Sponsor: Sanofi **Drug substance(s):** BIVV009	**Study Identifiers:** NCT03347396; EudraCT Number: 2017-003538-10 **Study code:** EFC16215 (BIVV009-03)

Title of the study:

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

Study center(s):

22 study sites screened at least 1 patient and 16 study sites enrolled at least 1 patient. The study was conducted at investigational sites in the United States, Australia, Germany, France, Italy, Japan, Norway, and the United Kingdom. Patients were screened in Austria and Belgium, but none were enrolled.

Study period:

Date first patient enrolled: 5 March 2018

Date last patient completed: 11 July 2019 (Part A)

Study Status: Completed.

Phase of development: 3

Objectives:

The primary objective of Part A was to determine whether sutimlimab administration resulted in a ≥2 g/dL increase in hemoglobin levels or increases hemoglobin to ≥12 g/dL and obviated the need for blood transfusion during treatment in patients with CAD who had a recent history of blood transfusion.

The efficacy objectives of Part A were as follows:

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

The safety objective of Part A was as follows:

- To evaluate the overall safety and tolerability of sutimlimab in patients with CAD

The exploratory objectives of Part A were as follows:

- To assess the effect of sutimlimab on specific complications of CAD (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

Methodology:

This is an open-label, single-arm, 2-part study designed to evaluate the efficacy, safety, and tolerability of sutimlimab in patients with the complement-mediated disorder, CAD, with 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.

During the 6-week Screening/Observation Period, the patient's diagnosis and eligibility was confirmed. Medical history was collected (including transfusions within 6 months of Screening and transfusions during the screening period), physical examinations were performed, and blood samples were collected on 3 occasions approximately every 2 weeks.

Patients were allowed to receive a transfusion(s) during the Screening/Observation Period prior to the first study drug infusion if medically indicated per the Investigator's discretion. However, the baseline visit (and the first infusion of study drug) had to occur at least 7 days following the transfusion.

Part A

In Part A, 24 patients with CAD who had a recent history of transfusion, defined as at least 1 transfusion during the last 6 months prior to enrollment were enrolled. Patients received sutimlimab IV on Days 0 and 7 and biweekly thereafter. Patients who missed a dose (ie, outside the dosing window or >17 days since the last dose) received an additional loading dose. Patients had an end-of-treatment (EOT) visit on Day 182 (Week 26).

Although there are no generally recognized criteria nor guidelines for RBC transfusion in CAD patients, this protocol included criteria accepted by most clinicians to support consistency and interpretability of the data from the study. For administration of transfusions independent of the clinical practice or decision of the investigator for the specific patient. Patients who met the transfusion criteria below during the 6-month treatment period were to receive a transfusion. Patients who received a transfusion during Part A were not withdrawn from the study and were eligible to participate in Part B. Part B is ongoing and the results will be provided in a separate report.

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.

Part B

Following the completion of dosing in the 6-month treatment period, eligible patients continued to receive sutimlimab dosing during Part B, the long-term safety and durability of response extension phase. Part B is ongoing.

Number of participants:

Planned: 20

Enrolled: 24

Treated: 24

Evaluated:

Efficacy/pharmacodynamics: 24
Safety: 24

Pharmacokinetics: 24

Diagnosis and criteria for inclusion:

Confirmed diagnosis of primary 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; IgG DAT ≤1+; no overt malignant disease. History of at least 1 documented blood transfusion within 6 months of enrollment and hemoglobin level ≤10.0 g/dL.

Study products

Investigational medicinal product: Sutimlimab

Formulation: Sterile solution containing 18 or 50 mg/mL sutimlimab with a 10 mM sodium phosphate buffer, 140 mM NaCl, 0.02% polysorbate 80 (Tween-80), and water for injection

Route(s) of administration: Intravenous (IV)

Dose regimen: 6.5 g (if <75 kg) or 7.5 g (if ≥75 kg); single dose on Day 0 and Day 7 followed by maintenance dosing every 14 days thereafter; dose administered over approximately 60 ± 5 minutes

Duration of treatment/participation: 25 weeks (Part A)

Duration of observation: 26 weeks

Criteria for evaluation:

Efficacy/pharmacodynamics:

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

- Hemoglobin level was ≥12 g/dL at the treatment assessment endpoint (defined as the mean value from Weeks 23, 25, and 26) or
- Hemoglobin level increased by ≥2 g/dL from baseline (defined as the last hemoglobin value before administration of the first dose of study drug) at the treatment assessment endpoint.

