15 September 2022
EMA/863061/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Enjaymo

International non-proprietary name: sutimlimab

Procedure No. EMEA/H/C/005776/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Table of contents

List of abbreviations

ADA	anti-drug antibody
ADCC	antibody-dependent cellular cytotoxicity
AE	adverse event
AMR	antibody mediated rejection
AUC	concentration versus time curve
BP	bullous pemphigoid
CAD	cold agglutinin disease
C1	complement component 1
C1q	complement component 1 q subcomponent
C1s	complement component 1 s subcomponent
C4	total complement component 4
CH50	total haemolytic complement
CHO	Chinese hamster ovary
CI	confidence interval
CE-SDS	Capillary sodium dodecyl sulfate gel electrophoresis
CEX	Cation exchange (chromatography)
Cmax	maximum plasma concentration
CMD	complement mediated disorders
COVID	coronavirus disease
CQA	Critical quality attribute
CP	Classical pathway
CPP	Critical process parameter
CPV	continued process verification
DAT	Direct antiglobulin test
DNA	deoxyribose nucleic acid
DoE	Design of experiments
DP	Drug product
DS	Drug substance
ECG	electrocardiogram
eCRF	electronic case report form
EEPCB	extended end of production cell bank
EOT	End of treatment
EQ-5D-5L	EuroQol - 5 dimensions questionnaire
FACIT	Functional Assessment of Chronic Illness Therapy
FAS	Full Analysis Set
FBS	foetal bovine serum
GCP	Good Clinical Practice
GERD	gastroesophageal reflux disease

HC	heavy chains
HCP	Host cell protein
HIC	hydrophobic interaction chromatography
HILIC	hydrophilic interaction liquid chromatography
HMWS	High molecular weight species
ICH	International Council for Harmonisation
ICP-MS	Inductively Coupled Plasma Mass Spectrometry
IgG4	immunoglobulin G4
IMP	investigational medicinal product
IPC	In-process control
ITP	immune thrombocytopenia
ITT	intent-to-treat
IWRS	Interactive Web-based System
KPP	Key process parameter
LDH	lactate dehydrogenase
LC	Light chain
mAb	monoclonal antibody
MCB	Master cell bank
MedDRA	Medical Dictionary for Regulatory Activities
mFAS	Modified Full Analysis Set
MMRM	mixed model for repeated measures
MMV	mouse minute virus
HNV	normal healthy volunteers
NOR	Normal operating range
PAR	Proven acceptable range
PCSA	Potentially clinically significant abnormality
pcVPC	prediction-corrected visual predictive checks
PCSA	potentially clinically significant abnormality
PD	pharmacodynamic
PDE	Permitted daily exposure
PGIC	Patient's Global Assessment of Change
PGIS	Patient's Global Assessment of [Fatigue] Severity
PK	pharmacokinetic(s)
PP	per-protocol
PS80	polysorbate 80
PT	preferred term
PPQ	process performance qualification
PV	process validation
QbD	Quality by design
QOL	quality of life
RBC	red blood cells

REO	reovirus type 3
RVLP	retrovirus-like particles
SAE	serious adverse event
SD	standard deviation
SE-HPLC	size exclusion HPLC
SF-12	12-Item Short Form Survey
SLE	systemic lupus erythematosus
SmPC	Summary of Product Characteristics
SOC	system organ class
TAT	treatment assessment timepoint
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
TCID50	50% tissue culture infective dose
TEM	transmission electron microscopy
TI	tolerance interval
UF/DF	ultrafiltration/diafiltration
WAIHA	warm autoimmune haemolytic anaemia
WCB	Working cell bank
XMuLV	xenotropic murine leukemia virus

1. Background information on the procedure

1. Submission of the dossier

The applicant Genzyme Europe BV submitted on 8 October 2021 an application for marketing authorisation to the European Medicines Agency (EMA) for Enjaymo, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 18 October 2018.

Enjaymo, was designated as an orphan medicinal product EU/3/16/1609 on 17 February 2016 in the following condition: Treatment of autoimmune haemolytic anaemia.

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Enjaymo as an orphan medicinal product in the approved indication. More information on the COMP's review can be found in the orphan maintenance assessment report published under the 'Assessment history' tab on the Agency's website: https://www.ema.europa.eu/en/medicines/human/EPAR/enjaymo.

The applicant applied for the following indication: Enjaymo is indicated for the treatment of haemolysis in adult patients with cold agglutinin disease (CAD).

2. Legal basis, dossier content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

3. Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included EMA Decisions P/0211/2019, P/0146/2021 on the granting of a product-specific waiver.

4. Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report, addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

5. Applicant's request(s) for consideration

New active Substance status

The applicant requested the active substance sutimlimab contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

6. Protocol assistance

The applicant received the following Protocol assistance on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
22 June 2017	H/SA/3586/1/2017/PA/III	*Dr Andreas Kirisits and Dr Hans Ovelgönne*

The Protocol assistance pertained to the following *non-clinical* aspects:

- Acceptability of the non-clinical development program to support a MAA.
- Enhanced Pre-/Postnatal Development (ePPND) study.

The Protocol assistance pertained to the following *clinical* aspects:

- Dose and dosing regimen in the pivotal clinical program.
- Proposed study design of the pivotal Cardinal study (TNT009-03) in primary CAD patients, and specifically with the proposed primary endpoint, inclusion and exclusion criteria, durability and statistical analyses.
- Acceptability of the selected Quality of Life Instrument, the Facit-Fatigue, to further inform the benefit/risk of the product and to support the labelling.
- Acceptability of the proposed open label extension study design to generate long-term safety and durability data.
- Overall clinical development plan to support a MAA for primary CAD.

7. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Kristina Dunder Co-Rapporteur: Paula Boudewina van Hennik

The appointed CHMP co-rapporteur had no such prominent role in Protocol assistance relevant for the indication subject to the present application.

The application was received by the EMA on	8 October 2021
The procedure started on	28 October 2021
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	17 January 2022
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	28 January 2022
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	24 February 2022
The applicant submitted the responses to the CHMP consolidated List of Questions on	21 April 2022
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	30 May 2022

The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	10 June 2022
The CHMP agreed on a list of outstanding issues to be sent to the applicant on	23 June 2022
The applicant submitted the responses to the CHMP List of Outstanding Issues on	11 August 2022
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	31 August 2022
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Enjaymo on	15 September 2022
Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product (see Appendix on NAS)	15 September 2022

2. Scientific discussion

1. Problem statement

Disease or condition

Enjaymo is proposed for the treatment of haemolysis in adult patients with cold agglutinin disease (CAD).

Epidemiology

Primary CAD is a rare disease. In retrospective reviews from Nordic countries, the incidence has been estimated at approximately 1 to 1.8 per million and the prevalence at approximately 13 to 16 per million with higher prevalence in colder climates. The prevalence is slightly higher in females than in males and the median age of diagnosis in the late 60s with a broad range (30s to 90s).

Aetiology and pathogenesis

CAD is characterized by the presence of autoantibodies (typically immunoglobin M [IgM]) called cold agglutinins that bind to the I antigen uniformly present on the surface of all RBCs at an optimum temperature of 3-4°C, but can also react at higher temperatures, depending on the thermal amplitude. This leads to agglutination of RBCs and/or to complement activation through the classical pathway (CP) with subsequent haemolysis. Not all individuals with circulating cold agglutinins have clinical disease, and some patients only present with symptoms if exposed to cold temperatures or in relation to infectious disease, trauma or surgery. The complement-coated RBCs are cleared from circulation predominantly through phagocytosis by liver macrophages causing extravascular haemolysis; however, also intravascular haemolysis could be found especially during periods of increased haemolysis, caused by activation of the terminal pathway of complement, leading to the formation of the membrane attack complex and RBC destruction.

