10%)	11 (14.5%)
Abdominal pain*	2 (20%)	4 (16.7%)	4 (18.2%)	0	10 (13.2%)
Constipation	2 (20%)	4 (16.7%)	2 (9.1%)	0	8 (10.5%)
Nervous system disorders					
Headache	3 (30%)	4 (16.7%)	5 (22.7%)	4 (20%)	16 (21.1%)
Dizziness*	5 (50%)	5 (20.8%)	2 (9.1%)	2 (10%)	14 (18.4%)
Vascular disorders					
Systemic hypertension*	0	6 (25%)	6 (27.3%)	4 (20%)	16 (21.1%)
Bleeding*	2 (20%)	6 (25%)	2 (9.1%)	1 (10%)	11 (14.5%)
Cyanosis	0	3 (12.5%)	3 (13.6%)	3 (15%)	9 (11.8%)
Blood and lymphatic system disorders					
Anemia*	1 (10%)	5 (20.8%)	5 (22.7%)	2 (10%)	13 (17.1%)
General disorders and administration site conditions					
Fatigue*	3 (30%)	6 (25%)	3 (13.6%)	1 (10%)	13 (17.1%)
Local administration reactions*	1 (10%)	2 (8.3%)	5 (22.7%)	2 (10%)	10 (13.2%)
Peripheral edema*	2 (20%)	5 (20.8%)	1 (4.5%)	0	8 (10.5%)
Respiratory, thoracic and mediastinal disorders					
Cough*	1 (10%)	6 (25%)	2 (9.1%)	1 (10%)	10 (13.2%)
Skin and subcutaneous tissue disorders					
Rash*	2 (20%)	3 (12.5%)	4 (18.2%)	1 (10%)	10 (13.2%)
Injury, poisoning and procedural complications					
Accident*	1 (10%)	3 (12.5%)	2 (9.1%)	2 (10%)	8 (10.5%)

Source: Clinical reviewer, ISS dataset

a) Including TEAEs which occurred during or after the first dose of BIVV009 in Part A to the data cutoff date of Part B based on BIVV009-treated

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patients in Part A.

(b) Including TEAEs which occurred during or after the first dose of BIVV009 in Part B to the data cutoff date of Part B based on placebo-treated patients in Part A (not including TEAEs which occurred during or after the first dose of placebo and up until the first infusion of BIVV009)

*The following preferred terms were combined

Abdominal pain: abdominal pain upper, abdominal pain lower, abdominal tenderness

Accident: fall, road traffic accident

Anemia: anemia, blood loss anemia, cold type hemolytic anemia, hemolytic anemia, iron deficiency anemia

Arthralgia, arthritis: arthralgia, osteoarthritis

Bleeding: epistaxis, gastrointestinal hemorrhage, hematoma, hemorrhoidal hemorrhage, occult blood positive, traumatic hematoma, vessel puncture site hematoma, vitreous hemorrhage

Cough: cough, productive cough

Dizziness: dizziness, postural dizziness, Meniere's disease, vertigo, positional vertigo, balance disorder

Dyspepsia: abdominal pain upper, dyspepsia

Fatigue: asthenia, fatigue, malaise, mental fatigue

Herpes virus: herpes simplex, herpes zoster, oral herpes

Infection, viral: oral herpes, herpes zoster, influenza, herpes simplex, viral infection, respiratory tract infection, viral upper respiratory tract infection

Local administration reaction: infusion related reaction, infusion site extravasation, injection site pruritis, vaccination site pain, vaccination site rash

Peripheral edema: peripheral edema, peripheral swelling

Nasopharyngitis: nasopharyngitis, rhinitis, allergic rhinitis

Rash: blister, dermatitis, erythema migraines, rash, maculo-papular rash, pustular rash, toxic skin eruption, vaccination site rash

Respiratory tract infection: nasopharyngitis, upper respiratory tract infection, rhinitis, influenza like illness, respiratory tract infection, sinusitis, respiratory tract infection viral, viral upper respiratory tract infection

Systemic hypertension: hypertension, blood pressure increased, essential hypertension

Urinary tract infection: cystitis, bacterial cystitis, Escherichia urinary tract infection, urinary tract infection, urinary tract infection bacterial, urosepsis

Based on the CADENZA Part A dataset, a higher proportion of patients in the sutimlimab group had at least one TEAE compared to the placebo group (95.5% vs 90%, respectively). The most common TEAEs by FMQs that occurred more frequently in the sutimlimab group included nasopharyngitis, headache, local administration reactions, systemic hypertension and rash (Table 8). The most common TEAEs by preferred terms that occurred more frequently in the sutimlimab group included headache, hypertension, Raynaud's phenomenon, rhinitis, and cyanosis (Table 9).

Table 8. Most Common (>5%) Treatment Emergent Adverse Events in Patients in the Sutimlimab Group in CADENZA Part A, FDA Medical Queries

Medical Query	Sutimlimab N=22 n(%)	Placebo N=20 n(%)
Infection	10 (45.5%)	8 (40%)
Respiratory tract infection*	7 (31.8%)	8 (40%)
Nasopharyngitis*	6 (27.3%)	2 (10%)
Infection, viral*	3 (13.6%)	2 (10%)
Herpes virus*	2 (9.1%)	0
Nervous system disorders		
Headache*	5 (22.7%)	3 (15%)
Paresthesia	2 (9.1%)	1 (5%)
General disorders and administration site conditions		

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Medical Query	Sutimlimab N=22 n(%)	Placebo N=20 n(%)
Local administration reactions*	5 (22.7%)	1 (5%)
Fatigue*	3 (13.6%)	2 (10%)
Injection site reactions*	3 (13.6%)	1 (5%)
Pyrexia*	2 (9.1%)	1 (5%)
Fall, dizziness, balance disorder*	2 (9.1%)	0
Vascular disorders		
Systemic hypertension	5 (22.7%)	0
Cyanosis	3 (13.6%)	0
Hemorrhage*	2 (9.1%)	2 (10%)
Hypotension	2 (9.1%)	0
Skin and subcutaneous tissue disorders		
Rash*	4 (18.2%)	2 (10%)
Pruritis*	2 (9.1%)	1 (5%)
Blood and lymphatic system disorders		
Anemia*	3 (13.6%)	4 (20%)
Gastrointestinal disorders		
Diarrhea	2 (9.1%)	4 (20%)
Dyspepsia*	2 (9.1%)	3 (15%)
Abdominal pain	2 (9.1%)	2 (10%)
Constipation	2 (9.1%)	0
Musculoskeletal and connective tissue disorders		
Arthralgia, arthritis	2 (9.1%)	3 (15%)
Respiratory, thoracic and mediastinal disorders		
Dyspnea	2 (9.1%)	2 (10%)
Chest pain*	2 (9.1%)	1 (5%)
Psychiatric disorders		
Anxiety	2 (9.1%)	1 (5%)
Insomnia	2 (9.1%)	0

Source: Clinical reviewer, CADENZA Part A ADAE.xpt and ADSL.xpt datasets

*The following preferred terms were combined:

Anemia: anemia, blood loss anemia

Arthralgia, arthritis: arthralgia, osteoarthritis

Chest pain: chest discomfort, musculoskeletal chest pain

Dyspepsia: abdominal pain upper, dyspepsia

Fall, dizziness, balance disorder: dizziness, fall

Fatigue: fatigue, asthenia, malaise

Hemorrhage: conjunctival hemorrhage, mouth hemorrhage, blood loss anemia, epistaxis

Herpes virus: herpes zoster, herpes simplex

Infection, viral: viral infection, viral upper respiratory tract infection, herpes zoster, influenza, oral herpes

Injection site reaction: injection site pruritus, vaccination site pain

Local administration reactions: infusion related reaction, vaccination site rash, injection site pruritus, vaccination site pain

Pruritis: injection site pruritus, pruritis

Nasopharyngitis: nasopharyngitis, rhinitis

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Pyrexia: febrile infection, pyrexia

Rash: toxic skin eruption, rash erythematous, rash, blister, dermatitis, vaccination site rash

Respiratory tract infection: upper respiratory tract infection, nasopharyngitis, sinusitis, viral upper respiratory tract infection, rhinitis, influenza like illness

Table 9. Most Common (>5%) Treatment Emergent Adverse Events in Patients in the Sutimlimab Group in CADENZA Part A, Preferred Terms

Preferred term	Sutimlimab N=22 n(%)	Placebo N=20 n(%)
Headache	5 (22.7%)	2 (10%)
Hypertension	5 (22.7%)	0
Raynaud's phenomenon	4 (18.2%)	0
Rhinitis	4 (18.2%)	0
Cyanosis	3 (13.6%)	0
Anemia	2 (9.1%)	4 (20%)
Diarrhea	2 (9.1%)	4 (20%)
Abdominal pain upper	2 (9.1%)	2 (10%)
Arthralgia	2 (9.1%)	2 (10%)
Dyspnea	2 (9.1%)	2 (10%)
Nasopharyngitis	2 (9.1%)	2 (10%)
Anxiety	2 (9.1%)	1 (5%)
Pruritus	2 (9.1%)	1 (5%)
Vaccination site pain	2 (9.1%)	1 (5%)

Source: Clinical reviewer, CADENZA Part A ADAE.xpt and ADSL.xpt datasets

Supportive safety population

In the CMD population, the most common TEAEs (occurring in >20% of the population) included; infection (34.4%), fatigue (28.1%), upper respiratory infection (URI) (25%), and headache (21.9%).

In the safety update with the BLA resubmission, 10 out of 12 patients (83.3%) with ITP had a TEAE. The most common TEAEs (occurring in >30% of the population) were fatigue, headache, an oropharyngeal pain.

Clinical reviewer comment: Similar to the original submission, most patients included in the primary safety database in the resubmission experienced a TEAE (~94%). While the most common TEAE was the same as the original submission were infections, specifically respiratory tract infections, other common (>15% of the population) TEAEs now included nasopharyngitis, arthralgia, arthritis, diarrhea, headache, and hypertension. This is likely more reflective of the safety profile of sutimlimab as the patient numbers are larger.

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In CADENZA Part A, the most common TEAEs by FMOs that occurred more frequently in the sutimlimab group included nasopharyngitis, headache, local administration reactions, systemic hypertension, and rash. The most common TEAEs by preferred terms that occurred more frequently in the sutimlimab group included headache, hypertension, Raynaud's phenomenon, rhinitis, and cyanosis. After reviewing grouped terms and considering causality related to sutimlimab the following ARs were most common (occurring in 3 or more patients receiving sutimlimab with a difference of ≥ 2 patients compared to placebo arm); headache, hypertension, Raynaud's phenomenon, cyanosis and rhinitis. The verbatim term for cyanosis was acrocyanosis for all patients.

It is difficult to determine if Raynaud's phenomenon and acrocyanosis was due to sutimlimab or due to CAD. The clinical team asked the Applicant if there was a proposed mechanism of action (MOA) that could have accounted for the increased events. The Applicant stated they did not know of a MOA that would explain these ARs (b) (4)

The clinical team agreed with the Applicant. It is not expected that sutimlimab would improve Raynaud's phenomenon or acrocyanosis as these are agglutination induced circulatory symptoms and not complement dependent[1].

Laboratory Findings

Hematology

In the original BLA submission, the most common (occurring in over 20% of the population) abnormal hematology laboratory values reported by the Applicant in the primary safety population was hematocrit $\leq 30\%$, lymphocytes $< 0.8 \times 10^9/L$, hemoglobin ≤ 10 g/dL, leukocytes $< 3 \times 10^9/L$, and absolute neutrophil count $< 1.5 \times 10^9/L$. There were no clinically meaningful significant trends in hematology laboratory values in the primary CAD safety population or supportive safety population.

In the BLA resubmission, the most common (occurring in over 20% of the population) abnormal hematology laboratory values reported by the Applicant in the primary safety population was hematocrit $\leq 30\%$ (39/72; 54.2% patients), lymphocytes $< 0.8 \times 10^9/L$ (30/75; 40% patients), and hemoglobin ≤ 10 g/dL (31/76; 40.8% patients). In total, 14 out of 76 patients (18.4%) had a TEAE of anemia (including terms; anemia, blood loss anemia, hemolysis, cold type hemolytic anemia and iron deficiency anemia). In addition, 1 out of 76 patients (1.3%) had white blood cell count decrease, lymphocytosis and leukocytosis.

In the ITP population, 9 out of 12 patients (75%) had thrombocytopenia. One patient (8.3%) had a TEAE of low hemoglobin.

Clinical reviewer comment: The most common hematology laboratory TEAE was anemia. This is

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not unexpected as anemia and hemolysis are hallmarks of CAD.

Chemistry

In the original BLA submission, the most common (>20% of patients) abnormal chemistry laboratory values included; blood urea nitrogen ≥ 10.7 mmol/L, direct bilirubin $>1.5x$ ULN, and total bilirubin $>1.5x$ ULN. Overall, no clinically meaningful significant trends were observed in chemistry laboratory values in the primary and supportive safety population.

In the BLA resubmission, the most common (>20% of patients) abnormal chemistry laboratory values included; blood urea nitrogen ≥ 10.7 mmol/L (15/66; 22.7%), direct bilirubin $>1.5x$ ULN (14/66; 21.2%), and total bilirubin $>1.5x$ ULN (17/76; 22.4%). One out of 76 patients (1.3%) had a grade 2 TEAE of increased blood creatinine. There were two out of 76 patients (2.6%) with TEAEs of alanine aminotransferase (ALT). One out of 76 patients (1.3%) had TEAE of aspartate aminotransferase. One out of 76 patients (1.3%) had a TEAE of alkaline phosphatase increased.

In the ITP population, the most common chemistry abnormality was high glucose (>8.9 mmol/L) in 4 out of 12 patients (33.3%). One patient had a TEAE of elevated GGT.

Clinical reviewer comment: TEAEs related to chemistry abnormalities were infrequent. Considering the complex patient population with multiple comorbidities causality is difficult to determine with small patient numbers. No patient had drug induced liver toxicity or acute kidney injury.

SLE panel

In the original BLA submission, 13 out of 34 patients (38.2%) had an all negative at baseline and at least one evaluation after sutimlimab exposure. Three of the 13 (23.1%) patients had at least one positive parameter that remained positive at the last SLE panel.

Of the patient 8 patients with ITP, 2 had negative results prior to sutimlimab exposure, one was positive at the last evaluation.

In the resubmission of the BLA, a total of 27 patients had all negative results prior to sutimlimab exposure and had at least 1 evaluation after sutimlimab exposure. In total, 8 (29.6%) had a positive result at least once postbaseline, and 7 (25.9%) were positive for at least 1 SLE panel parameter at the last postbaseline evaluation. Between 1 to 12 patients with CAD each shifted from negative at baseline to positive postbaseline for antinuclear antibody (3 patients), multiplex with double-stranded DNA (6 patients), anti-ribonucleoprotein antibody (1 patient), anti-Ro/SSA antibodies (1 patient), and circulating immune complexes (12 patients). Eleven patients shifted from at least 1 positive at baseline to at least 1 negative postbaseline.

In the supportive population, of the 12 patients with ITP, 4 (33.3%) had a negative baseline results. Of the 4 patients, 3 (75%) had a positive panel at any time, one remain positive.

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Clinical reviewer comment: A similar proportion of patients in the resubmission compared to the original BLA submission had a negative SLE panel at baseline and subsequently had at least one positive baseline SLE panel laboratory value turn positive at the end of treatment (25.9% vs 23.1%, respectively). Without clinical correlation, the significance of this is difficult to determine. See section 3.5.3 for further analysis.

3.4.6. Vital Signs

In the original BLA submission the most common abnormal vital signs were high systolic blood pressure, low systolic blood pressure, high diastolic blood pressure, low diastolic blood pressure, high heart rate, and low heart rate. Six out of 34 (17.6%) of patients had a TEAE of either hypertension or elevated blood pressure. There were no significant vital sign changes in the supportive safety population.

In the BLA resubmission, the most common abnormal vital signs were high/increased systolic blood pressure (17/71; 23.9%), low/decreased systolic blood pressure (22/71; 31%), high or increased blood pressure (10/721; 14.1%), low/decreased diastolic blood pressure (22/71; 31%), high or increased heart rate (17/71; 23.9%) and low/decreased heart rate in (27/71; 38%). In total, 16 out of 76 patients (21%) of patients had a TEAE of hypertension or elevated blood pressure.

In the ITP population, 1 out of 12 patients (8.3%) had a high or increased heart rate. No other clinically significant vital changes were noted.

Clinical reviewer comment Most vital sign changes continued to be consistent with pretreatment medical history. A similar proportion of patients has a TEAE of hypertension in the resubmission compared to the original submission (21% vs 17.6%, respectively). Hypertension is listed as an adverse reaction in the USPI.

3.4.7. Electrocardiograms (ECGs)

In the original BLA submission, 11 out of 27 (40.7%) patients had a normal ECG at baseline and 1 postbaseline ECG that was abnormal, no patient had a clinically relevant abnormal ECG in the primary CAD safety population or ITP population.

In the BLA resubmission, 21 out of 76 patients (39.6%) had a normal ECG at baseline and 1 postbaseline ECG that was abnormal, no patient had a clinically relevant abnormal ECG in the primary CAD safety population or ITP population.

Clinical reviewer comment: There were no clinically relevant ECG changes in patients with CAD who received sutimlimab.

3.4.8. Immunogenicity

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In the original BLA submission, anti-drug antibody (ADA) data was collected in studies BIVV009-01 part A,B &C, TNT009-02, and BIVV009-05 Part B. No patient with positive ADAs had evidence of a hypersensitivity reaction. One patient with CAD developed a positive ADA.

In the BLA resubmission, ADA data was collected in in studies BIVV009-01 part A,B, C and E, TNT009-02, BIVV009-05 Part B, along with BIVV009-03 and BIVV009-04. In total 5 out of 76 patients with CAD had a positive treatment emergent ADA. No patient with positive ADAs had evidence of a hypersensitivity reaction.

Clinical reviewer comment: See clinical pharmacology review further information.

3.5. Analysis of Submission-Specific Safety Issues

3.5.1. Infections

Primary Safety Population

In the original BLA submission serious infections were identified as an important safety signal as 20.6% of patients developed a serious infection. In total, one patient in the 90-day safety follow up report from study BIVV009-03 Part B developed *Streptococcus pneumoniae* bacteremia, despite receiving a vaccination. There were no other vaccine-related encapsulated organism infections.

Additional serious infections were described in the safety update with the resubmission. In total, 10 out of 76 patients (13.2%) had a serious infection. An updated table describing serious infections is provided below (Table 10). However, no new infections with vaccine-related encapsulated bacterium were reported, this included no meningococcal infections.

Table 10. Serious Infections in CAD Safety Population

Preferred Term	BIVV009-01 C&E	BIVV009-03 A&B	BIVV009-04 A&B		Total N=76 n(%)
	N=10 n(%)	N=24 n(%)	Sutimlimab N=22 n(%)	Placebo N=20 n(%)	
Serious Infection	2 (20%)	7 (29.2%)	1 (4.5%)	0	10 (13.2%)
Sepsis*	0	3 (12.5%)	0	0	3 (3.9%)
Pneumonia*	1 (10%)	1 (4.2%)	0	0	2 (2.6%)
Urosepsis	1 (10%)	1 (4.2%)	0	0	2 (2.6%)
Appendicitis	0	1 (4.2%)	0	0	1 (1.3%)
Erysipelas	0	1 (4.2%)	0	0	1 (1.3%)
Febrile Infection	0	0	1 (4.5%)	0	1 (1.3%)
Herpes Zoster	0	1 (4.2%)	0	0	1 (1.3%)
Respiratory tract	0	1 (4.2%)	0	0	1 (1.3%)

Preferred Term	BIVV009-01 C&E N=10 n(%)	BIVV009-03 A&B N=24 n(%)	BIVV009-04 A&B		Total N=76 n(%)
			Sutimlimab N=22 n(%)	Placebo N=20 n(%)	
infection					
Viral infection	0	0	0	0	1 (1.3%)
Staphylococcal wound infection	0	1 (4.2%)	0	0	1 (1.3%)

Source: Clinical reviewer, ISS dataset

a) Including TEAEs which occurred during or after the first dose of BIVV009 in Part A to the data cutoff date of Part B based on BIVV009-treated patients in Part A.

(b) Including TEAEs which occurred during or after the first dose of BIVV009 in Part B to the data cutoff date of Part B based on placebo-treated patients in Part A (not including TEAEs which occurred during or after the first dose of placebo and up until the first infusion of BIVV009)

*The following preferred terms were combined

Pneumonia: COVID-19 pneumonia, pneumonia, pulmonary sepsis

Sepsis: Escherichia sepsis, Pneumococcal sepsis, Streptococcal sepsis

Secondary safety population

In study BIVV009-201, 1 out of 12 patients (8.3%) had a serious infection. The serious infection was diverticulitis.

Clinical reviewer comment: Overall, the percentage of serious infections were less than the original BLA. In total, 10 out of 76 (13.1%) of patients had a serious infection based on the resubmission safety database. There were no further cases of vaccine-related infections described. A postmarketing requirement (PMR) will be issued to assess risk of serious infections by collecting additional long term safety data through a registry.

3.5.2. Hypersensitivity reactions

Primary safety population

In the original BLA submission, 2 patients (5.9%) in the primary CAD safety population clearly had infusion-related reactions to sutimlimab that responded to therapy. No patient had discontinued therapy.

In the resubmission safety update additional patients experienced hypersensitivity reactions. In total, 4 (5.3%) of patients experienced infusion related reactions. Also, 1 patient had pruritis accompanied by chest discomfort and hypotension within 24 hours of receiving sutimlimab.

The following TEAEs were reported as possible hypersensitivity reaction by the investigator:

- In study BIVV009-01 Part C there were no TEAEs concerning for a hypersensitivity reaction.
- In BIVV009-01 Part E there was on TEAE of rash that occurred 10 days after sutimlimab.

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- In BIVV009-03 Part A there were 2 (8.3%) patients with infusion related reactions, these were reported in the original BLA submission. In addition, one patient had a TEAE of erythema, that was originally thought to be related to sutimlimab but persisted and later was diagnosed as a basal cell carcinoma.
- In BIVV009-03 Part B, 1 patient had a TEAE of maculopapular rash that occurred on the same day as receiving sutimlimab and improved with antihistamines. In addition, one patient had efflorescence/skin change on the back. One patients had erythema reportedly due to a cold.
- In BIVV009-04 Part A, two patients had TEAEs within 24 hours of sutimlimab; infusion related reaction in one patient and one patient with pruritus, hypotension and chest discomfort. In addition, one patient had TEAE had injection site pruritus. One patient had a blister. And one patient had a rash.
- In BIVV009-04 Part B, one patient had a TEAE of infusion related reaction (itchy skin, chest tightness). One patient experienced 2 TEAEs of flushing within 24 hours of sutimlimab. One patient experienced 2 TEAEs of rash. One patient experienced 1 TEAE of pruritus. And one patient experienced seasonal allergy and erythema.

Secondary safety population

In the original BLA submission, one of the 8 (12.5%) patients with ITP experienced a non-serious TEAE of pruritis within 24 hours of the first infusion of sutimlimab and a non-serious event of an infusion-related reaction in the third infusion of sutimlimab.

In the safety update two additional patients out 12 (16.7%) with ITP experienced infusion related reactions. One those patients had a drug interruption due to infusion related reaction. In addition, one out of 12 patients (8.3%) developed a rash that resolved three days later. The investigator did not think the rash was related to sutimlimab.

Clinical reviewer comment: In total, the clinical reviewer considered 8 patients (10.5%) with hypersensitivity reactions due to sutimlimab. In addition to the two infusion related reactions reported in BIVV009-03 Part A from the original BLA submission the clinical reviewer considered the following also suggestive of hypersensitivity reactions related to sutimlimab. One patient in BIVV009-03 Part B experienced a maculopapular rash that occurred after sutimlimab administration and improved with antihistamines. In BIVV009-04 Part A one patient had an infusion related reaction (pain following the infusion) resulting in treatment discontinuation. In addition one patient had pruritis with hypotension, and chest discomfort. In BIVV009-04 Part B one patient had an infusion related reaction (itchy skin and chest tightness) this resulted in temporary interruption of sutimlimab and improved with antihistamines. In addition, one patient had 2 TEAEs of flushing which occurred within 24 hours of start of infusion.

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3.5.3. Autoimmune disease

In the original BLA submission, two out of 34 patients (5.9%) had possible worsening of a previously diagnosed autoimmune disease (i.e. polymyalgia rheumatica and multiple sclerosis).

In the safety update, 4 out of 76 patients (5.3%) had new or worsening autoimmune disease. The two additional events of autoimmune disease are described below.

In study BIVV009-03 Part B, one patient had a TEAE of systemic scleroderma. This patient had a history of arthralgia and pulmonary hypertension prior to starting sutimlimab. In Part A of the study the patient had a positive antinuclear antibody and anti-centromere B antibody at screening and at the end of Part A. During Part B, the patient was diagnosed with systemic scleroderma on day 353 of the study. No action was taken with sutimlimab.

