Sponsor: Sanofi **Drug substance(s):** BIVV009 (sutimlimab)	**Study Identifiers:** NCT03347422; EudraCT Number: 2017-003539-12 **Study code:** EFC16216 (BIVV009-04)

Title of the study:

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

Study center(s):

A total of 66 patients were screened and 42 were enrolled at 27 sites. The study was conducted in Australia, Austria, Canada, Germany, France, Italy, Israel,Japan, Netherlands, Norway, Spain, United Kingdom, and United States.

Study period:

Date first patient enrolled: 06 March 2018

Date last patient completed: 29 September 2020 (Part A)

Study Status: Completed

Phase of development: 3

Objectives:

The primary objective of Part A was to determine whether sutimlimab administration results in a ≥1.5 g/dL increase in hemoglobin level and avoidance of transfusion in patients with primary cold agglutinin disease (CAD) without a recent history of blood transfusion.

The secondary efficacy objectives of Part A were:

• To assess the effect of sutimlimab on clinical events and laboratory parameters related to hemolysis and anemia in patients with primary CAD

• To assess the effect of sutimlimab on specific complications of CAD (acrocyanosis, Raynaud's syndrome, hemoglobinuria, and thromboembolism)

• To assess the effect of sutimlimab on quality of life (QOL) in patients with primary CAD.

The safety objective of Part A was:

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

The exploratory objectives of Part A were:

• To evaluate the effect of sutimlimab on certain disease-related biomarkers in patients with primary CAD

• To evaluate the pharmacokinetics (PK) of sutimlimab

• To evaluate the immunogenicity of sutimlimab

Methodology:

This is a randomized, double-blind, placebo-controlled study designed to evaluate the efficacy and safety of sutimlimab in symptomatic patients with the complement-mediated disorder primary CAD with no recent history of blood transfusion.
Eligible patients were to be diagnosed with primary CAD at least 6 months prior to enrollment and not have a recent history of blood transfusion (ie, ≤1 transfusion during the last year and no transfusion during the last 6 months prior to enrollment). Patients could receive a transfusion(s) during the Screening/Observation Period prior to the first investigational medicinal product (IMP) infusion if medically indicated per the Investigator's discretion. However, the baseline visit (and first infusion of IMP) had to occur at least 7 days following the transfusion.
During the 6-week Screening/Observation Period, prospective patients had a detailed medical history collected that included transfusion history, physical evaluations, and blood samples collected on 3 occasions approximately every 2 weeks.
Part A
Eligible patients were randomized 1:1 to receive an IV infusion of sutimlimab or placebo over approximately 60 minutes on Day 0, Day 7, and every 14 days thereafter through Week 25 (ie, Days 21, 35, 49, 63, 77, 91, 105, 119, 133, 147, 161, and 175). Patients who missed a dose (ie, outside the 2-day dosing window or >17 days since last dose) 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. Patients had an end-of-treatment (EOT) visit in Part A on Day 182 (Week 26).
A patient received a transfusion during Part A or Part B if his or her hemoglobin level met either of the following criteria:
• Hemoglobin is <9 g/dL and the patient was symptomatic, or
• Hemoglobin is <7 g/dL and the patient was asymptomatic
Part B
Following completion of dosing in the initial 6-month treatment period, patients continue to receive open-label sutimlimab in Part B for up to 1 year after last patient completed Part A. A subset of patients from preselected countries are eligible for home infusion performed by a healthcare professional caregiver after receiving at least 3 months of treatment in Part B. In addition, at least 15 patients will receive infusions with IMP undiluted with saline solution. Part B is ongoing and the results are presented in a separate report; the data cutoff date for the Part B report was 29 September 2020.

Number of participants:

Planned: 40 (20 sutimlimab and 20 placebo)

Randomized: 42

Treated: 42

Evaluated:

Efficacy/pharmacodynamics: 42 patients (22 sutimlimab and 20 placebo)
Safety: 42 patients (22 sutimlimab and 20 placebo)

Pharmacokinetics: 42 patients (22 sutimlimab and 20 placebo)

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. No history of blood transfusion within 6 months of enrollment or more than one blood transfusion within 12 months of screening and hemoglobin level ≤10.0 g/dL.