Primary CAD is defined as an autoimmune haemolytic anaemia mediated by cold agglutinins without any obvious underlying disease such as aggressive lymphoma, other overt malignancies, or specific infections. (Secondary) cold agglutinin syndrome (CAS) pertains to the more uncommon, secondary cold agglutinin-mediated haemolytic anaemia occasionally complicating other specific diseases, such as certain infections or aggressive lymphoma. Most patients with primary CAD are however thought to have a low-grade clonal bone marrow disorder.

Clinical presentation, diagnosis

The main clinical presentation of cold agglutinin disease is twofold: cold-related symptoms such as acrocyanosis and Raynaud's phenomenon induced by agglutination of RBCs, in accordance with thermal amplitude of the cold agglutinins, and/or autoimmune-type haemolytic anaemia (AIHA) caused by IgM-induced CP activation. Chronic haemolysis is common in CAD, ranging from compensated haemolysis without anaemia to severe haemolytic anaemia requiring transfusion, with symptoms of anaemia such as fatigue, weakness, dizziness, and chest pain.

Generally accepted diagnostic criteria include the following: evidence of haemolysis (e.g., high reticulocyte count, high LDH, high indirect bilirubin, low haptoglobin), positive direct antiglobulin (Coombs) test for C3d only (or, in a minority, C3d plus weak IgG) and cold agglutinin titre of ≥64 at 4°C.

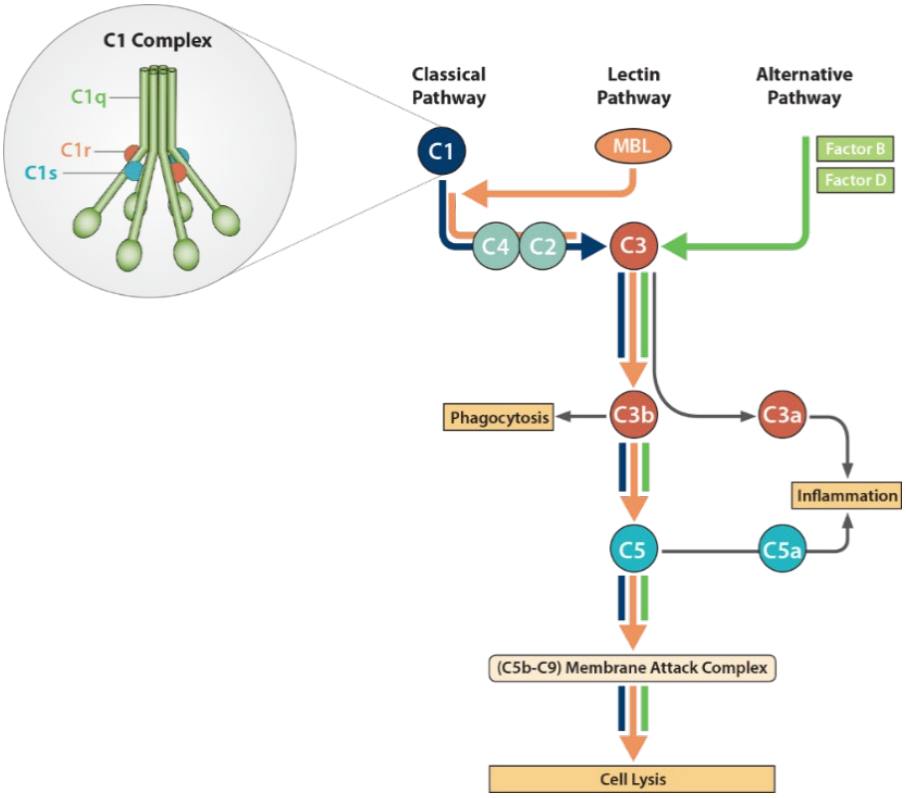
Management

In typical primary CAD, with or without a detectable low-grade bone marrow lymphoproliferative disorder, treatment is indicated for symptomatic individuals. Treatment is directed at minimizing cold-induced symptoms, maintaining an acceptable haemoglobin level, and, if required, addressing underlying disorders. Patients who have symptomatic anaemia or cold-induced ischemic symptoms interfering with daily living could receive therapy to reduce antibody production, primarily using rituximab alone or in combinations; none of these is however approved for CAD. Corticosteroids and/or splenectomy are usually not effective in primary CAD. Plasmapheresis may be used for immediate but transitory relief especially during periods of severe haemolysis. Red blood cell (RBC) transfusions could also be used to correct anaemia; the need of transfusions varies substantially between individuals with primary CAD and could be indicated only during periods of severe haemolysis precipitated by e.g., infectious disease or cold exposure.

2. About the product

Sutimlimab (BIVV009; TNT009) is a first-in-class, humanized immunoglobulin G (IgG), subclass 4 (IgG4) monoclonal antibody (mAb) that targets the classical pathway (CP) by inhibiting the classical CP-specific serine protease, specifically binding to complement component 1 (C1), s subcomponent (C1s). Complement C1s, which along with C1r and C1q is a part of the C1 complex that sits at the apex of the CP (see Figure 1). By binding C1s, sutimlimab prevents the enzymatic action of the C1 complex on its substrate, complement factors C4, and thereby blocks the formation of the C3 convertase. Upstream inhibition of the classical pathway is expected to retain the important immune surveillance functional activities of lectin and alternative pathways.

Figure 1. The Three Activation Pathways of the Complement System



Sutimlimab has been developed for the treatment of haemolysis in adult patients with cold agglutinin disease (CAD), a life-threatening chronic orphan disease. Sutimlimab inhibits haemolysis in patients with CAD through inhibition of the classical complement pathway. The proposed dose regimen of sutimlimab is 6.5 g (for patients >39 kg and <75 kg) or 7.5 g (for patients ≥75 kg), depending on the patient's body weight. Sutimlimab is to be administered by intravenous (IV) infusion over 1-2 hours once per week for the first 2 doses followed by every two weeks dosing thereafter. Enjaymo is intended for continuous use as chronic therapy only, unless the discontinuation of Enjaymo is clinically indicated. Patients with underlying cardiopulmonary disease may receive the infusion over 2 hours.

3. Quality aspects

Introduction

Sutimlimab, the active substance in Enjaymo, is an immunoglobulin G4 (IgG4) monoclonal antibody (MAb) produced in Chinese hamster ovary (CHO) cells by recombinant DNA technology.

Enjaymo is presented as solution for infusion in a single-use vial with a strength of 50 mg/mL. One vial contains 1100 mg of sutimlimab in 22 mL.

Sutimlimab is formulated with polysorbate 80, sodium chloride, sodium phosphate dibasic, sodium phosphate monobasic and water for injections.

Active Substance

General Information

Sutimlimab, also referred to as BIVV009, is a humanised IgG4 MAb specific for C1s esterase (EC 3.4.21.42). The antibody is expressed by recombinant CHO cells and produced in vitro using standard mammalian cell culture methods followed by chromatographic purification.