In study BIVV009-04 Part A, one patient with a history of Grave's disease, experienced worsening of Grave's disease on day 31. No action was taken with sutimlimab.

Secondary safety populations

In the original application, one patient with ITP, had sutimlimab interrupted due to a TEAE a positive RNP value. There were no clinical features associated with the positive RNP.

In the safety update, there were no TEAEs concerning for autoimmune disease.

Clinical reviewer comment: A similar proportion of patients had new or worsening autoimmune disease in the resubmission compared to the original submission (5.3% vs 5.9%, respectively). All patients had worsening of a pre-existing autoimmune disease, except one patient who had a new diagnosis of systemic scleroderma. This patient had symptoms suggestive of autoimmunity and a positive autoantibody panel prior to initiating sutimlimab. It's not clear if sutimlimab caused worsening/new autoimmune diseases. In addition, while 29.6% of patients had at least one parameter on the SLE autoantibody panel turn positive, the lack of clinical correlation makes it unclear if this is clinically meaningful. Therefore, the risk of autoimmune diseases remains theoretical. This risk will be further assessed by collecting long term safety data in a PMR.

3.5.4. Thromboembolic events

Primary safety population

In the original BLA submission, one out of 34 patients (2.9%) had a thromboembolic event (deep vein thrombosis).

With the resubmission of the BLA, 4 out of 76 patients (5.3%) had a thromboembolic event. This included one patient deep vein thrombosis (DVT), device related thrombosis, cerebral vein thrombosis, and transient ischemia attack.

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1. One patient in BIVV009-03 Part B developed a device related thrombosis. This patient was 81 years old and developed a DVT of the right arm due to an indwelling catheter.
2. One patient in BIVV009-04 Part A developed a cerebral venous thrombosis. The patient had risk factors including elderly age and steroid induced diabetes. Patient was receiving sutimlimab.
3. One patient in BIVV009-04 Part B developed a DVT. No further information was provided. Patient was receiving sutimlimab.
4. One patient in BIVV009-04 Part B had a transient ischemic attack (TIA). The patient had a history of TIA and stroke prior to starting sutimlimab. The patient received placebo in Part A, and then received sutimlimab in Part B.

Secondary safety population

No thromboembolic (TE) events were reported in the secondary safety population.

Clinical reviewer comment: While the proportion of patients with thromboembolic events (TE) increased in the resubmission compared to the original BLA submission (5.3% vs 2.9%, respectively). The significance of this is not clear given the small patient numbers. Also, this was a complex patient population that have increased risk factors such as comorbidities, older age, and indwelling catheters. In addition, there is an increased risk of thromboembolic events in patients with CAD[2]. At this time, it does not appear that sutimlimab causes an increased risk for TE events.

3.6. Additional Safety Explorations

3.6.1. Human Carcinogenicity or Tumor Development

Primary safety population

In the original BLA submission, 4 out of 34 patients (11.8%) had a neoplasm. This included hepatic cancer in one patient. In addition, one patient had increased in size of previous renal cell carcinoma and basal cell carcinoma. One patient with Waldenstroms macroglobulinemia. One patient with basal cell carcinoma. No events were thought to be related to sutimlimab.

In the resubmission, 9 out of 76 patients (11.8%) had a TEAE that was included under the neoplasm benign or malignant SOC. A table describing of all TEAEs is described below.

Table 11. Neoplasms Benign or Malignant in CAD Safety Population

Preferred Term	BIVV009-01 C&E N=10 n(%)	BIVV009-03 A&B N=24 n(%)	BIVV009-04 A&B		Total N=76 n(%)
			Sutimlimab (a) N=22 n(%)	Placebo (b) N=20 n(%)	
Basal cell carcinoma	0	2 (8.3%)	0	0	2 (2.6%)

Preferred Term	BIVV009-01 C&E N=10 n(%)	BIVV009-03 A&B N=24 n(%)	BIVV009-04 A&B		Total N=76 n(%)
			Sutimlimab (a) N=22 n(%)	Placebo (b) N=20 n(%)	
Bowen's disease	0	1 (4.2%)	0	0	1 (1.3%)
Colon adenoma	0	0	1 (4.5%)	0	1 (1.3%)
Hepatic cancer	0	1 (4.2%)	0	0	1 (1.3%)
Lipoma	0	0	1 (4.5%)	0	1 (1.3%)
Melanocytic nevus	0	0	1 (4.5%)	0	1 (1.3%)
Myelodysplastic syndrome	0	1 (4.2%)	0	0	1 (1.3%)
Renal cell carcinoma	0	1 (4.2%)	0	0	1 (1.3%)
Seborrheic keratosis	0	1 (4.2%)	1 (4.5%)		2 (2.6%)
Waldenstrom's macroglobulinemia	1 (10%)	0	0	0	1 (1.3%)

Source: Clinical reviewer, ISS dataset

a) Including TEAEs which occurred during or after the first dose of BIVV009 in Part A to the data cutoff date of Part B based on BIVV009-treated patients in Part A.

(b) Including TEAEs which occurred during or after the first dose of BIVV009 in Part B to the data cutoff date of Part B based on placebo-treated patients in Part A (not including TEAEs which occurred during or after the first dose of placebo and up until the first infusion of BIVV009)

Secondary safety population

No patient had an oncologic TEAE in the primary or secondary safety population.

Clinical reviewer comment: The proportion of patients with benign or malignant neoplasm was the same as resubmission compared to the original submission. The TEAEs of hepatic cancer, renal cell carcinoma, Waldenstroms macroglobulinemia, and myelodysplastic syndrome were all diagnosed prior to administration of sutimlimab. The remaining TEAEs were mostly skin lesions. It does not appear that sutimlimab increases the risk of malignancy.

3.6.2. Additional Safety Issues From Other Disciplines

There were no additional safety issues from other disciplines during the original review and resubmission.

3.7. Safety Summary

As requested in the Complete Response letter the Applicant has submitted a safety update with the resubmission of the BLA. This safety update included additional safety data from ongoing clinical trials. This included data from the following studies in patients with CAD; BIVV009-04 Parts A and B, BIVV009-03 Part B, and BIVV009-01 Part E. In addition, additional safety data was submitted from one ongoing trial in patient with ITP (BIVV009-201). The focus of the safety analysis was the CAD population, with particular emphasis on BIVV009-04 Part A (CADENZA), a

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randomized, double-blind, placebo-controlled trial in patients with CAD who had not received a recent blood transfusion (≤ 1 blood transfusion during the previous year and no transfusion during the 6 months prior to enrollment). The dosing of sutimlimab used in CADENZA Part A, was the same dose and regimen used in CARDINAL, patients < 75 kg received fixed doses of 6.5g, and patients > 75 g received fixed doses of 7.5g, on day 0, 7 and 14, followed by every two weeks. CADENZA Part A, which consists of 25 weeks of study drug, is now completed, and provides important safety information for sutimlimab..

While still manageable, the safety profile (i.e. most common ARs, types of ARs observed, and frequency of AESI) of sutimlimab has been modified after analyzing the additional data provided by the Applicant. With the safety update additional patients with CAD were included in the risk assessment of sutimlimab (N=76). In addition, patients with CAD were treated for a longer duration (median) compared to the original submission (63.9 weeks vs 38.4 weeks, respectively).

In the primary CAD safety population, the most common TEAEs (closely related terms were grouped or FMQs) in over 15% of the population included infections. respiratory tract infection, nasopharyngitis, arthralgia, arthritis, diarrhea, headache, and hypertension. In CADENZA Part A, the most common ARs (occurring in 3 or more patients receiving sutimlimab with a difference of ≥ 2 patients compared to placebo arm) were headache, hypertension, Raynaud's phenomenon, acrocyanosis and rhinitis.

Serious TEAEs occurred in 27.6% of patients in the primary safety population, the most common SAEs were infection and sepsis. In CADENZA Part A, the frequency of SAEs was higher in the sutimlimab arm compared to the placebo arm (13.6% vs 5%, respectively). There were two patients with SARs in the sutimlimab arm, this included Raynaud's phenomenon and febrile infection. There were no deaths due to sutimlimab. Overall the discontinuation rate was low, 7.9%. This supports the tolerability of sutimlimab.

Infections continued to be an adverse event of special interest (AESI) as the classical complement pathway is part of the innate immune system and therefore inhibiting this pathway may increase risk of serious infections, including infections by encapsulated organisms. While in the original BLAs submission one patient had pneumococcal sepsis, no additional patients experienced an infection of a vaccinated encapsulated bacteria. In total, serious infections occurred in 13.2% of patients in the primary safety population. The most common serious infections (≥ 2 patients) included sepsis, pneumonia and urosepsis. One patient discontinued therapy due to a febrile infection.

Hypersensitivity reactions occurred in 8 patients (10.5%) in the primary safety population. One patient discontinued sutimlimab due to an infusion related reaction.

Patients with inherited C1s deficiency are at increased risk of autoimmune diseases, therefore

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there is a theoretical risk of autoimmunity, in particular SLE in patients who receive sutimlimab. There continued to be no clear trend of autoantibody positivity and clinical symptoms of SLE. While 4 patients (5.3%) had new or worsening autoimmune disease, this was confounded by preexisting diagnosis and/or symptoms of autoimmunity. This risk thus remains theoretical, and it is unclear if long term exposure to sutimlimab (>3-5 years) would increase risk of developing autoimmune disease. The theoretical risk of SLE will be listed in the Warnings and Precautions of the USPI.

In summary, after reviewing the safety data with the resubmission, sutimlimab continues to be well tolerated and have low rates of discontinuations. The safety profile remains acceptable for patients with CAD. Toxicities can be addressed in labeling based on data collected from CARDINAL in the original BLA submission. The USPI will not be updated to reflect data collected with this resubmission. Uncertainties due remain given the small sample size and limited long-term data, it is possible that new safety signals will be revealed in ongoing studies. Therefore, PMRs will be issued to complete and submit results of ongoing studies (BIVV009-01 Part E, BIVV009-03 Part B, and BIVV009-04 Part B). In addition, a PMR will be issued to assess the risk of infections (including encapsulated organism) and autoimmune diseases in additional patients followed long-term in a registry.

4. Appendices

4.1. References

1. Berentsen, S., et al., *Cold agglutinin disease revisited: a multinational, observational study of 232 patients*. Blood, 2020. 136(4): p. 480-488.
2. Broome, C.M., et al., *Increased risk of thrombotic events in cold agglutinin disease: A 10-year retrospective analysis*. Res Pract Thromb Haemost, 2020. 4(4): p. 628-635.

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CLINICAL REVIEW

Application Type	BLA
Application Number(s)	761164
Priority or Standard	Priority
Submit Date(s)	03/13/2020
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Division/Office	DNH/OCHEN
Reviewer Name(s)	Clinical: Carrie Diamond, M.D. (Clinical Reviewer, DNH) Tanya Wroblewski, M.D. (Clinical Team Leader, DNH) Albert Deisseroth, MD, PhD, (Supervisory Associate Division Director, DNH) Statistics: Yaping Wang, PhD (Statistical Reviewer, DBIX) Yeh-Fong Chen, PhD (Statistical Team Leader, DBIX) Thomas Gwise, PhD (Division Director, DBIX)
Review Completion Date	11/05/2020
Established/Proper Name	Sutimlimab-jome
(Proposed) Trade Name	ENJAYMO
Applicant	Bioverativ Therapeutics, Inc
Dosage Form(s)	Injection: 1100 mg/22 mL (50 mg/mL)
Applicant Proposed Dosing Regimen(s)	Sutimlimab 6500mg (b) (4) or 7500mg (for patients $\geq$ 75kg), administered as an intravenous infusion over 1-2 hours once per week for the first 2 doses followed by every other week dosing
Applicant Proposed Indication(s)/Population(s)	Treatment of hemolysis in adult patients with cold agglutinin disease
Recommendation on Regulatory Action	Complete Response
Recommended Indication(s)/Population(s) (if applicable)	

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Figure 1. Plot of Mean Hemoglobin by Visit 46

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Glossary

ADA	anti-drug antibody
ADaM	Analysis Data Model Implementation
AE	adverse event
AIHA	autoimmune hemolytic anemia
ALT	alanine aminotransferase
AMR	renal allograft antibody-mediated rejection
ANA	anti-nuclear antibody
AR	adverse reaction
BLA	biologics license application
BP	bullous pemphigoid
C1	complement component 1
C1s	complement subcomponent 1
CA	cold agglutinin
CAD	cold agglutinin disease
CAS	cold agglutinin syndrome
CDER	Center for Drug Evaluation and Research
CIC	circulating immune complexes
CMC	chemistry, manufacturing, and controls
CMD	complement mediated disorder
CP	complement pathway
CR	complete response
CSR	clinical study report
CTCAE	Common Toxicity Criteria for Adverse Events
DAT	direct antiglobulin test
dsDNA	double stranded DNA
ECG	electrocardiogram
EOT	end of treatment
EQ-5D-5L	5-Level EuroQol 5 Dimensions Questionnaire
FACIT-F	Functional Assessment of Chronic Illness Therapy- Fatigue
FAS	full analysis set
FDA	Food and Drug Administration
FMQ	FDA medical query
GCP	good clinical practice
Hgb	Hemoglobin
ICH	International Council for Harmonization
IgG4	immunoglobulin G subclass 4
IND	Investigational New Drug Application

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ITP	immune thrombocytopenic purpura
IV	intravenous
LDH	lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Model for Repeated Measures
NHV	normal healthy volunteer
NME	new molecular entity
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PD	pharmacodynamics
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of [Fatigue] Severity
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PRO	patient reported outcome
PT	preferred term
QOL	quality of life
REMS	risk evaluation and mitigation strategy
RNP	anti-ribonucleoprotein antibody
SAE	serious adverse event
SAP	statistical analysis plan
SCS	summary of clinical safety
SF-12	12-Item Short Form
ScL-70	Anti-scleroderma antibody
SLE	systemic lupus erythematosus
SOC	systems organ class
SDTM	Study Data Tabulation Model
TEAE	treatment emergent adverse event
ULN	upper limit of normal
URI	upper respiratory infection
USPI	United States Prescribing Information
UTI	urinary tract infection
WAIHA	warm autoimmune hemolytic anemia

1. Executive Summary

1.1. Product Introduction

Sutimlimab-jome (proprietary name, ENJAYMO), a new molecular entity (NME), is a humanized immunoglobulin G subclass 4 (IgG4) monoclonal antibody that inhibits the classical complement pathway (CP) and specifically binds to complement protein component 1, s subcomponent (C1s), a serine protease which cleaves C4. The classical CP is activated in cold agglutinin disease (CAD) and leads to chronic hemolysis.

The Applicant proposes the following indication: the treatment of hemolysis in adult patients with CAD.

The proposed dosing regimen is 6.5g (b) (4) or 7.5g (patients ≥ 75 kg) depending on the patient's body weight at baseline, which is to be administered by intravenous (IV) infusion over 1-2 hours once per week for the first two doses followed by every other week dosing.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The Applicant has demonstrated substantial evidence of effectiveness. This conclusion is based upon the results of a global, multi-center, single-arm, open-label trial (BIVV009-03 Part A; CARDINAL study) in 24 adult patients with symptomatic CAD who had at least one transfusion in the previous 6 months and a hemoglobin (Hgb) level ≤ 10 g/dL.

The primary endpoint was the percent of patients who met criteria of the responder definition. Patients met the responder definition if they demonstrated an increase from baseline in Hgb level ≥ 2 g/dL or normalization of Hgb level ≥ 12 g/dL at the treatment assessment time point (mean value from weeks 23, 25, and 26) and did not receive a blood transfusion from week 5 through week 26, in addition to not receiving additional treatment for CAD beyond what was permitted in the protocol. The proportion of patients who met the primary composite endpoint was 54.2% (95% CI: 32.8%, 74.4%). CAD is a rare and serious life-long disease with significant morbidity for which there is no available therapy and has an unmet medical need.

Thus, the multicenter trial results indicate that in patients with CAD, the use of sutimlimab-jome confers substantial benefit in terms of transfusion independence and improvement in hemoglobin with a manageable toxicity profile. The benefits of sutimlimab-jome outweigh its risk. Approval on the basis of single study is entirely appropriate in a rare disease with unmet medical need the benefits which include transfusion independence with statistically significant results and concordance of secondary endpoints.

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However, this application will not be approved during this assessment cycle due to deficiencies identified for [REDACTED] ^{(b) (4)} facility. The Office of Pharmaceutical Manufacturing Assessment (OPMA), Office of Pharmaceutical Quality (OPQ), CDER is recommending that the application not be approved due to deficiencies related to readiness for commercial manufacturing and data integrity that were observed at the FDA pre-license inspection (PLI) of the [REDACTED] ^{(b) (4)} drug substance manufacturing facility. Thus, a complete response is recommended.

1.3. **1.3 Benefit-Risk Assessment**

Benefit-Risk Integrated Assessment

Sutimlimab is a first-in-class, humanized IgG4 monoclonal antibody that targets the classical complement pathway (CP) by inhibition of CP-specific serine protease, complement component 1 (C1), s subcomponent (C1s).

Cold Agglutinin Disease (CAD) is a rare type of autoimmune hemolytic anemia (AIHA). CAD is characterized by a low-grade clonal B-cell lymphoproliferative disorder and chronic hemolytic anemia. Cold agglutinins activate the classical CP leading to deposition of C3b on red blood cells which are phagocytosed in the liver resulting in extravascular hemolysis, the predominate mechanism of hemolysis. While hemolysis is chronic, disease severity can fluctuate throughout a patient's lifetime. CAD is a serious disease and patients may have increased mortality. Anemia can be mild to severe, it has been estimated that approximately half of patients require transfusions. Symptoms of anemia can greatly affect quality of life. Most patients have cold induced symptoms ranging from acrocyanosis to debilitating Raynaud's phenomenon. In addition, patients with CAD may be at increased risk for thrombosis. There are no approved therapies for CAD. Patients often require supportive therapies such as transfusions and avoidance of cold temperatures. Immunosuppressants that target the B cell clone such as rituximab as monotherapy or in combination with other cytotoxic agents are standard therapies for symptomatic patients. Limitations of these therapies may include; not all patients respond to treatment, response may not be durable, there is a slow onset to response, and depending on the regimen, significant toxicities may occur.

The determination of efficacy is based primarily upon the results from a single study (BIVV009-03 Part A, CARDINAL study). The CARDINAL study was a single-arm, open-label trial that included 24 adult patients with primary CAD who had at least one blood transfusion in the previous 6 months, Hgb $\leq$ 10g/dL and were symptomatic. The primary composite endpoint was the proportion of patients that met the responder definition. A patient was considered a responder if he or she did not receive a blood transfusion from Week 5 through Week 26 and did not receive treatment for CAD beyond what was permitted per protocol. Additionally, the patient's hemoglobin (Hgb) level must have met either of the following criteria; Hgb level $\geq$ 12 g/dL or Hgb level increased by $\geq$ 2 g/dL from baseline at the treatment assessment endpoint. In total, 13 out of the 24 (54.2%, 95% CI: 32.8, 74.4) patients in the full analysis set met the composite primary endpoint criteria and the lower bound of the response rate was $>$ 30%. As for each component of the composite endpoint; 15 (62.5%) patients met the Hgb endpoint, 17 (70.8%) patients were transfusion free from week 5 to 26, and 22 (91.7%) patients did not receive protocol prohibited CAD medications. To further support efficacy, markers of hemolysis including lactate dehydrogenase (LDH) and bilirubin were measured. Among 14 patients with baseline and follow-up bilirubin values, the mean was 55 μ mol/L (2.7-fold ULN) at baseline and 15 μ mol/L (0.8-fold ULN) at the treatment assessment timepoint. Among 17 patients with baseline and follow-up LDH values, the mean LDH was 424 U/L (1.7-fold ULN) at baseline and 301 U/L (1.2-

fold ULN) at the treatment assessment timepoint. The decrease in mean bilirubin and LDH values compared to baseline are further evidence of decreased hemolysis.

The determination of substantial evidence of efficacy was based on the clinically meaningful and statistically persuasive results of the proportion of patients that achieved the responder definition in a patient population with a serious, life-long disease, with significant disease burden, unmet medical need and no approved therapies.

The primary safety database consisted of 34 patients (30 patients with CAD, 3 with cold agglutinin syndrome (CAS) and 1 CAD/warm autoimmune hemolytic anemia (WAIHA)). The 24 patients with CAD from the pivotal study (BIVV009-03 Part A), were included in the primary safety population. An additional 96 normal healthy volunteers (NHVs) and 32 patients with other complement-mediated disorders (CMDs) were included to further support the safety database. In general, the safety profile for sutimlimab was manageable in a population compromised of older patients with multiple comorbidities and receiving concomitant medications. No patient discontinued therapy due to an adverse reaction (AR). Common ARs (>10%) reported in the pivotal study included; respiratory tract infections, viral infections, bleeding, hematoma, diarrhea, dyspepsia, cough, arthralgia, arthritis, and peripheral edema. In total, 6 out of 24 (25%) patients experienced a serious adverse reaction. The most common type of serious adverse reaction were infections in 3 out of 24 (12.5%) of patients. Six out of 24 (25%) patients had dose interruptions, with infection and infusion reactions as the most common ARs leading to dose interruption. Infusion-related reactions occurred in 2 out of 34 (5.9%) patients, no infusion-related reactions led to drug discontinuation.

Sutimlimab may increase the risk of serious infections, including encapsulated organisms. In the primary safety population (N=34), 58.8% of patient experienced infections and 20.6% had a serious adverse event (SAE) of infection. Serious infections included; urinary tract infection, pneumonia, pulmonary sepsis, erysipelas, Streptococcal sepsis, wound infection staphylococcal, Escherichia sepsis, acute cholecystitis, respiratory tract infection, and viral infection. No patient died due to a treatment emergent adverse event (TEAE) of infection. Infections with encapsulated bacteria occurred in clinical studies, including one patient with pneumococcal sepsis despite receiving a vaccination. No meningococcal infections were reported.

No clear trend was observed comparing autoantibody positivity and overt symptoms of autoimmune disease, including Systemic Lupus Erythematosus (SLE). One patient with Polymyalgia Rheumatica discontinued therapy due to pre-treatment serious event of Polymyalgia Rheumatica. The risk of autoimmune disease development or exacerbation is still under investigation as there is limited safety data regarding long term therapy.

In summary, CAD is a serious, life-long condition for which there is no Food and Drug Administration (FDA) approved therapy. Patients often have significant disease burden, including symptomatic hemolytic anemia and often require transfusions. In the pivotal study, 54.2% of patients with CAD and a recent blood transfusion met the responder definition, this included; meeting the predefined Hgb response and achieving transfusion independence, while not receiving any prohibited CAD therapies. Therapy that increases hemoglobin and decreases transfusion burden is considered direct clinical benefit for patients with CAD. The overall safety profile of sutimlimab is acceptable for a patient population with chronic hemolytic anemia.

