Sponsor: Sanofi **Drug substance(s):** TNT009 (BIVV009)	**Study Identifiers:** NCT02502903; EudraCT number: 2014-003881-26 **Study code:** LTS16214 (BIVV009-01)

Title of the study:

Safety, Tolerability and Activity of TNT009 in Healthy Volunteers and Patients with Completed-Mediated Disorders. A Single/Multiple Ascending Dose Phase 1 Study

Study center(s):

Parts A and Part B were conducted at the same site:

Medical University of Vienna

Department of Clinical Pharmacology

Waehringer Guertel 18-20

1090 Vienna, Austria

Phone: +43 1 40400 29810

Study period:

First Subject in (Informed Consent): Part A: 29-Jun-2015; Part B: 05-Oct-2015

Date of First Subject Treated: Part A: 13-Jul-2015 Part B: 20-Oct-2015

Date of Last Subject Last Treatment: Part A: 09-Oct-2015 Part B: 26-Nov-2015

Date of Last Subject Out: Part A: 23-Oct-2015 Part B: 10-Dec-2015

Phase of development: Phase 1

Objectives:

Primary Objective: Assessment of safety and tolerability of TNT009 (BIVV009) in humans

Secondary Objectives:

- To evaluate the pharmacokinetics of TNT009 (BIVV009)
- To evaluate the pharmacodynamics of TNT009 (BIVV009) with respect to CP function
- To determine the optimal dose regimen suitable for evaluation in Phase 2 studies

Methodology:

Part A and Part B were prospective, double-blind, randomized, placebo-controlled studies. Part A was a single ascending dose (SAD) study in normal human volunteers (NHVs) and Part B was a multiple ascending dose (MAD) study in NHVs.

Number of participants: Planned: Part A: 48 NHVs Part B: 16 NHVs Analyzed: Part A: 48 NHVs Part B: 16 NHVs
Diagnosis and criteria for inclusion: *Inclusion criteria Part A/B:* ● healthy male or female volunteers, age ≥ 18 years old ● if female, must be post-menopausal, surgically sterilised or willing and able to use highly effective methods of birth control throughout the study and for 30 days after the end-of trial visit ● previously vaccinated against encapsulated bacterial pathogens (Neisseria meningitidis, Haemophilus influenzae, and Streptococcus pneumoniae) or willing to undergo vaccination ● able to comprehend and to give informed consent ● able to co-operate with the investigator, to comply with the requirements of the study, and to complete the full sequence of protocol-related procedures *Exclusion criteria Part A/B:* ● clinically significant medical history or ongoing chronic illness that would jeopardize the safety of the subject or compromise the quality of the data derived from his/her participation in this study ● clinically relevant infection of any kind within the preceding month ● clinically relevant abnormal findings on physical examination or clinically relevant laboratory abnormalities ● history of infusion hypersensitivity, allergic or anaphylactic reactions to other therapeutic proteins ● substance abuse, mental illness, or any reason that makes it unlikely in the judgment of the investigator for the subject to be able to comply fully with study procedures ● use of medication during 2 weeks before the start of the study, which in the judgment of the investigator may adversely affect the subject's welfare or the integrity of the study's results (excluding hormonal contraception in female subjects) ● females who are pregnant (positive pregnancy test at screening or during study phase), lactating, or, if having reproductive potential, are considered potentially unreliable with respect to contraceptive practice

Test Product

Test Product: TNT009 (BIVV009) as a sterile solution for injection

Part A: single dose (0.3 – 100 mg/kg)

Part B: weekly dosing x 4 (30 / 60 mg/kg)

Reference Therapy

Comparator (placebo): sterile saline for injection (marketed product)

Part A: single dose

Part B: weekly dosing x 4

Duration of treatment:

Part A: One day (single dose)

Part B: Four weeks (weekly dosing)

Criteria for evaluation:

Criteria for Evaluation:

Safety (Primary Endpoints):

Overall safety and tolerability of TNT009 (BIVV009), assessed in terms of:

- Serious, drug-related adverse events
- Premature terminations due to drug-related adverse events
- Patterns of serious or non-serious, drug-related adverse events and/or clinical laboratory abnormalities suggestive of one or more specific target-organs for toxicity of TNT009 (BIVV009)

Secondary Endpoints

Pharmacokinetics:

Pharmacokinetic Endpoints:

- Measured concentration of TNT009 (BIVV009)
- Derived PK parameters
- Anti-Drug Antibodies (ADAs) against TNT009 (BIVV009)

Pharmacodynamic Endpoint:

- Complement System Classical Pathway WIESLAB®

Statistical methods:

Baseline data and safety data were analyzed descriptively. Adverse events rates, laboratory values over time, the number of laboratory values outside normal range and other safety and baseline parameters were presented by treatment group and for all subjects that received TNT009 (BIVV009) pooled to allow (descriptive) comparison with the subjects receiving placebo.

PK parameters of serum TNT009 (BIVV009) and PD parameters of various PD biomarkers (complement system classical pathway [CCP] activity, C1s, C1q and C1sC1INH concentration) were calculated using a validated version of Phoenix WinNonlin (version 7.0). Summary tables and/or figures of TNT009 (BIVV009) and PD biomarkers in serum were generated using WinNonlin® AutoPilot Toolkit™ (Version 7.0), a configurable software application that works with WinNonlin®, and reporting tools, including SigmaPlot® 2004 and Phoenix WinNonlin (version 7.0). Scatter plot correlation matrices were generated using R v.3.3.1. Modeling and simulations of serum TNT009 (BIVV009) were performed using a validated version of Phoenix NLME.

Summary Results:

Safety Results: In Part A and Part B there were a total of 48 NHVs treated with intravenous infusions of TNT009 (BIVV009), with single doses as high as 100 mg/kg and with repeated doses as high as 60 mg/kg weekly X 4. No serious adverse events (SAEs), drug-related SAEs, premature withdrawals due to adverse events, or ≥Grade 3 drug-related adverse events were observed. All adverse events were mild to moderate in severity. The most commonly reported AEs (incidence ≥ 10.0% per study part) in subjects receiving TNT009 (BIVV009) were nasopharyngitis, headache, influenza like illness, and oropharyngeal pain. There were 4 AEs reported in 3 of 48 (6.3%) Part A subjects, all in subjects receiving TNT009 (BIVV009), that were assessed as related by the investigator, which included 1 TEAE each of headache, oropharyngeal pain, rhinitis and vertigo. In Part B, there was a total of 7 AEs reported in seven (7) subjects assessed as related by the investigator. Five of these AEs occurred in 5 of 12 (41.7%) Part B subjects receiving TNT009 (BIVV009) and were as follows: 2 events of nasopharyngitis in 2 subjects and 1 event each of headache, abdominal pain and pruritus generalised. There were no clinically meaningful trends or patterns in clinical laboratory, vital sign, physical examination or ECG assessments.

Pharmacokinetic and Pharmacodynamic Results:

- Following a single intravenous infusion of TNT009 (BIVV009) at doses of 3-100 mg/kg, mean TNT009 (BIVV009) exposure (AUC_{0-168}) increased in a greater than dose proportional manner over 3 to 30 mg/kg dose range, but increased in an approximately dose-proportional manner over the 60 to 100 mg/kg dose range
- Following the once weekly regimen, the nonlinear clearance pathway was saturated at a dose of 60 mg/kg with a threshold for saturation at approximately 100µg/mL of TNT009 (BIVV009)
- Inhibition of CCP activity and decrease of C1s and C1sC1INH concentrations was maximal in most cases, less than 12 h post-dose. Prolonged PD effects were observed at dose levels equal to or greater than 30mg/kg
- A steep concentration-effect relationship was observed for the inhibition of CCP activity. A similar relationship was observed with C1s and C1sC1INH.The TNT009 (BIVV009) concentration associated with a 90% reduction of CCP activity (IC90) was 63.9 µg/mL
- Following repeated weekly dosing of 30 or 60 mg/kg, limited accumulation of TNT009 (BIVV009) as evidenced by a rapid decrease of CCP activity was observed. A rapid decrease of CCP activity, C1s and C1sC1INH concentrations in these TNT009 (BIVV009) treated subjects was observed. The PD was maintained over the study period for most of treated subjects
- No effect on C1q was observed at any dose