BIVV009 is composed of two heterodimers. Each of the heterodimers is composed of a heavy and a light polypeptide chain. Each heavy chain (HC) is composed of 445 amino acids and each light chain (LC) contains 216 amino acids.

BIVV009 contains a total of 12 intra-chain disulfide bonds, 4 within each of the two HCs and 2 within each of the two LCs. BIVV009 contains a serine-to-proline mutation (S241P), based on the Kabat numbering system, which stabilises the core-hinge region of the molecule. In addition, BIVV009 contains a leucine-to-glutamic acid mutation (L248E) that abrogates Fcγ receptor binding.

The predicted molecular weight (MW) of non-glycosylated, native BIVV009 is approximately 144,813 Da based on its amino acid sequence of 1322 residues.

The glycosylation site is located on the HC at N295.

The information in this section is considered sufficient.

Manufacture, process controls and characterisation

Manufacturer(s)

Sutimlimab active substance is manufactured by Biogen, Research Triangle Park, NC, USA. The name, address, and responsibilities of manufacturers involved in the manufacture, storage, and testing of the intermediates and the active substance is available in the dossier. The submitted information is considered sufficient. All sites operate in compliance with EU GMP.

Description of manufacturing process and process controls

The manufacturing process of sutimlimab active substance encompasses cell culture, harvest and primary capture, purification by three chromatography steps, low-pH viral inactivation, virus filtration, concentration, formulation and 0.2 um filtration to final fill and refrigerated storage. The manufacturing process and process controls are summarised in flow charts and tables. The purpose of each step is clearly stated, and a brief description is provided. Process parameters and in-process controls (IPC) are listed, including criticality assignment. Operating sequences, resin and filter materials, buffers, number of cycles, reuses (where applicable), and collection of fractions are provided for the chromatography steps and the filtration steps. The unprocessed bulk is tested for adventitious agents (viruses, bioburden, and mycoplasma). The level of detail is considered sufficient.

Each working cell bank (WCB) vial give rise to one active substance batch. The scale of the production bioreactor chromatography, virus filtration, and ultra-/diafiltration (UF/DF) and the final active substance steps are given.

In-process pool hold times and hold conditions are sufficiently described for each step. Resin and membrane reuse is, supported by small-scale data and at-scale validation activities. The approach to microbial control of the process is considered adequate.

Active substance transportation is sufficiently described.

Thus, reprocessing is not performed for the sutimlimab active substance manufacturing process.

In summary, it can be concluded that the description of the manufacturing process and process controls is acceptable.

Control of materials

Raw materials

Detailed descriptions of raw materials and consumables and the active substance storage container are presented. Specifications with acceptance criteria are provided for non-compendial raw materials including process solutions. No animal-derived material is used during manufacture of the active substance. However, animal-derived material was used during early development of the host cell line as mentioned below. The information regarding raw materials is sufficient.

Source, history and generation of the cell substrate

The history and development of the antibody and the CHO-M cell line lineage is sufficiently described as are the construction and rationale of gene constructs and expression vectors. The predicted amino acid sequences of both heavy and light chains are presented. The development of the CHO-M host cell line into the antibody producing research cell bank (RCB) is described and the route to monoclonality shown, in line with ICH Q5B and ICH Q5D guidelines.

Cell banks

The cell bank system and the preparation of the cell banks are sufficiently described for the master cell bank (MCB), WCB and extended end-of-production cell bank (EEOPCB), including storage, handling, identification and number of vials produced.

The cell banks, including the EEOPCB, were tested according to ICH Q5A (R1). The extended cell banks were tested for identity, sterility, mycoplasma and adventitious agents. Bovine and porcine cell lines were included for *in vitro* testing of the MCB. A Certificate of Analysis and Certificate of Suitability are provided and acceptable documents have been provided for raw materials of biological origin used in the establishment of cell substrate The testing of cell banks is in line with ICH Q5A and any risk of TSE is negligible.

Genetic stability was tested on the MCB, WCB and EEOPCB cells. The confirmation of genetic stability is in line with ICH Q5B and acceptable.

The MCB and WCB are stored under GMP conditions at two separate locations as a risk mitigation. Cell bank storage stability data is shown, MCB and WCB stability upon storage will be addressed at least every 5 and 3 years, respectively.

A protocol for new WCB is provided and found acceptable.

Control of critical steps and intermediates

Definitions for critical quality attributes (CQA), proven acceptable ranges (PAR), normal operating ranges (NOR), critical process parameters (CPP), key process parameters (KPP), IPCs, action limits and acceptance criteria are provided in 3.2.S.2.4 and aligned with relevant guidelines. This is endorsed.

Process parameter criticality is based on the impact to CQAs and process consistency and the IPCs are linked to consistent performance of relevant attributes. Process parameters are controlled within PARs. IPCs are tested against action limits or acceptance criteria.

Management of deviations to process parameters ranges and IPC limits is acceptably described.

The analytical procedures used for in-process testing are described in sufficient detail. They were also demonstrated to be suitable for their intended use.

In summary, process parameters and IPCs critical to the active substance manufacturing process are acceptably presented.

Process validation and evaluation

An extensive set of studies for process validation is presented, along with descriptions of methods and tools and completed for the active substance manufacturing process.

The process validation of the active substance manufacturing steps at commercial scale at Biogen is adequately described and reported. The manufacturing process was executed according to the description in 3.2.S.2.2.

The approach to demonstrate clearance of process-related and product-related impurities has been sufficiently demonstrated during process validation and is endorsed. A control for host cell proteins (HCP) is included in the active substance release specification.

Analytical methods used during process validation studies, were validated as appropriate for intended use The analytical method validations are provided. The level of information is considered sufficient, no concerns are raised.

Sufficient information is provided regarding impact of extractables and leachables from single use contact materials.

The hold times study approach for biochemical and microbial stability is considered acceptable (scale, containers/vessels, sampling, test panel, supportive small-scale studies). Biochemical and microbial hold times and hold conditions are considered validated.

Small-scale data support the proposed reuse of chromatography resins and UF/DF membranes. Concurrent validation of resin lifetime limits is performed during commercial manufacturing according to provided protocols. The overall strategy and proposed testing are approvable. The ultrafiltration membrane will be subjected to real-time testing – as long as the criteria are fulfilled, the membrane may be used. This is acceptable.

Reprocessing is not validated.

The outlined continued (ongoing) process verification program (trending and analysis to ensure that the process remains in its validated state) is endorsed.

In summary, it is agreed that the process validation results support the conclusion that the manufacturing processes for sutimlimab active substance can be considered validated.

Manufacturing process development

Manufacturing history and manufacturing process changes

Two different versions of the active substance manufacturing process have been used during clinical development. Changes between the clinical processes and the commercial process are clearly outlined. The description of the changes leading to the commercial active substance process is available in the validation section and the comparability section. The aspects considered and the panel of tests included in the comparability exercise are considered sufficient and in compliance with ICH Q5E.

CQAs

CQAs are defined in accordance with ICH Q8. This is endorsed. Identification of CQAs encompass a multidisciplinary risk assessment of the potential impact on biological activity or efficacy, pharmacokinetic/pharmacodynamic, immunogenicity and safety of the product, and the uncertainty of the knowledge regarding the impact. The approach as such is supported and considered sufficiently described. The scoring system is explained and a summary table describing the outcome of the risk assessment is provided. The scoring of the uncertainty is partly based on prior knowledge from "related molecules/similar class of molecules". The use of prior knowledge is considered appropriately justified. The proposed classification of CQAs and non-CQAs is acceptable.