Thus, the trial results indicate that in patients with CAD, the use of sutimlimab-jome confers substantial benefit in terms of transfusion independence and improvement in hemoglobin with a manageable toxicity profile. The benefits of sutimlimab-jome outweigh its risk. Approval on the basis of a single study is entirely appropriate given the benefits which include transfusion independence demonstrated in a multicenter trial with statistically significant results and concordance of secondary endpoints in a rare disease with unmet medical need. ,

As summarized above, the clinical data submitted supports the conclusion of substantial evidence of efficacy and safety of sutimlimab-jome. However, during the facility site inspection of [REDACTED] (b) (4) facility for this BLA, the field investigator observed objectionable conditions at the facility and conveyed that information to the representative of the facility at the close of the inspection. Deficiencies identified at [REDACTED] (b) (4) included lack of quality oversight and significant data integrity concerns, in addition to failure to conduct a comprehensive data integrity assessment to ensure the accurate and reliable results submitted to the BLA application. Satisfactory resolution of the observations observed at the facility is required before this BLA may be approved. Therefore, a complete response (CR) action is recommended.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Cold Agglutinin Disease CAD is a form of AIHA that results from a clonal B-cell proliferative disorder of the bone marrow. This rare disease primarily affects middle aged adults and the elderly. The classical complement pathway is activated by cold agglutinins (autoantibodies) binding to the erythrocyte surface, which results in chronic hemolytic anemia. Anemia may be mild to severe, and patients may require transfusions. Symptoms related to anemia such as chronic fatigue, dyspnea, and weakness can be associated with substantial impairment of quality of life. In addition, patients often have cold-induced symptoms such as acrocyanosis and may be at an increased risk for thromboembolic events.	CAD is a rare, serious disease that results in complement mediated hemolysis. Many patients experience symptomatic anemia and require blood transfusions. The extent of anemia, which may be severe, and be associated with significant impairment in quality of life.
Current Treatment Options	• There are no approved therapies for the treatment of CAD. Treatment often consists of supportive therapies, including blood transfusions. Other therapies, including rituximab as monotherapy or in combination with cytotoxic agents may not be effective or durable, and can be associated with significant toxicities. Most patients have received one or more therapies for the treatment of CAD.	There is an unmet medical need for an effective treatment for patients with CAD.
Benefit	• In a single-arm, open-label trial (BIVV009-03 Part A), 24 patients with symptomatic CAD and a recent blood transfusion, received sutimlimab, administered on day 0, 7, followed by every two weeks for 26 weeks. • The proportion of patients that met the responder definition was 54.2% (95% CI: 32.8, 74.4). • In total, 62.5% of patients met the predefined hemoglobin endpoint (Hgb level $\geq$12 g/dL or Hgb level increased by $\geq$2 g/dL from baseline at	Of the 24 patients with CAD included in the study, 54.2% of patients responded to sutimlimab therapy. Sutimlimab improved hemolysis in patients with CAD, demonstrated by an increase in hemoglobin, transfusion independence and not receiving other therapies for CAD that were prohibited in the protocol.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	the treatment assessment endpoint), 70.8% were transfusion free from week 5 to 26, and 91.7% of patients did not receive protocol prohibited CAD medications. To support efficacy, patients also demonstrated improvement in hemolysis markers, including LDH and bilirubin.	
Risk and Risk Management	- Primary safety results included 34 patients pooled from BIVV009-01 Part C&E and BIVV009-03 Part A and B. - The most common type (>10%) of TEAEs in the 24 patients included in the pivotal study (BIVV009-03 Part A) were; respiratory tract infections, viral infections, bleeding, hematoma, diarrhea, dyspepsia, cough, arthralgia, arthritis, and peripheral edema. - In total, 6 out of 24 (25%) patients included in the pivotal study experienced a serious adverse reaction. The most common type of serious adverse reaction were infections in 3 out of 24 (12.5%) of patients. - In the primary safety population, the most common type of treatment-emergent SAEs were infections in 7 out of 34 (20.6%) of patients. Serious infections included; urinary tract infection, pneumonia, pulmonary sepsis, erysipelas, Streptococcal sepsis, wound infection staphylococcal, Escherichia sepsis, cholecystitis acute, respiratory tract infection, and viral infection. - Infections from encapsulated bacteria were reported. One patient had pneumococcal sepsis despite receiving a vaccination. - There is a theoretical risk of autoimmunity with inhibition of early components of the classical complement pathway. While no clear trend was demonstrated in studies with sutimlimab, this risk needs	Overall the safety profile of sutimlimab is acceptable for the proposed indication. Risks of sutimlimab can be sufficiently addressed through Warnings and Precautions in the United States Prescribing Information (USPI). To minimize risk, labeling should include Warning and Precautions for serious infections, infusion related reactions and autoimmune disease. The long-term risk of autoimmune disease and serious infections would have been further assessed in a postmarketing requirement (PMR) if the application was approved. Long term safety of sutimlimab will be further assessed with ongoing studies, if the

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
	further monitoring as there is limited long term data with sutimlimab exposure. • Hypersensitivity reactions, including infusion-related reactions were observed in 5.9% of the 34 patients. No patient discontinued therapy due to a hypersensitivity reaction. • Deficiencies related to readiness for commercial manufacturing and data integrity were observed at FDA pre-license inspection of one of the manufacturing sites.	application was approved PMRs would have been issued for the Applicant to complete ongoing studies. Ultimately, due to significant quality oversight deficiencies and data integrity issues identified during the (b) (4) site inspection, a CR is recommended.

1.4. Patient Experience Data

In the pivotal CARDINAL study (BIVV009-03 Part A), patient reported outcomes (PROs) were assessed with the Functional Assessment of Chronic Illness Therapy- Fatigue (FACIT-F) score as a secondary endpoint. The 5-Level EuroQol 5 Dimensions Questionnaire (EQ-5D-5L), 12-Item Short Form (SF-12), Patient Global Impression of Change (PGIC) and Patient Global Impression of [Fatigue] Severity (PGIS) were exploratory endpoints. Given this was a single arm study with no comparator, the PRO endpoints were not included in the USPI.

Patient Experience Data Relevant to this Application (check all that apply)

☒	The patient experience data that was submitted as part of the application include:	Section where discussed, if applicable
☒	Clinical outcome assessment (COA) data, such as	
☒	Patient reported outcome (PRO)	Discussed in Section 6
☐	Observer reported outcome (ObsRO)	
☐	Clinician reported outcome (ClinRO)	
☐	Performance outcome (PerFO)	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
☐	Patient-focused drug development or other stakeholder meeting summary reports	
☐	Observational survey studies designed to capture patient experience data	
☐	Natural history studies	
☐	Patient preference studies (e.g., submitted studies or scientific publications)	
☐	Other: (Please specify)	
☐	Patient experience data that were not submitted in the application, but were considered in this review:	
☐	Input informed from participation in meetings with patient stakeholders	
☐	Patient-focused drug development or other stakeholder meeting summary reports	
☐	Observational survey studies designed to capture patient experience data	
☐	Other: (Please specify)	
☐	Patient experience data was not submitted as part of this application.	

2. Therapeutic Context

2.1. Analysis of Condition

Autoimmune hemolytic anemias (AIHAs) is a group of disorders characterized by autoantibodies targeting red blood cell surface antigens resulting in hemolysis and anemia[1]. AIHA is further subdivided into cold or warm mediated disease based on the optimum temperature used to detect autoantibodies and CAD accounts for roughly 15-25% of AIHAs[2]. CAD is a primary chronic clonal B-cell lymphoproliferative disorder of the bone marrow that is characterized by the presence of cold induced clinical symptoms and AIHA [3]. It should be distinguished from secondary CAS, as CAS occurs in the presence of overt malignancies (lymphoid malignancies), autoimmune disease, and infections[2]. CAD is rare, in a Norwegian study it was estimated the prevalence was 16.2 cases per million[4]. It mostly affects middle aged and elderly patients (median age of onset is 67 years old), rare cases have been reported in patients as young as 30 years old[3]. There is a female predominance, although this may also be secondary to women living longer than men[3].

CAD is caused by cold agglutinins (CA) which are autoantibodies (mostly of immunoglobulin M class) that binds predominantly to the I carbohydrate antigen on the surface of erythrocytes resulting in agglutination maximally at a low temperatures (optimally at 3-4°C)[1, 2]. The complex of antigen bound to CA on the erythrocyte cell surface triggers activation of the of the classical complement pathway by interaction with the C1 complex ultimately leading to C3b-coated red blood cells [2]. Hemolysis occurs predominantly through extravascular destruction in the liver of C3b coated red blood cells, although C5-mediated intravascular hemolysis can occur[2].

Diagnostic criteria for CAD includes; chronic hemolysis, positive polyspecific DAT, monospecific DAT strongly positive for C3d, CA titer ≥ 64 at 4°C and absence of an underlying clinical disease such as overt malignancy[2]. Hemolysis is typically assessed by markers such as lactate dehydrogenase, bilirubin, and haptoglobin[3]. In addition, a work up should include a bone marrow biopsy which typically shows a lymphoid infiltration consisting of nodular B-cell aggregates (without characteristics of lymphoplasmacytic lymphoma), consistent with lymphoproliferative disorder[3].

The severity of CAD is mostly dependent on the thermal amplitude of cold agglutinins and the intensity of symptoms can fluctuate throughout a patient's lifetime[5]. There are conflicting reports regarding the risk of increased mortality, although it is likely there is at least slight increase in mortality for patients with CAD[6]. Anemia is more often mild to moderate, but it can be severe. Hemolysis tends to exacerbate in the setting of infections, cold temperatures, surgery, and trauma[7]. Patients often have symptoms related to anemia such as chronic

fatigue, dyspnea, and weakness which can be associated with substantial impairment of quality of life[5]. The majority of patients need transfusions at some point in their disease[5]. The percentage of patients that are transfusion dependent is difficult to quantify, larger studies have estimated 40-50% of CAD patients are transfusion dependent[3]. In a retrospective longitudinal study in the United States, it was estimated that transfusions were given to at least 65% of patients [5]. Alloimmunization and iron overload may occur in individuals who require frequent blood transfusions[8]. Most patients have symptoms related to cold-induced circulatory symptoms, such as acrocyanosis to Raynaud's phenomena[2]. Jaundice and hemoglobinuria may also occur secondary to hemolysis. Patients are likely at increased risk for venous and arterial thrombosis, particularly if they have severe anemia[3].

2.2. Analysis of Current Treatment Options

There are currently no FDA approved therapies for the treatment of CAD. Treatments are considered if the patient develops symptomatic anemia or disabling cold-induced circulatory symptoms. It has been estimated at 70-80% of patients have received therapy for CAD and many patients require trials of 1 or more therapies [3]. Supportive nonpharmacologic therapies include keeping warm, avoidance of cold infusions, and blood transfusions[2]. During a blood transfusion the extremity should be kept warm, and an in-line blood warming tubing is recommended, failure to adhere to these precautions may result in significant morbidity and could be life threatening[9]. Folic acid and erythropoietin may be used as supportive therapies.

Corticosteroids, azathioprine, and cyclophosphamide are not effective in CAD [7]. Splenectomy is not effective, which is expected as extravascular hemolysis is mostly localized to the liver.

Most successful treatments have been with targeting the pathogenic B-cell clones[3]. Rituximab monotherapy has been used with success as a single-agent and is often considered for first-line therapy. In prospective uncontrolled trials, rituximab has had an overall response rate of approximately 50%, with a median Hgb increase of 4g/dL[7]. Although, response time was often slow (median time to response was 1.5 months) and not durable (median duration approximately one year)[7]. Rituximab has also been studied in combination with bendamustine and can be considered as first-line therapy in fit patients or second-line therapy[7]. In a non-randomized study, 71% of the 45 patients had a response and only 10% of patients relapsed after 32 months. The median hemoglobin response in complete responders was 4.4g/dL, and 3.9g/dL in partial responders. Still significant toxicities were noted, 33% of patients experienced grade 3-4 neutropenia and 11% had infections[10].

As for second-line therapies, rituximab has also been combined with fludarabine. In a prospective uncontrolled trial, a response rate of 76% was observed in 29 patients. Median increase in Hgb was 3.1g/dL and median response of duration was 66 months. Increased toxicities were observed, 41% of patient experienced grade 3-4 hematologic toxicities and 59%

experienced grade 1-3 infection[11]. Bortezomib has been studied as well as monotherapy, with an overall response rate of 32% out of 19 patients[12]. While some case reports have reported benefit with eculizumab (C5 monoclonal antibody), a prospective study that was not randomized demonstrated a reduction in transfusions and intravascular hemolysis in 7 out of 13 patients, but an increase in hemoglobin level of only 0.9g/dL [13].

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Sutimlimab is an NME and is not currently marketed in the United States.

3.2. Summary of Presubmission/Submission Regulatory Activity

Table 1 below summarizes the regulatory interactions that have occurred between the Applicant and the Agency.

Table 1 . Regulatory History

Date	Regulatory Interaction
December 12 th , 2015	Pre-investigational new drug written responses were issued to discuss the clinical development program of sutimlimab, in particular to gain feedback on the design of the phase 1 study.
January 18 th , 2017	Study may proceed letter was issued for the phase 1 dose confirmation study in healthy volunteers under IND 128190.
May 30 th , 2017	End-of-phase 1 and initial comprehensive multidisciplinary breakthrough therapy meeting was held to discuss the registrational path for the treatment of hemolysis in patients with CAD. Agreement was reached regarding the proposed population, endpoints, and study duration of the pivotal CARDINAL study.
March 23 rd , 2018	Meeting to discuss the statistical analysis plan for the pivotal CARDINAL Study (BIVV009-03 Part A).
December 10 th , 2018	Written comments were provided obtaining to the presentation of the anticipated BLA.

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Date	Regulatory Interaction
July 12 th , 2019	Pre-BLA meeting (Written comments were provided).
September 26 th , 2019	Pre-BLA chemistry, manufacturing, and controls (CMC) meeting.
November 4 th , 2019	Pre-BLA meeting (written comments provided) to discuss the final components of the BLA submission and review topline data from the pivotal CARDINAL study.
April 6 th , 2020	A type A meeting was held to discuss the integrity investigation pertaining to the sutimlimab BLA.

Orphan drug designation was granted on July 27th, 2016 for the treatment of autoimmune hemolytic anemia.

Breakthrough therapy designation was granted on May 17th, 2017 for the treatment of hemolysis in patients with CAD.

Rolling submission components of the application were received; Part 1 the non-clinical portion was submitted Sept 5, 2019, Part 2 the clinical portion submitted February 26, 2020 and Part 3 the CMC and labeling was submitted on March 13, 2020. Priority review was granted at the time of filing.

3.3. Foreign Regulatory Actions and Marketing History

Sutimlimab is not approved or marketed in any other country.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

The Office of Scientific Investigations (OSI) conducted inspections for the pivotal study BIVV009-03 at a single investigator site: site No. 931 (Dr. David Kuter at Massachusetts General Hospital) and at the Applicant site (Bioverativ USA, Inc), in support of BLA 761164.

At the investigator site No. 931, (b) (4) The primary efficacy endpoint was verifiable and there was no under reporting of adverse events. OSI concluded the clinical investigator was in compliance with Good Clinical Practice.

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Based on the results of the inspections the clinical study data was reliable and the study appeared to have been conducted adequately. For details refer to the Clinical Inspection Summaries by Dr. Anthony Orenca, MD (July 13th, 2020).

4.2. Product Quality

Refer to review by Office of Product Quality. This was conducted by the review team as listed in the table below. The Product Quality reviews are filed in Panorama.

Quality Review Team		
Discipline	Reviewer	Office/Branch/Division
Product Quality (Drug Substance (DS) and DP)/Immunogenicity Assay	Xiaoshi Wang	OPO/OBP/DBRR11
Labeling	Scott Dallas James Barlow Xiaoshi Wang	OPO/OBP OPO/OBP OPO/OBP/DBRR11
Facility	Viviana Matta (DS) Maria (Gema) Martin Manso (DP)	OPO/OPMA/DBM/BMB2 OPO/OPMA/DBM/BMB2
Microbiology	Viviana Matta (DS) Maria (Gema) Martin Manso (DP)	OPO/OPMA/DBM/BMB2 OPO/OPMA/DBM/BMB2
Inspection	Viviana Matta (lead) Cyrus Agarabi	OPO/OPMA/DBM/BMB2 OPO/OBP/DBRR11
Team Lead	Yan Wang (product quality) Candace Gomez-Broughton (microbiology, DS) Maria (Reyes) Candau-Chacon (microbiology, DP) Peter Qiu (facility)	OPO/OBP/DBRR11 OPO/OPMA/DBM/BMB2 OPO/OPMA/DBM/BMB2 OPO/OPMA/DBM
Application Team Lead	Yan Wang	OPO/OBP/DBRR11
OBP Review Chief	Xianghong (Emily) Jing	OPO/OBP/DBRR11
RBPM	Florence Aisida	OPO/OPRO

As stated in the Office Product Quality review in the executive summary; this application will not be approved during this assessment cycle due to deficiencies identified for (b) (4) facility. The Office of Pharmaceutical Manufacturing Assessment (OPMA), Office of Pharmaceutical Quality (OPQ), CDER is recommending that the application not be approved due to deficiencies related to readiness for commercial manufacturing and data integrity that were observed at the FDA pre-license inspection (PLI) of the (b) (4) drug substance manufacturing facility (b) (4). From a product quality perspective, the Office of Biotechnology Products (OBP), OPO, CDER, does not note any product quality deficiencies that would preclude approval of STN 761164 for Enjaymo (sutimlimab-jome) manufactured by Bioverativ UAS Inc at this time.

Deficiencies identified included;

1. Lack of quality oversight
2. Significant data integrity concerns and failure to conduct a comprehensive data integrity assessment to ensure the accurate and reliable results submitted to the BLA application

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4.3. **Clinical Microbiology**

4.4. **There were no approvability issues from a microbiology product quality perspective. Please refer to the review by the Office of Product Quality and the microbiology reviewer for additional details. Nonclinical Pharmacology/Toxicology**

In summary, based on a chronic toxicity study in monkeys in which monkeys received 5 times the clinical exposure at the 7.5g dose, sutimlimab demonstrated robust and prolonged inhibition of C1s component. No significant adverse effects were observed. Sutimlimab is unlikely to have significant carcinogenic risk and no further carcinogenicity assessments are recommended at this time. In addition, sutimlimab did not cause adverse reproductive or developmental outcomes when administered to pregnant monkey up to 4 times the clinical exposure at the 7.5g dose.

See nonclinical review by Dr. Shaji Theodore on 10/01/2020.

4.5. **Clinical Pharmacology**

In summary, clinical pharmacology determined the proposed dosing regimen is supported by the CARDINAL study which demonstrated statistically significant and clinically meaningful improvement in the composite endpoints using a high hemoglobin threshold and transfusion avoidance through 26 weeks in patients with CAD. The proposed dosing regimen depends on the patient's body weight at baseline. The impact of immunogenicity is inconclusive due to low incidence of treatment-emergent ADA formation in patients with CAD.

Please see the review by Xiaolei Pan, clinical pharmacology reviewer.

4.6. **Devices and Companion Diagnostic Issues**

There are no companion diagnostic devices required for the proposed use of sutimlimab-jome.

4.7. **Consumer Study Reviews**

Not applicable.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

The Applicant submitted six completed or ongoing studies shown in Table 2.

The efficacy of sutimlimab was based on the CARDINAL study, BIVV009-03 Part A, a single phase 3, open-label study evaluating the safety and efficacy of sutimlimab in patients with CAD and a recent blood transfusion. Additional supportive efficacy data was obtained from BIVV009-03 Part B and BIVV009-01 Part C&E.

The safety of sutimlimab was primarily based on pooled studies consisting of patients with CAD. This included studies BIVV009-01 Parts C (CAD patients only) &E, and BIVV009-03 Part A&B. Additional support for safety was based on pooled healthy volunteer studies (BIVV009-01 Parts A&B, TNT009-02, and BIVV009-05 Part A&B), pooled complement mediated disorder studies (BIVV009-01 part C (non-CAD patients), BIVV009-201 Part A&B), and the ongoing study BIVV009-04 part A&B which is a phase 3, randomized, placebo-controlled, double-blind study with patients with CAD and without a history of a recent blood transfusion.

Table 2. Listing of Clinical Trials Relevant to this BLA

Trial Identity	NCT number	Population	Design	Treatment Dosing	Primary Objectives	Sample Size ¹	Status
Pivotal Study to Support Safety and Efficacy							
BIVV009-03 (Part A and Part B)²	NCT03347396	CAD (recent blood transfusion)	Phase 3, open label, single arm, multicenter study <u>Part B:</u> Extension of Part A with assessment of long term safety	<u>Part A:</u> Sutimlimab fixed 6.5g (<75kg) or 7.5g (≥75kg), dosing at week 0, 7, and every other week to week 25 <u>Part B:</u> Following completion of part A, every 2 weeks (same dosing as Part A) for up to 2 years following the last patient out of Part A	<u>Part A:</u> To determine whether sutimlimab administration results in a ≥ 2 g/dL increase in hemoglobin (Hgb) levels or increases Hgb to ≥ 12 g/dL and obviates the need for blood transfusion during treatment in patients with primary CAD who had a recent history of blood transfusion. <u>Part B:</u> Evaluate	<u>Part A:</u> 24 <u>Part B:</u> 21	<u>Part A:</u> Completed <u>Part B:</u> Ongoing

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Trial Identity	NCT number	Population	Design	Treatment Dosing	Primary Objectives	Sample Size ¹	Status
					the long-term safety and tolerability		
22 sites screened at least one patient, 16 study sites enrolled at least 1 patient: United States, Australia, Germany, France, Italy, Japan, Norway, United Kingdom, Austria, Belgium							
Additional Studies to Support Safety, Efficacy, or PK							
BIVV009-01 (Part A,B,C,E)	NCT02502903	<u>Part A,B:</u> NHV <u>Part C:</u> CMD (BP, AMR, WAIHA, CAD) <u>Part E:</u> CAD and previously treated with sutimlimab	<u>Part A:</u> Phase 1, double-blind, randomized, placebo controlled, single dose <u>Part B:</u> Phase 1, double-blind, randomized, placebo controlled, multiple ascending dose <u>Part C,E:</u> Phase 1, open label	<u>Part A:</u> Single dose Sutimlimab (0.3-100mg/kg) <u>Part B:</u> Weekly dosing x 4 Sutimlimab (30 or 60 mg/kg) <u>Part C:</u> Single dose Sutimlimab of 10mg/kg followed by 4 weekly doses of 60mg/kg <u>Part E:</u> Initially Sutimlimab 5.5g, modified to 6.5g (<75kg) or 7.5g (≥75kg) weekly for the first two doses followed by every other week	Part A,B,C,E: Safety and tolerability of Sutimlimab	<u>Part A:</u> 48 (36 sutimlimab, 12 placebo) <u>Part B:</u> 16 (12 sutimlimab, 4 placebo) <u>Part C:</u> 34 (10 with CAD, 4 with WAIHA, 10 with AMR, 10 with BP) <u>Part E:</u> 4 with CAD	<u>Part A,B,C:</u> Completed <u>Part E:</u> Ongoing
BIVV009-04 (Part A and B)	NCT03347422	CAD (no recent blood transfusion)	<u>Part A:</u> Phase 3, double-blind, randomized, placebo-controlled <u>Part B:</u>	<u>Part A:</u> Sutimlimab 6.5g (<75kg) or 7.5g (≥75kg), dosing at week 0, 1, and every other week to week 25 <u>Part B:</u> Following	Part A: To determine whether sutimlimab administration results in a ≥1.5g/dL increase in hemoglobin level and avoidance of	<u>Part A:</u> 27 <u>Part B:</u> 9	Ongoing

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Trial Identity	NCT number	Population	Design	Treatment Dosing	Primary Objectives	Sample Size ¹	Status
			Phase 3, open label, extension, long term safety	completion of Part A, Sutimlimab 6.5g(<75kg) or 7.5g (≥75kg) every 2 weeks for up to 1 year after the last patient out of part A	transfusion and CAD prohibited medications between week 5 and 26 <u>Part B</u> : Long-term safety and tolerability		
BIVV009-201 (Part A and B)	NCT03275454	Chronic ITP	<u>Part A</u> : Phase 1, open label, single-arm <u>Part B</u> : Phase 1, open label, extension with long term safety	<u>Part A</u> : Sutimlimab fixed 6.5g (<75kg) or 7.5g (≥75kg), dosing at week 0, 7, and every other week for approximately 21 weeks <u>Part B</u> : Sutimlimab 6.5g (<75kg) or 7.5g (≥75kg) biweekly for up to 2 years following completion of last patient included in part B	Safety and tolerability in patients with chronic ITP	<u>Part A</u> : 8 <u>Part B</u> : 4	Ongoing
TNT009-02	--	NHV	Phase 1, randomized, double-blind, controlled parallel group	Sutimlimab 75mg/kg x 4 (days 1, 8, 22, 36)	To assess safety and tolerability of multi-dose sutimlimab in NHVs	18 sutimlimab, 6 placebo	Completed
BIVV009-05	--	NHV	Phase 1, randomized, open label	<u>Part A</u> : Sutimlimab single dose of either 30mg/kg, 60mg/kg, or 100mg/kg <u>Part B</u> : Sutimlimab 6.5 (<75kg) or 7.5g (≥75kg) on day 1, 8, 22	Evaluate the PK of a single-dose and multi-dose sutimlimab in healthy Japanese subjects	<u>Part A</u> : 18 <u>Part B</u> : 12	Completed

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¹sample size is based on number of treated patients at the initial data cut-off

²Pivotal study includes Part A of BIVV009-03. Part B of BIVV009-03 is supportive.

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5.2. Review Strategy

The FDA clinical and statistical review consisted of one primary clinical reviewer and one primary statistical reviewer.

The review of efficacy was based on the analysis of study BIVV009-03 Part A.

The review of safety was based primarily on the analysis of study BIVV009-03 Part A and B, and BIVV009-01 Parts C (patients with CAD) and E. Supportive safety analysis is based on the analysis of studies from healthy volunteers (BIVV009-01 Part A and B, TNT009-02, and BIVV009-05) and patients with other CMDs (Studies BIVV009-01 Part C with non-CAD indications and BIVV009-201).

The Applicant submitted this BLA to the FDA Center for Drug Evaluation and Research (CDER) Electronic Document Room. The data included in this submission are in electronic Common Technical Documents Format, in accordance with FDA guidance on electronic submission. The datasets were well documented and included definition files.

The key materials used for the review of efficacy and safety include the following:

- BLA 761164 including; clinical study report (CSR), patient narratives, protocol and amendments, statistical analysis plan (SAP) and amendments, and data sets are located at: <\\CDSESUB1\evsprod\BLA761164\0002>
- Relevant published literature
- Relevant information in the public domain

Clinical data was provided in Study Data Tabulation Model (SDTM) and Analysis Data Model Implementation (ADaM). The clinical and statistical reviewers were able to duplicate the analysis based on the Applicant's submitted datasets.