The secondary efficacy endpoints for Part A were as follows:

- 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 Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue 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

Safety assessments were performed throughout the study as shown in Table 5. Safety endpoints included:

- Incidence of treatment-emergent adverse events (TEAEs) and treatment-emergent serious adverse events (SAEs)
- Change from baseline in clinical laboratory evaluations
- Change from baseline in systemic lupus erythematosus (SLE) panel
- Change from baseline in vital signs
- Change from baseline in electrocardiogram (ECG) data
- Physical examination findings
- Incidence of infections of ≥ Grade 3 severity (ie, requiring IV antibiotics)
- Incidence of thromboembolic events

Pharmacokinetics:

- Plasma concentrations of sutimlimab
- PK exposure parameters will be provided in a separate report using a population approach.

Pharmacodynamics:

- Pharmacodynamic primary outcome measure: Wieslab-CP
- Exploratory complement system measures: CH50, Total C4, complement component 1 q subcomponent (C1q), C1s

Pharmacokinetic/Pharmacodynamics sampling times and bioanalytical methods:

Pharmacokinetic and PD blood samples were collected predose and 1 hour 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 analysis was collected during the EOT visit on Day 182 or at early termination (ET) if a patient withdrew early.

Statistical methods:

The Full Analysis Set (FAS) population consisted of all patients who received at least 1 dose (including partial dose) of study drug.

Analyses of efficacy were performed on the FAS. Patients who received at least 1 dose (including partial dose) of study drug were included in the Safety Analysis Set. In this study the FAS and Safety analysis set were the same.

Efficacy

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 (nonresponder) and the 95% CI for the proportion of responders was calculated using Clopper-Pearson exact method.

Any patient who withdrew from the study after Week 5 and prior to the Week 23 visit was considered a nonresponder.

To assess the hematology component of response, the mean of the nonmissing hemoglobin assessments at the Week 23, Week 25, and Week 26 analysis visits (treatment assessment endpoint) was used. Patients missing all 3 analysis visits were counted as nonresponders.

With the determination that a response rate ≤30% is not clinically relevant, the success criteria for the primary endpoint was that the 95% lower bound CI for response rate excludes 30% using the exact Clopper-Pearson method. That is, this criterion is equivalent to demonstrating at the 2 sided 0.05 level of significance that the true response rate is >30%.

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.

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). For these analyses, if there were <5 patients in a category, the cutoff may have been modified to adjust distribution.

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. Additional sensitivity analyses were carried out using multiple imputations.

Safety endpoints

Adverse events were classified using the Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and preferred term (PT) version 21.0. Tabulations of TEAEs and TESAEs by frequency, relatedness, and severity were presented. Tabulations of serious TEAEs by frequency and relatedness were presented. Patient listings were provided for AEs, SAEs, AEs resulting in discontinuation of the study or study treatment, and all deaths. In addition, specific summary tables were presented for hemolytic breakthrough and infections (Grade 3 or above).

Changes from baseline in clinical laboratory parameters (except those considered efficacy and PD endpoints), vital signs, and ECG parameters were summarized over time using descriptive statistics.

Clinically significant physical examination findings were to be reported as AEs.

Summary Results:

Population characteristics:

Twenty-four patients were enrolled in Part A of the study; 22 patients completed 6 months of sutimlimab treatment in Part A and are continuing treatment in Part B. The study population was mostly female (62.5%) and elderly, with a median age of 71.5 years. Patients were transfusion dependent and received a median of 2 transfusions in the 6 months prior to screening. As expected in a patient population with hemolytic anemia, the patients generally had elevated levels of bilirubin, LDH, and reticulocytes and decreased levels of hemoglobin and haptoglobin. Within 5 years of screening, 62.5% of patients had received prior CAD directed therapy within the last 5 years.

Efficacy/pharmacodynamic results:

In summary, in this single blind, open-label study conducted in patients with CAD, the primary endpoint was met. Given that this was a single arm study in patients with a high unmet need, stringent criteria consistent with amelioration of the hemolytic anemia that is responsible for the clinical presentation of this severe condition, were set for the primary endpoint. A total of 54.2% of the patients met the high threshold set for the primary composite endpoint. Moreover, 6 of the 11 patients who did not meet the criteria for the primary endpoint did achieve important clinically meaningful improvements in their disease as measured by normalization of bilirubin levels, improvements in hemoglobin levels, and improvement in FACIT-Fatigue. The improvements in clinical efficacy measures related to hemolysis (bilirubin), anemia (hemoglobin), and fatigue (FACIT-Fatigue) were rapid and clinically significant within the first few doses. All patients who completed Part A (22 of 24 patients) elected to continue in Part B.