Control strategy

An extensive process development program is submitted, including justifications for all stages of the proposed active substance manufacturing process which consists of a traditional set of PARs (proven acceptable range), and in some cases NORs (a minimal level of variation around the target setpoint). PAR is defined in accordance with ICH Q8. Overall, the approach for control strategy development is considered scientifically sound.

Process parameter criticality was determined by preliminary risk assessment (unit operation impact to CQAs), process characterisation studies which included evaluation of practical significance, and a final updated risk assessment (seemingly traditional failure modes and effects analysis (FMEA) taking severity, occurrence and detectability into account). Process parameters identified as not impacting CQAs or process performance were identified as non-KPPs. This methodology is supported.

Quality by Design (QbD) elements such as risk assessments and design of experiments (DoE) were included during process development.

The applied strategy for small-scale model (SSM) qualification is supported and is considered qualified and representative of the commercial scales.

Process characterization development studies were performed to identify PARs for process parameters.. Process parameter impact to quality and performance, respectively, determined the severity ranking for the final risk assessment and criticality assignment of process parameters. The final outcome of the FMEA analysis, including justified changes made due to PPQ, is found acceptable. The proposed process parameter criticality assignment is approvable.

In summary, the process development program and the resulting proposed final control strategy is considered appropriate and supportive of the proposed manufacturing process.

Comparability

Three different comparability studies are presented for the clinical processes and the commercial process to demonstrate comparability across the process versions.

The comparability studies encompass release tests, characterisation testing, stability studies and forced degradation (temperature, light).

The aspects considered and the panel of tests included in the comparability exercise are considered sufficient and in compliance with ICH Q5E. Results are presented in tables displaying individual results for post-change batches, historical ranges for pre-change batches, comparability criteria, and clinical active substance specification. Individual batches are not plotted but chromatograms, electropherograms and spectras are provided, and conclusions are clearly stated.

Comparability criteria for several attributes are based on tolerance intervals. The resulting comparability criteria are wider than the historical range but tighter than the clinical active substance specifications in use at the time.

There were no new peaks or variants detected in any of the comparability studies.

Results from stability comparability studies are assessed in S.7.

In summary, it is concluded that the proposed commercial manufacturing process is representative of the active substance and finished product that has been used in clinical studies included in this application.

Characterisation

Sutimlimab is a humanised IgG4 monoclonal anti-C1s esterase antibody expressed in CHO cells. Sutimlimab contains two specific mutations: serine-to-proline (S241P) to stabilise the core-hinge region, and leucine-to-glutamic acid mutation (L248E) to abrogate the Fcγ receptor binding.

A comprehensive physicochemical and biological characterisation of the sutimlimab molecule is presented. In general, the results show that sutimlimab has the covalent structure, post-translational modifications, and other characteristics of a typical humanised IgG4 antibody derived from CHO cells. Studies of primary, secondary and higher order structure, various physicochemical properties, carbohydrate structure, heterogeneity pattern and biological functions were included.

An extensive panel of state-of-the-art and orthogonal tests were applied. Characterisation methods and preparations of variants for characterisation studies are sufficiently described. All peaks are defined and relevant chromatograms, electropherograms and spectras with sufficient resolution are provided.

Sutimlimab contains N-linked glycosylation at position Asn295 of each HC. The dominant forms are core fucosylated biantennary glycans. The proposed mechanisms of action include binding to the C1s esterase, thereby inhibiting further escalation of the classical complement pathway. Binding studies confirm that the Leu-to-Glu mutation (L248E) obviates, or significantly decrease, binding to Fcγ receptors. In summary, except for a recommendation to the approval, the submitted information regarding characterisation of the active substance is acceptable and demonstrates a sufficient product understanding. The monosaccharide profile is currently missing. The Applicant is recommended to update section 3.2.S.3.1 with the missing monosaccharide profile within 6 months from approval. This is listed as Recommendation 1.

Active substance product-related and process-related impurities, respectively, are described together with the analytical methods for control. All peaks are defined and relevant chromatograms, electropherograms and spectras are provided. Amounts of the process-related impurities are measured and calculated (assuming a worst-case scenario) to be well below safety limits and clearance can be considered sufficiently demonstrated.

Sufficient information is provided regarding impurities.

Specification

Specifications

The commercial release and stability specifications for BIVV009 active substance include control of identity, purity and impurities, potency and other general tests and are adequately justified.

Active substance release and stability (end-of-shelf life) specifications are presented.

The proposed list of attributes is considered suitable.

The specifications were developed in accordance with ICH Guideline Q6B, for most parts. The approach takes future variability into account by including assay and process variability, while guidelines (ICH Q6B) expect justifications based on variability during clinical trials and process validation. However, as the active substance specification in the end is adapted to clinically justified criteria in the finished product end-of-shelf life and release specifications, the proposed active substance specification is considered approvable.

In conclusion, the proposed active substance specification is considered approvable.

Analytical procedures

Descriptions were provided for all analytical procedures. Most of the methods described in this part are used for testing of both active substance and finished product.

The non-compendial analytical procedures are generally described with a sufficient level of detail. Representative chromatograms, electropherograms, and dose-response curves are provided.

Compendial procedures have been appropriately verified for their intended use.

The non-compendial procedures applicable to control of both active substance and finished product have been appropriately validated. The validations were performed in accordance with the requirements in ICH Q2(R1). Successful execution of the method verification and method transfer protocols is demonstrated for most parts.

Reference standards

A two-tiered system of primary and working reference standard is applied. The selection, preparation, qualification, and re-qualification of reference standards have been described in sufficient detail, including specifications and characterisation testing.

Batch analysis

Batch release results, and batch usage overview, for three manufacturing versions of the active substance lots are provided. Further batch genealogy is presented in 3.2.S.2.6.

Each batch was tested to the specification in place at the time of manufacture. All limits were met.

Container closure

The applicant has provided an adequate description of the container closure system, including drawings and CoAs and acceptable specifications.

Stability

A shelf life for sutimlimab active substance of 21 months at the recommended long-term storage condition of 5 ± 3 °C is proposed.

The subjects covered by the description of the stability studies (recommended, accelerated and stressed conditions, and forced degradation) and the stability data are appropriate, in compliance with ICH Q1A(R2) and Q5C, and the chosen analytical methods appear adequately stability indicating.

The submitted data is considered supportive of the proposed shelf life and long-term storage conditions (21 months at 5 ± 3 °C).

Finished Medicinal Product

Description of the product and Pharmaceutical Development

The BIVV009 finished product is a sterile solution for intravenous (IV) infusion in a single-dose vial. Packs of 1 or 6 vials are proposed.

The qualitative and quantitative composition of the BIVV009 has been provided . All excipients in the composition comply with the Ph. Eur. or USP grade (USP grade tested to closely related chemicals available as Ph. Eur.). No novel excipients and no human or animal derived materials are used.

Each single-use vial contains a nominal volume of 22 mL of 50 mg/mL BIVV009 (1100 mg BIVV009/vial). An overfill volume of 1.0 mL is included to allow for withdrawal of the labelled amount of 22 mL bringing the target fill volume to 23.0 mL. No overages are applied.

The vials and stoppers are compliant with appropriate Ph. Eur. monographs for primary containers and closures as described in section P.7.