Summaries of the data and analysis by the reviewer were performed using JMP 14.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. Study BIVV009-03 Part A (CARDINAL)

6.1.1. Study Design

Overview and Objective

Trial Name: A Phase 3 Pivotal, Open-Label, Multicenter Study to Assess the Efficacy and Safety of BIVV009 in Patients with Primary Cold Agglutinin Disease Who Have a Recent History of

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Blood Transfusion (CARDINAL)

The purpose of this study was to provide pivotal efficacy and safety data for the evaluation of sutimlimab for patients with primary CAD and a recent blood transfusion.

Study initiation: March 5th, 2018

Study completion: July 11th, 2019 (Part A)

Primary Objective

- To determine whether sutimlimab administration resulted in a ≥ 2 g/dL increase in hemoglobin levels or increased hemoglobin to ≥ 12 g/dL and obviated the need for blood transfusion during treatment in patients with CAD who had a recent blood transfusion.

Secondary Efficacy Objectives:

- To assess the effect of sutimlimab on clinical events and laboratory parameters related to hemolysis and anemia in patient with CAD
- To assess the effect of sutimlimab on quality of life (QOL) in patients with CAD

Exploratory objectives:

- To assess the effect of sutimlimab on specific complications of CAD including; acrocyanosis, Raynaud's syndrome, hemoglobinuria, and thromboembolism
- To evaluate the effect of sutimlimab on certain disease-related biomarkers in patients with CAD
- To evaluate the pharmacokinetics of sutimlimab

Trial Design

Study BIVV009-03 (CARDINAL study) is an open-label, single-arm, 2-part study designed to evaluate the efficacy, safety, and tolerability of sutimlimab in patients with CAD and a recent history of blood transfusion in Part A. Part B is ongoing and will evaluate the long-term safety, tolerability and durability of response of sutimlimab in patients with CAD.

In the study, which includes part A only, 24 patients with a diagnosis of CAD who had at least one blood transfusion in the previous 6 months prior to enrollment were enrolled. Patients were administered sutimlimab IV of either 6.5g (if <75 kg) or 7.5g (if ≥ 75 kg) on days 0, 7, and biweekly thereafter, to day 175 (week 25). Patients who missed a dose (>17 days) received an additional loading dose. End of treatment was defined as day 182 (week 26).

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The dose regimen used in this study was based on the population PK model from studies BIVV009-01 (Part A,B&C) and BIVV009-02, in order to maintain complement pathway inhibition at the minimum concentration.

Patients received blood transfusions as needed based on predefined criteria (Table 3).

Table 3. Transfusion Criteria

A patient was to receive a transfusion during Part A or Part B if his or her hemoglobin level met either of the following criteria:

- The hemoglobin level was <9 g/dL, and the patient was symptomatic.
 - The hemoglobin level was <7 g/dL, and the patient was asymptomatic.
-

Source: Table 1 of Applicant's CSR

Beyond the permitted concomitant medications, study drug, and transfusions, patients were not allowed to receive other therapies for the treatment of CAD while on study. Prohibited therapies included rituximab monotherapy or rituximab combination therapies (bendamustine, fludarabine, ibrutinib or cytotoxic agents). Erythropoietin and or steroids (equivalent to ≤ 10 mg/day of prednisone) were acceptable as long as patients had been on a stable dose for the previous 3 months.

The study included patients ≥ 18 years of age with a confirmed diagnosis of CAD based on the following criteria; chronic hemolysis, polyspecific direct antiglobulin test (DAT) positive, monospecific DAT strongly positive for C3d, cold agglutinin titer ≥ 64 at 4°C, and IgG DAT $\leq 1+$. In addition, patients must have had at least one blood transfusion in the preceding 6 months and hemoglobin ≤ 10 g/dL. Lastly, patients were symptomatic defined as the presence of 1 or more signs or symptoms within 3 months of screening; symptomatic anemia, acrocyanosis, Raynaud's syndrome, hemoglobinuria, disabling circulatory symptoms, and major adverse vascular events. Patients had a bone marrow biopsy 6 months prior to screening and were included if there was no overt evidence of lymphoproliferative disease or other hematological malignancy. Patients were excluded if they had cold agglutinin syndrome secondary to infection, rheumatologic disease or active hematologic malignancy.

The following immunizations were required within 5 years prior to enrollment; Neisseria meningitidis (including serogroup B meningococcus where available), Hemophilus influenzae, and Streptococcus pneumoniae.

A total of 22 sites screened at least one patient and 16 sites enrolled at least one patient from 8 countries (Australia, Germany, France, Italy, Japan, Norway, United Kingdom and the United States).

Table 4. Schedule of Events for Study BIVV009-03 Part A.

Study visit (week/day)	Screening/ Observation Period ^a	Baseline	Part A		Part B extension phase	ET/EOS/Safety Follow-up ^b
			Weeks 1–25			
			Weeks 1–25	Week 26 (EOT)		
	Days -42, -28, and -14	Day 0	Days 7, 21, 35, 49, 63, 77, 91, 105, 119, 133, 147, 161, 175	Day 182	Every 2 weeks after Week 25	9 weeks after the last dose
Visit windows	±3 days	N/A	±2 days	±2 days	±2 days	±2 days
Written informed consent	X					
Demographic and baseline characteristics	X					
Detailed medical history	X					
Inclusion/exclusion criteria	X	X				
Immunization review/vaccination ^c	When applicable, vaccinations should be initiated on Day -42 or as soon as possible during Screening. The primary vaccine series should be completed during Screening when possible and otherwise prior to Week 5 of Part A.					
Bone marrow biopsy report review ^d	X					
Optional bone marrow testing for MYD88 status for consenting patients	X					
Pregnancy test (if applicable) ^e	X	X	X (Prior to study drug infusion on Days 21, 49, 77, 105, 133, and 161) ^e	X	X ^e	X
Body weight and height ^f	X	X		X	X ^f	X
Physical examination, full	X			X		X
Physical examination, brief		X	X		X ^f	
Vital signs (BP, PR, RR, body temperature) ^g	X	X	X	X	X ^f	X
12-lead electrocardiogram (predose and 1 hour after infusion on dosing days)	X	X	X (Day 91 only)		X ^o	
Virology/serology panel ^h	X					
Gilbert's syndrome test (UGT1A1 gene)	X					
SLE panel ^h	X			X		X
Iron panel and erythropoietin ^h	X					

Study visit (week/day)	Screening/ Observation Period ^a	Baseline	Part A		Part B extension phase	ET/EOS/Safety Follow-up ^b
			Weeks 1–25			
			Weeks 1–25	Week 26 (EOT)		
	Days -42, -28, and -14	Day 0	Days 7, 21, 35, 49, 63, 77, 91, 105, 119, 133, 147, 161, 175	Day 182	Every 2 weeks after Week 25	9 weeks after the last dose
Visit windows	±3 days	N/A	±2 days	±2 days	±2 days	±2 days
Hematology panel ^h	X	X	X	X	X	X
Coagulation panel ^h	X	X		X		X
Clinical chemistry panel ^h	X	X	X	X	X	X
Urinalysis ^h	X	X		X	X ^f	X
FACIT-Fatigue ^g		X	X	X	X ^f	X
PGIS ^g		X	X (Days 35, 77, and 119 only)	X	X ^f	X
PGIC ^g		X	X (Days 35, 77, and 119 only)	X	X ^f	X
SF-12 ^g		X	X (Days 35, 77, and 119 only)	X	X ^f	X
EQ-5D-5L ^g		X	X (Days 49, 91, and 133 only)	X	X ^f	X
Solicited symptomatic anemia	X (Day -42 only)	X	X	X	X	X
Study drug administration ⁱ		X	X		X	
ADAs against sutimlimab		X				X
PK samples ^j		X	X	X	X ^f	X
PD samples ^{h,j}	X ^m	X	X	X	X ^f	X
Disease-related biomarkers ^h	X	X	X ⁿ (Day 91 only)	X		
Prior and concomitant medications, including transfusions	X	X	X	X	X	X
Healthcare resource utilization	X	X	X (Days 21, 49, 77, 105, 133, and 161)	X	X ^p	X
Adverse events ^k	X	X	X	X	X	X

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ADA=antidrug antibodies; BP=blood pressure; EOS=End of Study; EOT=End of Treatment; EQ-5D-5L=5-Level EuroQol 5 Dimensions Questionnaire; SF-12=12-Item Short Form Survey; ET=Early Termination visit; FACIT=Functional Assessment of Chronic Illness Therapy; N/A=not applicable; PD=pharmacodynamic; PGIC=Patient's Global Impression of Change; PGIS=Patient's Global Impression of [Fatigue] Severity; PK=pharmacokinetic; PR=pulse rate; QOL=quality of life; RR=respiratory rate; SLE=systemic lupus erythematosus

- a The 6-week Screening/Observation Period could be extended by 1 week for patients requiring a blood transfusion prior to study drug administration.
- b Patients were to return to the site 9 weeks after the last dose for ET procedures, EOS assessment, or Safety Follow-up procedures upon the completion of dosing in the study. If a patient experienced a hematologic breakthrough event, a PK, PD, and ADA sample was collected at the time of the event.
- c Applicable to patients who did not have documented vaccination against encapsulated bacterial pathogens within 5 years of enrollment. A blood sample for vaccine titers was collected on Day 0 prior to study drug infusion to be used to determine serum relevant antibody titers should the patient be diagnosed with an infection associated with an encapsulated organism during the course of the study. A second sample was collected during the study period if the patient presented with symptoms of infection.
- d Prior bone marrow biopsy report review, prior tissue assessment, or new bone marrow biopsy (as applicable). Sites were to submit deidentified biopsy reports to an independent central reader for eligibility adjudication. If the biopsy was deemed unsuitable or insufficient to determine eligibility, either prior tissue could be submitted for additional hematopathology assessment or a new bone marrow biopsy was performed during the Screening Period.
- e Females of childbearing potential only. Serum pregnancy test was performed at Screening. Serum or urine pregnancy test was to be performed on Days 0, 21, 49, 77, 105, 133, and 161 and at Week 26/EOT or at the ET Visit. Serum or urine pregnancy test is repeated every 4 weeks during Part B.
- f Height was measured at Screening only. Body weight is measured every 3 months during Part B.
- g Vital signs measurements (supine BP, PR, RR, and oral temperature) were to be obtained at Screening and at each subsequent visit, with measurements performed predose and 1 hour (± 5 minutes) after the completion of administration of each dose of study drug.
- h For a complete list of analytes, see 16-1-1-protocol [Appendix A].
- i Sutimlimab doses of 6.5 g (if <75 kg) or 7.5 g (if ≥ 75 kg) based on the patient's baseline body weight were administered via IV infusion over approximately 60 ± 5 minutes on Day 0, Day 7, and every 14 days thereafter during Part A and every 2 weeks starting at Week 27 during Part B. Patients with underlying cardiopulmonary disease could receive a 2-hour infusion with Sponsor approval. If a patient missed a scheduled dose (outside of the 2-day window or >17 days since the last dose), he or she was required to return to the site (unscheduled visit) to receive another loading dose 1 week prior to the next scheduled dose.
- j During Part A, PK and PD samples were collected at predose and 1 hour (± 15 minutes) postdose (ie, 1 hour after the completion of study drug infusion) from all patients on Days 0, 7, 21, 35, 49, 63, 77, 91, 105, 119, 133, 147, 161, and 175. An additional blood sample for PK and PD analysis was collected during the EOT visit on Day 182 or at ET if a patient withdrew early. During Part B, PK and PD samples were collected routinely at 3-month intervals. PK and PD samples were also collected if a patient experienced a hematologic breakthrough event at any point during the study.
- k AEs were recorded from the time the patient signed the informed consent form until 9 weeks after administration of the last dose of study drug.
- l Performed every 3 months.
- m Refer to the Laboratory Manual for details of sample collection during Screening.
- n Samples were collected for a subset of the disease-related biomarkers at Day 91 only. Refer to the Laboratory Manual for details.
- o During Part B, a 12-lead ECG was conducted predose and postdose at 3 months (Day 273).
- p During Part B, the healthcare resource utilization data were recorded every 4 weeks.
- q Performed in the following order: FACIT-Fatigue first, PGIS second, PGIC third, SF-12 fourth, and EQ-5D-5L fifth.

Source: Table 2 of Applicant's CSR

Reviewer comment:

A control group was not included in the study. This was determined to be acceptable prior to the BLA submission given the stringent composite efficacy endpoints and lack of available effective therapies for a patient population that is symptomatic and requiring blood transfusions. The CAD patient population while mostly enrolled in Europe, has similar characteristics to the US population. The inclusion criteria clearly defined a symptomatic patient population with CAD and in need of therapy for hemolytic anemia. Diagnostic criteria for CAD used in the study is consistent with what is widely accepted as diagnostic for CAD in the community.

Study Endpoints

Primary Endpoint

The primary efficacy endpoint was responder rate, which was a composite endpoint. A patient was considered a responder if he or she did not receive a blood transfusion from Week 5 through Week 26 (end of treatment) and did not receive treatment for CAD beyond what was permitted per protocol. Additionally, the patient's Hgb level must have met either of the following criteria:

- Hgb level ≥ 12 g/dL at the treatment assessment endpoint (defined as the mean value from Weeks 23, 25, and 26) or
- Hgb level increased by ≥ 2 g/dL from baseline (defined as the last hemoglobin value

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before administration of the first dose of study drug) at the treatment assessment endpoint.

Secondary Endpoints

- Mean change from baseline in bilirubin (excluding patients with Gilbert's syndrome) at the treatment assessment endpoint (defined as the mean value of Weeks 23, 25, and 26)
- Mean change from baseline in QOL, as assessed by the change in FACIT-F scale scores at the treatment assessment endpoint
- Mean change from baseline in lactate dehydrogenase (LDH) at the treatment assessment endpoint
- Number of transfusions and number of units after the first 5 weeks of study drug administration
- Mean change from baseline in hemoglobin at the treatment assessment endpoint

Exploratory Endpoints

- Time to first transfusion after the first 5 weeks
- Multiple endpoints considering QOL measures
- Incidence of solicited symptomatic anemia at EOT (end of treatment)
- Proportion of patients with hemoglobin level >12 g/dL at EOT
- Median time to normalization and proportion of patient with normalization of bilirubin, LDH, and haptoglobin
- Incidence of hemolytic breakthrough

Clinical reviewer comment: The reviewer agrees that the primary composite endpoint of responder rate represents clinical benefit. All three components (hemoglobin increase, transfusion independence, and not receiving other therapies for CAD) are equally important to assessing the response to sutimlimab. Inclusion of primary and secondary endpoints in the USPI was based on robustness of results and on the number of evaluable patients. Interpretation of PROs is limited given the open-label design and lack of a comparator arm, and therefore was not included in the USPI.

Statistical Analysis Plan

Sample Size and Power Considerations

It was planned that approximately 20 patients with CAD who had a recent history of transfusion would be enrolled (24 were actually enrolled). If the true responder rate was estimated to be 66% and a minimum of 30% was required for success, then with 20 patients there was 90% probability that the lower limit of the 95% CI was at least 30%.

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Analysis Populations

- Full analysis set (FAS) included all patients who received at least 1 dose (including partial dose) of study drug. Efficacy analysis was performed on the FAS.
- Per-protocol (PP) set included a subset of FAS patients who did not have any important protocol deviations impacting efficacy assessments.
- Safety analysis set included patients who received at least 1 dose (including partial dose) of study drug.
- PK analysis set included all patients who received at least one dose of study drug and had at least 1 evaluable sample for baseline and PK concentrations.
- PD (pharmacodynamic) analysis set included all patients who received at least one dose of study drug and had at least 1 evaluable sample for baseline and PD concentrations.

Analyses of the Primary Efficacy Endpoint

Efficacy analyses were performed on the FAS. Each patient in the FAS population was classified as meeting the criteria of the primary endpoint (responder) or not meeting the criteria of the primary endpoint (non-responder). The 95% CI for the proportion of responders was calculated using Clopper-Pearson exact method. Any patient withdrawing from the study prior to the Week 23 visit was considered a non-responder.

The primary analysis of the primary endpoint was based on the Composite Estimand, for which any missing response was considered a non-responder. Sensitivity analyses were carried out based on the Completer Estimand and the Per-protocol Estimand, respectively. Subgroup analyses for the primary endpoint were performed by age (<65 and ≥65 years), gender, baseline weight (<75 and ≥75 kg), number of transfusions within 12 months prior to study entry (≤2, 3-4, >4), baseline hemoglobin level (<8.5 and ≥8.5 g/dL), and previous rituximab therapy and/or cytotoxic therapy (yes/no). For these analyses, if there were <5 patients in a category, the cutoff may have been adjusted.

Analyses of Secondary Efficacy Endpoints

All secondary efficacy endpoints (change from baseline in hemoglobin, bilirubin, LDH, and FACIT-Fatigue) were analyzed using the Mixed Model for Repeated Measures (MMRM) at the treatment assessment endpoint. Analyses were performed based on the Hypothetical Estimand and the De-facto Estimand, respectively. Additional sensitivity analyses were carried out using multiple imputations.

Clinical reviewer comment: The Agency agreed with the SAP and agreed that it would be overall clinically meaningful if the responder rate was ≥30% of patients

Protocol Amendments

There were 5 global amendments and 5 country specific amendments. Only Amendments 4 and
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5 were implemented after patients were enrolled, see Table 5.

Table 5. Protocol Amendments

4 Global	29 June 2018	• Added the PGIS [Fatigue] as a QOL assessment at the request of the US FDA. • Increased the frequency of sample collection for PK and PD assessments. Specified that PK and PD samples were to be collected predose and 2 hours (± 15 minutes) postdose (1 hour after the completion of study drug infusion) from all patients on Days 0, 7, 21, 35, 49, 63, 77, 91, 105, 119, 133, 147, 161, and 175. An additional blood sample for PK and PD analysis was to be collected during the EOT visit on Day 182 or at ET if a patient withdraws early. • Added that "documentation" of all vaccinations was required in text where it was not previously included • Added the vaccine schedule for Japan as an appendix. • Changed the PGIC assessment from every 6 months to every 3 months in Part B to coincide with the timing of PGIS assessments.
5 Global	17 July 2018	• Clarification as to how data corrections would be shown • Changed PK and PD postdose sample collection time from 2 hours to 1 hour postdose

Source: Table 4 of Applicant's CSR

After database lock, additional analyses were performed to further evaluate the effects of sutimlimab in the FAS population, regardless whether patients met the criteria for the primary endpoint. These additional analyses inform the efficacy profile across the study population beyond the definition of the primary endpoint.

- Mean change in hemoglobin from baseline to the treatment assessment endpoint by threshold (≥ 1 g/dL, ≥ 1.5 g/dL, ≥ 2 g/dL, and ≥ 3 g/dL)
- Number of patients with either a mean change from baseline in hemoglobin ≥ 1 g/dL or normalized total bilirubin for at least half times of the post-baseline visits and the number of patients meeting both criteria
- Number of patients with LDH $\leq 1.5 \times$ ULN at the treatment assessment endpoint
- Separate analyses of the change in hemoglobin levels in patients who met the criteria of the primary endpoint and in patients who did not meet the criteria of the primary endpoint

Clinical reviewer comment: Protocol amendments were minor and did not impact the integrity of the trial.

6.1.2. Study Results

Compliance with Good Clinical Practices

The Applicant provided a statement that the study was conducted in accordance with consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki, and the International Council for Harmonization (ICH) Guidelines for Good Clinical Practice (GCP), all applicable laws, rules, and regulations. The protocol and

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amendments were submitted to Independent Ethics Committees and/or Institutional Review Boards for review and written approval.

Financial Disclosure

The Applicant adequately disclosed financial interests/arrangements with clinical investigators for protocol BIVV009-03. There were 78 clinical investigators who screened at least one patient. Two investigators self-disclosed financial interests. Dr. [REDACTED] self-disclosed research and education grant in the financial disclosure form. Dr. [REDACTED] self-disclosed travel and scientific advice. Despite a financial search this could not be reconciled.

The Applicant took appropriate measures to prevent potential bias. This included;

- Additional screening tests may have been repeated at the discretion of the principal investigator
- Upon completion of screening assessments, the site compiled de-identified, key eligibility data for each patient and sent to the medical monitor for review and confirmation of eligibility prior to study enrollment
- Each component of the primary efficacy endpoint was subject to source document verification by the Clinical Research Associate
- Key secondary endpoints were measured by a vendor laboratory, independently from the PI
- PK/PD assays were not disclosed to investigators
- The study does not have a comparator

Clinical comment: The financial disclosures likely did not affect the integrity of this application given the measures the Applicant took to minimize bias and the distribution of patient across multiple sites.

Patient Disposition

A total of 24 patients received at least one dose (full or partial) of sutimlimab and were included in the Safety and Full Analysis Sets. Two patients were excluded from the PP Analysis Set due to protocol deviations.

Of the total 24 patients, twenty-two (91.7%) of the treated patients completed Part A (16 of 17, 94.1% and 6 of 7, 85.7%] in the 6.5 g and 7.5 g groups, respectively) and 22 of the treated patients are continuing in Part B. Of the 2 patients who did not complete Part A, 1 patient in the 7.5 g group discontinued from the study due to death on Day 32 from a fatal treatment-emergent SAE of hepatic cancer that was diagnosed on Day 22 and 1 patient in the 6.5 g group discontinued due to a pretreatment SAE of polymyalgia rheumatica that started on Day -8.

Patient disposition is summarized in Table 6 and includes details regarding completion status and reasons for discontinuation.

Table 6. Patient Disposition

Disposition Status	Dose: 6.5g (N=17)	Dose: 7.5g (N=7)	Total (N=24)
Analysis Sets; n (%)			
Safety Analysis Set	17 (100)	7 (100)	24 (100)
Full Analysis Set	17 (100)	7 (100)	24 (100)
Per-protocol Set	16 (94.1)	6 (85.7)	22 (91.7)
Completion Status; n (%)			
Completed Part A	16 (94.1)	6 (85.7)	22 (91.7)
Discontinued Part A	1 (5.9)	1 (14.3)	2 (8.3)
Adverse event	1 (5.9)	0	1 (4.2)
Death	0	1 (14.3)	1 (4.2)

Source: Statistical Reviewer

Protocol Violations/Deviations

Major protocol deviations occurred in 10 (41.7%) of patients. Two patients had deviations that could impact efficacy; one patient missed two consecutive doses (weeks 24 and 25) and the other patient missed the week 23, 25, 26 assessment. These two patients were excluded from the PP analysis set.

Four patients did not receive transfusions as planned, including 2 patients with study conduct deviations and 2 patients as part of visit procedures. None of these patients met the primary endpoint.

Five patients had safety deviations including; SAE not reported within 24 hours for 3 patients, transfusion given to 1 patient who was symptomatic but had a hemoglobin value of 9.1 g/dL (i.e., not <9.0 g/dL), and HIB vaccination not given until after Week 5. One of the patients had an SAE (pneumonia) during the screening period, which was not reported within 24 hours. The SAE would have resulted in the patient meeting exclusion criteria if it had been reported.

Two patients missed scheduled visits. One patient missed the Week 25 visit (visit schedule error) and 1 patient missed the Week 9 visit due to an SAE.

*Clinical comment: Patients who had protocol violations were included in the FAS. Based on the CDER Clinical Review Template
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type of violations (incomplete data), this was unlikely to impact the primary efficacy results and this was evenly balanced between responder and non-responder group. While four patients did not receive transfusions as indicated by the predefined criteria, none of the patients had met the primary efficacy endpoint and therefore does not impact the efficacy conclusions.

Table of Demographic Characteristics

Overall, patients had a median age of 71.5 years (range 55 to 85), and most patients were ≥65 years old (19, 79.2%) and female (15, 62.5%). Race and ethnicity were not reported for 18 patients due to local laws. Of the 6 patients with race and ethnicity data; 3 were Asian, 3 were white, and none were Hispanic or Latino. Most of the patients were from Europe (17, 70.8%). This study utilized the weight-based dosing strategy. As specified per protocol, all patients in 6.5 g arm had baseline weight <75 kg and all patients in the 7.5 g group had baseline weight ≥75 kg. Demographic characteristics of patients enrolled are summarized in Table 7.

Table 7. Demographic Characteristics (Full Analysis Set)

Demographic Characteristic	Dose: 6.5g (N=17)	Dose: 7.5g (N=7)	Total (N=24)
Age (years)			
Mean (SD)	71.8 (9.05)	70.1 (6.01)	71.3 (8.18)
Median	72.0	70.0	71.5
Min, Max	55, 85	63, 77	55, 85
Age Group (years), n (%)			
<65 years	3 (17.6)	2 (28.6)	5 (20.8)
≥65 years	14 (82.4)	5 (71.4)	19 (79.2)
Sex, n (%)			
Female	11 (64.7)	4 (57.1)	15 (62.5)
Male	6 (35.3)	3 (42.9)	9 (37.5)
Race, n (%)			
Asian	3 (17.6)	0	3 (12.5)
White	2 (11.8)	1 (14.3)	3 (12.5)
Black or African American	0	0	0
Not collected ¹	12 (70.6)	6 (85.7)	18 (75.0)
Ethnicity, n (%)			
Hispanic or Latino	0	0	0
Not Hispanic or Latino	5 (29.4)	1 (14.3)	6 (25.0)
Not collected ¹	12 (70.6)	6 (85.7)	18 (75.0)
Region, n (%)			
Europe	12 (70.6)	5 (71.4)	17 (70.8)

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North America	2 (11.8)	1 (14.3)	3 (12.5)
Asia	3 (17.6)	0	3 (12.5)
Other	0	1 (14.3)	1 (4.2)

¹ Data on race and/or ethnicity were not collected because of local regulations.