Issue date: 13-Jul-2023

Sponsor: Sanofi **Drug substance(s):** TNT009 (BIVV009)	**Study Identifiers:** NCT02502903; EudraCT number: 2014-003881-26 **Study code:** LTS16214 (BIVV009-01)

Title of the study:

Safety, tolerability and activity of TNT009 in healthy volunteers and patients with complement-mediated disorders. A single/multiple ascending dose phase 1 study

Study center(s):

Medical University of Vienna
Department of Clinical Pharmacology

1090 Vienna, Austria

Study period:

First Patient In: 09-Nov-2015

First Patient Treated: 04-Jan-2016

Last Patient Treatment Completed: 17-Feb-2017

Last Patient Out: 10-Mar-2017

Phase of development: Phase 1

Objectives:

Primary Objective:

- Assessment of safety and tolerability of TNT009 (BIVV009) in humans

Secondary Objectives:

- To evaluate the pharmacokinetics of TNT009 (BIVV009)
- To evaluate the pharmacodynamics of TNT009 (BIVV009) with respect to CP function
- To evaluate the effect of TNT009 (BIVV009) on disease-related biomarkers in patients
- To prioritize therapeutic indications for further clinical development
- To determine the optimal dose regimen suitable for evaluation in Phase 2 studies

Methodology:

Part C was a multiple dose (MD) study in patients with a complement-mediated disorder. All patients were treated with TNT009 (BIVV009), which was conducted sequentially after Part A and B of this study.

Number of participants:

Planned: Up to 50 patients with bullous pemphigoid (BP), cold agglutinin disease (CAD), warm autoimmune hemolytic anemia (WAIHA), or Antibody-Mediated Rejection (AMR) (acute or chronic) after kidney transplantation. The enrolled number of patients was 34. Ten patients with CAD, 10 with BP, 4 with WAIHA and 10 with AMR.

Diagnosis and criteria for inclusion:

Inclusion criteria Part C:

- male or female, age ≥ 18 years old
- if female, must be post-menopausal, surgically sterilised or willing and able to use highly effective methods of birth control throughout the study and for 30 days after the end-of trial (EOT) visit
- previously vaccinated against encapsulated bacterial pathogens (Neisseria meningitidis, Haemophilus influenzae, and Streptococcus pneumoniae) or willing to undergo vaccination
- able to comprehend and to give informed consent
- able to co-operate with the investigator, to comply with the requirements of the study, and to complete the full sequence of protocol-related procedures
- History of one of the following complement-mediated disorders:

o bullous pemphigoid (BP)
o cold agglutinin disease (CAD)
o warm autoimmune hemolytic anemia (WAIHA)
o active Antibody-Mediated Rejection (AMR) (acute or chronic) after kidney transplantation

- If CAD, by medical history within the 3 months preceding enrollment, and again at the screening visit:

o has hemoglobin <11.0 g/dL

- If AMR:

o is ≥180 days post-kidney transplantation with biopsy-proven late AMR
o has a functioning kidney graft with eGFR ≥20 mL/min/1.73 m2
o has evidence of late, active AMR (acute or chronic) present on renal allograft biopsy:

- molecular signature indicating AMR (molecular AMR score >0.2)
- morphological and immunohistochemical findings consistent with AMR according to the criteria of the Banff 2013 classification
- morphological findings consistent with an active rejection process:presence of glomerulitis (g score >0) and/or peritubular capillaritis (ptc score >0)

o has IgG type DSA present in serum (at time of renal allograft biopsy) with MFI>1000 in single antigen bead assays
o is willing and able to take routine antibiotic prophylaxis with ciprofloxacin