Formulation development

All BIVV009 finished products manufactured during development are sterile solutions intended for intravenous (IV) administration. The study designs, results and chosen buffer components are found acceptable. A commercial formulation of 50 mg/mL BIVV009 in 10 mM sodium phosphate, 140 mM sodium chloride, 0.02% (w/v) polysorbate 80, pH 6.1 was selected.

In-use time and dilution/compatibility stability of BIVV009 finished product was studied. Finished product was diluted with normal saline in IV bags and infused through an IV set with in-line filter. It was demonstrated that the IV infusion bag could be stored for up to 8 hours at ambient temperature (20–25°C) and with room light conditions if not used immediately. From a microbiological point, appropriate text from NfG on maximum shelf life for sterile products for human use after first opening or following reconstitution (CPMP/QWP/159/96 corr.) is included in the SmPC.

Manufacturing process development

Active substance batch, finished product dosage form, manufacturer, location, finished product lot and allocation of lots are listed.

Process development studies have been performed to optimise the processing conditions and confirm equipment suitability, including at-scale studies supporting the manufacture of finished product BIVV009 50 mg/mL vial on the filling line. The product CQAs are determined at the level of the active substance. Process characterisation studies on the manufacturing process were performed.

Compatibility of product with contacting materials was tested. Hold times and storage conditions were confirmed. Extractable volume was confirmed as well as effectiveness of crimp pressure for the container closure system.

Nomenclature and definitions with rationales for process controls and control strategy is presented as well as a list of process controls. The controls and tests are assessed as adequate and justified.

Container closure

Extractable and leachable (E&L) assessments of the primary packaging components and the key product-contact materials associated with the filling lines were performed. The levels of any potential leachable or extractable compound were considerably lower than the Analytical Evaluation Threshold and do not pose a toxicological safety concern for the finished product. No elemental impurity above the ICH Q3D limits for parenteral compounds was detected in the course of the leachable study. The container closure system is considered suitable for use. An acceptable approach is in place to ensure microbial safety.

Compatibility

An in-use stability/compatibility study was performed. The results of the refrigerated hold study demonstrated that finished product diluted with 0.9% sodium chloride at concentrations between 13 to 50 mg/mL (undiluted) can be stored at 2-8ºC for up to 72 hours prior to infusion.

Manufacture of the product and process controls

All sites involved in manufacture control and storage of the finished product operate in accordance with EU GMP.

The manufacturing process is of standard type with pooling, mixing, bioburden reduction, sterile filtration, filling and capping, however the active substance is not frozen. Batch formula both in volume and weight is provided with minimum and maximum batch sizes.

All product contacting equipment and materials, single use or as dedicated equipment, are listed. Equipment used for sterilisation is identified with conditions for sterilisation and specifications/limits. Vials are depyrogenated, the stoppers are autoclaved and used equipment is identified. Sterilisations are performed.

Maximum hold and processing times with temperature requirements are defined as are shipping conditions for subsequent finished product vial labelling and secondary packaging. No reprocessing has been suggested for the finished product manufacture.

Control of critical steps and intermediates

The nomenclature and definitions for process controls and control strategy with categories and attributes are explained and defined. The definitions for control strategy are found acceptable.

Process operations with parameters and ranges are presented with criticality classifications. CPPs are listed together with acceptance criteria and control methods for critical IPCs, critical in-process tests as well as the key-controlled parameters and critical-controlled parameters. The overall control strategy, with process parameters and IPCs are found adequate leading to consistent finished product quality.

Process validation and/or evaluation

The Applicant describes the process validation with pooling and mixing of finished product followed by bioburden reduction and in-line sterile filtration. Homogeneity of filling, subvisible particle verification, visual inspection, yields and container closure verification with capping validation was performed. Validation also included hold times and the aseptic process by media fill, sterilising filters with bacterial filter retention tests, integrity testing and compatibility, bacterial challenge studies and extractable/leachable as well as shipping studies.

Consecutive lots were included in the process qualification and the finished product manufacturing process is considered validated.

Overall, the finished product manufacturing process is considered validated.

Product specification

Specifications

The commercial release and stability specifications for BIVV009 finished product include control of identity, purity and impurities, potency and other general tests.

The proposed list of attributes is considered suitable. Polysorbate 80 is included in both the release and stability specification which is endorsed. A justification for routine batch release and stability testing is presented. Specifications for the active substance release, active substance end of shelf life, and finished product release are adjusted to assure that the clinically justified finished product limits can be met during the entire shelf life.

Analytical methods

Short descriptions of the analytical procedures and validation/qualification reports are provided.

The methods common for the active substance and finished product are described in the active substance section. Specific tests for the finished product are appearance-visible particles, sub-visible particulates, extractable volume, polysorbate 80, sterility, endotoxin and container closure integrity. The methods specific to the finished product are validated with exception for the compendial methods that are verified.

Reference standard

The reference standards used for testing of the BIVV009 finished product are the same as those used for testing of the active substance.

Batch analysis

Batch analysis release data have been provided for all batches manufactured (preclinical, clinical and PPQ).

All test results including lots released to the clinic met the release specification in place at time of testing.

Characterisation of impurities

Product-related impurities are the same as those present or potentially present in BIVV009 active substance except for sub-visible particles.

The level of specific elemental impurities was assessed following ICH Q3D.The results were for all elements tested below the control threshold (30% of the PDE), thus not posing any risk. The risk assessment carried out for BIVV009 indicates that the finished product complies with ICH Q3D requirements. A risk assessment on the potential presence of nitrosamines was performed on the BIVV009 finished product manufacturing process. The assessment includes potential sources of nitrosamines and their potential chemically related substances entering the final commercial finished product. The Applicant concluded that due to the design of the manufacturing process as well as the quality systems applied, there is no risk of release or potential release of nitrosamines into the finished product during production. This is endorsed.

Stability of the product

A claim is made for 2 years shelf life for the finished product when stored at 2°C to 8°C, as stated in the SmPC.

The stability program with tests and test interval is in line with ICH Q5C and found acceptable.

The requested shelf life is based on primary and supportive stability studies from lots manufactured throughout development.

Photostability was studied with the conclusion that prolonged light exposure should be avoided, to protect from light and store in the original carton as stated in the SmPC. Temperature cycling and time out of refrigeration with post-cycling long-term stability storage was performed. Studies determined that this did affect the ability of BIVV009 finished product to conform to the final proposed commercial stability specifications. This is acceptable.

Testing for leachables is ongoing on long term storage. The in-use stability and compatibility portion of the in-use study will be repeated on an end of shelf life finished product lot stored at 5 ± 3°C, which is acceptable. A post-approval stability protocol and stability commitment for long-term storage condition of 5±3 °C has been provided. Overall, the shelf life of 2 years at 2°C to 8°C protected from light is acceptable.

Chemical and physical in-use stability has been demonstrated for 16 hours at 18°C to 25°C or for 72 hours at 2 °C to 8 °C. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would not normally be for longer than 24 hours at 2°C to 8 °C or 8 hours at room temperature, unless vial opening and pooling into the infusion bag has taken place in controlled and validated aseptic conditions.

Adventitious agents

The adventitious agents safety testing is stated to be according to ICH Q5A. Testing on cell banks and EEOPCB is sufficiently described and in line with ICH Q5A.

Unprocessed bulk harvest is tested for mycoplasma and adventitious viruses.