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 Route of administration: Intravenous (IV) Dose regimen: 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
Non investigational medicinal product(s) Formulation: Sterile solution of 10 mM sodium phosphate buffer, 140 mM NaCl, 0.02% polysorbate 80 (Tween-80), and water for injection Route of administration: IV Dose regimen: 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: 26 weeks in Part A **Duration of observation:** 26 weeks in Part A

Criteria for evaluation:

Efficacy/pharmacodynamics:
The primary efficacy endpoint in Part A was defined as meeting all 3 of the following criteria:
• Hemoglobin increased ≥1.5 g/dL from baseline (defined as the last hemoglobin value before administration of the first dose of IMP) at treatment assessment endpoint (defined as mean value from Weeks 23, 25, and 26) and
• The patient did not receive a blood transfusion from Week 5 through Week 26 (EOT), and
• The patient did not receive treatment for CAD beyond what was permitted per protocol from Week 5 through Week 26 (EOT)
The secondary efficacy endpoints in Part A were:
• Mean change from baseline in hemoglobin at treatment assessment endpoint (mean of values at Week 23, 25, and 26)
• Mean change from baseline in bilirubin (excluding patients with Gilbert's Syndrome) at treatment assessment endpoint
• Mean change from baseline in QOL, as assessed by the change in Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue scale (Appendix 16.1.1 Amended Protocol 7, Appendix C) scores at the treatment assessment endpoint
• Mean change from baseline in lactate dehydrogenase (LDH) at the treatment assessment endpoint
• Incidence of solicited symptomatic anemia at EOT

Safety:

Safety assessments were performed throught the study. The safety endpoints included:

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

• Change from baseline in clinical laboratory evaluations

• Change from baseline in 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

• For patients with home infusions, safety assessments also included AEs with onset within 24 hours of the of infusion

• For patients receiving undiluted infusions, safety assessments also included AEs with onset within 24 hours of the infusion

Pharmacokinetics:

• Sutimlimab plasma concentrations

• Sutimlimab exposure parameters including maximum plasma concentration (Cmax) and area under the concentration versus time curve (AUC)

Pharmacodynamics:

The primary PD analysis was the Complement Classical Pathway (Wieslab CP) assay.

Pharmacokinetic/Pharmacodynamics sampling times and bioanalytical methods:

During Part A, PK and PD blood samples were collected at predose and 1 hour (±15 minutes) post-dose (ie, 1 hour after 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 samples for PK and PD analysis were 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 predose and 1 hour (±15 minutes) postdose on Days 189, 217, and 245, then routinely at 3-month intervals starting at Day 273 through the remainder of the study. PK and PD samples were also collected if a patient experienced a hematologic breakthrough event at any point during the study.

Statistical methods:

The primary efficacy analysis was to compare the proportion of patients meeting primary endpoint criteria ("responder rate") in the sutimlimab treatment arm with the placebo treatment arm using the COVID-adjusted Composite estimand. If no patients missed both the Week 23 and 25 study visits due to COVID-19, the primary efficacy analysis was to be performed using the Composite estimand as shown in Table 1.

To reject the null hypothesis of no treatment difference, the pooled 2-sided p-value based on a stratified Cochran-Mantel-Haenszel (CMH) test had to be <0.05. The test was to be stratified by baseline hemoglobin (<median baseline hemoglobin versus ≥median baseline hemoglobin) and geographic region (Japan/Australia, United States, Europe). In the case of completely unbalanced strata (all records within any strata fall within a single treatment arm), the CMH test was to be stratified only by baseline hemoglobin.

Subgroup analyses for the primary endpoint were performed by age (<65 and ≥65 years), gender (female/male), baseline weight (<75 kg and ≥75 kg), baseline hemoglobin level (<median, ≥median g/dL), previous rituximab monotherapy and/or cytotoxic therapy (yes/no), previous eculizumab therapy, and prior thromboembolic events within the last year.

Table 1: COVID-adjusted Composite Estimand

Population	FAS
Response variable	To meet primary endpoint criteria, a patient had to fullfill all 3 of the following components:
ICEs handling	• Change from baseline in hemoglobin at treatment assessment timepoint ≥1.5 g/dL • Free of post-baseline transfusion within the range of Week 5 and Week 26 visit dates • Receive no protocol prohibited medications within the range of Week 5 and Week 26 visit dates • Patients who early discontinued study prior to Week 23, for reasons other than COVID, were considered as not having met primary endpoint criteria ("non-responders") • Patients with no hemoglobin data from Week 23, 25, and 26, for reasons other than COVID, were considered as not having met primary endpoint criteria ("non-responders"). If a patient had a COVID-related infusion gap (defined as ≥2 consecutive missed infusions due to COVID), transfusions received and protocol-prohibited CAD medications taken during the infusion gap and within the 5 weeks following the infusion gap were not to be included in the primary endpoint ("responder") derivation.
Measure of treatment effect	• Odds ratio of the proportion of responders in sutimlimab and placebo using the Cochran-Mantel-Haenszel test • Patients missing infusions at Week 23 and 25 due to COVID had their hemoglobin at treatment assessment timepoint imputed using multiple imputation with an MMRM approach.