Test Product, Dose and Mode of Administration:

Test Product: TNT009 (BIVV009) as a sterile solution for injection

o Single IV test dose of 10 mg/kg followed by 4 weekly doses of 60 mg/kg

Duration of treatment:

Dose at day 0, 4*, 11, 18 and 25
Overall treatment duration: a maximum of 26 days
* Per the amendment introducing CSP Version 9.0, the first maintenance dose of 60 mg/kg previously scheduled for Nominal Day 4 was changed to be infused 24 hours after the test dose given on Day 0 if a review of adverse effects, routine clinical chemistry and hematology parameters showed no contraindication for further treatment. The Day 1 and Day 2 visit procedures were omitted, and further treatment and study assessments continued according to the Nominal Day 11, Day 18, Day 25 visit schedules.

Criteria for evaluation:

Primary Endpoints:

Safety:

Overall safety and tolerability of TNT009 (BIVV009), assessed in terms of:

- Serious, drug-related adverse events
- Premature terminations due to drug-related adverse events
- Patterns of serious or non-serious, drug-related adverse events and/or clinical laboratory abnormalities suggestive of one or more specific target-organs for toxicity of TNT009 (BIVV009)

Secondary Endpoints:

Pharmacokinetics:

- Measured concentration of TNT009 (BIVV009)
- Derived PK parameters
- Anti-Drug Antibodies (ADAs) against TNT009 (BIVV009)

Pharmacodynamic:

- Complement System Classical Pathway WIESLAB®

Exploratory Complement System parameters:

- Complement System Alternative Pathway WIESLAB
- CH50
- C4
- C1s
- C1s-C1INH
- C1q
- CIC-C3d
- CIC-C1q
- *Ex vivo* HLA antibody-triggered C3d deposition on Single Antigen Beads exposed to HLA-sensitized sera from ESRD patients

Exploratory Coagulation System parameters:

- Fibrin D-dimer (WAIHA and CAD patients)
- Prothrombin Fragment F1.2 (WAIHA and CAD patients)

Disease-Related Biomarkers:

- Cold Agglutinin titer in sera from CAD patients
- Haptoglobin (plus routine clinical lab parameters of hemolysis, e.g. hemoglobin, hematocrit, reticulocyte count, LDH, bilirubin) in blood samples from WAIHA and CAD patients
- Ex vivo C3b deposition on normal donor RBCs exposed to sera from CAD and WAIHA patients.

- Serial C3-DAT in blood samples from WAIHA and CAD patients
- ROTEM in blood samples from WAIHA and CAD patients – this will be done only at the clinical site at the Medical University of Vienna in Austria
- FACS for RBCs with bound C3d in blood samples from WAIHA and CAD patients –this will be done only at the clinical site at the Medical University of Vienna in Austria
- erythropoietin in blood samples from WAIHA and CAD patients
- transferrin in blood samples from WAIHA and CAD patients
- soluble transferrin receptor in blood samples from WAIHA and CAD patients
- Total Iron Binding Capacity in blood samples from WAIHA and CAD patients
- iron in blood samples from WAIHA and CAD patients
- ferritin in blood samples from WAIHA and CAD patients
- BFU-E and CFU-E counts in blood samples from WAIHA and CAD patients
- Anti-RBC IgM in blood samples from CAD patients
- Anti-BP-180 titer in sera from BP patients
- Anti-BP-230 titer in sera from BP patients
- *Ex vivo* C3c deposition on monkey esophagus tissue sections exposed to sera from BP patients
- Direct immunofluorescent detection of C3 deposition and IgG in skin punch biopsies taken from BP patients (OPTIONAL)
- Morphologic and molecular signature of rejection on the Day 32 study visit renal allograft biopsy from AMR patients
  - o Molecular rejection score
  - o Molecular AMR score
  - o Gene expression microarray Principal Component Analysis (molecular microscope®)
  - o Histopathologic scores of AMR lesion: glomerulitis (g 0-3); peritubular capillaritis (ptc 0-3); transplant glomerulopathy (cg 0-3); C4d (0-3) on the renal allograft biopsy from AMR patients
- Serological and immunological parameters of AMR in serum from AMR patients
  - o MFI of IgG type DSA
  - o C1q-fixing capability of DSA
  - o C3-fixing capability of DSA
  - o B-cell ELISPOT assay for anti-HLA antibodies
  - o Overall activity of the classical complement pathway in patient sera assessed on anti-HLA antibody-coated screening beads (C3d-fixation assay)
- Renal function parameters in serum from AMR patients
  - o eGFR
  - o Spot Urinary Protein: Creatinine ratio