There are no animal-derived raw materials used in the manufacture of BIVV009 active substance. During early development of the CHO-M host cell line, materials of animal origin were used. A Certificate of Analysis and Certificate of Suitability are provided. The materials were trypsin of porcine origin, cod liver oil, ovine cholesterol and FBS heat inactivated. Some ancillary materials (e.g., bags, tubes, and filters) used in the process were manufactured using bovine tallow derivatives as lubricants and/or release agents. All bovine tallow derivatives were TSE compliant in line with EMA/410/01.

Virus clearance studies are in line with expectations and have been performed using qualified scale-down models The suitability of the scaled-down models has been sufficiently demonstrated. An appropriate panel of model viruses is used. Four viruses were chosen for the BIVV009 virus clearance validation study: Xenotropic Murine Leukemia Virus (X-MuLV), Minute Mouse Virus (MMV), Porcine Pseudorabies Virus (PRV) and Reovirus Type 3 (Reo3).

Chromatography parameters such as resin type, column bed height, diameter, loading, linear flow rate, elution end of collection and resin lifetime were compared side-by-side. Differences were essentially in column sizes, linear flow rates were kept within range.

Any cytotoxic or viral infectivity interference of process buffers on the cell lines used for the virus assay was evaluated prior virus validation studies. Also, potential effect on a unit operation from the virus formulation matrix on performance when virus is spiked into the feed-stream was tested.

The summary of clearance validation results only add up the lowest obtained values which is endorsed being a conservative approach. The overall clearance values and viral safety of the process is acceptable. The retrovirus safety margin for retrovirus like particles found in the bulk harvests by TEM

is sufficient and acceptable. In summary, the characterisation and control of the cell substrates, the use of non-animal derived materials in the process, in-process testing and virus clearance capability of the manufacturing process provides sufficient assurance of safety regarding adventitious agents in the BIVV009 process.

Discussion and conclusions on chemical, pharmaceutical and biological aspects

The dossier is of good quality.

Characterisation of sutimlimab was performed using an extensive panel of appropriate methods.

A science- and risk-based approach with QbD elements was used for process development and process characterisation, supporting the proposed manufacturing process control strategy and demonstrating a solid process understanding. The active substance and finished product manufacturing processes and process controls are appropriately described and the processes are appropriately validated.

Four versions of the active substance manufacturing process are presented. Changes are clearly described. Comparability between process versions is demonstrated. It is concluded that active substance manufactured with the commercial process version is representative of the active substance used in clinical trials.

The claimed stability for the active substance of 21 months at 2°C to 8°C, and for finished product of 2 years at 2°C to 8°C is considered acceptable based on the provided stability data.

Conclusions on the chemical, pharmaceutical and biological aspects

The overall quality of Enjaymo is considered acceptable when used in accordance with the conditions defined in the SmPC. The different aspects of the chemical, pharmaceutical and biological documentation comply with existing guidelines.

In conclusion, based on the review of the data provided, the marketing authorisation application for Enjaymo is considered approvable from the quality point of view.

Recommendation(s) for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends several points for investigation.

2. Non-clinical aspects

Introduction

The pharmacology, drug disposition, and nonclinical safety profile of sutimlimab were evaluated in support of the use of sutimlimab for conditions in which the classical complement pathway plays an important role in the pathophysiology such as CAD, immune thrombocytopenic purpura (ITP), bullous pemphigoid (BP) and other indications in which CP activation is induced by pathogenic patient autoantibodies.

The nonclinical toxicology program was claimed to be consistent with the Guidance for Industry: S6(R1) Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals (2012). The nonclinical toxicology program was claimed to be conducted under Good Laboratory Practices (GLP), as appropriate.

Pharmacology

Primary pharmacodynamic studies

In vitro pharmacology studies were performed to assess sutimlimab and/or TNT003 binding affinity to human (and other species) C1s and to determine the specificity and potency of sutimlimab inhibition of CP activity. Additionally, *in vitro* studies with samples from CAD, ITP and BP patients were performed to assess the ability of sutimlimab to inhibit complement fragment deposition on human RBCs, platelets and skin.

The affinity of mouse antibody TNT003 and 12 humanized variants to active and inactive forms of human C1s was determined using biolayer interferometry. All variants bound C1s with higher affinity than the parental mouse antibody, TNT003. The humanized lead antibody (TNT009, variant VH4Nk2) bound active and inactive C1s with an affinity of 2.624 x 10-10 M and 2.616 x 10-10 M respectively.

The *in vitro* pharmacology of sutimlimab (TNT009) was evaluated using both sutimlimab and TNT003. Using normal human serum (NHS) or human CP proteins *in vitro*, sutimlimab was shown to have high affinity (10^{-10} M) and specificity for human C1s and to be a potent (IC50 of 10^{-9} M) and complete (100%) inhibitor of serum CP activity but not of the alternative pathway or lectin pathway (AP or LP, respectively) activity. Cynomolgus monkey (*Macaca fascicularis*) was the only pharmacologically relevant species identified, as the binding affinity for C1s (10^{-10} M) and the pharmacologic activity of sutimlimab in this species are identical to those for humans. TNT003 IC50 values for inhibition of CP activity were 14.7 and 15.6 µg/mL in 80% human and monkey serum, respectively.

As was observed *in vitro*, sutimlimab displayed a steep threshold concentration-response curve; *in vivo* this resulted in rapid loss of CP inhibition when the serum sutimlimab concentration declined below the threshold concentration.

TNT003 was demonstrated *in vitro* to inhibit: CA-mediated C3 fragment opsonization of human RBCs, erythrophagocytosis of C3 fragment-opsonized RBCs, CA-mediated hemolysis; CAmediated production of anaphylatoxins (C3a, C4a, C5a) in CAD patient samples and C1q, C3b, C4d, and C5b-9 deposition on platelets with ITP patient samples. In addition, TNT003 was demonstrated to inhibit complement C3 fragment deposition, mediated by auto-antibodies from patients with BP, at the dermal-epidermal junction of human skin.

Secondary pharmacodynamic studies

In vitro studies of autoimmunity

In vitro autoimmunity studies demonstrated that TNT003 does not inhibit C1q deposition on early apoptotic cells (EACs). Furthermore, TNT003 does not inhibit the desirable immunosuppressive effects of efferocytosis of EACs.

Effect of C1s inhibition on bacterial killing

To evaluate the risk of *Neisseria meningitidis* and *Streptococcus pneumoniae* infections when inhibiting the classical pathway studies were performed with another well characterized and specific inhibitor of C1s, the mouse monoclonal antibody TNT005. TNT005 specifically inhibits the protease activity of C1s and achieves complete inhibition of the CP at concentrations like those of sutimlimab *in vitro*. The data suggest that killing of *N. meningitidis* or *S. pneumoniae* in whole blood containing specific anti-capsular antibodies is unimpeded by inhibition of the CP. Meningococcal and pneumococcal capsular conjugate vaccines which may mitigate risk of these infections in patients receiving C1s inhibitors.

Safety pharmacology programme

No dedicated safety pharmacology studies were conducted with sutimlimab. Instead, safety pharmacology endpoints were incorporated into the 5- and 26-week repeat-dose toxicology studies in monkeys. No secondary PD effects related to AP activity were observed in the 5-week GLP repeat-dose toxicity study in monkeys. No sutimlimab-related central nervous system (CNS), cardiovascular or respiratory safety pharmacology effects were noted for the parameters evaluated in the 5- and 26-week GLP repeat-dose toxicity studies.