CAD=cold agglutinin disease; COVID=coronavirus disease; FAS=full analysis set; ICE=intercurrent events; MMRM=mixed peated measures

Secondary efficacy endpoints
All secondary efficacy endpoints (change from baseline in hemoglobin, bilirubin, lactate dehydrogenase [LDH], and FACITFatigue) 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.
Safety
Adverse events were classified using the Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and preferred term (PT) version 23.0. 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:

Forty-two patients were enrolled in Part A of the study (22 sutimlimab and 20 placebo). Three patients discontinued Part A due to TEAEs. All of the other patients completed 6 months of sutimlimab or placebo treatment in Part A. The study population was mostly female (78.6%) and elderly, with a mean age of 66.7 years. As per protocol, no patients had received a transfusion within 6 months of screening. Within >6 months to 12 months prior to screening, 3 patients in the sutimlimab arm had received 1 transfusion each, versus no patient in the placebo arm. 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, 73.8% of patients had received prior CAD directed therapy, including rituximab and chemotherapy.

Efficacy/pharmacodynamic results:

Primary endpoint

• The study met the primary endpoint based on the proportion of patients who met all three primary endpoint criteria achieved with sutimlimab treatment compared with placebo. A statistically significant treatment effect was observed favoring sutimlimab over placebo. The results showed that the odds of meeting the primary response criteria in the sutimlimab group were significantly higher than in the placebo group; the odds ratio between sutimlimab and placebo estimated using a stratified CMH test with the FAS was 15.94 (95% CI: 2.88 to 88.04; p<0.001). No patients with COVID-related infusion gaps received a transfusion or prohibited medication obviating the need for a COVID-adjusted analysis.

- At the treatment assessment timepoint, 72.7% and 15.0% of patients in the sutimlimab and placebo groups, respectively, were observed to have a ≥1.5 g/dL increase in hemoglobin. From Weeks 5 to 26, 81.8% and 80.0% of patients in the sutimlimab and placebo groups, respectively, had no transfusions; and 86.4% and 100% of patients, respectively did not receive a prohibited CAD medication during that period.
- Treatment response analyzed based on demographics and baseline disease characteristics was generally consistent with the primary endpoint and favored sutimlimab over placebo.

Secondary endpoints

・The LS mean change in hemoglobin from baseline to TAT was 2.66 g/dL (95% CI: 2.09 to 3.22) in the sutimlimab group and 0.09 g/dL (95% CI: -.050 to 0.68) in the placebo group, with an LS mean difference of 2.56 g/dL (p<0.001; 95% CI: 1.75 to 3.38), showing there was a statistically significant difference in treatment effect on hemoglobin increase in favor of sutimlimab as compared to placebo. Clinically meaningful increases in hemoglobin were observed in the sutimlimab group beginning at Week 1.

・Improvements from baseline to Week 26 in anemia symptoms were observed in the sutimlimab group, while minimal or no improvement was observed for symptoms in the placebo group.

・The LS mean change in FACIT-Fatigue score from baseline to TAT increased 10.83 points (95% CI: 7.45 to 14.22) in the sutimlimab group and 1.91 points (95% CI: -1.65 to 5.46) in the placebo group, with an LS mean difference of 8.93 points (p<0.001; 95% CI: 4.0 to 13.85). Based on the results, there was a statistically significant difference in treatment effect on FACIT-Fatigue score improvement in favor of sutimlimab. Clinically meaningful increases in FACITFatigue score were observed in the sutimlimab group beginning at Week 1.

・Patients in the sutimlimab group had substantial mean reductions in bilirubin from baseline to TAT compared with insignificant changes in the placebo group (-22.129 µmol/L versus -1.829 µmol/L). At the TAT, mean bilirubin levels were normalized at 12.124 µmol/L in the sutimlimab group compared with 33.949 µmol/L in the placebo group. Clinically meaningful decreases in bilirubin were observed in the sutimlimab group beginning at Week 1.

・Patients in the sutimlimab group had substantial mean reductions in LDH from baseline to TAT compared with no change in the placebo group (-150.833 U/L versus 7.600). At the TAT, mean LDH values were 269.535 U/L in the sutimlimab group and 388.400 U/L in the placebo group. Clinically meaningful decreases in LDH were observed in the sutimlimab group beginning at Week 9.

Exploratory endpoints

・Patients who received sutimlimab showed greater improvement than patients who received placebo in patient reported quality-of-life assessments including EQ-5D-5L, SF-12, PGIC, and PGIS. Few patients were hospitalized and there was no difference in incidence between groups.

・Among patients who achieved hemoglobin ≥12 g/dL (81.8% sutimlimab and 20.0% placebo) at any time after Week 5, the median time to reach first normalization was 39 days (range 29 to 78) in the sutimlimab group and was not estimable in the placebo group as fewer than 50% of the placebo patients achieved such increases.

・Median times to first normalization of bilirubin, LDH, haptoglobin were 8.5 days, 37 days, and 89.0 days in the sutimlimab group and was not estimable in the placebo group as fewer than 50% of the placebo patients achieved such increases.