Primary endpoint

- A total of 13 patients (54.2%, 95% CI: 32.8 to 74.4) of patients met the criteria for the primary endpoint (ie, lower bound of the 95% CI was >30%). Furthermore, the robustness of the results were supported by 3 sensitivity analyses: PP population; excluding patients who discontinued prior to Week 23; and using hemoglobin ≥LLN as a cutoff.

  - At the treatment assessment endpoint, 9 (37.5%) patients had normalized hemoglobin (≥12 g/dL), 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. At any time during the study after Week 5, 15 (62.5%) patients had normalized hemoglobin (≥12 g/dL).

  - Treatment response analyzed based on intrinsic variables and disease severity was consistent with the primary endpoint.

Secondary endpoints

- Reductions in bilirubin were observed from 55.26 µmol/L (2.7-fold ULN) at baseline and 15.48 µmol/L (0.8-fold ULN) at the treatment assessment endpoint. Mean bilirubin was maintained below ULN after Week 3.
- An increase in FACIT-Fatigue LS mean score of 10.85 points was observed at the treatment assessment endpoint, with improvements observed beginning Week 1. At least 75% of patients had meaningful improvements in FACIT-F scores (Interquartile range [IQR]: 5.00 to 15.50 points).
- Reductions in mean LDH observed beginning at Week 1 were sustained through EOT. A total of 14 (58.3%) patients had LDH values ≤1.5 × ULN at the treatment assessment endpoint.
- Seventeen (70.8%) patients did not receive a transfusion between Weeks 5 and 26.
- Mean baseline hemoglobin levels increased by 2.62 g/dL from 8.64 g/dL to 11.26 g/dL between Weeks 5 and 26. At any time during the study after Week 5, 17 (70.8%) patients had a ≥2 g/dL increase in hemoglobin, and 19 (79.2%) patients had either a ≥2 g/dL increase or normalization of hemoglobin.
- Increases in mean hemoglobin were observed beginning at Week 1 and were sustained through the treatment assessment endpoint. From Week 3 onward, the mean hemoglobin level was >11 g/dL and the change from baseline ≥2 g/dL at all time points. At the treatment assessment timepoint, 18 (75.0%) patients had achieved means increase in hemoglobin level of ≥1 g/dL, 15 (62.5%) patients had achieved ≥1.5 g/dL increases, 15 (62.5%) patients had achieved ≥2 g/dL increases, and 8 (33.3%) patients had achieved ≥3 g/dL increases.
- At the treatment assessment endpoint, patients who met the primary endpoint criteria had a mean hemoglobin value of 12.3 g/dL (increase of 3.9 g/dL) and patients not meeting the criteria had a mean hemoglobin value of 9.8 g/dL (increase of 0.7 g/dL).

Exploratory endpoints

- At any time during the study after Week 5, 17 (85.0%) patients had normalized bilirubin, 11 (68.8%) patients had normalized LDH, and 12 (54.2%) patients had normalized haptoglobin. Fourteen (58.3%) patients had LDH values ≤1.5 × ULN at the treatment assessment endpoint. Fifteen (62.5%) patients had a ≥1 g/dL in hemoglobin and concurrent normalization of bilirubin at >50% of study visits.
- Patients showed improvement in patient reported quality-of-life assessments including EQ-5D-5L, SF-12, PGIC, and PGIS.
- Improvements in solicited anemia symptoms were observed for fatigue, weakness, shortness of breath, palpitations, and chest pain. A reduction in the incidence of hemoglobinuria was observed.
- No patient experienced a treatment-emergent thromboembolic event.
- Other PD markers

- No clinically meaningful changes in IgG, IgM, IgA, and IgD were observed.

- Near complete inhibition of mean CP activities was observed after the 1st dose and sustained throughout the treatment period, consistent with maintained suppression of CH50.

- The decreased C4 levels seen at baseline were rapidly restored to normal shortly after the 1st dose of sutimlimab.

Safety results:

● Overall, the safety profile of sutimlimab in patients with CAD who had a history of a recent blood transfusion in Study BIVV009-03 was assessed in 24 patients in Part A. Patients were between 55 to 85 years of age with a median age of 71.5 years. Patients received amedian 26.14 weeks of sutimlimab. Sutimlimab was generally well tolerated. The primary safety results included the following:

● One death occurred during the study due to hepatic cancer on Day 32; the patient was diagnosed with hepatic cancer on Day 22 and the death was assessed as not related to sutimlimab

● A total of 124 TEAEs were reported in 22 (91.7%) patients. Nine (37.5%) patients experienced a total of 13 TEAEs assessed by the Investigator as related to sutimlimab. The TEAEs reported in 2 patients were abdominal pain upper, anemia, arthralgia, confusional state, cough, cyanosis, diarrhea, edema peripheral, fall, gastroenteritis, hemorrhoids, headache, infusion related reaction, nasopharyngitis, and upper respiratory tract infection. No TEAEs were reported in more than 2 patients.