Pharmacodynamic drug interactions

No pharmacodynamic drug interaction studies were conducted with sutimlimab. Please see Clinical pharmacology section for more detail.

Pharmacokinetics

The pharmacokinetic (PK) and toxicokinetic (TK) exposure parameters of sutimlimab have been characterized in single- and multiple-dose cynomolgus monkey studies over the same dose range as the pharmacodynamic (PD) studies, 5 to 180 mg/kg. After an IV dose of sutimlimab C_{max} are observed at the end of infusion, increasing with increasing dose. The exposure, as determined by the AUC, was dose-proportional at doses ≤45 mg/kg; a greater than dose-proportional increase in exposure was observed for doses above 45 mg/kg. The $t_{1/2}$ of serum sutimlimab appears to be concentration dependent. At 30 mg/kg, the $t_{1/2}$ was approximately 18 to 25 hours. When the dose is doubled from 30 to 60 mg/kg, the mean $t_{1/2}$ increased to 50 hours.

No specific studies were done to assess the distribution of sutimlimab. Sutimlimab is a humanized IgG4 monoclonal antibody (mAb) intended to be administered intravenously. It is anticipated to be present within the vasculature (blood and plasma) and interstitial and extracellular fluids throughout the body, as evidenced by the low volume of distribution *in vivo*. No tissue distribution, protein binding, or placental transfer studies have been conducted. No formal metabolism studies were conducted with sutimlimab. As a large protein, sutimlimab is expected to be metabolized by non-saturable proteolytic catabolism processes. As these pathways of degradation are generally well understood, classical biotransformation studies are generally not needed (ICH S6[R1]). Small peptides and individual amino acids generated during the metabolism of biologics such as sutimlimab are excreted and/or re-incorporated into new protein production via normal metabolic pathways. As these pathways of

excretion and re-incorporation are generally well understood, classical excretion studies are generally not needed and have not been performed for sutimlimab. Pharmacokinetic drug interaction studies have not been conducted with sutimlimab. As monoclonal antibodies are generally highly target specific and do not interact with the protein/enzymatic systems responsible for the metabolism of small molecule drugs, drug interactions are not anticipated to occur.

Toxicology

A limited toxicology program with sutimlimab has been evaluated in non-clinical studies in agreement with relevant guidelines.

The toxicity profile of has been characterized in cynomolgus monkeys via GLP-compliant repeat-dose toxicity studies for up to 6 months and in an enhanced pre-and postnatal development (ePPND) toxicology study with a 3-month postnatal evaluation. Evaluation of safety pharmacology parameters on CNS, respiration and cardiovascular endpoints were included in the repeat-dose toxicity studies. The repeat-dose toxicology studies and the ePPND study also included TK analysis and evaluation of immunogenic potential of sutimlimab, and the risk for autoimmunity and circulating immune complexes. Furthermore, a human tissue cross-reactivity study has been conducted.

The intravenous route of administration was utilized in the repeated toxicology studies and the enhanced pre and postnatal study to match the intended clinical administration route.

Relevance of selected species

The choice of cynomolgus monkey as the toxicology species, was based upon comparable binding affinity to human C1 and the functional cross-reactivity to inhibit CP-mediated haemolysis of antibody-sensitized red blood cells (RBCs) in humans. In other species tested (mice, rats, rabbits, minipigs and dogs) no binding to C1 and/or no inhibition of CP-mediated haemolysis in serum occurred. Based on binding and functional properties of sutimlimab, the selection of cynomolgus species as the only relevant toxicology species is supported.

Single dose toxicity

No single-dose toxicity studies were conducted with sutimlimab.

Repeat dose toxicity

Sutimlimab has been evaluated in repeat-dose studies in cynomolgus monkey for 5 (up to 100 mg/kg/week) and 26 weeks (up to 180 mg/kg/week) with 8 weeks of recovery. In addition, as part of the studies evaluation of inhibition of classical component pathway was evaluated. Further, blood samples from animals in these monkeys was evaluated for autoimmunity and the levels of circulating immune complexes in non-GLP compliant studies (TN-1501).

In both the 5- and 26-weeks studies no mortality, clinical signs, effects on body weight, food consumption, body temperature or clinical pathology parameters (hematology, coagulation, serum chemistry, and urinalysis) or any histopathological findings were observed.

In the 5-week study, inhibition of serum CP was noted at 30 mg/kg/week, however, sustained high inhibition during 5- weeks of treatment of sutimlimab was observed at 60 and 100 mg/kg/week. After a recovery period of 8 days at 100 mg/kg/week, the CP levels remained reduced in males and females (13% and 50% of controls, respectively) that was return to normal reference range (81.9-126.2%) after 15 days of recovery. In the 26-week study, the activity of the complement system for each dose level is at the same level at the pre-dose sampling; however, the activity of the complement system is significantly inhibited even at the pre-dose sampling at day 29 for the highest dose level. In recovery

animals administered 60 or 180 mg/kg/week, serum CP activity returned to baseline values by Days 197 or 232, respectively. No inhibition of alternative complement pathway (AP) was not observed in the studies.

Toxicokinetics

Toxicokinetic analysis was performed in the repeat toxicology studies and the ePPND study. In the 5-weeks study, there was no significant difference in exposure between genders. Over-proportional AUC_{0-145} exposure and accumulation at 100 mg/kg/week were seen.

In the 26-weeks toxicity study, the applicant concludes that no sex differences in sutimlimab C_{max} and $AUC_{0-48.5}$ were present. As a consequence, the results and discussion were based on combined sex values. This in not completely agreed. There are data points (60 mg/kg/week: dose 13 show a decrease in exposure in females vs. males in $AUC_{0-48.5}$ and C_{max} with a 2.6-fold and 2.4-fold change, respectively; 180 mg/kg/week: dose 26 show a decrease in exposure in females vs. males in $AUC_{0-48.5}$ with a 2.0-fold), thus sex-dependent PK is indicated. In the same study, the company concludes that exposure to sutimlimab increased with the increase in dose level from 60 to 180 mg/kg/dose and that this increase (mean Cmax and AUC0-48.5 values) was roughly dose proportional on Days 1, 29, 85, and 176. This claimed dose-proportionality is not agreed as the data rather point at a more than dose proportional relationship. Accumulation was observed following multiple doses.

In dams in the e-PPND study an overproportioned AUC and C_{max} exposure was seen at day 48 and 146 pc and an approximately 2-fold accumulation at the 180 kg/mg/week dose. No exposure was observed in the F_1 infants.

Safety pharmacology

Safety pharmacology endpoints were evaluated in the 5- and 26-week repeat-dose toxicology studies in monkeys dosed up to 180 mg/kg/week sutimlimab administered IV.

The endpoints included clinical CNS and respiratory daily examinations, physical weekly examinations, neurobehavioral examinations, and heart rate or ECG evaluations.

No treatment-related CNS clinical signs or body temperature effects, changes in heart rate or electrocardiogram (ECG) parameters or respiratory clinical signs or changes in respiratory rate was observed in any of the animals in the repeat-dose toxicology studies.

Exposure margins

The proposed clinical dose of sutimlimab in humans is 6.5 grams (> 39kg and <(<75kg) and 7.5 grams (≥75kg) administrated weekly for the first two doses followed by every two weeks dosing thereafter. In CAD populations this results in an exposure to sutimlimab of mean AUC of 74290 µg*h/mL (using the population PK model) and mean C_{max} of 3370 µg/mL at the 6.5 grams dose.