・Decreases in reticulocyte counts were observed beginning at Week 3 that leveled off at Week 5 in the sutimlimab group. No consistent changes in reticulocyte count were observed in the placebo group.

・Substantial reductions in the incidence of CAD symptoms at Week 26 versus baseline were observed in the sutimlimab group compared with minimal changes in the placebo group for acrocyanosis, Raynaud's syndrome, and hemoglobinuria.

・Other disease-related and PD markers

- No clinically meaningful changes in IgG, IgM, IgA, were observed in either treatment group. IgD levels increased nearly 2-fold in the placebo group with little change observed in the sutimlimab group.

- Near complete inhibition of mean CP activities was observed after the first dose and sustained throughout the treatment period, consistent with maintained suppression of CH50 in the sutimlimab group with no comparable changes observed in the placebo group.

- The decreased C4 levels seen at baseline were restored to normal shortly after the first dose of sutimlimab. No increase in C4 levels were observed in the placebo group.

Safety results:

Overall, the safety profile of sutimlimab in patients with CAD was assessed in 42 patients (22 sutimlimab and 20 placebo) in Part A. Patients had a mean age of 66.7 years (range 46 to 88). Patients received a median 26.14 weeks of sutimlimab or 26.14 weeks of placebo. Overall sutimlimab was generally well tolerated. While all patients except 1 patient in the sutimlimab group had ≥1 TEAE, the total number of TEAEs was higher in the sutimlimab arm. 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 included the following:

・No deaths were reported.

・A total of 146 TEAEs were reported in 21 (95.5%) patients in the sutimlimab group and 90 TEAEs were reported in 20 (100%) in the placebo group. Treatment-emergent AEs reported more frequently in the sutimlimab group than in the placebo group (≥2 patient difference in incidence) were hypertension (5 [22.7%] sutimlimab and 0% placebo), headache (5 [22.7%] and 2 [10.0%]), Raynaud's phenomenon (4 [18.2%] and 0%), rhinitis (4 [18.2%] and 0%), cyanosis (investigator term acrocyanosis) (3 [13.6%] and 0%]), constipation (2 [9.1%] and 0%), rash (2 [9.1%] and 0%), vaccination complication (2 [9.1%] and 0%), and insomnia (2 [9.1%] and 0%). Treatment-emergent AEs reported more frequently in the placebo group than in the sutimlimab group (≥2 patient difference in incidence) were anemia (2 [9.1%] sutimlimab and 4 [20.0%] placebo), diarrhea (2 [9.1%] and 4 [20.0%]), upper respiratory tract infection (1 [4.5%] and 3 [15.0%]), hemolysis (0% and 2 [10.0%]), sciatica (0% and 2 [10.0%]), and vomiting (0% and 2 [10.0%]).

・Vascular disorders were reported more frequently in the sutimlimab group than in the placebo group (40.9% versus 0%). Treatment-emergent AEs of Raynaud's phenomenon and cyanosis were reported more frequently in the sutimlimab group (with no events in placebo-treated patients). One patient with a history of Raynaud's phenomenon had a TESAE of Raynaud's phenomenon associated with an event of extremity necrosis that required amputation of all digits on both hands and bilateral below knee amputation as well as staphylococcal skin infection (Investigator term pyoderma of both legs methicillin-susceptible Staphylococcus aureus).

・One TESAE of cerebrovascular thrombosis was reported in the sutimlimab group which was assessed as related to the study drug by the investigator. No thromboembolic events were reported in the placebo group.

・Eight (36.4%) patients in the sutimlimab group experienced a total of 28 TEAEs assessed by the Investigator as related which was higher than the number reported in the placebo group (4 [20.0%] patients with 7 related TEAEs). Related TEAEs reported in >1 patient in either group were hypertension (3 [13.6%] sutimlimab and 0 placebo) and cyanosis (2 [9.1%] sutimlimab and 0 placebo).

・No Grade 4 or Grade 5 TEAEs were reported.

・Three (13.6%) patients in the sutimlimab group had 4 TESAEs and 1 (5.0%) patient in the placebo group had 3 TESAEs. No TESAE by PT was reported in >1 patient. The type and incidence of TESAEs observed in the study were similar to what is expected for a medically complex, elderly study population.

・Eighteen TEAEs of infection were reported in 10 (45.5%) patients in the sutimlimab group and 19 TEAEs of infection were reported in 10 (50.0%) patients in the placebo group. One patient in each group reported a serious infection which included febrile infection (sutimlimab group) and vascular device infection (placebo group). The serious infections occurred in patients with other risk factors for infection. Treatment-emergent AEs of infection with encapsulated bacteria, including Staphylococcus aureus and E coli were reported. No TEAEs of infection with encapsulated bacteria, which required vaccination per protocol, were reported in either group. No meningococcus infections or TEAEs of meningitis were reported in either treatment group. Overall, the type and frequency of TEAE infections was generally consistent with the demographics and comorbidities of the study population.