Summary Results:

Safety Results: In Part C there were a total of 34 patients treated with intravenous infusions of TNT009 (BIVV009), with a single test dose of 10 mg/kg followed by 4 weekly doses of 60 mg/kg. Overall, 31 of 34 patients (91.2 %) experienced a total of 99 TEAEs. The most common TEAEs reported by patients were fatigue, headache, edema peripheral, dizziness and nausea. Four patients (11.8 %) experienced 4 TEAEs assessed as related to treatment with TNT009 (BIVV009) by the Investigator, where 2 patients were from the BP group, 1 from the mixed AIHA & CAD group and 1 from the secondary CAD group. The TEAEs assessed as related to study drug by the Investigator for which an association with TNT009 (BIVV009) cannot be excluded include: alopecia, purpura, urinary tract infection and dizziness. Two patients experienced serious TEAEs, including 1 patient from primary CAD group who experienced a spinal fracture and one patient from BP group who experienced cardiac failure. There were no serious TEAEs reported that were assessed as related to treatment with TNT009 (BIVV009) by the Investigator. All TEAEs were assessed by the Investigator as either mild or moderate in severity with one exception: the serious adverse event of cardiac failure with a fatal outcome in a BP patient that occurred approximately 4 weeks after the last dose of study drug. Two patients permanently discontinued study drug and withdrew early from the study due to a TEAE including 1 WAIHA patient due to a TEAE of hemolysis and the 1 BP patient who had a fatal TEAE of cardiac failure. The pattern of infections in the study does not suggest an increased risk of infections with TNT009 (BIVV009) treatment. Although 3 patients reported a total of 5 TEAEs of pruritus, none of these events were assessed by the investigator as possibly or probably related to TNT009 (BIVV009). No TEAEs were reported concerning the development of lupus or other autoimmune diseases.

Pharmacokinetic Results:

No obvious PK differences were noted across patient populations. Following either single (10 mg/kg) or multiple doses (60 mg/kg), serum Cmax and AUC values appeared similar across patient populations. The clearance across patient populations (19.2 – 24.7 mL/h at steady-state) was also similar.

Pharmacodynamic Results:

There was a difference in baseline levels of CCP across the patient populations, with lower baselines and higher variability for CAD and WAIHA patient populations. The C1q concentration observed was similar across patient populations. CCP activity displayed nearly complete inhibition over the entire treatment period across all patient populations. C1s and C1sINH levels demonstrated near complete binding by TNT009 (BIVV009) across all patient populations. Exploratory exposure response (PK/PD) analyses suggested that TNT009 (BIVV009) concentrations above ~50 - 100 µg/mL consistently resulted in maximal CCP inhibition and C1s and C1sC1INH binding independent of the patient population.