● The TEAEs assessed related to sutimlimab included infusion related reaction which was reported in 2 patients and all of the other related TEAEs were reported in one patient each and included: cyanosis, abdominal distension, application site hemorrhage, edema peripheral, cystitis bacterial, blood pressure increased, tendonitis, rhinorrhea, erythema, and hypertension. All of the TEAEs assessed by the Investigator as related to sutimlimab were Grade 1 or 2 in severity.

● Seven (29.2%) patients experienced a total of 16 TESAEs, all assessed by the Investigator as not related to sutimlimab. The type and incidence of TESAEs observed in the study were similar to what is expected for a medically complex, elderly study population, with no TESAE reported in ≥1 patient.

● Thirteen patients experienced 23 TEAEs of infection and of these, 2 patients had serious infections including 1 patient with TESAEs of streptococcal sepsis and wound infection staphylococcal (infected hematoma after Lichtenstein surgery) following inguinal hernia surgery and 1 patient with 2 TESAEs of respiratory tract infection. No AEs of meningitis or infections with meningococcus were reported, though other serious infections with encapsulated bacteria (Streptococcus pyogenes and Staphylococcus species) were reported. The type and frequency of TEAE infections was generally consistent with the demographics, medical history and prior/concomitant medication use of the study population.

● One patient permanently discontinued study drug due to TESAEs of gastrointestinal haemorrhage and hepatic cancer and subsequently discontinued from the study due to the fatal TESAE of hepatic cancer. A second patient discontinued from the study due to a pretreatment SAE of polymyalgia rheumatica.

● There were no TEAEs of anaphylaxis associated with sutimlimab administration. Three patients experienced TEAEs suggestive of a potential hypersensitivity reaction associated with sutimlimab treatment. The events included 2 TEAEs reported as infusion related reactions and 1 event of erythema. All of the TEAEs suggestive of a potential hypersensitivity reaction associated with sutimlimab administration were assessed as Grade 1 or 2 in severity.

● Six (25.0%) patients experienced 6 TEAEs within 24 hours of the start of study drug infusion. Infusion related reaction (2 patients) was the only TEAE reported in >1 patient. All of the events were Grade 1 or 2 except Grade 3 air embolism (dyspnea probably due to air embolism). Three TEAEs within 24 hours of the start of study drug infusion were assessed by the Investigator as related to sutimlimab: 2 events of infusion related reaction 1 event of blood pressure increased.

● No TEAEs suggestive of autoimmune disease, including SLE, were reported. One patient had a pre-treatment TESAE of [Medical History] on Day [**] that led to permanent study drug discontinuation and study withdrawal. This patient shifted from a negative ANA result at Day [**] to positive post-baseline. Other shifts in SLE panel parameters from negative at baseline to positive post-baseline or positive at baseline to negative post-baseline were not associated with clinical symptoms or reported TEAEs of autoimmune diseases.

● Clinical laboratory parameters: The majority of clinical laboratory abnormalities and shifts were consistent with clinical response to sutimlimab administration or due to underlying CAD disease process. Other than the changes noted below, no clinically meaningful patterns or trends in mean changes were noted. The data do not indicate that sutimlimab administration adversely affects hematology, chemistry or coagulation panel values.

- Shifts to low lymphocyte and platelet counts occurred more frequently than shifts to high values and shifts to high neutrophil values occurredmore frequently than shifts to low values. Few patients had PCSA values associated with shifts, with the exception of lymphocyte count <0.8 × 109/L (11 patients). In most cases, the lymphocyte count was low or PCSA low at screening and/or baseline and the low value only persisted for a few weeks. The only TEAEs in patients with PCSA hematology values were associated with anemia.
- One patient with at PCSA high ALT value had a Grade 2 TEAE of increased ALT that resolved by the following visit.

● No apparent clinically meaningful patterns or trends in vital signs were observed.

● No clinically meaningful patterns or trends were observed in ECG changes.