・Three patients in the sutimlimab group permanently discontinued IMP due to TEAEs. The first patient had multiple TEAEs of cyanosis (investigator term acrocyanosis) with concurrent Raynaud's phenomenon and was later diagnosed with progression of lymphoproliferative disease; the second patient had blood IgM increased and was diagnosed with low grade B-cell lymphoma; and the third patient had infusion related reaction. No patient in the placebo group discontinued treatment.

・Overall, 50% of patients in the sutimlimab group had TEAEs within 24 hours of the start of IMP infusion compared with 35% of patients in the placebo group. Of these, 7 TEAEs in 4 patients in the sutimlimab group compared with 1 TEAE in 1 patient in the placebo group were assessed by the Investigator as related to IMP. One patient in the sutimlimab group permanently discontinued IMP due to a TEAE of PT infusion related reaction that occurred within 24 hours of IMP infusion versus none in the placebo group. One TESAE within 24 hours of start of infusion of IMP was reported in both groups. Five TEAEs in 2 patients in the sutimlimab group were suggestive of potential hypersensitivity reaction versus 1 event in 1 subject in the placebo group.

・There were no serious TEAEs of hypersensitivity reaction or anaphylaxis or a TESAE suggestive of a potential hypersensitivity reaction reported in either treatment group. Nonserious events suggestive of potential hypersensitivity reactions were reported in both groups (5 patients sutimlimab versus 3 patients placebo) and were all Grade 1 or 2. Seven TEAEs in 3 patients were assessed as related to IMP by the investigator in the sutimlimab group versus 2 TEAEs in 2 patients in the placebo group. The IMP was permanently discontinued in 1 sutimlimab-treated patient due to infusion related reaction.

・No TEAEs suggestive of the development of autoimmune disease, including SLE, were reported.

・Two patients developed treatment-emergent ADA. One of the patients permanently discontinued treatment due to a TESAE of blood IgM increased as noted above and the other patient had no concurrent TEAEs.

・The observed changes in hematology and chemistry laboratory parameters were either consistent with the observed changes in efficacy parameters (erythroid changes associated with hemoglobin increases) or were not considered to be clinically insignificant. There was an increase in d-dimers observed in the sutimlimab group, but this and other coagulation changes were not considered clinically meaningful.

・While minimal increases in systolic and diastolic blood pressure were observed during sutimlimab treatment, they were not associated with a higher incidence of PCSA values compared with the placebo group.

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

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. The 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.

Issue date: 13-Jul-2023

Sponsor: Sanofi **Drug substance(s):** BIVV009 (sutimlimab)	**Study Identifiers:** NCT03347422; EudraCT Number: 2017-003539-12 **Study code:** EFC16216 (BIVV009-04)

Title of the study:

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

Study center(s):

For Part B, 34 study sites screened at least 1 patient and 25 study sites enrolled at least 1 patient. The study was conducted at investigational sites in Austria, France, Germany, Israel, Italy, Norway, Spain, Netherlands, the United Kingdom, Japan, Australia, Canada, and the United States.

Study period:

Date first patient enrolled: 06 March 2018 (Part A)

Date last patient completed: 03 December 2021 (Part B)

Study Status: Completed

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 primary 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 primary CAD.

Methodology:

BIVV009-04 was a Phase 3, randomized, double-blind, placebo-controlled study (Part A) followed by an open-label period (Part B) and designed to evaluate the efficacy and safety of sutimlimab in symptomatic patients with primary CAD with no recent history of blood transfusion. In Part A, patients were randomized and received sutimlimab or placebo in a double-blind fashion over a 26-week period, and Part A was completed on 29 September 2020. Results for the Part A study are presented in a separate report.

Part B was an open-label extension study with a duration of running for 1 year after last patient completed Part A to evaluate long-term safety and tolerability, as well as durability of efficacy of sutimlimab in patients with CAD. The results for Part B are presented in this study report.

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 A, eligible patients were randomized 1:1 to receive an intravenous (IV) infusion of sutimlimab or placebo over approximately 60 minutes on Day 0, Day 7, and every 14 days thereafter through Week 25. After completion of all Part A end of treatment assessments, patients who qualified to roll-over into Part B received a cross-over loading dose, in a blinded manner, at the Week 26 visit. Patients who were randomized to placebo during the 6-month treatment period in Part A, received sutimlimab; patients who were randomized to sutimlimab during the 6-month treatment period received a placebo dose in order to maintain the blinding. In Part B, patients were dosed with open-label sutimlimab every 2 weeks beginning at Week 27, and Part B ran for 1 year after last patient completed Part A.