Source: Table 8 of Applicant's CSR and confirmed by statistical reviewer

Clinical review comment: Patients were older (median age 71.5 years) and more patients were female, this is consistent with the historical CAD population. Race and ethnicity were largely unknown because of restrictions from local regulations. Most patients were from Europe, but 12.5% of patients were from the US.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Table 8. Other Baseline Characteristics

Demographic Characteristic	Dose: 6.5g (N=17) n (%)	Dose: 7.5g (N=7) n (%)	Total (N=24) n (%)
Hospitalization due to CAD in previous 2 years	11 (64.7)	5 (71.4)	16 (66.7)
CAD-related anemia symptoms¹			
Fatigue	16 (100)	6 (100)	22 (100)
Weakness	13 (81.3)	5 (83.3)	18 (75)
Shortness of breath	13 (81.3)	4 (66.7)	17 (77.3)
Palpitations	8 (50)	3 (50)	11 (50)
Light headedness/presyncope	3 (18.8)	0 (0)	3 (13.6)
Chest pain	3 (18.8)	0 (0)	3 (13.6)
CAD-related disease characteristics¹			
Acrocyanosis	4 (25)	1 (16.7)	5 (22.7)
Raynaud's syndrome	2 (12.5)	1 (16.7)	3 (13.6)
Hemoglobinuria	8 (50)	0 (0)	8 (35.4)
Disabling circulatory symptoms	0 (0)	0 (0)	0 (0)
Major adverse vascular event (including thrombosis)	2 (12.5)	1 (16.7)	3 (13.6)
Transfusion in the last 6 months			
Number of transfusions			
Mean	3	3.7	3.2
Median	1	2	2
Min, Max	1, 19	1, 9	1, 19
Targeted prior therapy within 5 years	10 (58.8)	5 (71.4)	15 (62.5)

Demographic Characteristic	Dose: 6.5g (N=17) n (%)	Dose: 7.5g (N=7) n (%)	Total (N=24) n (%)
Rituximab single agent	7 (41.2)	4 (71.4)	12 (50)
Corticosteroids	8 (41.7)	2 (28.6)	10 (41.7)
Bendamustine/Rituximab	2 (11.8)	2 (28.6)	4 (16.7)
Bortezomib	2 (11.8)	1 (14.3)	3 (12.5)
Cyclophosphamide	1 (5.9)	1 (14.3)	2 (8.3)
Fludarabine/Rituximab	2 (11.8)	0 (0)	2 (8.3)
CHOP-R	1 (5.9)	0 (0)	1 (4.2)
Ibrutinib single agent	0 (0)	1 (14.3)	1 (4.2)
Plasmapheresis	0 (0)	1 (14.3)	1 (4.2)

[†]CAD related anemia symptoms and CAD-related disease characteristics were based on day -42 assessment, collecting data from the previous 3 months and included 22 patients.

Source: Adapted from Applicant's CSR

Clinical reviewer comment: While all patients met the inclusion criteria of receiving a transfusion in the previous 6 months, the median number of transfusions was 2, indicating that this patient population did not have a high transfusion burden at the time of enrollment. Although, most patients (62.5%) received prior therapy in the previous 5 years.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

All patients were $\geq$ 85% compliant. In total, 10/24 (41.7%) of patients received at least 1 dose out of window.

The most commonly used concomitant medications were drugs to prevent or treat anemia 15/24 (62.5%) and drugs for acid related disorders 15/24 (62.5%). Medications to prevent or treat anemia included; folic acid, vitamin B12, cyanocobalamin, darbepoetin alfa, epoetin beta, and iron preparations. Other concomitant medications included antithrombic agents 14/25 (58.3%), antibacterial for systemic use 9/24 (37.5%), and corticosteroids for systemic use 6/24 (25%).

Clinical comment: Concomitant medications are unlikely to impact efficacy results. Only one patient each were taking darbepoetin alpha, epoetin beta, and iron preparations. These medications were unlikely to impact hemoglobin level or need for transfusions as these were therapies patients were taking prior to starting the study and on a stable dose. Corticosteroids were used in 25% of patients, corticosteroids are typically not effective in treating CAD.

Efficacy Results – Primary Endpoint

Primary Endpoint Analysis

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The primary endpoint was defined as the proportion of patients that met the responder definition. Patients were classified as a responder if they met the following criteria; no blood transfusion between week 5 to 26 and no treatment for CAD beyond what was permitted per protocol. In addition, achieved a hemoglobin level ≥ 12 g/dL or an increase from baseline in hemoglobin ≥ 2 g/dL at the treatment endpoint (mean value from week 23, 25, and 26).

Among the 24 patients in the Full Analysis Set, 13 patients met the composite primary endpoint criteria and the lower bound of the response rate was $>30\%$ (54.2%, 95% CI: 32.8% to 74.4%), a predefined efficacy threshold.

Seventeen (70.8%) patients remained transfusion free from Week 5 to Week 26 and none received a prohibited CAD medication. At the treatment assessment endpoint, 9 (37.5%) patients had normalized hemoglobin (≥ 12 g/dL) and 15 (62.5%) patients had a ≥ 2 g/dL increase in hemoglobin, and 15 (62.5%) patients had either a ≥ 2 g/dL increase or normalization of hemoglobin.

Table 9. Summary of Primary Endpoint (Full Analysis Set)

	N=24
Response Rate	
n (%)	13 (54.2)
(95% CI)	(32.8, 74.4)
Components of the Primary Endpoint	
Subjects with either Hgb ≥ 12 g/dL or increased ≥ 2 g/dL from baseline at treatment assessment timepoint, n (%)	15 (62.5)
Subjects with Hgb ≥ 12 g/dL at treatment assessment timepoint, n (%)	9 (37.5)
Subjects with Hgb increased ≥ 2 g/dL from baseline at treatment assessment timepoint, n (%)	15 (62.5)
Subjects free of transfusions during Week 5 to Week 26 (EOT), n (%)	17 (70.8)
Subjects receiving no protocol prohibited CAD medications during Week 5 to Week 26 (EOT), n (%)	22 (91.7)

Source: Statistical Reviewer

Subgroup Analysis of the Primary Endpoint

The responder rate results by age, gender, and baseline weight are presented in Table 10 shown below. All results from the subgroups are descriptive.

Table 10. Response Rate by Age, Gender, Race and Region

Subgroup	Responder (%)	95% CI
Age		

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≤65 (n=5)	3 (60)	(14.7, 94.7)
>65 (n=19)	10 (52.6)	(28.9, 75.6)
Gender		
Male (n=9)	2 (22.2)	(2.8, 60.0)
Female (n=15)	11 (73.3)	(44.9, 37.7)
Race		
Asian (n=3)	2 (66.7)	(9.4, 99.2)
White (n=3)	3 (100.0)	(29.2, 100.0)
Black (n=0)	0 (0)	(NA, NA)
Not collected (n=18)	8 (44.4)	(21.5, 69.2)
Region		
Europe (n=17)	8 (47.1)	(23.0, 72.2)
North America (n=3)	3 (100.0)	(29.2, 100.0)
Asia (n =3)	2 (66.7)	(9.4, 99.2)
Other (n=1)	0 (0)	(NA, NA)

Source: Statistical Reviewer

Clinical Reviewer Comment: The primary endpoint was met in 54.2% of patients and the lower bound response rate was >30%. This is clinically meaningful in a patient population who are symptomatic from their disease, had a recent transfusion, and no approved therapies. It is worth noting that 5 of the 11 patients who did not meet the primary endpoint possibly had evidence of some treatment response. Four patients had an increase in hemoglobin level $\geq 1\text{g/dL}$ and one patient had an increase in hemoglobin level $>2\text{g/dL}$ and reached a hemoglobin level $\geq 12\text{ g/dL}$, without transfusions beyond week 15. Most patients (70.8%) became transfusion independent, not receiving a blood transfusion between week 5 to 26. Also, 15 of the 24 (62.5%) patients had an increase in hemoglobin of $\geq 2\text{g/dL}$.

There were no significant differences in the subgroup analysis with the exception for gender. Only 2 out of 9 males met the primary endpoint (22.2%) compared to 11 out of 15 (73.3%) of females. Results of the subgroup analysis are difficult to interpret given the small sample size and data could be unbalanced.

Data Quality and Integrity

There are no concerns regarding the submitted data quality or integrity that raise questions about the reported efficacy results.

Efficacy Results – Secondary and other relevant endpoints

A. Mean change from baseline in bilirubin levels

Table 11 displays the statistical reviewer’s analysis results for mean change from baseline in bilirubin (umol/L) at treatment assessment timepoint. Patients with Gilbert’s syndrome were excluded. Among 14 patients with evaluable baseline and treatment assessment endpoint bilirubin values, the mean was 55.26 µmol/L (2.7x ULN) at baseline and 15.48 µmol/L (0.8x ULN) at the treatment assessment endpoint. The LS mean change in bilirubin at the treatment assessment endpoint was reduction of -38.18 umol/L (95% CI: -42.52 to -33.84). The sponsor also states that decreases in mean bilirubin were observed at week 1, with mean bilirubin levels maintained below the ULN from week 3 through the treatment assessment timepoint.

Table 11. Summary of Change from Baseline in Bilirubin (umol/L) at Treatment Assessment Timepoint – Full Analysis Set

	N=14
Baseline mean	55.26
Mean at assessment timepoint	15.48
LS Mean for change from baseline, 95% CI	-38.18 (-42.52, -33.84)

Source: Statistical Reviewer

B. Mean Change from Baseline in FACIT-F Score

Table 12 displays the statistical reviewer’s analysis results for mean change from baseline in FACIT-Fatigue score at treatment assessment timepoint. Among 17 patients with evaluable baseline and treatment assessment endpoint FACIT-F values, the mean score was 31.24 at baseline and 44.26 at the treatment assessment endpoint, a mean increase of 13.03 points. The LS mean change at the treatment assessment endpoint was an increase of 10.85 points (95% CI: 8.00 to 13.70). A 3-10 point increase in FACIT-F score was considered clinically meaningful by the Applicant, this was achieved in at least 75% of patients. Increase in FACIT-F scores were observed beginning at Week 1 that continued through week 5 and were maintained through the treatment assessment endpoint.

Table 12. Summary of change from baseline in FACIT-Fatigue score at treatment assessment timepoint – Full Analysis Set

	N=17
Baseline mean	31.24
Mean at assessment timepoint	44.26
LS Mean for change from baseline, 95% CI	10.85 (8.00, 13.70)

Source: Statistical reviewer

C. Mean change from baseline in lactate dehydrogenase

Table 13 displays the statistical reviewer’s analysis results for mean change from baseline in lactate dehydrogenase (U/L) at treatment assessment timepoint. The normal range for LDH was

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120-246 U/L. Among 17 patients with evaluable baseline and treatment assessment endpoint LDH values, the mean LDH was 424.06 U/L (1.7x ULN) at baseline and 301.91 U/L (1.2x ULN) at the treatment assessment endpoint. The LS mean change in LDH at the treatment assessment endpoint was reduction of -126.95 (95% CI: -218.47 to -35.42). The sponsor states LDH values were variable across patients. Mean decrease in LDH was observed starting week 1.

Table 13. Summary of change from baseline in lactate dehydrogenase (U/L) at treatment assessment timepoint – Full Analysis Set

	N=17
Baseline mean	424.06
Mean at assessment timepoint	301.91
LS Mean for change from baseline, 95% CI	-126.95 (-218.47, -35.42)

Source: Statistical reviewer

D. Transfusions received before and after initiating sutimlimab treatment

Table 14 displays descriptive statistics which showed that the number of transfusions administered and the number of patients receiving transfusions were reduced for the periods from the baseline with the first dose to Week 5, and from Week 5 to Week 26 when compared with the 6 months prior to enrollment and the screening period. As a comparison, the median number of transfusions 6 months prior to enrollment was 2 (range; 1-19) and the median number of transfusions during the 6-week screening period was 1 (range; 0-8).

Table 14. Summary of Transfusions by Study Period – Full Analysis Set

Number of transfusions per subject	Before Week 5 (n=24)	Week 5- Week 26 (n=23)
0	19 (79.2)	17 (70.8)
1	3 (12.5)	3 (12.5)
2	2 (8.3)	1 (4.2)
3	0	1 (4.2)
4	0	0
≥ 5	0	1 (4.2)

Source: Statistical reviewer

E. Mean change from baseline in hemoglobin (Hgb) levels

Table 15 displays the statistical reviewer’s analysis results for mean change from baseline in hemoglobin (g/dL) at treatment assessment timepoint. Among 17 patients with evaluable baseline and treatment assessment endpoint hemoglobin values, mean hemoglobin was 8.45

g/dL at baseline and 11.63 g/dL at the treatment assessment endpoint. The LS mean change at the treatment assessment endpoint was an increase of 2.60 g/dL (95% CI: 0.74 to 4.46).

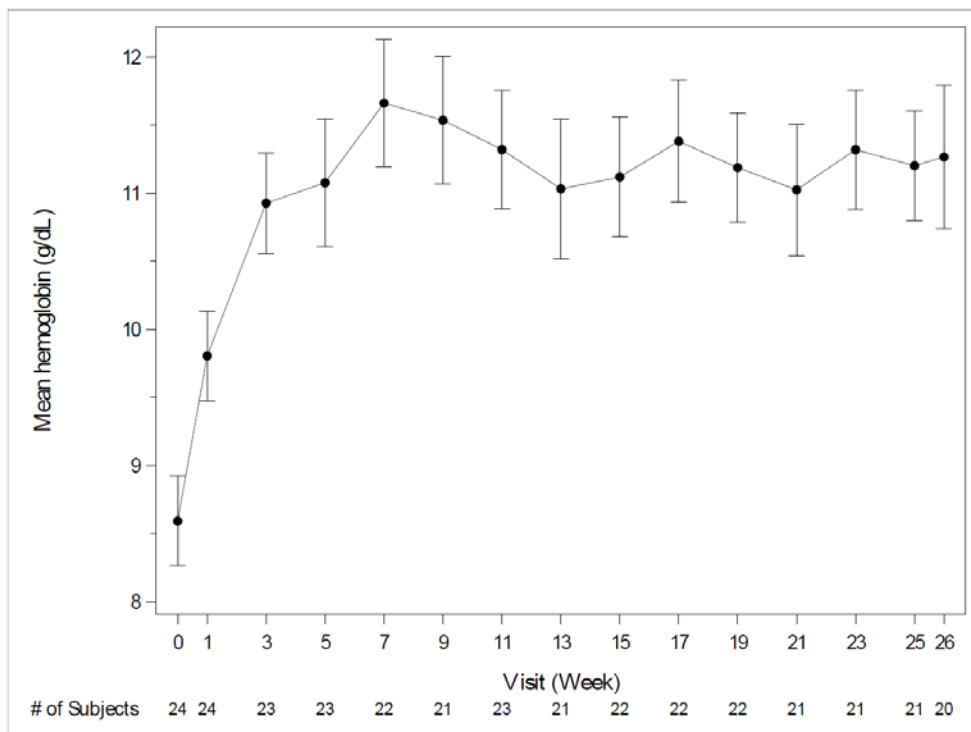
Table 15. Summary of change from baseline in hemoglobin (g/dL) at treatment assessment timepoint – Full Analysis Set

	N=17
Baseline mean	8.45
Mean at assessment timepoint	11.63
LS Mean for change from baseline, 95% CI	2.60 (0.74, 4.46)

Source: Statistical reviewer

While not predefined as an endpoint in the SAP, the sponsor states the mean increases in hemoglobin were observed beginning at Week 1, with a maximum increase observed at Week 7 that was generally maintained through the treatment assessment timepoint (Figure 1). After week 3, the mean change from baseline was an increase in >2g/dL at all time points.

Figure 1. Plot of Mean Hemoglobin by Visit



Source: Applicant's CSR Figure 5

Clinical reviewer comment: Secondary endpoints were not evaluated at baseline and at the treatment assessment timepoint in all 24 patients of the FAS. The mean change in bilirubin at

the treatment assessment endpoint was a reduction of -38.2 μmol/L, this was only evaluated in 14 patients. The mean change in LDH at the treatment assessment endpoint was reduction of -127 U/L, this was evaluated in 17 patients. The decrease in bilirubin and LDH is evidence of decreased hemolysis and will be described in the USPI. The decrease in bilirubin was more substantial than LDH, which is not surprising as LDH is a marker of intravascular hemolysis and extravascular hemolysis is the predominant mechanism of hemolysis in CAD. The FACIT-F^{(b) (4)} is an open label, single-arm study with no comparator arm. A clear benefit is the relatively quick onset of response, demonstrated by a mean increase in hemoglobin by 2g/dL starting at week 3 and maintained through the treatment assessment endpoint. It should be noted that time to hemoglobin, LDH and bilirubin response was a post-hoc evaluation and not pre-specified,

Dose/Dose Response

Please refer to clinical pharmacology review for additional details

Durability of Response

The durability of response was demonstrated by response at week 26. Ongoing studies; BIVV009-03 Part B and BIVV009-01 Part E will continue to assess durability beyond 26 weeks.

Persistence of Effect

Ten patients had a dosing interval exceed 17 days and 6 of the 10 (60%) patients had evidence of rebound anemia. Five of the 6 patients with rebound anemia required a transfusion.

Additional Analyses Conducted on the Individual Trial

A post hoc analysis conducted by the Applicant of hemoglobin was performed by threshold to assess mean change of hemoglobin (Table 16).

Table 16. Summary of Mean Change from Baseline in Hemoglobin by Threshold

	BIVV009 (N=24)
Number of subjects with mean change from baseline in hemoglobin	
>=1 g/dL	18 (75.0%)
>=1.5 g/dL	15 (62.5%)
>=2 g/dL	15 (62.5%)
>=3 g/dL	8 (33.3%)

NOTE: 1: Percentage are based on the number of subjects in the Full Analysis Set.

2: The treatment assessment timepoint is defined as the average of the values from the Week 23, 25, and 26 visits. In the case of any missing value at any of those visits, it will be calculated as the average of the available values, unless no value is available from all three visits.

Source: Table 28 of Applicant's CSR

In addition, a post hoc analysis conducted by the Applicant evaluated changes in hemoglobin levels comparing responders and non-responders. Patients in the responder group had a mean hemoglobin level of 12.3g/dL (median 12.4, range 9 to 14) and a mean increase of 3.9 g/dL (median 3.5, range 2 to 7) at the treatment assessment endpoint. Compared to non-responders who had a mean hemoglobin levels of 9.8g/dL (median 10, range 6 to 13) and mean increase 0.7g/dL (median 1, range -1 to 2) at the treatment assessment endpoint.

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

This is not applicable as efficacy is supported by a single study (BIVV009-03 Part A).

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

While the pivotal study was multi-center, it was mostly conducted in sites outside of the US. In addition, race and ethnicity was not collected from the majority of patients due to local regulations. It is unknown if differences in race and or ethnicity will impact the efficacy of sutimlimab.

7.2.2. Other Relevant Benefits

An additional benefit of this drug is the relatively quick improvement of hemoglobin within the first few doses of sutimlimab. Compared to standard therapies such as rituximab, which may take several weeks to show a response.

7.3. Integrated Assessment of Effectiveness

A single pivotal study, BIVV009-03 part A (CARDINAL study), was submitted to determine efficacy of sutimlimab for patients with CAD and a recent blood transfusion. The efficacy of sutimlimab was demonstrated by the proportion of patients that met the responder definition. Patients were classified as a responder if they met the following criteria; no blood transfusion from week 5 to 26 and no treatment for CAD beyond what was permitted per protocol; and achieved a hemoglobin level ≥ 12 g/dL or an increase from baseline in hemoglobin ≥ 2 g/dL at

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the treatment endpoint (mean value from week 23, 25, and 26). In total, 13 out of the 24 (54.2%) patients in the full analysis set met the composite primary endpoint criteria and the lower bound of the response rate was >30%. It was pre-determined (and agreed upon by the Agency) to be successful the lower bound of the 95% CI had to exceed 30%. As for each component of the composite endpoint; 62.5% of patients met the hemoglobin endpoint, 70.8% were transfusion free from week 5 to 26, and 91.7% of patients did not receive protocol prohibited CAD medications. Each component of the composite endpoint is important to defining clinical benefit and will be presented in the USPI. The proportion of patients who met the responder definition is clinically meaningful to a patient population who are symptomatic from their disease, had a recent transfusion, and there are there are no approved therapies.

Patients with CAD have chronic hemolytic anemia, that can be exacerbated in the setting of febrile infections or cold temperatures. Patients are often symptomatic from anemia and may require transfusions. Symptoms related to anemia can be severe and debilitating. Furthermore, standard therapies often consist of immunosuppressive agents such as rituximab alone or in combination with other agents. These therapies may be ineffective, not durable, or associated with significant toxicities. Therefore, therapy that increases hemoglobin and decreases transfusion burden, while not receiving immunosuppressant therapies is considered direct clinical benefit.

Efficacy of sutimlimab is further supported by secondary endpoints of the study, such as decreased bilirubin and LDH. Among 14 patients with baseline and follow-up bilirubin values, the mean was 55 $\mu\text{mol/L}$ (2.7-fold ULN) at baseline and 15 $\mu\text{mol/L}$ (0.8-fold ULN) at the follow-up time point. Among 17 patients with baseline and follow-up LDH values, the mean LDH was 424 U/L (1.7-fold ULN) at baseline and 301 U/L (1.2-fold ULN) at the follow-up time point. This data demonstrates that sutimlimab decreases hemolysis. It was expected that the decrease in bilirubin would be more dramatic than the decrease in LDH, as the mechanism of hemolysis in CAD is predominately extravascular and not all LDH is RBC derived.

(b) (4)

As the duration of the pivotal study was 6 months, durability of sutimlimab will be further assessed with ongoing studies, including BIVV009-part B in which patients will continue on sutimlimab for an additional 2 years. A PMR will be issued for the Applicant to complete ongoing studies. This will be an important consideration as CAD is a life-long disease.

In conclusion, the Applicant has proposed sutimlimab for the indication of hemolysis secondary to CAD. The Pivotal CARDINAL Study presented by the Applicant was an adequate and well

conducted study in which the efficacy data demonstrates substantial evidence of effectiveness for the proposed indication.

8. Review of Safety

8.1. Safety Review Approach

The Applicant’s safety database consisted of 6 completed or ongoing studies. The safety population consisted of patients or subjects that received at least one dose of sutimlimab. The primary safety population included 34 patients with CAD from two pooled studies; BIVV009-01 Parts C and E (10 patients) and BIVV009-03 Parts A and B (24 patients) (Table 17).

The data cut-off date for the primary CAD safety database was July 11th, 2019. In addition, the Applicant submitted a 90 day safety update for the four ongoing studies; BIVV009-01 Part E, BIVV009-04 Part A and B, and BIVV009-201 Part A and B with a data cut-off November 20th, 2019. In addition, BIVV009-03 Part B was included with a data cut off of January 16th, 2020.

Table 17. Primary CAD Safety Population Completion Status

	BIVV009-01		BIVV009-03		Total N=34 n (%)
	Part C N=10 n (%)	Part E N=4 n (%)	Part A N=24 n (%)	Part B N=21 n (%)	
Completion status					
Completed	10 (100)	0 (0)	22 (91.7)	0 (0)	7 (20.6)
Ongoing	0 (0)	3 (75)	0 (0)	21 (100)	24 (70.6)

Source: Derived from Applicant’s SCS

Supportive safety data consisted of pooled NHV studies of 96 patients from studies; BIVV009-01 parts A and B, TNT009-02, and BIVV009-05, and pooled CMD studies which included 32 patients from studies; BIVV009-01 part C with non-CAD indications and BIVV009-201. In addition, 27 patients from the ongoing phase 3, randomized, double-blind, placebo-controlled CAD study; BIVV009-04. This study remains blinded, and therefore only limited safety data was included.

Review of safety was based upon:

- Clinical Study Reports (CSR) for studies
- Protocol for studies

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- Data sets for the populations described above
- Summary of clinical safety (SCS)
- 90-day safety update
- Patient narratives
- Case report forms

Case report forms and narratives were provided and reviewed for adverse events (AE) of interest, serious adverse events (SAEs), and deaths that occurred in the primary and supportive safety populations. TEAEs of special interest were not predefined, but the following TEAEs of special interest were described by the Applicant and included; thromboembolic events, hypersensitivity reactions, infections, and development of systemic lupus erythematosus (SLE).

The ADAE.xpt data file was reviewed for accuracy of translation of the verbatim to preferred term by manual review. Based on this review a modified table was produced where additions of preferred terms were added based on the verbatim term. With additions of preferred terms, the adverse event file was copied with the new preferred term. Similar preferred terms were grouped by standardized groupings of related preferred terms through FDA Medical Queries (FMQs).