Pharmacokinetic results:

- After 4 doses of sutimlimab, 6.5 g or 7.5 g, the plasma concentrations appeared to reach steady-state, on average, by Week 5. The PopPK trough and peak sutimlimab concentrations remained constant throughout the treatment period.
- The plasma concentration-time profiles of sutimlimab over the treatment period overlapped between the two dose groups, indicating that the body weight stratified dose levels was appropriate.
- The coefficients of variability, %CV, of the measured plasma concentrations were similar between two groups with values of 19.34 to 78.45% (6.5 g) and 39.53 to 79.50% (7.5 g).
- Only 2 patients had plasma concentrations less than 100 µg/mL during the 26-week treatment period, and no patients had levels less than 20 µg/mL, which was consistent with the prediction from the population analysis of Studies BIVV009-01 and BIVV009-02 (Population PK report TNTH-CSC-103).

Issue date: 13-Jul-2023

Sponsor: Sanofi **Drug substance(s):** BIVV009	**Study Identifiers:** NCT03347396; EudraCT Number: 2017-003538-10 **Study code:** EFC16215 (BIVV009-03)

Title of the study:

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

Study center(s):

22 study sites screened at least 1 patient and 16 study sites enrolled at least 1 patient. The study was conducted at investigational sites in the United States, Australia, Germany, France, Italy, Japan, Norway, and the United Kingdom. Patients were screened in Austria, Belgium, and the Netherlands, but none were enrolled.

Study period:

Date first patient enrolled: 05 March 2018 (first patient enrolled in Part A)

Date last patient completed: 11 July 2019 (Part A); 05-Oct-2021 (Part B).

Phase of development: 3

Objectives:

The primary objective of Part B was to evaluate the long-term safety and tolerability of sutimlimab in patients with cold agglutinin disease (CAD).

The secondary objective of Part B was to investigate the durability of response during long-term treatment with sutimlimab in patients with CAD.

Methodology:

BIVV009-03 was an open-label, single-arm, 2-part, Phase 3 study designed to evaluate the efficacy/durability of effect, safety, and tolerability of sutimlimab (BIVV009) in patients with the complement-mediated disorder, CAD. The study enrolled symptomatic CAD patients with evidence of active hemolysis and who had a history of recent blood transfusion in the prior 6 months. Part A of the study was a 6-month pivotal safety and efficacy treatment phase, which was completed on 11 July 2019. Patients who were on the study treatment at the end of Part A rolled over from Part A into long-term extension Part B to evaluate the long-term safety, tolerability, and durability of effect of sutimlimab treatment.

Beyond the permitted concomitant medications, study drug, and transfusions, patients were not supposed to receive other therapies for the treatment of CAD while enrolled in this study.

In Part B, patients were dosed with sutimlimab every 2 weeks, as in Part A. Should patients deviate from their scheduled dosing (ie, outside the dosing window or >17 days since the last dose), a repeat loading dose was required. If patients missed a dose (ie, outside the 2-day dosing window or >17 days since the last dose), they were to return to the site for an unscheduled visit, 1 week prior to the next scheduled dose in order to receive an additional loading dose. Then they were to resume subsequent dosing visits every 14 days (±2 days) after the loading dose.

Patients requiring treatment with permitted concomitant medications and/or transfusions were not to be discontinued from either Part A or Part B of the study. Patients in Part B were to be transfused if his or her hemoglobin level met either of the following criteria:

• Hemoglobin was <9 g/dL and the patient was symptomatic, or

• Hemoglobin was <7 g/dL and the patient was asymptomatic

A safety follow-up (SFU) visit for collection of adverse event (AE) data, pharmacokinetics (PK), pharmacodynamics (PD), and antidrug antibody (ADA) samples was performed 9 weeks after administration of the last dose of study drug in all patients, including those who discontinued early. Samples for PK, PD, and ADA were also collected from patients who experienced a hemolytic breakthrough event.

Part B of the study was completed 24 months following last patient out for Part A. At that time, all ongoing patients receiving treatment in Part B entered 9-week follow-up period followed by an end of study visit 9 weeks after the last dose.

Number of participants:

Treated in Part A: 24

Planned for Part B: 22 (all patients who completed Part A; 2 patients elected to withdraw during Part A and did not enter into Part B)

Treated in Part B: 22

Evaluated in Part B:

Efficacy: 22

Safety: 22

Diagnosis and criteria for inclusion:

Part A of this study enrolled 24 adult patients with CAD who had a recent history of transfusion, defined as at least 1 transfusion during the last 6 months prior to enrollment. Patients who met all the inclusion criteria and for whom none of the exclusion criteria applied were eligible for enrollment. Patients who were on the study treatment at the end of Part A rolled over from Part A into long-term extension Part B.

Study products

Investigational medicinal product(s): Sutimlimab

Formulation: Sterile solution containing 18 or 50 mg/mL sutimlimab with a 10 mM sodium phosphate buffer, 140 mM NaCl, 0.02% polysorbate 80 (Tween-80), and water for injection. The sutimlimab drug product originally contained 18 mg/mL sutimlimab and later 50 mg/mL after the 50 mg/mL concentration was formally introduced through an amendment to the protocol; and as sites received Institutional Review Board approval, the adoption of the 50 mg/mL concentration took place at the site pharmacy.