On-site visits were completed every 2 weeks when samples for safety and efficacy measures were collected; pharmacokinetic (PK) and pharmacodynamic (PD) samples were collected at visits approximately every 3 months. Samples for antidrug antibodies (ADA) were collected every 3 months (at a minimum). The study treatment completed 12 months after last patient completed Part A, at which time all patients receiving ongoing treatment proceeded to an end of study visit approximately 9 weeks after the last administration of study drug.

After Week 39, a subset of patients from preselected countries, who met pre-specified entry criteria, were eligible for home infusion performed by a healthcare professional caregiver.

In addition, at least 15 patients in Part B were expected to receive infusions with sutimlimab undiluted with saline solution. Patients who were not selected for home infusion administration were eligible for undiluted infusions following treatment for at least 3 months in Part B, if they consented and had no history of hypersensitivity reaction to sutimlimab.

Number of participants:

Planned: 40 (Part A)

Enrolled: 42 (Part A)

Treated: 42 (Part A)

Evaluated:

Efficacy: 39

Safety: 39

Pharmacokinetics: 39

Pharmacodynamics: 39

Diagnosis and criteria for inclusion:

Part A of this study enrolled adult patients with CAD without a recent history of transfusion, defined as any transfusion within 6 months of screening or more than one transfusion within 12 months of screening. 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 Part B were enrolled. All 39 patients who completed Part A were eligible and continued in Part B of the study.

Study treatments in Part B

Investigational medicinal product: Sutimlimab

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

Route of administration: IV

Duration of treatment in Part B: 12 months after last patient completed Part A
Duration of observation: Screening for 6 weeks, Part A for 26 weeks, Part B through 1 year after the last patient completed Part A, and Follow-up observation at 9 weeks after last dose

Criteria for evaluation:

Efficacy:

The following parameters of disease activity were assessed:

• Mean change from baseline in hemolytic parameters including hemoglobin, total bilirubin, lactate dehydrogenase, and haptoglobin

• Mean change from baseline in quality of life assessments, as assessed by the change in functional assessment of chronic illness therapy fatigue (FACIT-Fatigue) score, the five-level EuroQol five dimensions questionnaire scores, the 12-item short form survey, Patient's Global Impression of [Fatigue] Severity, and Patient's Global Impression of Change by visit

• Transfusion requirements including the number of transfusions and total transfusion units, and annualized number of transfusions and annualized transfusion units

Safety:

Safety assessments included:

• Incidence of treatment-emergent adverse events (TEAEs) and treatment-emergent serious adverse events (TESAEs)
• 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
• Incidence of infections of ≥ Grade 3 severity (ie, requiring IV antibiotics)
• Incidence of hemolytic breakthrough through end of treatment
• Incidence of thromboembolic events
• For patients with home infusions, safety assessments also included AEs with onset within 24 hours of the of infusion
• For patients receiving undiluted infusions, safety assessments also included post-infusion AEs with onset within 24 hours of the infusion

Pharmacokinetic/Pharmacodynamics sampling times and bioanalytical methods: Blood samples for PK analysis of sutimlimab levels and ADA and PD analysis were routinely collected at 3-month intervals during Part B. Samples were also collected if a patient experienced a hematologic breakthrough event or withdrew from study.

Statistical methods:

Part B was an open-label study with no blinding or randomization. No formal statistical hypotheses were tested. Analyses of efficacy endpoints were primarily descriptive.

The Full Analysis Set (FAS) consisted of all patients who enrolled into Part B who received at least 1 dose (including partial dose) of study drug. Analyses of efficacy were performed on the FAS. The Safety Analysis Set is the same as FAS in this study.

Efficacy Endpoints:

The continuous endpoints were summarized by visit and treatment arm using descriptive statistics for the FAS. Change from baseline was also summarized by visit. Line plots of hemoglobin, bilirubin, and FACIT-Fatigue score over time, starting at Baseline/Day 0, were presented. Additionally, line plots of mean change from baseline in hemoglobin, bilirubin, and FACITFatigue score over time, starting at Baseline/Day 0, were presented. The endpoints related to transfusions and transfusion units were summarized by study period.

The categorical endpoints were summarized descriptively by visit and treatment arm using the FAS with the exception of total healthcare resource utilization, which was presented in a listing.

The number of healthcare visits by type (office visit, hospital emergency room visit, hospitalization, and intensive care unit stay) were collected and presented in a listing.

Safety Endpoints:

All safety data were summarized for patients in the Safety Analysis Set. Adverse events (AEs) were classified using the Medical Dictionary for Regulatory Activities system organ class and preferred term (PT) version 24.1. Tabulations of TEAEs and TESAEs by frequency, relatedness, and severity were presented. Patient listings are provided for all AEs. Tabulations of TEAEs and TESAEs by frequency and relatedness were presented. Patient listings were provided for AEs, serious adverse events (SAEs), AEs resulting in discontinuation of the study or study drug, and all deaths. In addition, specific summary tables were presented for hemolytic breakthrough and Grade ⩾3 infections, and TEAEs within 24 hours after the start of infusion.