Clinical comment: The Agency agrees with the pooling strategy used by the Applicant. This included pooling patients with CAD for the primary safety analysis, and pooling subjects NHV and CMD for supportive safety assessment.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

A total of 162 patients or subjects (34 patients with CAD or CAS, 32 patients with other CMDs, and 96 NHVs) were treated with sutimlimab. An additional 27 patients with CAD were treated on an ongoing study (BIVV009-04) that remains blinded (not included in Table 18). Twenty-two subjects were treated with placebo. In the entire safety population, the median number of sutimlimab administrations is 4 (range 1 to 48). Duration of weeks of exposure to sutimlimab was a median of 5.1 weeks (range 2.1 to 90.3). The total median dose was 17.1 g (range 0-275).

Table 18. Sutimlimab Exposure in the Safety Populations

	CAD Population N=34	NHV Population N=96	CMD Population N=32	Total N=162
Total number of administrations Median, (range)	20 (2,48)	1 (1,4)	5 (2,26)	4 (1,48)
Duration of study treatment (weeks) Median, (range)	38.4 (3.1-90.3)	2.1 (2.1-7.1)	5.3 (2.3-53.6)	5.1 (2.1-90.3)
Total Dose (grams) Median (range)	143.8 (14-275)	5.8 (0-32)	20.4 (5-170)	17.1 (0-275)

Source: Derived from Applicant's SCS

The overall extent of exposure for patients in the primary safety population (N=34) is summarized in Table 19. This included 10 patients from study BIVV009-01 Part C, in which patients were administered a single IV test dose of 10mg/kg dose of sutimlimab followed by four weekly doses of 60mg/kg. Four of the 10 patients continued onto study BIVV009-01 Part E, patients were administered a single test dose of 5.5g at week 0, 1 and then every two weeks. Dosing was modified following an amendment (version 15.0), patients <75kg received fixed doses of 6.5g, and patients ≥75g received fixed doses of 7.5g. The primary safety population also included 24 patients from study BIVV009-03 Part A (pivotal study), in which patients <75kg received fixed doses of 6.5g, and patients ≥75g received fixed doses of 7.5g, on day 0, 7 and 14, followed by every two weeks for 25 weeks. Of the 24 patients, 21 patients continued on to part B which consisted of the same dosing. This study is ongoing and subjects will continue treatment for an additional 2 years following part A.

In the primary safety population, the median number of administrations were 20 (range 2-48) and the median total dose was 143.8g (range 14-275). Overall the median duration of exposure was 38.4 weeks (range 3.1-90.3), with the majority of patients (19/34; 55.9%) exposed for ≥ 35 weeks and 10/34 (29.4%) patients were exposed for ≥55 weeks.

Table 19. Total Exposure for the Primary CAD Safety Population

	BIVV009-01 C&E N=10	BIVV009-03 A&B N=24	Total N=34
Total number of administrations Median, (range)	5 (5-48)	21 (2-36)	20 (2-48)
Total Duration of study treatment (weeks) Median, (range)	5.5 (5.3-90.3)	39.3 (3.1-70.6)	38.4 (3.1-90.3)

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	BIVV009-01 C&E N=10	BIVV009-03 A&B N=24	Total N=34
Duration of study treatment (weeks) n (%)			
≥5 weeks	10 (100)	23 (95.8)	33 (97.1)
≥15 weeks	4 (40)	22 (91.7)	26 (76.5)
≥25 weeks	4 (40)	22 (91.7)	26 (76.5)
≥35 weeks	4 (40)	15 (62.5)	19 (55.9)
≥45 weeks	4 (40)	9 (37.5)	13 (38.2)
≥55 weeks	4 (40)	6 (25)	10 (29.4)
≥65 weeks	3 (30)	2 (8.3)	5 (14.7)
≥75 weeks	2 (20)	0 (0)	2 (5.9)
Total Dose (grams) Median (range)	19.1 (14-275)	150 (15-270)	143.8 (14-275)

Source: Derived from Applicant's SCS

8.2.2. Relevant characteristics of the safety population:

In the primary safety population, most subjects had primary CAD, 30/34 (88.2%). Three subjects from BIVV009-01 Part C had secondary CAS, and one subject from BIVV009-01 part C had mixed WAIHA and CAD. The CMDs population consisted of patients with WAIHA, bullous pemphigoid (BP), renal allograft antibody-mediated rejection (AMR) and immune thrombocytopenic purpura (ITP). Table 20 shows the diagnosis of all populations included in this safety review.

Table 20. Populations Included in the Safety Review

	Primary CAD	Secondary CAS	Mixed WAIHA/CAD	WAIHA	BP	AMR	ITP	NHV
Primary safety population	30	3	1					
Supportive safety population				4	10	10	8	96

Source: FDA clinical reviewer

Primary Safety Population Demographic Characteristics

In the primary safety population, the median age was 70.5 years (range 55-85). Overall, there were more females (23/34; 67.6%). More patients (23/34; 67.6%) weighed less than 75kg. Most

patients were from Europe (27/34; 79.4%). A summary of demographic characteristics is shown in Table 21.

Table 21. Summary of Demographic Characteristics in the Primary CAD Safety Population

	BIVV009-01 C&E N=10	BIVV009-03 A&B N=24	Total N=34
Age (years)			
Median	69.5	71.5	70.5
Mean	68.7	71.3	70.5
Range	55-76	55-85	55-85
Gender			
Male, n (%)	2 (20%)	9 (37.5%)	11 (32.3%)
Female, n (%)	8 (80%)	15 (62.5%)	23 (67.6%)
Weight			
<75kg, n (%)	6 (60%)	17 (70.8%)	23 (67.6%)
≥75kg, n (%)	4 (40%)	7 (29.2%)	11 (32.4%)
Race			
White, n (%)	9 (90%)	3 (12.5%)	12 (35.3%)
Asian, n (%)	1 (10%)	3 (12.5%)	4 (11.8%)
Not collected, n (%)	0 (0%)	18 (75%)	18 (52.9%)
Ethnicity			
Hispanic or Latino, n (%)	0 (0%)	0 (0%)	0 (0%)
Not Hispanic or latino, n (%)	0 (0%)	6 (25%)	6 (17.6)
Not collected, n (%)	10 (100%)	18 (75%)	28 (82.5%)
Geographic location			
Europe, n (%)	10 (100%)	17 (70.8%)	27 (79.4%)
North America, n (%)	0 (0%)	3 (12.5%)	3 (8.8%)
Asia, n (%)	0 (0%)	3 (12.5%)	3 (8.8%)
Other, n (%)	0 (0%)	1 (4.2%)	1 (2.9%)

Source: Derived from Applicant's SCS

Supportive safety population demographic characteristics

In the CMD population, the mean age of the 4 patients with WAIHA was 61 years (range 53-75). Patients were equally male and female. All were enrolled in Europe. The mean age of the 10 patients with BP was 73.8 (range 47-88) years. Patients were equally male and female. Most were from Europe 9/10 (90%). The mean age of the 10 patients with AMR 54.5 years (range 36-77). Majority of patients were male, 6/10 (60%). All were enrolled in Europe. Among the 8 patients with ITP the mean age was 42.6 (27-65) years. The majority of patients were female 6/8 (75%). Most patients were enrolled in North America 7/8 (87.5%).

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In the NHV population, the mean age was 35.1 (range 19-59) years. The majority of subjects were male 68/96 (70.8%). Most subject were enrolled in Europe and North America 48/96 (50%).

Clinical reviewer comment: The patients in the primary safety population are older, with a median age of 70.5 years and the majority of patients were females (67.7%). Race and ethnicity were not collected in the majority of patients due to local regulations, therefore it is not clear if the patient population is sufficiently diverse. Overall the demographic characteristics in the primary safety population (age and gender) is representative of patients likely to receive sutimlimab in clinical practice.

8.2.3. Adequacy of the safety database:

The safety database of the primary safety population represents a patient population consistent with the patient demographics (age and gender) and disease characteristics of CAD. Most patients were from Europe with limited information regarding race and ethnicity. The course of the disease is not known to be impacted by race and ethnicity. While the safety database is small, safety can be adequately assessed. Given the rarity of the disease, the patient exposure seems adequately representative to be marketed to the US patient population.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

The quality of the safety data submitted was well organized and relevant data was easily identified. The Applicant provided all clinical data sets with the initial submission. The Applicant also provided narratives for all patients resulting in death, SAEs and AEs of interest. There are no concerns regarding the quality and integrity of this submission.

8.3.2. Categorization of Adverse Events

Adverse events were classified using the Medical Dictionary for Regulatory Activities (MedDRA) system organ classes (SOC) and preferred terms (PT). MedDRA version 21.0 was used for the integrated analysis. An AE was determined to be TEAE if it had an onset date after receiving the first administration of study drug. TEAEs were collected from the first study drug administration to discontinuation or the safety follow up. Adverse events were classified using Common Toxicity Criteria for Adverse Events (CTCAE) version 4.03 in all studies except the healthy volunteer study for BIVV009-05, in which severity was classified as mild, moderate, and severe. Events were classified as serious adverse events if the AE resulted in death, life-threatening,

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inpatient hospitalization, prolongation of existing hospitalization, persistent or significant disability, or birth defect. An event could also be deemed a SAE if the event jeopardized the subject or required intervention to prevent the above listed outcomes. Adverse events of special interest included; thromboembolic events, infections, development of SLE and hypersensitivity reactions.

The ADAE.xpt datafile was reviewed for accuracy of translation from the verbatim to preferred terms by manual review. There were 9 terms out of 535 terms for which translation was incomplete and additional terms were added, see Table 22.

Table 22. Additions of Preferred Terms to ADAE Data File

AETERM (verbatim term)	AEDECOD (preferred term)	Added preferred term 1	Added preferred term 2
ABDOMINAL INFECTION WITH VOMITING AND DIARRHEA ORGANISM UNKNOWN	Abdominal infection	Vomiting	Diarrhea
FATIGUE AND CHANGE IN SLEEP PATTERN SECONDARY TO WORK STRESS	Stress at work	Fatigue	Sleep disorder
PAIN ABDOMEN WITH SUSPECTED COHERENCE TO HERNIA INGUINALI RIGHT GROIN	Hernia pain	Abdominal pain	
BRUISE L THENAR EMINNENCE DUE TO DOG BITE	Animal bite	Contusion	
DYSPNOEA PROBABLY DUE TO AIR EMBOLISM	Air embolism	Dyspnea	
FEVER IN CAUSE OF URINARY TRACT INFECTION	Urinary tract infection	Fever	
INFECTED HEMATOMA (WOUND INFECTION) AFTER LICHTENSTEIN SURGERY WITH STAPHYLOCOCCUS AUREUS AND STAPHYLOCOCCUS EPIDERMIDIS	Wound infection staphylococcal	Hematoma	
PAIN BOTH HANDS RELATED TO ACROCYANOSIS	Cyanosis	Pain	
CARDIAC TROPONIN T INCREASED RELATED TO CORONARY HEART DISEASE	Coronary artery disease	Troponin T increased	

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Source: FDA clinical reviewer

8.3.3. Routine Clinical Tests

Safety assessments included physical examinations, vital signs, laboratory measurements, electrocardiograms (ECGs), and anti-drug antibody. Laboratory evaluations were determined to be clinically significant if worsened from baseline and grade 2 or higher (based on CTCAE).

In study BIVV009-01 Part C hematology assessments were collected at screening, day 0, 4, 11, 18, 25, 32, 39, 46, and 53. Coagulation and chemistry assessments were collected on day 0, 4, 11, 25, 32, and 53. Day 1 assessments were discontinued following an amendment (version 9). SLE panels were collected before treatment, during treatment and at post treatment assessments. The SLE panel consisted of anti-double stranded DNA (dsDNA), antinuclear antibodies (ANA), anti-smith, anti-phospholipid, anti-Rho antibodies, antineutrophil cytoplasmic antibodies, and circulating immune complexes (CICs).

In study BIVV009-01 Part E hematology and chemistry assessments were collected at screening, day 0, 7, 14 and every 2-3 weeks. Coagulation assessments were collected every 2-3 weeks. SLE panel will be collected at end of treatment.

In study BIVV009-03 Part A hematology and chemistry assessments were collected at screening, day 0, 7, followed by every 2 weeks. Coagulation assessments were collected at screening, day 0 and week 26. Systemic lupus erythematosus (SLE) panel were collected at baseline and post-treatment and consisted of; ANA, multiplex with dsDNA, anti-smith antibody, anti-phospholipid, anti-Ro/SSA antibody, anti-La/SSB antibody, anti-ribonucleoprotein antibody (RNP), anti-scleroderma antibody (Scl-70), anti-chromatin antibody, anti-Jo-1 antibody, anti-Centromere B antibody, and CICs: C1q.

In study BIVV009-03 Part B hematology and chemistry assessments were collected every two weeks. SLE panel will be collected at end of study.

Clinical reviewer comment: The safety assessments and safety monitoring schedule are appropriate to capture AEs and SAEs that may occur during the study.

8.4. Safety Results

8.4.1. Deaths

There were two deaths in the entire clinical development program. There was 1 death out of 34 patients (2.9%) in the primary safety population due to progressive hepatic cancer. In addition, there was 1 death in the supportive patient population in a patient with bullous pemphigoid

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who died due to cardiac failure. There were no deaths in the NHV population. Events leading to death are described below:

Primary Safety Population:

Patient (b) (6): The patient was diagnosed with CAD in (b) (6), and had a significant past medical history of hypertension, atrial fibrillation, coronary artery disease and cardiac insufficiency. The patient was enrolled into BIVV009-03 Part A (pivotal CARDINAL study). On day -14 of the study (prior to the first dose of study drug) the patient developed an ischemic stroke that was cardioembolic in origin. The patient successfully received thrombolysis and continued on apixaban. The patient weighed >75kg so therefore received 7.5g dosing of sutimlimab. On study day 18 (after receiving two doses of sutimlimab) the patient was hospitalized for grade 3 SAE of gastrointestinal (GI) bleeding and was transfused. During this hospitalization the patient deteriorated and developed altered mental status. A computed topography (CT) scan of the abdomen and liver biopsy revealed poorly differentiated hepatic cancer. The last dose of sutimlimab was received on day 8 of study. The patient recovered from the GI bleeding event. Shortly after discharge from the hospital, the patient died due to progressive hepatic cancer on day 32 of study. No autopsy was performed.

Supportive Safety Population:

Patient (b) (6): The patient was an 84-year-old female with a diagnosis of bullous pemphigoid. Significant past medical history included; diabetes mellitus, atrial fibrillation, chronic myocardial failure, hypertension and obesity. The patient was hospitalized for bullous pemphigoid and during her inpatient stay she was enrolled in study BIVV009-01 Part C. During the study, the patient had two TEAEs of urinary tract infections. The patient died suddenly in her sleep 28 days after the last dose of sutimlimab. There was no autopsy, but the probable cause of death was listed as “cardiac decompensation”.

Clinical reviewer comment: The two described patient deaths do not appear to be related to sutimlimab. The patient who died of hepatic cancer only received two doses of sutimlimab and had advanced disease, therefore it is unlikely that sutimlimab was related to the hepatic cancer. The second patient who died of likely heart failure, had multiple serious underlying comorbidities (atrial fibrillation, cardiac insufficiency, and diabetes mellitus) that likely contributed to the cause of death and the death occurred a month after the last dose of sutimlimab.

8.4.2. Serious Adverse Events

Primary Safety Population

In total, 12 out of 34 (35%) of the patients in the primary safety population experienced a treatment-emergent SAE. All treatment-emergent SAEs (including grouping of closely related

adverse events) are shown in Table 23. The most common type of treatment-emergent SAEs were infections in 7 out of 34 (20.6%) of patients, including sepsis in 3 out of 34 (8.8%) patients. Other treatment-emergent SAEs that occurred in more than 1 patient included; bacterial infection, bleeding, anemia, cholecystitis/cholelithiasis, and malignancy.

In the pivotal study BIVV009-03 Part A (included in the primary safety population), 7 out of 24 (29.2%) of patients had a treatment-emergent SAE. The most common treatment-emergent SAE occurring in 3 out of 24 (12.5%) of the patients was infection, which included the following preferred terms; streptococcus sepsis, wound infection staphylococcal, acute cholecystitis, and respiratory tract infection. Other treatment-emergent SAEs that occurred in more than one patient was bleeding, anemia, and malignancy.

Table 23. All Serious Treatment Emergent Adverse Events in the Primary CAD Safety Population

FDA Medical Query	BIVV009-01 C&E N=10	BIVV009-03 A&B N=24	Total N=34
Infection, all*	2 (20%)	5 (20.8%)	7 (20.6%)
Sepsis*	1 (10%)	2 (8.3%)	3 (8.8%)
Infection, bacterial*	0 (0%)	2 (8.3%)	2 (5.9%)
Infection, viral	0 (0%)	1 (4.2%)	1 (2.9%)
Erysipelas	0 (0%)	1 (4.2%)	1 (2.9%)
Respiratory tract infection	0 (0%)	1 (4.2%)	1 (2.9%)
Pneumonia	1 (10%)	0 (0%)	1 (2.9%)
Urinary tract infection	1 (10%)	0 (0%)	1 (2.9%)
Bleeding*	0 (0%)	2 (8.3%)	2 (5.9%)
Gastrointestinal bleed	0 (0%)	1 (4.2%)	1 (2.9%)
Ocular hemorrhage	0 (0%)	1 (4.2%)	1 (2.9%)
Anemia	0 (0%)	2 (8.3%)	2 (5.9%)
Cholecystitis, cholelithiasis	0 (0%)	2 (8.3%)	2 (5.9%)
Malignancy	0 (0%)	2 (8.3%)	2 (5.9%)
Arthralgia	0 (0%)	1 (4.2%)	1 (2.9%)
Coronary artery disease	0 (0%)	1 (4.2%)	1 (2.9%)
Extrapyramidal symptoms	0 (0%)	1 (4.2%)	1 (2.9%)
Fracture	1 (10%)	0 (0%)	1 (2.9%)
Hematoma	0 (0%)	1 (4.2%)	1 (2.9%)
Hemolysis	0 (0%)	1 (4.2%)	1 (2.9%)
Hernia	0 (0%)	1 (4.2%)	1 (2.9%)
Retinal disorders	0 (0%)	1 (4.2%)	1 (2.9%)

Source: FDA clinical reviewer

*The following terms were combined

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Bleeding includes: gastrointestinal hemorrhage, vitreous hemorrhage

Infection, all includes: urinary tract infection, pneumonia, pulmonary sepsis, erysipelas, streptococcal sepsis, wound infection staphylococcal, Escherichia sepsis, cholecystitis acute, respiratory tract infection, viral infection

Sepsis includes: pulmonary sepsis, streptococcal sepsis, Escherichia sepsis

Supportive Safety Population

In the CMD population, no patient with WAIHA or AMR reported a SAE. One out of 10 (10%) patients had a serious TEAE of cardiac failure that resulted in death, see section 8.4.1 for the detailed narrative. Two out of 8 (25%) with ITP experienced serious TEAEs including; thrombocytopenia, migraine, and dural arteriovenous fistula.

No healthy volunteers experienced a serious TEAE.

Clinical reviewer comment: Infections were the most common treatment-emergent SAEs in the primary safety population, occurring in approximately 20% of patients. Infections occurred as similar frequencies in both studies. Bacterial infections were slightly more common than viral infection, 5.9% vs 2.9%, respectively. As the patient population consists of older patients with multiple underlying comorbidities it is difficult to fully understand the relationship of infections to the study drug as there is no placebo arm. Although, it is possible sutimlimab increases the risk of serious infections given the mechanism of action of inhibiting the classical complement pathway which is an integral part of the immune system. Serious infections will be added to the Warning and Precautions section of the label.

Bleeding events occurred in 2 out of 34 (5.9%) patients. This included a TEAE of ocular hemorrhage in a patient with a history of ocular hemorrhage. One TEAE of gastrointestinal hemorrhage, resulting in a hospitalization and need for transfusion. Of note, the patient was diagnosed with hepatic cancer shortly after the event of gastrointestinal hemorrhage. The relationship between bleeding and sutimlimab is not known. It is notable that both patients had underlying risk factors for the bleeding event.

Two patients developed malignancy that were unlikely associated with sutimlimab. One patient developed hepatocellular carcinoma which was diagnosed just after receiving two doses of sutimlimab. The other malignancy was renal cell carcinoma, in a patient with a history of renal cell carcinoma. In addition, anemia and hemolysis were described as treatment-emergent SAEs, the verbatim terms for anemia and hemolysis both stated, "due to CAD". Patient narratives were reviewed and agreed the events of anemia and hemolysis were not likely due to sutimlimab.

Seven out of 24 (29.2%) of patients in the pivotal study (BIVV009-03 Part A) had a treatment-emergent SAE. After review, 6 out of 24 (25%) of patients had an SAE possible due to sutimlimab, as anemia and malignancy were not considered adverse reactions for reasons stated above. Similar to the entire safety population, infectious were the most common serious

TEAE.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

Three out of 34 (8.8%) from the primary safety population discontinued the study early due to TEAEs (Table 24).

Patient (b) (6) from study BIVV009-01 Part E, discontinued due to worsening Waldenstrom Macroglobulinemia. The patient had a history of Waldenstrom Macroglobulinemia since (b) (6). During the study multiple transfusions were required for anemia. The patient also had treatment-emergent non-serious events of cough, dysphonia, and urinary tract infection, in addition to treatment emergent SAEs of pneumonia and pulmonary sepsis. The patient discontinued the study due to worsening Waldenstrom's Macroglobulinemia, the last dose of study drug was on day 367. At the time of the data cut-off the patient was still in the hospital.

Patient (b) (6) from study BIVV009-03 Part A, discontinued the study due to polymyalgia rheumatica. The patient had a medical history significant for polymyalgia rheumatica and reported on day -8 (prior to receiving first dose of sutimlimab) grade 3 serious events of shoulder and knee pain secondary to Polymyalgia Rheumatica. The shoulder pain was described as debilitating. During the study the patient received pain medication (ibuprofen and morphine) and IV flucloxacillin for polymyalgia rheumatica related pain. On day 26 the patient was hospitalized with knee pain, swelling and difficulty mobilizing. The left knee was drained and work up was consistent with pseudogout. The patient received colchicine and pain medication. On day 43, the patient had another left knee aspiration (not consistent with pseudogout) and was administered steroids for polymyalgia rheumatica. The patient was subsequently hospitalized for pain, a total body positron emission tomography-computed tomography without contrast showed multifocal joint avidity, rheumatology determined findings were consistent with polymyalgia rheumatica. The patient was treated with analgesics and steroids. The patient discontinued therapy due to PMR on day 65. Of note, at the safety follow up the patient's ANA was positive (1:160) when previously negative at baseline. The patient continued to have arthralgias at the safety follow up on day 127 despite discontinuing sutimlimab.

Patient (b) (6) from study BIVV009-03 Part A discontinued the study due to death from hepatic cancer. Narrative of this death is in section 8.4.1.

Table 24. Dropouts and Discontinuations in the Primary CAD Safety Population

	BIVV009-01		BIVV009-03		Total N=34
	Part C N=10	Part E N=4	Part A N=24	Part B N=21	
Discontinued prematurely	0 (0)	1 (25)	2 (8.3)	0 (0)	3 (8.8)
Adverse event	0 (0)	1 (25)	1 (4.2)	0 (0)	2 (5.9)
Death	0 (0)	0 (0)	1 (4.2)	0 (0)	1 (2.9)

Source: Adapted from Applicant's SCS

Supportive Safety Population

Of the 4 patients with WAIHA, 3 (75%) withdrew due to predefined criteria (2 due to treatment not successful and one due to acute hemolysis). Of the 10 patients with BP, 2 (20%) discontinued prior to the study ending (one was lost to follow up and one due to death of cardiac failure). All patients with AMR completed the study. One (12.5%) out of 8 patients with ITP discontinued prematurely due to withdrawal of consent, the patient also required rescue therapy for thrombocytopenia.

In the healthy volunteer population 3/96 (3.1%) patients discontinued the study prematurely. One patient discontinued due to protocol violation, one lost to follow up, and one due to a TEAE of first-degree AV heart block.

Reviewer comment: The low rates of discontinuations support the tolerability of this drug in the CAD population despite consisting of an elderly population with underlying comorbidities. There were 2 (8.8%) patients in the primary safety population who discontinued the study early due to TEAEs. Both discontinuations were related to underlying diseases and unlikely related to sutimlimab. Of note, studies are ongoing and therefore there may be more dropouts due to TEAEs.

8.4.4. Significant Adverse Events

Adverse Events Leading to Dose Interruption

Primary Safety Population

Dose interruption due to AEs occurred in 9 out of 34 (26.5%) patients. The most common (occurring in 2 or more patients) reason was dose interruption was infection occurring in 11.8% of patients and infusion related reaction occurring in 5.9% of patients.

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In the pivotal study alone, 6 out of 24 (25%) of patients had dose interruptions with infection and infusion reactions as the most common TEAEs leading to dose interruption.