Route(s) of administration: Intravenous (IV)

Dose regimen: 6.5 g (if <75 kg) or 7.5 g (if ≥75 kg); single dose on Day 0 and Day 7 followed by maintenance dosing every 14 days thereafter during Part A and every 14 days starting at Week 27 during Part B; dose administered over approximately 60 ± 5 minutes

Duration of treatment: 2 years following last patient out for Part A

Duration of observation:

- Part A (up to 26 weeks)
- Part B (starting at Week 27 and continuing for up to 2 years after last patient out in Part A with a 9-week follow-up period after last treatment in Part B)

Criteria for evaluation:

Efficacy:
The efficacy endpoints included the following parameters of disease activity:

- Hemoglobin
- Bilirubin (total)
- Quality of life assessments - functional assessment of chronic illness therapy (FACIT)-Fatigue only (5-level EuroQol 5-dimensions questionnaire, 12-item short-form survey, patient's global impression of [fatigue] severity, and patient's global impression of change)
- Lactate dehydrogenase (LDH)
- Transfusion requirements
- Haptoglobin
- Reticulocyte count
- Incidence of solicited symptomatic anemia
- Total healthcare resource utilization parameters
- Satisfaction with home infusion. Note that home infusion methodology was planned but not implemented in this study; therefore, this endpoint was not analyzed.

Safety:

Safety assessments included the following:

• Incidence of treatment-emergent AEs (TEAEs) and serious AEs (SAEs)

• Change from baseline in clinical laboratory evaluations

• Change from baseline in systemic lupus erythematosus (SLE) panel

• Change from baseline in vital signs

• Change from baseline in electrocardiogram data

• Physical examination findings

• Serum disease-related biomarkers

• Incidence of infections of Grade ≥3 severity (ie, requiring IV antibiotics)

• Incidence of thromboembolic events

• Incidence of hemolytic breakthrough (rapid fall in hemoglobin ≥2 g/dL associated with an increase in LDH/total bilirubin and/or decrease in haptoglobin since the last scheduled visit through the end of treatment at Week 26)

• For patients with home infusions, safety assessments included AEs with onset within 24 hours of the infusion at home. Note that home infusion methodology was planned but not implemented in this study; therefore, this endpoint was not analyzed.

Pharmacokinetics:

Pharmacokinetic samples were routinely collected at 3-month intervals during the first year of treatment in Part B and then at 6-month intervals for the remainder of the time on study. Samples were also collected if a patient experienced a hematologic breakthrough event or a patient withdrew from study.

Pharmacodynamics:

Pharmacodynamic samples were routinely collected at 3-month intervals during the first year of treatment in Part B and then at 6-month intervals for the remainder of the time on study. Samples were also collected if a patient experienced a hematologic breakthrough event or a patient withdrew from the study.

Immunogenicity:

In Part B, immunogenicity endpoints included the evaluation of pre-existing ADA and treatment-emergent ADA.

Statistical methods:

All patients who completed Part A, including those who received transfusions, were eligible for Part B. Patients who withdrew from the study in Part A, including those who received prohibited concomitant medications, were not eligible to participate in Part B.

No power and sample size analysis was conducted for Part B. Patients from Part A were enrolled into Part B following the Part A end of treatment visit.

The Full Analysis Set (FAS) was defined as all patients who enrolled into the Part B study and received at least 1 dose (including partial dose) of study drug. Patients who received at least 1 dose (including partial dose) of study drug were included in the Safety Analysis Set. In this study, the FAS and Safety Analysis Set were the same.

Efficacy Endpoints:

Analysis of Efficacy Endpoints (Part B Study Period):

Continuous endpoints including LDH, haptoglobin, reticulocyte count, and FACIT-Fatigue score, as well as categorical endpoints including incidence of thromboembolic events and incidence of hemolytic breakthrough, were summarized for the Part B study period, starting at Week 27.

The endpoints were summarized by visit descriptively, including change from baseline for continuous endpoints, starting at Week 27. Baseline summaries were included for comparison.

Analysis of Efficacy Endpoints (Combined Study Period):

Continuous endpoints including hemoglobin and total bilirubin were summarized descriptively by visit, starting at baseline/Day 0. Summary tables included change from baseline and individual summary statistics.