All thromboembolic events reported were adjudicated by the Sponsor. In case of discrepancies between the medical review and Investigators' assessment, separate analyses were carried out for both sets of events. The incidence of thromboembolic events and hemolytic breakthrough events were summarized using all data in Part B (including data from the Week 79 visit and beyond).

Summary Results:

Population characteristics:

All 39 patients who had completed Part A enrolled into the long-term extension Part B. In total, 32 (82.1%) patients completed Part B, including the safety follow-up (SFU) visit, without early termination, including 16 (84.2%) ex-sutimlimab and 16 (80.0%) ex-placebo).

Overall, at Part A baseline, patients who entered Part B had a median age of 66.0 years (range 46 to 88 years) and more than half of patients were ⩾65 years (59.0%); most were female (79.5%). Race and ethnicity were not reported for a majority of patients (28 of 39 patients) due to local laws. Of the 11 patients with race and ethnicity data, 7 (17.9%) patients were Asian and 4 (10.3%) patients were White. Most of the patients were from the Europe geographic region (64.1%). Baseline weight was <75 kg for 32 (82.1%) patients and ⩾75 kg for 7 (17.9%) patients. The baseline demographic characteristics were generally similar between the ex-sutimlimab and ex-placebo groups.

Efficacy and Pharmacodynamic results:

Part B of the study was intended to assess the long-term safety and durability of response of sutimlimab treatment. In patients treated with placebo in Part A, over the first weeks of sutimlimab treatment in the Part B open-label phase, markers of hemolysis and anemia reached levels comparable to those seen in sutimlimab-treated patients. Citing lack of efficacy, 3 patients (1 ex-sutimlimab and 2 ex-placebo) withdrew from the study in Part B. Collectively, the data suggest that, with long-term treatment with sutimlimab, hemoglobin levels remain increased over baseline, extravascular hemolysis was controlled, as evidenced by continued normalization of total bilirubin levels, and fatigue remained improved as demonstrated by sustained FACIT-Fatigue scores through the end of treatment.

For the other PD markers assessed, near complete inhibition of mean classical complement pathway (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 complement component 4 (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. Similar trend in PD markers (Wieslab-CP, CH50, C4) was observed in patients that transitioned from placebo to sutimlimab treatment during Part B.

In contrast, once sutimlimab was no longer administered during the 9-week SFU, a return of hemolysis activity was evidenced by the following observed changes in laboratory parameters and biomarkers. At SFU (9 weeks after the last dose of sutimlimab), mean levels of total bilirubin (the most relevant marker of extravascular hemolysis) increased while mean hemoglobin levels and mean FACIT-Fatigue scores decreased from the last available on-treatment value. During SFU, the near-complete inhibition of CP activity observed throughout the treatment period was reversed, and CH50 and C4 levels returned toward baseline.

Safety results:

Sutimlimab was generally well tolerated. Overall, the type and frequency of TEAEs were generally consistent with the underlying disease indication, reported medical history, and an elderly medically complex patient population. Safety results for this report included the following:

• One fatal TEAE of squamous cell carcinoma of lung was reported in the 6.5 g cohort. The event was assessed as not related to sutimlimab by the Investigator. This was the only event in Part B of the study that led to study discontinuation. The patient died approximately 50 days after the last dose of sutimlimab.

• A total of 395 TEAEs were reported in 36 (92.3%) patients. The most frequently (>10% of patients) reported PTs were: fatigue (12 [30.8%] patients); anemia (11 [28.2%] patients), arthralgia (8 [20.5%] patients); diarrhea, hypertension, and nasopharyngitis (7 [17.9%] patients each); asthenia, headache, and pyrexia (6 [15.4%] patients each); dizziness, dyspnea, fall, hemoglobinuria, nausea, and upper respiratory tract infection (5 [12.8%] patients each); and cyanosis, cystitis, gastroenteritis, insomnia, and iron deficiency anaemia (4 [10.3%] patients each).

• During the 9-week SFU period, 16 patients had a total of 55 TEAEs. One event was a TESAE of anaemia. None of the events reported in the post-treatment follow-up period were assessed as related to sutimlimab by the Investigator except 1 event (Grade 2 upper respiratory tract infection). Most of the events experienced by the patients during the 9-week post-treatment follow-up period could be attributed to the worsening of the underlying CAD; fatigue (10 [25.6%] patients), anemia (7 [17.9%] patients), dyspnoea (4 [10.3%] patients), asthenia and hemoglobinuria (3 [7.7%] patients, each), and Raynaud's phenomenon (1 [2.6%] patient).