Results for analysis of biomarkers and exploratory assay parameters:

The efficacy data describe results for 6 patients classified as primary CAD, 3 patients classified as secondary CAD and 1 patient with mixed AIHA/CAD. Notably, circulating levels of C1s, the molecular target of TNT009 (BIVV009), were reduced to < 10% of pre-dose levels following TNT009 (BIVV009) administration in the 6 primary CAD patients. In addition to near complete inhibition of CCP activity, serum CH50 activity was effectively inhibition by TNT009 (BIVV009) for the duration of the treatment in primary CAD patients. Similar reductions in C1s levels were also seen in 3 patients with secondary CAD and 1 patient with mixed AIHA/CAD. However, levels of CH50 increased in 2 patients classified as having secondary CAD. Disease related biomarkers of hemolysis improved consistently in the patients with primary CAD with either normalization or near normalization of hemoglobin, bilirubin and LDH.

Data are available for 10 patients with AMR. These patients had signs of antibody-mediated rejection with alloantibody-triggered CP activation at baseline. TNT009 (BIV009) administration led to a substantial and sustained blockade of serum CH50 activity in all patients. TNT009 (BIV009) substantially reduced the C3q-fixing capability of DSA but did not affect the MFI or C1q-fixing capability of DSA. Based on biopsy data, C4 deposition (C4d) declined substantially from screening to the end of treatment. The histomorphology and molecular biopsy results were essentially unchanged with TNT009 (BIV009) administration, based on measurements of glomerulitis, peritubular capillaritis, transplant glomerulopathy, and molecular ABMR scores. Spot urine protein:creatinine ratio and renal function were essentially unchanged with TNT009 (BIV009) administration. eGFR was similar at the beginning and end of the treatment period.

Data are available for 10 patients with BP. TNT009 (BIVV009) effectively inhibited CH50 for the duration of treatment. Circulating anti-BP-180 and anti-BP-230 antibody titers were essentially unchanged. Biopsy data showed important reductions in complement deposition (C3) and IgG reductions at the dermal-epidermal junction.

Issue date: 13-Jul-2023

Sponsor: Sanofi **Drug substance(s):** TNT009 (BIVV009)	**Study Identifiers:** NCT02502903; EudraCT number: 2014-003881-26 **Study code:** LTS16214 (BIVV009-01)

Title of the study:

Safety, tolerability and activity of BIVV009 in healthy volunteers and patients with complement-mediated disorders: A single/multiple ascending dose phase 1 study (Part E - An Open Label Study in Patients with Cold Agglutinin Disease)

Study center(s):

Medical University of Vienna, Department of Clinical Pharmacology, 1090 Vienna, Austria.

Study period:

Date first patient enrolled: 12-OCT-2017

Date last patient completed: 31-MAR-2021

Study Status: Completed

Phase of development: Phase 1

Objectives:

Primary Objective:

- To evaluate the safety and tolerability of sutimlimab in humans

Secondary Objectives:

- To evaluate the pharmacokinetics (PK) of sutimlimab
- To evaluate the pharmacodynamics (PD) of sutimlimab with respect to classical complement pathway (CP) function
- To evaluate the effect of sutimlimab on disease-related biomarkers in patients in Parts C and E
- To prioritize therapeutic indications for further development
- To determine the optimal dose regimen suitable for evaluation in Phase 2 studies

Methodology:

Part E was a treatment extension enrolling cold agglutinin disease (CAD) patients who previously responded to treatment with sutimlimab in a clinical trial or named patient program (NPP).

Number of participants:

Treated: 4

Evaluated:

Pharmacodynamics: 4

Safety: 4

Diagnosis and criteria for inclusion:

Patients to be enrolled had to have a history of CAD, and previously had been treated with sutimlimab in a sutimlimab clinical trial or NPP with evidence of treatment response. If not currently receiving sutimlimab at Screening, patients had to have hemoglobin ≤ 10.5 g/dL at Screening/Day 1. Any underlying malignancy or warm autoimmune hemolytic anemia had to have been successfully treated.

Patients who had received rituximab, azathioprine, or other immune-suppressive therapy (except corticosteroids equivalent to ≤10 mg/day prednisone) in the previous 3 months; and rituximab combination therapy or other cytotoxic therapy (eg, fludarabine, bendamustine, cyclophosphamide, ibrutinib, or other cytotoxic drugs) in the previous 6 months were excluded. Patients with abnormally low ferritin or erythropoietin or diagnosis of systemic lupus erythematosus or other autoimmune disorder with antinuclear antibodies were excluded.