Additionally, the following continuous endpoints were summarized by study period using the FAS:

- Number of transfusions and total transfusion units
- Annualized number of transfusions and annualized transfusion units

For annualized number of transfusions and annualized transfusion units, all Part B data (and Part A data in appendix and in clinical study report Table 8) will be considered. Annualized values will be calculated for each patient using the following formula:

$$\text{Annualized value} = \frac{\text{Number of events during the study period}}{\text{Total number of days during the study period}} \times 365.25$$

Safety Endpoints:
All safety data were summarized for patients in the Safety Analysis Set. Adverse events were classified using the Medical Dictionary for Regulatory Activities system organ class (SOC) and preferred term (PT) version 23.0. Tabulations of TEAEs and serious TEAEs by frequency, relatedness, and severity were presented. Patient listings were provided for all AEs.

Summary Results:

Population characteristics:

Part A of this study enrolled 24 adult patients with CAD who had a recent history of transfusion, defined as at least 1 transfusion during the last 6 months prior to enrollment. Patients who met all the inclusion criteria and for whom none of the exclusion criteria applied were eligible for enrollment. Patients who completed Part A of the study and were able and willing to enter the long-term extension Part B were enrolled. All 22 patients who had completed Part A enrolled into Part B, with 19 (86.4%) patients completing Part B without an early termination (ET), including 18 (81.8%) patients who completed the SFU visit. One (4.5%) patient died during SFU due to exacerbation of CAD approximately 1.5 months after receiving the last dose of sutimlimab in the treatment phase and did not complete the SFU visit. Three (13.6%) patients discontinued the study drug and/or the study due to TEAEs. Two of the patients discontinued treatment due to treatment-emergent SAEs (TESAEs) of fatal pneumonia Klebsiella and cyanosis in one patient and vitreous hemorrhage in another patient.

One patient was discontinued due to nonserious events of dyspepsia, dysphagia, erosive gastritis, and cyanosis.

The study population had a median age of 71.5 years, and most patients (81.8%) were ≥65 years of age. Most patients (68.2%) were from Europe, and most (68.2%) were female.

Efficacy and pharmacodynamics results:

Part B of the BIVV009-03 study was designed to assess the safety and tolerability as well as durability of response to sutimlimab treatment. Collectively, the data suggest that, with long-term treatment with sutimlimab, hemoglobin levels remain increased over baseline; hemolysis continues to be inhibited, as evidenced by continued normalization of bilirubin levels; and fatigue remains improved, as demonstrated by sustained FACIT-Fatigue scores. For the other PD markers assessed, near complete inhibition of mean CP activities (Wieslab-CP) observed after the first dose was sustained through the Part B treatment period, consistent with maintained suppression of CH50. The decreased C4 levels seen at baseline were rapidly restored to normal shortly after the first dose of sutimlimab and maintained through the treatment period of Part B.

In contrast, once sutimlimab was no longer administered during the 9-week SFU, there was evidence of a return of hemolysis activity as evidenced by the following observed changes in laboratory parameters and biomarkers. At SFU (9 weeks after the last dose of sutimlimab), in the majority of patients, levels of bilirubin (the most relevant marker of extravascular hemolysis) increased while hemoglobin levels and FACIT-Fatigue scores decreased from the last available treatment value, the near-complete inhibition of CP activity observed throughout the treatment period was reversed, and CH50 and C4 levels returned toward baseline. These findings are also consistent with a concomitant decrease in measurable sutimlimab concentrations upon the discontinuation of sutimlimab. Without sutimlimab CP inhibition, there was a resumption of the CP-mediated hemolysis that is the hallmark pathophysiology of CAD.

Safety results:

In Part A/B, patients received a median duration of 144.1 weeks (range 54.0 to 177.1) of sutimlimab and a median of 72.5 administered doses of sutimlimab (range 22.0 to 89.0). In Part B, patients received a median of 77.6 weeks (range 27.9 to 107.9 weeks) of sutimlimab and a median of 88.0 administered doses of sutimlimab.

The type and frequency of AEs were generally consistent with the underlying disease indication, reported medical history, and an elderly, medically complex patient population. The primary safety results in Part B included the following:

- Two deaths due to TEAEs occurred: one patient due to a TEAE of Klebsiella pneumonia 14 days after the last dose of sutimlimab and another patient due to TEAE of exacerbation of cold-type hemolytic anemia approximately 1.5 months after the last dose of sutimlimab in the treatment phase. Both fatal events were considered to be not related to the study drug by the investigator.
- All 22 patients reported at least 1 TEAE; a total of 380 TEAEs were reported. The most frequently reported (>10% of patients) TEAE PTs were anemia (7 [31.8%] patients); fatigue (6 [27.3%] patients); cyanosis, diarrhea, nausea, pyrexia, and urinary tract infection (5 [22.7%] patients each); arthralgia, constipation, dizziness, headache, hypertension, and nasopharyngitis (4 [18.2%] patients each); and abdominal pain upper, cold type hemolytic anemia, cystitis, dyspnea, Escherichia urinary tract infection, non-cardiac chest pain, edema peripheral, and urinary tract infection bacterial (3 [13.6%] patients each).