Supportive Safety Population

In the CMD population, 3 out of 32 (9.4%) patients had dose interruptions. Reasons for dose interruptions included infusion reaction, antinuclear antibody positive and thrombocytosis.

In the NHV population, 2 out of 96 (2.1%) patients had dose interruptions. Reasons for dose interruption included a moderate event of diarrhea and mild event of alanine aminotransferase increased.

Clinical reviewer comment: Dose interruptions occurred for a variety of reasons. In the primary safety population (including the pivotal study) the most common reason for dose interruption was due to infection and infusion related reactions.

Severity of Adverse Events

Primary Safety Population

Grading was based on CTCAE criteria. AEs graded as grade 1 = mild, grade 2= moderate and grade ≥ 3 = severe. The majority of patients experienced AEs that were grade 1 or grade 2 in intensity as shown in Table 25.

Table 25. TEAE Toxicity Grade Summary

	BIVV009-01 C&E N=10	BIVV009-03 A&B		Total N=34
		6.5g N=17	7.5g N= 7	
Any TEAE	8 (80%)	17 (100%)	7 (100%)	32 (94%)
Patients with grade 1 TEAE	8 (80%)	14 (82.4%)	6 (85.7%)	28 (82.4%)
Patients with grade 2 TEAE	7 (70%)	13 (76.5%)	6 (86%)	26 (75.5%)
Patients with ≥ 3 grade TEAE	3 (30%)	7 (41.2%)	3 (42.9%)	13 (38.2%)
SAEs	3 (30%)	6 (35.3%)	3 (42.9%)	12 (35.3%)

Source: FDA clinical reviewer

In total, 13 out of 34 (38.2%) of patients in the primary safety population experienced at least 1 Grade 3 (severe) TEAE. The most common (occurring $\geq 5\%$ of the total population) TEAEs Grade ≥ 3 is shown in Table 26.

Table 26. Most common (>5%) TEAEs Grade $\geq$ 3 in the Primary Safety Population

FDA Medical Query	BIVV009-01 C&E N=10	BIVV009-03 A&B N=24	Total N=34
Infection, all*	2 (20%)	5 (20.8%)	7 (20.6%)
Sepsis	1 (10%)	2 (8.3%)	3 (8.8%)
Infection, bacterial	0 (0%)	2 (8.3%)	2 (5.9%)
Bleeding*	0 (0%)	2 (8.3%)	2 (5.9%)
Anemia	0 (0%)	2 (8.3%)	2 (5.9%)

Source: FDA clinical reviewer

*The following terms were combined

Bleeding includes: gastrointestinal hemorrhage, vitreous hemorrhage

Infection, all includes: urinary tract infection, pneumonia, pulmonary sepsis, erysipelas, streptococcal sepsis, Escherichia sepsis, cholecystitis acute, respiratory tract infection, viral infection

Sepsis includes: pulmonary sepsis, streptococcal sepsis, Escherichia sepsis

Supportive Safety Population

In the ITP population, 3 out of 8 (37.5%) patients experienced a total of 5 grade 3 TEAEs including pyrexia, cough, migraine, dural arteriovenous fistula and thrombocytopenia. No other patient populations reported grade $\geq$ 3 TEAEs.

No healthy volunteers experienced a grade $\geq$ 3 TEAE.

Clinical reviewer comment: Frequency of adverse events and intensity of adverse events were similar across studies and dosing groups. Most TEAEs were grade 1 or grade 2. The most common TEAE grade $\geq$ 3 were infections.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

In total, 32/34 (94%) of patients in the primary safety population had a TEAE. TEAEs (including grouping of closely related adverse events) are shown in Table 27. The most common type of TEAEs (>20%) were respiratory tract infection, urinary tract infections and fatigue.

Table 27. Most Common (>10%) Treatment Emergent Adverse Events in the Primary CAD Safety Population

Medical Query	BIVV009-01 C&E N=10	BIVV009-03 A&B N=24	Total N=34
Infection	4 (40%)	16 (66.7%)	20 (58.8%)
Respiratory tract infection*	4 (40%)	7 (29.2%)	11 (32.4%)
Urinary tract infection*	2 (20%)	5 (20.8%)	7 (20.6%)
Infection, viral*	2 (20%)	4 (16.7%)	6 (17.6%)
Nasopharyngitis	4 (40%)	2 (8.3%)	6 (17.6%)
Infection, bacterial*	2 (20%)	3 (12.5%)	5 (14.7%)
Vascular disorders			
Systemic hypertension*	0 (0%)	6 (25%)	6 (17.6%)
Hematoma*	2 (20%)	3 (12.5%)	5 (14.7%)
Bleeding*	0 (0%)	3 (12.5%)	3 (12.5%)
General disorders and administration site conditions			
Fatigue*	3 (30%)	4 (16.7%)	7 (20.6%)
Peripheral edema	2 (20%)	3 (12.5%)	5 (14.7%)
Pyrexia*	1 (10%)	3 (12.5%)	4 (11.8%)
Gastrointestinal disorders			
Abdominal pain*	2 (20%)	4 (16.7%)	6 (17.6%)
Diarrhea	1 (10%)	5 (20.8%)	6 (17.6%)
Nausea	3 (30%)	2 (8.3%)	5 (14.7%)
Constipation	2 (20%)	2 (8.3%)	4 (11.8%)
Dyspepsia*	1 (10%)	3 (12.5%)	4 (11.8%)
Gastroenteritis	1 (10%)	3 (12.5%)	4 (11.8%)
Nervous system disorders			
Dizziness*	5 (50%)	1 (4.2%)	6 (17.6%)
Headache	2 (20%)	2 (8.3%)	4 (11.8%)
Blood and lymphatic system disorders			
Anemia	1 (10%)	4 (16.7%)	5 (14.7%)
Musculoskeletal and connective tissue disorders			
Back pain	4 (40%)	1 (4.2%)	5 (14.7%)
Respiratory, thoracic and mediastinal disorders			
Cough	1 (10%)	4 (16.7%)	5 (14.7%)
Injury, poisoning and procedural complications			
Fall	1 (10%)	3 (12.5%)	4 (11.8%)

Source: FDA clinical reviewer

*The following terms were combined:

Abdominal pain includes; abdominal pain, abdominal pain upper, abdominal pain lower, abdominal tenderness

Bleeding includes; gastrointestinal hemorrhage, epistaxis, vitreous hemorrhage

Dizziness includes; dizziness, vertigo, balance, disorder, Meniere’s disease
Dyspepsia includes; abdominal pain upper, dyspepsia
Fatigue includes; fatigue, asthenia, malaise, mental fatigue
Hematoma includes; hematoma, traumatic hematoma, vessel puncture site hematoma
Infection, bacterial includes; urinary tract infection bacteria, bacteremia, streptococcal sepsis, wound infection, staphylococcal, Escherichia sepsis, cystitis bacteria
Infection, viral includes; herpes zoster, oral herpes, respiratory tract infection viral, viral infection
Pyrexia includes; pyrexia, fever
Systemic hypertension includes; hypertension, essential hypertension, blood pressure increased
Upper respiratory infection includes; nasopharyngitis, respiratory tract infection, influenza like illness, viral upper respiratory tract infection, upper respiratory tract infection
Urinary tract infection includes; urinary tract infection, cystitis, cystitis bacterial

Within the primary safety population, the most common (occurring in >5% of the population) adverse reactions from the pivotal study BIVV009-03 Part A (CARDINAL study) is presented in Table 28. Adverse reactions occurring in >10% are; respiratory tract infections, viral infections, bleeding, hematoma, diarrhea, dyspepsia, cough, arthralgia, arthritis, and peripheral edema.

Table 28. Most Common (>5%) Adverse Reaction in the Pivotal Study (BIVV009-03 Part A)

FDA Medical Query	All Grades (%) N=24	Grade $\geq$ 3 (%) N=24
Infections*	58	13
Respiratory tract infection*	25	4
Viral infection*	13	0
Urinary tract infection*	8	0
Bacterial infection*	8	4
Vascular disorders		
Bleeding*	13	8
Hematoma*	13	0
Cyanosis	8	0
Systemic hypertension *	8	0
Gastrointestinal disorders		
Diarrhea	13	0
Dyspepsia*	13	0
Gastroenteritis	8	0
Abdominal pain	8	0
Respiratory, thoracic and mediastinal disorders		
Cough *	13	0
Musculoskeletal and connective tissue disorders		
arthralgia, arthritis*	13	4
General disorders and administration site conditions		

FDA Medical Query	All Grades (%) N=24	Grade $\geq$ 3 (%) N=24
Peripheral edema	13	0
Infusion reaction	8	0
Fatigue*	8	0
Fall	8	0
Nervous system disorders		
Headache	8	0
Confusional state	8	0

Source: FDA clinical reviewer

*The following terms were combined:

Arthralgia, arthritis includes: arthralgia, osteoarthritis

Bacterial infection includes: cystitis bacterial, streptococcal sepsis, wound infection staphylococcal

Bleeding includes: epistaxis, gastrointestinal hemorrhage, vitreous hemorrhage

Cough includes: cough, productive cough

Dyspepsia includes: dyspepsia, abdominal pain upper

Fatigue includes: asthenia, fatigue, mental fatigue

Hematoma includes: hematoma, vessel puncture site hematoma

Infection includes: abdominal infection, bronchitis, acute cholecystitis, bacterial cystitis, gastroenteritis, infection, nasopharyngitis, oral herpes, respiratory tract infection, respiratory tract infection viral, skin infection, streptococcal sepsis, upper respiratory tract infection, urinary tract infection, viral infection, viral upper respiratory tract infection, wound infection staphylococcal

Respiratory tract infection includes: nasopharyngitis, respiratory tract infection, respiratory tract infection viral, upper respiratory tract infection, viral upper respiratory tract infection

Systemic hypertension includes: hypertension, blood pressure increased

Urinary tract infection includes: cystitis bacterial, urinary tract infection

Viral infection includes: oral herpes, respiratory tract infection viral, viral infection, viral upper respiratory tract infection

Supportive Safety Population

In the CMD population, the most common TEAEs (occurring in >20% of the population) included; infection (34.4%), fatigue (28.1%), upper respiratory infection (URI) (25%), and headache (21.9%).

In the NHV population the most common TEAEs (occurring in >5% of the population) were; infection (13.5%), URI (11.5%), headache (9.4%) and nasopharyngitis (6.3%).

Clinical reviewer comment: Most patients in the primary safety population (94%) experienced 1 or more TEAEs. The most common term reported was infections. The most common type of infection was respiratory tract infection, followed by urinary tract infection (UTI). The safety profile of the supportive safety population was similar to the primary safety population.

The USPI section 6.1 will contain safety information from the 24 patients enrolled in the pivotal

study (BIVV009-03 Part A), shown in Table 28. The most common (>10%) TEAEs included; respiratory tract infections, viral infections, bleeding, hematoma, diarrhea, dyspepsia, cough, arthralgia, arthritis, and peripheral edema. Reasons for including only the pivotal study in the label is the pivotal study is complete, unlike BIVV009-03 part B and BIVV009-01 part E which are still ongoing. In addition, the pivotal study used the same dosing regimen as recommended in the USPI and consisted only of a CAD population. In BIVV009-01 the dosing regimen was not the same as what is recommended in the USPI and four patients had CAS or mixed CAD/WAIHA patients. Overall the safety profile in the pivotal study was similar to the primary safety population. (b) (4)

8.4.6. Laboratory Findings

Hematology

The most common (occurring in over 20% of the population) abnormal hematology laboratory values reported by the Applicant in the primary safety population was hematocrit $\leq 30\%$ (18/32, 56.3%), lymphocytes $< 0.8 \times 10^9/L$ (18/34, 52.9%), hemoglobin ≤ 10 g/dL (16/34, 47.1%), leukocytes $< 3 \times 10^9/L$ (7/34, 20.6%) and absolute neutrophil count $< 1.5 \times 10^9/L$ (7/34, 20.6%). In total, 5 out of 34 patients had a TEAE of anemia, and one patient had a TEAE of hemolytic anemia. Overall, the Applicant concluded there were no clinically meaningful significant trends in hematology laboratory values in the primary CAD safety population

No significant trends were observed in the supportive safety populations.

Clinical reviewer comment: The majority of patients with abnormal leukocyte, lymphocyte, and neutrophils had abnormal results at some point in the screening process, in addition low values were often transient or intermittent. The only hematologic laboratory tests that were TEAEs of anemia and hemolysis. These TEAEs are likely secondary the primary disease process of CAD and not sutimlimab.

Chemistry

The most common (>20% of patients) abnormal chemistry laboratory values included; blood urea nitrogen ≥ 10.7 mmol/L (7/24, 29.2%), direct bilirubin $> 1.5 \times$ ULN (7/24, 29.2%), and total bilirubin $> 1.5 \times$ ULN (9/34 26.5%). One patient had a grade 2 TEAE of increased blood creatinine on day 274 of the study. The patient did have elevated creatine levels during screening. The grade 2 event of increased blood creatinine is ongoing as the patient continues on BIVV009-03 Part B. There was one patient with a grade 2 nonserious TEAE of increased alanine aminotransferase (ALT), the patient had a single elevated ALT level on day 162 of 190U/L which normalized at the following visit. Overall, no clinically meaningful significant trends were observed in chemistry laboratory values.

No significant trends were observed in the supportive safety populations. One patient in the

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NHV population developed a grade 1 nonserious TEAE of increased ALT on day 35 of the study. Sutimlimab was discontinued due to this TEAE. By day 43 the patients ALT normalized.

Clinical comment: According to the Applicant the direct bilirubin was either transient, isolated, or occurred in patients with elevated bilirubin at baseline. Elevation in total bilirubin is expected given the underlying disease and chronic hemolysis. There was one TEAE of increase blood creatinine that is ongoing and one TEAE of alanine aminotransferase that quickly resolved without intervention. Overall it does not appear there are any trends in chemistry laboratory data.

SLE panel

Overall, 19 of 34 (55.9%) patients in the primary safety population had at least one positive SLE panel parameter prior to sutimlimab exposure. In total, 13 (38.2%) patients had an all negative at baseline and at least one evaluation after sutimlimab exposure. Three of the 13 (23.1%) patients had at least one positive parameter that remained positive at the last SLE panel. Nine out of 34 (26.5%) patients had one or more SLE panel parameters that were previously negative or missing at baseline that subsequently turned positive post-baseline. The following SLE panel parameters turned positive; ANA (2 patients), anti-dsDNA (2 patients), RNP (1 patient), anti-scleroderma antibody (1 patient), anti-centromere B antibody (1 patient), and CICs (3 patients).

One out of 9 (11%) patients with AMR had a negative SLE panel at baseline and positive at value at postbaseline (CIC:C1q). Of the patient 8 patients with ITP, 2 had negative results prior to sutimlimab exposure, one was positive at the last evaluation.

One patient (1.2%) of the 83 NHVs who had a negative baseline SLE panel had at least one positive baseline value that remained positive at the last visit (antinuclear antibody).

Clinical reviewer comment: Of the 13 patients with a completely negative baseline SLE panel at baseline, 23% developed one or more positive autoantibodies. It was further reported that about 26% of the 34 patients had a negative autoantibody value at baseline that subsequently turned positive. In addition, 1.2% of healthy volunteers developed positive autoantibodies.

8.4.7. Vital Signs

No clinically meaningful trends were observed in mean temperature, heart rate, or respiratory rate in the primary CAD safety population. The most common abnormal vital signs were high systolic blood pressure (6/34, 17.6%), low systolic blood pressure (8/34, 23.5%), high diastolic blood pressure (6/34, 17.6%), low diastolic blood pressure (10/34, 29.4%), high heart rate (6/34, 17.6%), and low heart rate (13/34, 38.2%). Six of 34 (17.6%) of patients had a TEAE of either hypertension or elevated blood pressure.

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Supportive safety population

One (10%) patient with AMR with a history of hypertension, developed a TEAE of hypertension. No trends were noted in the CMD or NHV populations.

Clinical comment: Most vital sign changes were consistent with pretreatment medical history. Hypertension may be associated with sutimlimab. While 17.6% of patients had TEAE of systemic hypertension, most patients had elevated blood pressure at baseline or cardiac disease.

8.4.8. **Electrocardiograms (ECGs)**

In total, 11 out of 27 (40.7%) patients had a normal ECG at baseline and 1 postbaseline ECG that was abnormal, no patient had a clinically relevant abnormal ECG in the primary CAD safety population.

One patient in the healthy volunteer study had a normal baseline ECG and developed 1st degree atrioventricular (AV) block on study day 8. This was assessed by a cardiologist who concluded this was secondary to a vasovagal reaction prior to sutimlimab administration. The event resolved without intervention after 1.5 hours.

Clinical reviewer comment: There was one healthy volunteer with the TEAE of 1st degree AV heart block that was unlikely related to sutimlimab as the event occurred after a single dose of sutimlimab and evaluated by a cardiologist who believed it was not secondary to sutimlimab.

8.4.9. **QT**

No formal QT clinical trials were conducted. Since sutimlimab is a monoclonal antibody it is not expected to affect cardiac ion channels or prolong the QT interval.

8.4.10. **Immunogenicity**

No patient in the pivotal study developed treatment-emergent ADA. See clinical pharmacology review for further information. Anti-drug antibody (ADA) data was collected in studies BIVV009-01 part A,B&C, TNT009-02, and BIVV009-05 Part B. No patient with positive ADAs had evidence of a hypersensitivity reaction. One patient with CAD developed a positive ADA.

8.5. **Analysis of Submission-Specific Safety Issues**

8.5.1. **Infections**

Primary Safety Population

Patients were monitored for infections and vaccinated against encapsulated organisms (*Neisseria meningitidis*, *Haemophilus influenzae*, *Streptococcus pneumoniae*) within 5 years of enrollment, in the case patients were not already vaccinated, vaccination was performed at least 14 days prior to study drug administration during the screening period. Antibiotic prophylaxis was not administered to prevent meningococcal infections.

Infections were the most common TEAE, infections occurred in 20/34 (58.8%) of patients in the primary safety population. The most common type of infection was URI, this occurred in 11/34 (32.4%) of patients in the primary safety population. This FMQ included preferred terms such as influenza like illness, nasopharyngitis, respiratory tract infection, and upper respiratory tract infection. The second most common type of infection was UTI, this occurred in 7/34 (20.6%) of patients, followed by viral infection which occurred in 6/34 (17.6%) and bacterial infection in 5/34 (14.7%) of patients. A list of all infections in the primary safety population is shown in Table 29.

Table 29. All Infections in the Primary Safety Population

FDA Medical Query	BIVV009-01 C&E N=10	BIVV009-03 A&B N=24	Total N=34
Infection, all	4 (40%)	16 (66.7%)	20 (58.8%)
URI*	4 (40%)	7 (29.2%)	11 (32.4%)
UTI*	2 (20%)	5 (20.8%)	7 (20.6%)
Infection, viral*	2 (20%)	4 (16.7%)	6 (17.6%)
Nasopharyngitis	4 (40%)	2 (8.3%)	6 (17.6%)
Infection, bacterial*	2 (20%)	3 (12.5%)	5 (14.7%)
Herpes virus*	2 (20%)	1 (4.2%)	3 (8.8%)
Sepsis*	1 (10%)	2 (8.3%)	3 (8.8%)
Bacteremia*	1 (10%)	2 (8.3%)	3 (8.8%)
Infection, fungal*	0 (0%)	2 (8.3%)	2 (5.9%)
Pneumonia *	2 (20%)	0 (0%)	2 (5.9%)
Abscess	1 (10%)	0 (0%)	1 (2.9%)
Erysipelas	0 (0%)	1 (4.2%)	1 (2.9%)

Source: FDA clinical reviewer

*The following terms were combined:

Bacteremia includes; bacteremia, streptococcal sepsis, Escherichia sepsis

Herpes virus includes; herpes zoster, oral herpes

Infection, bacterial includes; urinary tract infection bacteria, bacteremia, streptococcal sepsis, wound infection, staphylococcal, Escherichia sepsis, cystitis bacteria

Infection, fungal includes; skin candida, tinea pedis

Infection, viral includes; herpes zoster, oral herpes, respiratory tract infection viral, viral infection

Pneumonia includes; pneumonia, pulmonary sepsis

Sepsis includes; pulmonary sepsis, streptococcal sepsis, Escherichia sepsis

Upper respiratory infection includes; nasopharyngitis, respiratory tract infection, influenza like illness, viral

upper respiratory tract infection, upper respiratory tract infection

Urinary tract infection includes; urinary tract infection, cystitis, cystitis bacterial

Seven of the 34 (20.6%) had a serious infection. No patient discontinued therapy due to TEAE infection. The most common infectious SAE was sepsis, occurring in 3/34 (8.8%) of patients.

Narratives of SAEs of infection included:

- Patient (b) (6) in BIVV009-01 Part E had a grade 3 serious TEAE of UTI. Significant past medical history included diabetes mellitus and urinary incontinence. On day 375 of the study the patient developed a UTI and was subsequently hospitalized. Blood and urine culture were positive for Escherichia coli. The patient recovered from the event after receiving fluids and antibiotics. Sutimlimab was continued. The patient had four previous events of UTIs while on study that were not serious.
- Patient (b) (6) in BIVV009-01 Part E had grade 3 serious TEAE of pneumonia and pulmonary sepsis. On day 383 the patient developed pneumonia and was hospitalized for shortness of breath, cough and tiredness. The patient was also noted to have anemia and was transfused. With a course of antibiotics and steroids the patient improved. On day 397 the patient developed pulmonary sepsis and was hospitalized with shortness of breath, cough and dark urine. The patient received IV antibiotics and blood transfusions. The study drug was interrupted and never restarted due to TEAE of Waldenstrom's macroglobulinemia (pre-existing condition).
- Patient (b) (6) in study BIVV009-03 Parts A and B has serious events of staphylococcal wound (hematoma) infection, Streptococcal pyogenes sepsis and erysipelas. Of note the patient has a history of receiving multiple immunomodulatory therapies for CAD including; bendamustine, rituximab, bortezomib, and cyclophosphamide. On day 57 of Part A, the patient developed worsening painful inguinal hernia and underwent surgery for repair. The surgery was uncomplicated and there were no bleeding complications. On day 62 of the study the patient was hospitalized for grade 2 infected hematoma. The wound culture grew Staphylococcus aureus and Staphylococcus epidermidis. The patient underwent a wound debridement and vacuum assisted closure. Sutimlimab was temporarily interrupted for the surgery and wound infection. On day 96, the patient was diagnosed with a grade 3 serious event of Streptococcal pyogenes sepsis. The patient was hospitalized and received IV antibiotics. Sutimlimab was temporarily interrupted. On day 249 (part B) the patient was hospitalized for erysipelas and received IV antibiotics. Sutimlimab was temporarily interrupted.
- Patient (b) (6) in study BIVV009-03 Part A had a serious TEAE of acute cholecystitis. On day 159 of the study the patient was hospitalized with a grade 3 acute cholecystitis and was treated with IV fluids, IV antibiotics and pain medications. The patient subsequently underwent a retrograde cholangiopancreatography endoscopy and was found to have calculi in the left bile duct and terminal hepatic duct, a sphincterotomy was performed. The patient had no prior history of cholecystitis. Sutimlimab was temporarily

interrupted.

- Patient (b) (6) in study BIVV009-03 Part A had two grade 3 serious events of respiratory tract infections. The patient had a significant past medical history of receiving multiple chemotherapy agents and had a history of pulmonary tuberculosis. On day 24 the patient developed a respiratory tract infection. Symptoms included were; cough, shortness of breath and anemia related symptoms. The patient hospitalized, transfused and received oral antibiotics. The other TEAE of respiratory tract infection occurred on day 49 of the study. Symptoms included fever and productive cough. The patient was hospitalized and developed septic shock and pneumonia. The organism was not identified. The patient received transfusion, IV antibiotics and fluids for treatment. Sutimlimab was temporarily interrupted.
- Patient (b) (6) in study BIVV009-03 Part B had a grade 3 serious event of viral infection. On day 290 of the study the patient developed a headache and fever. Lumbar puncture and blood cultures were negative. Patient received IV antibiotics. Sutimlimab was temporarily interrupted.
- Patient (b) (6) in study BIVV009-03 Part B had a grade 3 serious event with Escherichia coli sepsis. Past medical history was significant for history of receiving multiple immunomodulatory therapies in the past for CAD including; rituximab, prednisone, and bortezomib. On day 272 of the study, the patient developed abdominal pain and fever. The patients' blood culture grew Escherichia coli and was treated with IV antibiotics. Sutimlimab was continued during the event of sepsis.

Secondary safety population

No patients with WAIHA experienced a TEAE of infection. Four of the 10 (40%) patients with BP had an infection related TEAE, this included nasopharyngitis, rhinitis, and urinary tract infection. One (10%) patient with AMR experienced at least 1 TEAE of rhinitis. Five of 8 patients (62.5%) with ITP had TEAEs of infection which included; sinusitis, upper respiratory tract infection, bronchitis, gastroenteritis, and nasopharyngitis.

In the healthy volunteer population, 13/96 (13.5%) of patients had a TEAE of infection. The most common types of infection was URI in (11/96; 11.5%), nasopharyngitis (6/96; 6.3%) and viral respiratory tract infection (2/96; 2.1%). All events were non-serious.