Study products

Investigational medicinal product(s):

Investigational medicinal product: Sutimlimab (BIVV009)

Formulation: Sutimlimab (BIVV009) as a sterile, 18 and 50 mg/mL solution for injection

Route of administration: Intravenous

Dose regimen: Sutimlimab 5.5 to 7.5 g doses administered intravenously at Visits 1 (Week 0), 2 (Week 1), and every 2 weeks thereafter during the study. Under Version 13.0 (21 June 2017) of the protocol, patients received 5.5 g sutimlimab at each infusion; under Version 15.0 of the protocol (17 April 2018), patients in Part E who weighed <75 kg were to receive fixed sutimlimab doses of 6.5 g; patients who weighed ≥75 kg were to receive infusions of fixed sutimlimab doses of 7.5 g.

For patients with evidence of biochemical breakthrough hemolysis (rapid fall in hemoglobin ≥2 g/dL and increase in lactate dehydrogenase [LDH]/bilirubin and/or decrease in haptoglobin since last scheduled visit), re-loading with an additional dose of sutimlimab was permitted. If a patient missed a scheduled dose (outside of the 2-day window or >17 days since last dose), they had to return to site (unscheduled visit) to receive another loading dose.

Duration of treatment: The duration of treatment was patient specific in this study and the first patient began treatment in Oct 2017 and the treatment ended for all patients in Mar 2021.

Duration of observation: During 9-week Safety Follow-up period after the last dose of study medication

Criteria for evaluation:

Pharmacodynamics: Secondary endpoints included CP activities assessments.

Safety:

Overall safety and tolerability of sutimlimab, assessed in terms of:

- Serious, drug-related adverse events (AEs)
- Premature terminations due to drug-related AEs
- Patterns of serious or non-serious AEs, drug-related AEs, and/or clinical laboratory abnormalities suggestive of one or more specific target organs for toxicity of sutimlimab

Pharmacokinetics:

- Measured concentration of sutimlimab
- Derived PK parameters
- Anti-drug antibodies (ADAs) against sutimlimab

Pharmacokinetic/Pharmacodynamics sampling times and bioanalytical methods: Sutimlimab PK samples were taken predose at each treatment visit and at the End of Treatment (EOT)/End of Study (EOS) visit and the Safety Follow-up visits. Predose PD samples were taken at each treatment visit, the EOT/EOS visit, and the Safety Follow-up visit.

Statistical methods: All analyses were descriptive in nature.

Summary Results:

Pharmacodynamic results:

In the first 3 weeks of treatment, hemoglobin increased and markers of hemolysis (bilirubin and LDH) decreased in all 4 patients, consistent with sutimlimab's effect of inhibiting hemolysis. Clinically meaningful improvements in hemoglobin were observed, with median increases from baseline of 2.20 g/dL (range, 1.3 to 3.8 g/dL) by Week 3 and 2.65 g/dL (range, 2.40 to 4.50 g/dL) by Week 7; hemoglobin assessments in 3 patients reached the normal range at least once and 1 patient discontinued early due to SAE at Week 53. As would be anticipated with improvement in hemolytic anemia and coinciding with improvement and stabilization in hemoglobin, reticulocytes initially increased in the first week of treatment and then decreased to below baseline levels thereafter. Bilirubin and LDH trended upward from the EOT to end of Safety Follow-up. Hemoglobin for 1 patient (Patient C2125) remained relatively stable, but declined for 2 patients (Patients C0992 and C7784) with a hemolytic event noted for 1 patient (Patient C0992) from EOT to end of Safety Follow-up.