- During the 9-week safety follow up period, TEAEs experienced by the majority of patients (10/11) were attributed to exacerbation of underlying CAD following completion of treatment with sutimlimab.
- Twelve (54.5%) patients had at least 1 TESAE. A total of 37 TESAEs were reported, including for 7 (31.8%) patients who experienced at least 1 event each within the SOC of infections and infestations.
- Eleven (50.0%) patients had a total of 16 TEAEs assessed by the Investigator as related to sutimlimab. Additionally, two patients had a TESAE (viral infection in 1 patient and vitreous hemorrhage in 1 patient) that was assessed by the Investigator as related to sutimlimab.
- Two patients discontinued treatment due to TESAEs of Klebsiella pneumonia and cyanosis in 1 patient and vitreous hemorrhage in another patient. One patient was discontinued due to nonserious events of dyspepsia, dysphagia, gastritis erosive, and cyanosis. The events of dysphagia, vitreous hemorrhage, and 1 nonserious event of cyanosis were assessed by the Investigator as related to sutimlimab. All events of cyanosis were reported as acrocyanosis.
- Eight (36.4%) patients had an infection of ≥Grade 3. All events were reported as TESAEs, except for 2 nonserious TEAEs of urinary tract infection. Serious infections with encapsulated bacteria were reported, including 1 TESAE of pneumococcal sepsis caused by encapsulated protocol-defined vaccine-related organism. Two TESAEs involving COVID-19 infection were reported. No infections with meningococcus or TEAEs of meningitis were identified. One of the TESAEs (viral infection) was assessed as related to sutimlimab by the Investigator, and study drug was interrupted. One patient died due to pneumonia caused by *Klebsiella pneumoniae*.
- Two patients reported a thromboembolic TEAE. One patient had a TESAE of peripheral artery thrombosis and 1 patient had a nonserious TEAE of device-related thrombosis.
- Two TEAEs were assessed as autoimmune conditions, each with a prior history of symptoms consistent with preexisting autoimmune disorders. One patient with a history of [Medical History] and [Medical History] experienced [Medical History] relapse. A second patient with a medical history of [Medical History], [Medical History], and [Medical History] at screening, was diagnosed with systemic scleroderma during the study.
- No TEAEs suggestive of a serious hypersensitivity reaction or anaphylaxis were identified. One TEAE of rash maculo-papular occurred on the same day as sutimlimab infusion, and the event was assessed as related by the Investigator. One TEAE of rash pustular which was suggestive of a potential hypersensitivity reaction was reported. The event was assessed as not related to sutimlimab by the Investigator.
- Five patients had a TEAE within 24 hours of the start of the infusion; stress cardiomyopathy (reported as Tako-Tsubo cardiomyopathy due to stress), rash maculo-papular, constipation, hypertension, ankle fracture.
- Of the 22 patients evaluable for ADAs, 2 (9.1%) patients developed treatment-induced ADA. Antidrug antibody did not impact PK and PD in these 2 patients, indicating the low immunogenic potential of sutimlimab.

Pharmacokinetic results:

- After 5 doses of sutimlimab, 6.5 g or 7.5 g, the plasma concentrations appeared to reach steady state, on average, by Week 7 during Part A treatment period. The trough and peak sutimlimab concentrations remained constant and sustained through Part B treatment period.
- The plasma concentration versus time profiles of sutimlimab over the treatment period overlapped between the 2 dose groups, indicating that the body weight stratified dose levels was appropriate.
- The coefficients of variability, %CV, of the measured plasma concentrations were similar between the two dose groups during Part B.
- Only 3 patients had plasma concentrations less than 20 µg/mL during Part B treatment period whilst remaining patients had concentrations above 100 µg/mL. Two of the 3 patients showed dose interruptions which contributed to concentrations <20 µg/mL. This is consistent with the prediction from the population PK analysis report POH0797 of studies BIVV009-01, BIVV009-02, BIVV009-03 (Part A, interim Part B), BIVV009-04 (Part A), and BIVV009-05.
- Sutimlimab concentration at ET/SFU visit decreased to below the lower limit of quantification in most patients except for 3 patients had concentration >100 µg/mL.

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