Clinical review comment: Infections can cause exacerbation of hemolysis, therefore prompt recognition and treatment is critical for patients with CAD[2].

In the primary safety population, 58.8% of patient experienced TEAEs of infections and 20.6% had an SAE of infection. Bacterial and viral infections occurred at similar rates. No patient died due to a TEAE of infection. Secondary safety populations including healthy volunteers and CMD

patients also experienced infections, most commonly nasopharyngitis, and upper respiratory tract infections.

The high rate of patients experiencing infections in the primary safety population was likely confounded by an older population with multiple underlying comorbidities and many patients had previously received immunomodulatory therapy.

In total, 3 out of 34 (8.8%) patients in the primary safety population had an encapsulated organism infection. This included infections such as; Escherichia coli, Streptococcus pyogenes, Staphylococcus aureus, and Staphylococcal epidermidis. In addition, one patient in the 90-day safety follow up report from study BIVV009-03 Part B developed Streptococcus pneumoniae bacteremia, despite receiving a vaccination. There were no meningococcal infections or events of meningitis. Patients did not receive prophylaxis for meningococcal infections but they were required to have a vaccination for Neisseria meningitidis. Streptococcus pneumonia, and Haemophilus influenzae vaccinations were also required for study entry.

It is possible that sutimlimab contributes to the increase risk of infections given the mechanism of action of inhibiting the complement pathway which is part of the innate immune system. The complement system has important roles in the recognition and elimination of pathogens through direct killing and/or phagocytosis[14]. Direct killing of gram negative bacteria is done thorough the membrane attack complex (C5b-9). Gram positive bacteria and fungi tend to be resistant to the membrane attack complex. Sutimlimab does not inhibit the alternative complement pathway, therefore this function may remain intact. It has been estimated that approximately 65% of complement deficient patients experience severe infections mostly caused by encapsulated bacteria, including Neisseria meningitidis and Streptococcus pneumoniae[15]. Even more relevant to sutimlimab, patients with inherited complement deficiencies in the classical complement pathway (including C1s) are at increased risk for encapsulated bacteria such as Neisseria meningitidis, Streptococcus pneumoniae, and Haemophilus influenzae[16].. While there are important differences between inherited complement deficiency of C1s and acquired by pharmacologic suppression, this is a relevant comparison we have to assess this risk. Serious infections including increased susceptibility to encapsulated bacteria will be included in the Warnings and Precautions of the USPI. Patient should be closely monitored for infection and if suspected warrant early and immediate intervention. Vaccination will be recommended against encapsulated bacteria and noted while vaccination will likely decrease the risk of infection, it does not prevent it.

8.5.2 Hypersensitivity reactions

Primary safety population

Allergic reactions are described to be associated with monoclonal antibody therapies therefore, patients were monitored for hypersensitivity or allergic reactions. In total, 4/34 (11.8%) of patients experienced a hypersensitivity reaction.

- One patient in BIVV009-01 Part E experienced a grade 1 TEAE of rash on day 361 of treatment. This was described as exanthem left upper arm. The event did not begin within 24 hours of sutimlimab administration and resolved without intervention. The investigator believed this was associated with the administration of sutimlimab.
- One patient in BIVV009-03 Part A, experienced grade 1 erythema, described as red area of the skin that was elevated on the leg and not elevated on the forehead. This occurred on day 133 of the study. The patient was not receiving any other concomitant therapies. The erythema had not resolved as the subject continued on to part B of the study. No corrective therapy was given. The investigator thought it was suggestive of a potential hypersensitivity associated with sutimlimab.
- Two patients in BIVV009-03 Part A experienced infusion-related reactions. One TEAE was a grade 2 infusion related reaction, occurred on day 1 within 24 hours of administration of sutimlimab. The reaction consisted of shortness of breath and rapid heartbeat. The patient received loratadine and hydrocortisone. Sutimlimab was temporarily interrupted but was restarted and completed the same day. With the next two administrations of sutimlimab the patient received loratadine prior to administration. No further events of infusion related reactions occurred, and the patient did not receive any further prophylaxis.

The other patient experienced a grade 1 infusion-related reaction with the third administration of sutimlimab. The patient had received fexofenadine (antihistamine) for prophylaxis. During the event the patient experienced nausea, feeling flushed and a headache. The patient received diphenhydramine, famotidine, and prochlorperazine. The infusion was temporarily interrupted, and then reinitiated shortly after without incident. Of note, the patient also received a blood transfusion that same day for symptomatic anemia. The patient was premedicated with famotidine and diphenhydramine with subsequent administrations of sutimlimab up to day 92 of the study. The investigator believed both TEAEs of infusion-related reactions were possibly related to sutimlimab.

Supportive safety population

In the CMD population, one of the 8 (12.5%) patients with ITP experienced a non-serious TEAE of pruritis within 24 hours of the first infusion of sutimlimab and a non-serious event of an infusion-related reaction in the third infusion of sutimlimab. The infusion-related reaction consisted of dizziness, chest tightness, and facial flushing. The patient received Decadron (steroids) and Benadryl (antihistamine). Sutimlimab was temporarily interrupted, but then reinitiated shortly after. The patient received the fourth dose of sutimlimab without reoccurrence. No other patients in the CMD population had event of a hypersensitivity reaction.

In the NHV population 2 out of 96 (2.1%) patients experienced potential hypersensitivity reactions. One patient had generalized pruritis and one patient experienced urticaria. Both events occurred >7 days after administration of sutimlimab.

Clinical review comment: In total 4 out of 34 (11.8%) of patients had an event that may be a hypersensitivity reaction. Two (5.9%) patients in the primary CAD safety population clearly had infusion-related reactions to sutimlimab that responded to therapy. In the supportive population an additional patient had an infusion-related reaction. Prophylaxis for hypersensitivity reactions was not routinely administered without a history of a reaction to sutimlimab. Infusion-related reactions will be included in the Warnings and Precautions of the USPI. Patient should be closely monitored for infusion-related reactions and if suspected warrant early and immediate intervention.

8.5.3 Autoimmune Disease

Primary Safety Population

There is a theoretical risk of autoimmune disease development with inhibition of the classical complement pathway. Patients were monitored for autoimmune disease development and had full autoantibody panels at baseline, during and/or end of treatment. In the primary safety population, there were two (5.9%) out of 34 patients with possible worsening of a previously diagnosed autoimmune disease.

Patient (b) (6) from BIVV009-03 Part A, had a grade 3 serious TEAE of polymyalgia rheumatica including shoulder and knee arthralgias that began prior to sutimlimab administration. The pain reoccurred and persisted and/or worsened during the study, ultimately leading to study discontinuation at day 65. The full patient narrative can be found in section 8.4.3. At baseline the patient had a negative ANA. At the safety follow up the patient had a positive ANA (1:160). At the time of the safety follow up (day 127) the arthralgias and polymyalgia rheumatica persisted. Following an information request, the Applicant provided further information that following the safety follow up the patient followed with a rheumatologist, and while events of polymyalgia rheumatica and arthralgias continued the ANA had reverted back to negative.

Patient (b) (6) from BIVV009-03 Part B, had a history of multiple sclerosis prior to sutimlimab administration. The patient had a multiple sclerosis relapse (optic nerve attack flare) on day 194 of the study resolved without further reoccurrence. The patient received steroids. The autoantibody test was negative pre and post administration of sutimlimab.

Supportive safety populations

One patient with ITP, had sutimlimab interrupted due to a TEAE a positive RNP value. Due to this TEAE the patient did not receive the last administration of sutimlimab. At the last safety

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follow up the RNP value returned back to negative. There was no clinical correlation with the positive RNP value. The patient had a baseline positive ANA and MDSDNA, in addition to history of Hashimoto disease.

No healthy volunteers developed autoimmune disease.

Clinical reviewer comment: The risks of autoimmunity associated with inhibition of the proximal component of the classical CP are not known, but theoretically inhibition of the classical CP could increase the risk for development or worsening of autoimmune diseases such as SLE or immune complex diseases. This risk is based on observations that patients with certain types of autoimmune diseases, in particular SLE have low individual CP components. In addition, patients with hereditary deficiency of complement components of the early phase of the classical CP such as C1q, C1r, C1s, C4 and C2 are associated with increased susceptibility to SLE and SLE-related diseases[17]. The increased risk of SLE is likely most strongly associated with C1q deficiency. Deficiencies in C1r and/or C1s have been linked to glomerulonephritis, SLE, SLE-like disease and other autoimmune diseases[18]. The components of the classical complement pathway may be protective against SLE due to its roles in clearance of immune complexes and apoptotic cell debris, in addition to the role of complement-dependent B cell tolerance [15, 19]. For these reasons the Applicant monitored autoantibody panels and the development or worsening of autoimmune disease in patients exposed to sutimlimab, an inhibitor of the classical complement pathway.

Thirteen patients had an all negative SLE panel at baseline and three (23.1%) patients had at least one positive parameter that remained positive at the last SLE panel. Nine out of 34 (26.5%) patients had one or more SLE panel parameters that were previously negative or missing at baseline that subsequently turned positive post-baseline. No patient developed a new autoimmune disease. There was one patient with CAD with a history of polymyalgia rheumatica and a negative autoantibody panel at baseline that did develop a positive ANA and had arthralgias during the study. It's not clear if there was a correlation between the positive ANA and arthralgia, especially considering the patients ANA test returned to negative at a later follow up evaluation. The patients had a history of arthralgia due to polymyalgia rheumatica prior to exposure to sutimlimab and was diagnosed with gout (diagnostic by fluid aspiration) during the study. Autoantibody panels are typically negative in patients with polymyalgia rheumatica [20]. In addition, one patient with multiple sclerosis did have a flare on study, there was no correlation with the autoantibody panel. On note, one (1.2%) healthy subjects had a negative baseline SLE panel and had at least one positive post-treatment value that remained positive. There were no clinical symptoms of autoimmunity.

Sutimlimab inhibits C1s and therefore there is a theoretical risk of autoimmune disease development. The Applicant states C1q levels were not depressed with sutimlimab administration and therefore may offer some protection against autoimmunity. In the safety

populations, there was no clear trend of autoantibody panels turning positive and overt symptoms of autoimmune disease, although the median time a patient was exposed to sutimlimab was relatively short, and therefore long-term risk has not been assessed. As there remains a theoretical risk of autoimmunity, and development or worsening of autoimmune disease can be serious and is associated with significant morbidity, autoimmune disease will be listed in the Warnings and Precautions in the USPI. In addition, a PMR will be issued to continue to follow the long-term outcomes of autoimmune disease in patients exposed to sutimlimab in order to further understand this theoretical risk.

8.6. Safety Analyses by Demographic Subgroups

Age, gender and race subgroups were too small to make meaningful safety comparisons.

8.7. Specific Safety Studies/Clinical Trials

No specific studies were conducted to evaluate any specific safety concern.

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

The TEAE of hepatic cancer was reported in one patient. The event of hepatic cancer occurred only after two doses of sutimlimab. See a full description of the event in section 8.4.1. The patient ultimately died due to hepatic cancer shortly after the diagnosis.

The TEAEs of basal cell carcinoma and renal cell carcinoma were reported in one patient. The patient had a history of clear cell renal cell carcinoma and anal cancer. On day 92 of the study the patient had a magnetic resonance imaging (MRI) revealed increase size of the left renal cell carcinoma lesion. On day 154 of the study the patient was diagnosed with basal cell carcinoma and it was excised.

Clinical reviewer comment: It does not appear that sutimlimab increases in the risk for malignancy. The event of hepatic cancer was likely present before treatment given its advanced stage after only two doses of sutimlimab. In addition, the events of renal cell carcinoma and basal cell carcinoma occurred in a patient with a history of multiple malignancies.

8.8.2. Human Reproduction and Pregnancy

Not applicable.

8.8.3. Pediatrics and Assessment of Effects on Growth

No pediatric patients were enrolled in any of the studies.

8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Not applicable.

8.8.5 Additional safety issues

The Applicant submitted a 90-day safety update pertaining to the 4 ongoing studies. This included 3 studies in patients with CAD (BIVV009-01 Part E, BIVV009-03 Part B, BIVV009-04) and one study in patients with ITP (BIVV009-201).

BIVV009-01 Part E (data cut-off November 20, 2019)

No additional patients were enrolled in this study. Syncope was the only additional serious TEAE reported within the 90-day safety update. Waldenstrom Macroglobulinemia was previously reported as a TEAE, it was later reassessed and changed to a serious TEAE which had led to discontinuation of sutimlimab.

BIVV009-03 Part B (data cut-off January 16, 2020)

One additional patient was enrolled in this study following completion of Part A, increasing the total to 22 patients. One patient discontinued due to multiple non-serious TEAEs including; cyanosis, dysphagia, dyspepsia and gastritis erosive. The following additional serious TEAEs were reported in the 90-day safety update; angina pectoris, iridocyclitis, occult blood positive, and peripheral vascular disorder. There were 2 additional serious TEAEs of infections; grade 3 herpes zoster and grade 3 pneumococcal sepsis.

Study BIVV009-04 Part A and B (data cut-off November 20, 2019)

Three additional patients were enrolled in this study, increasing the total to 30 patients. All data from BIVV009-04 remains blinded. One patient discontinued therapy due to TEAEs of cyanosis and Raynaud's phenomenon. Potential hypersensitivity reactions were reported; pruritus, injections site pruritus, toxic skin eruption, and rash erythematous. In addition, one patient experienced pruritus, hypotension, and chest discomfort concurrently with study drug administration. No hypersensitivity reactions were serious.

BIVV009-201 Part A and B (data cut-off November 20, 2019)

Three additional patients were enrolled in this study. There was one additional serious TEAE of diverticulitis. Additional hypersensitivity reactions were noted, including pruritus and infusion related reaction.

Reviewer comment: There were no new deaths in the safety follow up. In study BIVV009-03 Part

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B one patient discontinued therapy due to multiple non-serious TEAEs. TEAEs reported in the 90-day safety update were consistent with what was observed during with the original study report. Additional hypersensitivity reactions, including infusion-related reactions were observed. Infections (serious and non-serious) continue to occur.

There was an event of pneumococcal sepsis in a patient previously vaccinated against Streptococcal pneumonia. Further information was requested, the Applicant explained the patients was a 63-year-old man with a complicated past medical history including; non-Hodgkin Lymphoma with secondary hypogammaglobulinemia, bladder carcinoma, chronic obstructive pulmonary disease (COPD) and serious pretreatment infections. The Applicant confirmed the patient received streptococcal pneumoniae (13-valent) vaccine on day -28 of the study and received streptococcal pneumoniae (23-valent) on (b) (6). The patient received the first dose of 7.5g sutimlimab on (b) (6). On (b) (6) the patient experienced an exacerbation of COPD and was treated with prednisolone 80mg on (b) (6) followed by prednisolone 10mg daily until (b) (6). The patient developed pneumococcal sepsis on (b) (6). Vaccine titer prior to the event on (b) (6) was 22.1mg/L, and following the event on (b) (6) was 18.8mg/L. It appears the patient was appropriately vaccinated, but the case is confounded by the patient's significant comorbidities and concomitant medications that may have increased the risk of infection. Still, the label will state that vaccinations reduces but does not eliminate the risk of encapsulated bacteria.

The 90-day safety update information does not significantly change the safety assessment from the original safety assessment.

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Postmarket Experience

Not applicable.

8.9.2. Expectations on Safety in the Postmarket Setting

Expectations of safety in the postmarketing setting are similar to what was observed in the primary CAD patient population. Given the small patient numbers and rarity of the disease it is possible that additional safety signals will be detected in the postmarketing setting. Safety with long term administration of sutimlimab will continued to be assessed in ongoing studies. In addition, a PMR will be issued to further understand the risk of autoimmune disease development and serious infections.

8.9.3. Additional Safety Issues From Other Disciplines

No additional safety issues were identified from other disciplines.

8.10. Integrated Assessment of Safety

The safety analysis for sutimlimab-jome was focused on the primary safety population, which consisted of 34 patients with CAD from the following studies; BIVV009-01 Part C and Part E (N=10), and BIVV009-03 Part A and B (N=24). Studies BIVV009-01 Part E and BIVV009-03 Part B were ongoing at the time of this report. The primary safety population consisted mostly of patients with CAD (88%), a few patients with CAS (8.8%), and one patient with mixed CAD/WAIHA (2.9%). Given the sample size of the primary safety population was small, supportive safety populations were also included. This included 32 patients with other CMDs (AMR, WAIHA, BP, ITP) and 96 NHVs.

In the primary safety population, the median duration of dosing was 38.4 weeks, with a range of 3.1-90.3. In study BIVV009-01 Part C, patients were administered a single IV test dose of 10mg/kg dose of sutimlimab followed by four weekly doses of 60mg/kg. In study BIVV009-01 Part E, patients were administered a single test dose of 5.5g at week 0, 1 and then every two weeks. Dosing was modified to patients <75kg received fixed doses of 6.5g, and patients $\geq$ 75g received fixed doses of 7.5g. In study BIVV009-03 Part A and B, patients <75kg received fixed doses of 6.5g, and patients $\geq$ 75g received fixed doses of 7.5g, on day 0, 7 and 14, followed by every two weeks.

The most common TEAEs (closely related terms were grouped or FMQs) reported in >20% the primary safety population included respiratory tract infections, UTI, and fatigue. In the pivotal study BIVV009-03 Part A, the most common TEAE by FMQ reported in >10% of the population were respiratory tract infections, viral infections, bleeding, hematoma, diarrhea, dyspepsia, cough, arthralgia, arthritis, and peripheral edema.

Serious TEAEs occurred in 35% of the 34 patients of the primary safety population and 25% of 24 patients within the pivotal study. The most frequent SAEs in the primary safety population included sepsis (8.8%), bacterial infection (5.9%), bleeding (5.9%), cholecystitis or cholelithiasis (5.9%), malignancy (5.9%) and anemia (5.9%). The events of malignancy and anemia were related to underlying pathologies and are likely not adverse reactions.

Infections are of particular concern for patients with CAD as it may exacerbate hemolysis. As the classical complement pathway is part of the innate immune system, it is possible that sutimlimab may increase the risk of non-serious and serious infections. Infections occurred in 58.8% of the 34 patients in the primary safety population and 58.3% of the 24 patients in the pivotal study. Infections with encapsulated organisms occurred in 8.8% of the 34 patients in the primary safety population. Following the 90-day safety update, one patient who received

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required vaccinations developed pneumococcal sepsis. This was the only case of a patient developing an infection of a vaccinated encapsulated bacteria. Overall, bacterial and viral infections occurred at similar frequency, fungal infections were less common. No patient died or discontinued therapy due to infections.

Infusions reactions occurred in 2 out of 34 (5.9%) patients in the primary safety population and in one out of the 32 (3.1%) patients with CMDs. There were no events of anaphylaxis. Sutimlimab dosing was interrupted but not discontinued.

There is a theoretical risk that inhibition of the classical complement pathway may increase the risk of development of autoimmune disease, in particular SLE. During the study there was no clear trend of autoantibody positivity and clinical symptoms of SLE. There was one patient with who experienced arthralgias during the study and developed a positive ANA after exposure to sutimlimab. This case is confounded by the patient's pretreatment history of polymyalgia rheumatica and arthralgias prior to exposure to sutimlimab, and ultimately the ANA reverted back to negative at a later date. The risk of autoimmune development is difficult to assess given the small patient population and lack of long-term data, therefore a PMR will be issued to continue to assess autoimmune disease development and/or worsening.

Two of the 34 (5.9%) patients in the primary safety discontinued treatment. One patient due to death from hepatocellular carcinoma that was diagnosed after only two doses of sutimlimab, and one patient discontinued due to polymyalgia rheumatica, which was diagnosed prior to exposure to sutimlimab. Both patients' discontinuations were likely unrelated to sutimlimab.

In summary, sutimlimab was well tolerated and had low rates of discontinuations and deaths, in an older population with multiple comorbidities and concomitant medications. The relatively high incidence of AEs and SAEs is therefore not unexpected. The most common SAE associated with sutimlimab were infections, which in most cases the infections were manageable with screening and aggressive supportive care. Overall the safety profile is acceptable for patients with CAD. Uncertainties remain given the small sample size, lack of a placebo arm, and limited data on long term outcomes, and it is possible that new safety signals will be revealed in ongoing studies and the postmarketing period. Therefore, a PMR was issued to complete and submit the ongoing studies and a PMR to assess the risk of autoimmune disease and serious infections including encapsulated bacteria.

9. Advisory Committee Meeting and Other External Consultations

The content of this BLA was not presented at an Advisory Committee meeting or any other external consultants.

10. Labeling Recommendations

10.1. Prescription Drug Labeling

Substantial changes were made to the proposed USPI. Changes recommended by the Agency are summarized in the table below. Labeling negotiations were ongoing at the time of this review and not completed.

Summary of Significant Labeling Changes (High Level Changes)		
Section	Proposed Labeling	Approved Labeling
Indications and Usage	ENJAYMO is a classical complement inhibitor indicated with cold agglutinin disease (CAD)	ENJAYMO is a classical complement inhibitor indicated with cold agglutinin disease (CAD).
Dosage and Administration		Added text to vaccinate against encapsulated bacteria at least two weeks prior to treatment. Converted dosing recommendations from table to text; • Weight-based dosage weekly for two weeks then every two weeks: ○ For patients weighing 39 kg to less than 75 kg: 6,500 mg by intravenous infusion. ○ For patients weighing 75 kg or more: 7,500 mg by intravenous infusion.
Warnings and Precautions	1. 2. 3.	1. Revised to serious infections and included rate and types of infections observed in clinical trials. 2. Revised to infusion-related reactions for consistency with other labels. Also included rate of infusion-related reactions and included description of symptoms.

		3. Revised to autoimmune diseases. (b) (4) Patients with C1s deficiency have developed SLE, SLE-like symptoms, glomerulonephritis, and other autoimmune diseases.
Adverse Reactions	The most frequently reported (>5%) adverse reactions with ENJAYMO (b) (4)	Most common adverse reactions (incidence > 10%) are respiratory tract infection, viral infection, (b) (4), diarrhea, dyspepsia, cough, arthralgia, arthritis, and peripheral edema. The division revised data presented based on FDA Medical Queries (FMQs) to derive the ADR table in section 6.1. FMQs are standard groupings of related adverse reactions and are designed to avoid splitting of terms that represent the same or similar medical concept. As stated in the Adverse Reactions Section of Labeling Guidance; events that are reported under different terms in the database, but that represent the same phenomenon should ordinarily be grouped together as a single adverse reaction to avoid diluting or obscuring the true effect. In addition, attributions in a single-arm trial are not acceptable. Adverse reactions that are grade 3 or higher are the most important because they may lead to morbidity and/or more dose interruptions. Current labels have used this approach. Included rate of serious ARs and dose interruptions.
Clinical Studies	Included data (b) (4)	Efficacy results table only included the pre-specified composite primary endpoint.

	(b) (4)	Did not include information (b) (4) Did not include (b) (4)

10.2. Nonprescription Drug Labeling

Not applicable.

11. Risk Evaluation and Mitigation Strategies (REMS)

No safety issues were identified during the review of the application that warranted a REMS.

12. Postmarketing Requirements and Commitments

The following PMRs were proposed by the clinical team however due to recommendation of complete response, agreement was not reached on these requirements and commitments

PMR1: Complete part B of study BIVV009-03, “A Phase 3, Pivotal, Open-Label, Multicenter Study to Assess the Efficacy and Safety of BIVV009 in Patients With Primary Cold Agglutinin Disease Who Have a Recent History of Blood Transfusion “. Include updated summary safety and efficacy analysis and submit datasets at the time of final clinical study report submission.

PMR 2: Complete part E of study BIVV009-01, “Safety, Tolerability and activity of TNT009 in Healthy Volunteers and Patient with Complement-Mediated Disorders. A Single/Multiple Ascending Dose Phase 1 Study”. Include updated summary safety and efficacy analysis in the final clinical study report.

PMR 3: Complete Study BIVV009-04, “A Phase 3, randomized, double-blind, placebo-controlled study to assess the efficacy and safety of BIVV009 in patients with primary Cold Agglutinin Disease without a recent history of blood transfusion”. (b) (4)

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(b) (4)
Include updated safety information and submit datasets at the time of final clinical study report submission.

PMR 4: Conduct a study to characterize the long-term safety (up to 5 years) of exposure to sutimlimab in patients with primary Cold Agglutinin Disease (b) (4). Submit yearly safety follow-up data for a (b) (4). The final study report should include an integrated safety dataset and a summary of the major safety findings for all patients, including the development or worsening of autoimmune diseases and the development of serious infections, including encapsulated organisms.

The following CMC PMC was recommended;

(b) (4)

13. Appendices

13.1. References

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13.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): BIVV009-03

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from

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Total number of investigators identified: <u>78</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>2</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>0</u> Significant payments of other sorts: <u>0</u> Proprietary interest in the product tested held by investigator: <u>0</u> Significant equity interest held by investigator in S Sponsor of covered study: <u>0</u>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u>		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

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