• In total, 11 TESAEs were reported in 7 (17.9%) patients. One TESAE of hypertension was assessed as related to sutimlimab by the Investigator.

• TEAEs assessed by the Investigator as related to sutimlimab were reported in 16 (41.0%) patients (58 events). All related TEAEs were reported in only 1 patient with the exception of headache (4 [10.3%] patients), and cyanosis, cystitis, fatigue, hypertension, injection site erythema, nausea, and pyrexia (2 [5.1%] patients each). Other related TEAEs were reported in one patient each.

• A total of 59 TEAEs of infection were reported in 24 (61.5%) patients, including 2 TEAEs of Grade ⩾3 infection (TESAE of Grade 3 urinary tract infection and a nonserious TEAE of Grade 3 urinary tract infection). One patient had a nonserious event of infection with an encapsulated bacterium (Escherichia Urinary Tract Infection). No TEAEs of infection with encapsulated bacteria, which required vaccination per protocol, were reported. No meningococcus infections or TEAEs of meningitis were reported.

• One TEAE was identified as consistent with autoimmune disease: one patient, with a history of Graves' disease, experienced one event of worsening of Graves' disease (PT of Basedows's disease). No other TEAEs reported were consistent with development of a new autoimmune disease or worsening of an underlying autoimmune disease. No patients developed a TEAE consistent with diagnosis of SLE.

• No TEAEs of serious hypersensitivity reaction or anaphylaxis were identified. All events suggestive of potential hypersensitivity reaction to sutimlimab were assessed as nonserious.

• Thirty-four (34) TEAEs occurring within 24 hours after the start of sutimlimab infusion were reported in 17 patients (43.6%). All events were reported in one patient in either dose cohort with the exception of nausea in 3 patients, and diarrhea, hypertension, injection site erythema, pyrexia, which were reported in 2 patients each. The TEAEs of infusion related reaction, injection site erythema, eczema, flushing, pruritus, nausea, dizziness, and hypotension were suggestive of potential hypersensitivity reactions.

• Thromboembolic events were reported in 2 patients. One patient reported an event of transient ischemic attack and the other patient reported an event of deep vein thrombosis. Both events were reported as nonserious and assessed as unrelated to sutimlimab by the Investigator.

• For the 3 patients who received home infusions, no TEAEs occurred within 24 hours of a home infusion.

• Among 23 patients who received at least one undiluted infusion, 9 (39.1%) patients had a total of 15 TEAEs with an onset within 24 hours of receiving an undiluted infusion and 6 (26.1%) patients had a total of 9 TEAEs with an onset within 24 hours of receiving a diluted infusion. Overall, all TEAEs within 24 hours of undiluted infusion were reported in 1 (4.3%) patient each except for hypertension, and injection site erythema (2 [8.7%] patients each). All TEAEs by PT within 24 hours of diluted infusion occurred in only 1 (4.3%) patient, each. A total of 5 (21.7%) patients had 9 related TEAEs within 24 hours of receiving an undiluted infusion and 1 patient had 1 related TEAE of dyspepsia within 24 hours of receiving a diluted infusion. The only related event within 24 hours of receiving an undiluted infusion that occurred in >1 patient was injection site erythema (2 [8.7%] patients). No patients had Grade ⩾3 AEs within 24 hours of receiving an undiluted infusion or diluted infusion. No patient had a TESAE within 24 hours of receiving an undiluted infusion and 1 patient had a TESAE of lumbar spinal stenosis within 24 hours of receiving a diluted infusion. The event was resolved and assessed as not related to sutimlimab. No fatal TEAEs were reported in subjects within 24 hours of start of undiluted or diluted infusion of sutimlimab.

• Of the 39 patients evaluable for ADA, 6 (14.4%) patients developed treatment-induced ADA. Anti-drug antibody did not impact PK and clinical outcome of these 6 patients; thus, there was no indication that ADA had neutralizing effect.

Pharmacokinetic results:

• After 5 doses of sutimlimab, 6.5 g or 7.5 g, the plasma concentrations appeared to reach steady-state, on average. After reaching steady state, the trough and peak sutimlimab concentrations were constant and remained sustained throughout the Part B treatment period for all patients, including ex-placebo patients.

• The coefficients of variability, %CV, of the measured plasma concentrations were similar between the 2 groups during Part B treatment period with values of 25.74 to 68.66% (6.5 g) and 10.10 to 76.50% (7.5 g).

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• Ten patients had plasma concentrations less than 20 µg/mL at some time point during Part B treatment period of which nine patients had dose interruptions. In addition, one patient had plasma concentration between 20 and 100 µg/mL whilst remaining patients had concentrations above 100 g/mL, which was 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 after Part B treatment period decreased to below the lower limit of quantification in most patients except for 2 patients. One patient had concentration >100 µg/mL and another patient had concentration between 20 and 100 µg/mL at ET/SFU visit.

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