Safety results:

The long-term safety profile of sutimlimab (18 mg/mL) was evaluated in 4 female patients with CAD aged 56 to 78 years at enrollment in Part E of Study BIVV009-01. Long-term treatment with sutimlimab was generally well tolerated, and no new safety concern arose over a median treatment duration of 156.21 weeks (range, 54.4 to 167.9 weeks) including the Safety Follow-up period. Primary safety results for Part E of BIVV009-01 included the following:

・No death was reported.

・A total of 130 treatment-emergent AEs were reported during the study, with each patient experiencing at least 1 TEAE. A total of 10 TEAEs in 3 of 4 patients were assessed by the Investigator as related to sutimlimab treatment. A total of 4 TEAEs in 3 patients were assessed with Grade 3 severity; the same events were considered treatment-emergent serious adverse events (TESAEs). No event was assessed by the Investigator as Grade 4 or 5 in severity. No TESAE was assessed by the Investigator as related to sutimlimab.

・Frequent treatment-emergent events included nasopharyngitis and back pain and occurred in all the patients. The TEAEs that occurred in at least 3 patients included nausea, dizziness, and headache. Other TEAEs reported in at least 2 patients included anaemia, vertigo, constipation, toothache, fatigue, pneumonia, urinary tract infection, fall, skin abrasion, arthralgia, and hematoma. In general, the type and frequency of AEs reported was consistent with an older patient population and individual patients' medical histories.

・Treatment-emergent events assessed by the Investigator as related to sutimlimab treatment included events of dry mouth, paraesthesia oral, pyrexia, balance disorder, dizziness, rash, and pallor. None of the TESAEs were assessed as related by the Investigator.

・Two patients were discontinued from the study prematurely: 1 patient with pre-existing medical history of [Medical History] experienced a TEAE of worsening of Waldenstroem's disease and was discontinued from the treatment, and 1 patient who completed the treatment was discontinued prematurely from the follow up phase due to TEAE of haemolysis (approximately 2 months after having received the last dose of sutimlimab); the events were assessed by the Investigator as serious and not related to sutimlimab.

・Treatment-emergent events with Grade ≥3 severity included events with preferred terms of pneumonia, pulmonary sepsis, urosepsis, and joint dislocation; all were TESAEs.

・Overall, 7 TESAEs were observed in the 4 patients, 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.

・All 4 patients had at least 1 TEAE in the system organ class of infections and infestations. Two patients reported 3 serious infections. One patient reported TESAEs of pneumonia and pulmonary sepsis, and another patient reported 1 TESAE of urosepsis. Causative organisms were not reported for the majority of infections. Infections with encapsulated organisms were reported; however, no event of meningitis or infection due to meningococcus or other specific organism targeted by a protocol-required vaccine was reported. The pattern of infections reported in the study is consistent with an elderly, medically complex patient population. The 2 patients with TESAE infections had underlying risk factors for infection.

・One patient reported a TEAE of rash that was suggestive of potential hypersensitivity reaction. Upon further review the event was unlikely to represent hypersensitivity reaction to sutimlimab. No TESAEs suggestive of potential hypersensitivity reaction to sutimlimab administration were reported.

・No reported TEAE corresponded to a development or worsening of systemic lupus erythematosus (SLE) or other autoimmune disease.

・Consistent with clinical responses to sutimlimab observed in other studies, improvements in hematological safety parameters (hemoglobin, hematocrit, erythrocytes) and blood chemistry parameters associated with hemolysis (bilirubin, LDH) were observed after the first week of treatment. Aside from these observations in safety laboratory parameters, no other clinically meaningful pattern or trend in abnormalities of hematology or blood chemistry values was observed.

・While post baseline blood pressure values were generally slightly higher than baseline, no clinically meaningful pattern or trend in electrocardiograms (ECGs) or vital signs was observed.

Pharmacokinetic results:
There were inter- and intra-individual variabilities among PK samples. However, the steady-state Cmin and AUC appeared to be consistent with other sutimlimab clinical studies. ADAs were not detected and thus did not influence the PK of sutimlimab in this study.

Issue date: 13-Jul-2023