The proposed NOAELs in the general toxicity studies and the ePPND study were set to the highest dose (100 mg/kg/week in the 5-weeks study and 180 mg/kg/week in the 26-week and ePPND studies). In these studies, the AUC and C_{max} exposure was approximately 3 to 7.7-fold and 0.9 to 4.4-fold, respectively, at the proposed NOAELs. It can be concluded that at the current NOAELs the margins ranged from no to modest margins to the proposed clinical exposure.

Genotoxicity

Sutimlimab is a recombinant protein made up entirely of naturally occurring amino acids and contains no inorganic linkers, synthetic organic linkers or other non-protein portions. Therefore, sutimlimab would not react directly with DNA or other chromosomal material and no genotoxicity studies have been conducted. This is in line with the ICH S6 (R1).

Carcinogenicity

No carcinogenicity studies were conducted which was justified by that the high molecular weight of monoclonal antibodies, such as sutimlimab, cause a low risk for a genetic damage to patients.

The applicant has performed a weight-of-evidence assessment of carcinogenic potential of sutimlimab. The non-clinical part of this assessment included a review of published literature regarding the inhibition of C1s of the classical complement pathway and its relationship to tumour development, as well as analysis of pertinent data obtained from non-clinical toxicology studies with sutimlimab.

In the repeated toxicology studies, no signs of treatment related neoplastic proliferative lesions were found. In the 5 weeks study hyperplastic changes that involved the thyroid tissue and fibrotic changes at the infusion site were observed. In the 26 weeks study testicle-, epididymis-, seminal vesicle- and prostate weights (% of total weight) with increased exposure to test article was observed (see discussion).

Reproductive and developmental toxicity

Fertility and embryonal development

The applicant has not conducted a fertility and early embryonic study as the male and female reproduction organs were stated to be evaluated in the repeated toxicology studies. Such an approach is in line with ICH S5.

Enhanced pre and postnatal study

An enhanced pre- and postnatal development study was conducted in cynomolgus monkeys. No sutimlimab-related effects on maternal parameters at doses up to 180 mg/kg/week given from day 20 p.c. to day 146 p.c. (parturition). Pregnancy loss occurred in all groups. During the first trimester (Days 21 through 50 p.c.) abortions occurred for one maternal control animal, three maternal animals administered 60 mg/kg/week, and one maternal animal administered 180 mg/kg/week and during the third trimester (Days 101 through 144 p.c.) one abortion occurred for a maternal animal administered 180 mg/kg/week. In addition, stillbirths were noted for two maternal animals administered 60 mg/kg/week.

In F1 generation there was no sutimlimab related effects on the parameters evaluated which included clinical observations, neonatal muscle tone (PND28 grip strength), hematology, serum chemistry, coagulation and morphological development parameters arm length, crown-rump length, crown-heal length, distance between eyes, head circumference, leg length, tail comment, tail length, male and female anogenictal distance, thorax circumference), external abnormalities, visceral abnormalities, skeletal abnormalities, organ weights, macroscopic observations, and microscopic findings.

Inhibition of serum CP was observed at 60 and 100 mg/kg/week, but not so high inhibition seen in females treated with the same doses in the 26-week study. After 28 days of recovery the levels returned pre-dose and control levels. There were no inhibition of serum CP observed in infants.

No change markers of autoimmune risk (anti-dsDNA IgG, anti-ENA IgG) in maternal and infant animals. No change of levels of circulating immune complexes (CIC-C1q) was recorded maternal animals. However, analysis of CIC-C1q in infants is inconclusive based on too low number of samples with measurable CIC-C1q.

Local tolerance

Local tolerance was evaluated as part of the general toxicity studies. In these studies, sutimlimab was formulated in 10 mM sodium phosphate, 140 mM sodium chloride, 0.02% polysorbate 80, pH 6.1 and

administrated by 30-minute IV infusion at doses of up to 180 mg/kg/week for a duration of up to 26-weeks (26 doses). No local irritation was observed in neither studies.

Immunogenicity

Evaluation of ADA was recorded in blood sample of animals in the 5- and 26-weeks repeated toxicity studies and in maternal and infant animals in the ePPND study.

In the 5-weeks study, ADA was observed in 2 males and 1 female at 30 mg/kg/week and in 1 female at 60 mg/kg/week but not at 100 mg/kg/week. A decrease of serum concentrations of sutimlimab was recorded in these animals. In the 26-weeks study, all animals had ADA titers ≤10 prior to dosing. All values at all time points remained ≤10 for animals administered the vehicle control article (0 mg/kg/dose), with the exception of a titer of 50 in one male (Animal I10642) on the last day of recovery (Day 232). TNT009 was not detected in control animals at any time point. Two animals administered 60 mg/kg/dose (Animal I10644, male and Animal I10658, female) and one female administered 180 mg/kg/dose (Animal I10665), first observed on Day 57, displayed ADA titers >50. In these three animals, ADA titers were typically elevated prior to weekly dosing and subsequently reduced at 5 minutes after dosing, consistent with the binding of serum ADA to the IV-administered TNT009. ADA returned to titers of ≤10 in all recovery animals.

In the ePPND study, presence of ADA was seen in maternal and infant animals in the vehicle control group. The titer values for most animals was ≤10 but in few animals the titer values was 50. In maternal and infant animals in sutimlimab-dosed groups also in most animals the ADA titer values was ≤50. Higher titer values were observed in few maternal animals, along with their respective infants, which ranged from 250 to 31300 in maternal animals and from 10 to 625 in infants at Day 146 pc. Nearly 20-fold lower AUC0-48.5 exposure was noted in one maternal animal which was excluded from the TK analysis on p.c. day 146. Overall, sutimlimab was minimally immunogenic.

Immunotoxicity

In non-GLP studies evaluation of autoimmunity in terms of anti-dsDNA IgG, anti-ENA IgG, and of levels of circulating immune complexes was recorded in blood sample of animals in the 5- and 26-weeks repeated toxicity studies and in maternal and infant animals in the ePPND study. Additionally, in a non-GLP study the immunogenic potential of sutimlimab was profiled for potential neutralizing or cross-reacting immune responses in patients using a T cell proliferation assay with human blood.

In the 5-weeks study, no change of markers of autoimmune risk (anti-dsDNA IgG, anti-ENA IgG) was recorded in cynomolgus monkeys treated with 60 and 100 mg/kg/week with sutimlimab. In the 26-week study, serum anti-ENA reactivity was observed in a similar incidence comparing controls to animals in exposure groups; 9 of 10 subjects in controls and 8 of 10 or 9 of 10 animals receiving 60 or 180 mg/kg TNT009, respectively, showed reactivity over the course of the study. Thus, there were no TNT009-related effects on serum anti-ENA IgG levels. No change of autoimmune parameters (anti-dsDNA IgG, anti-ENA IgG) in maternal and infant animals were recorded.

No change in levels of serum CIC-C1q was recorded in the 5-weeks study were animals dosed up to 100 mg/kg/week with sutimlimab. In the 26-week study, serum CIC-C1q reactivity was observed in 2 of 10 or 1 of 10 animals administered 60 or 180 mg/kg/dose TNT009, respectively, over the course of the study. The incidence and relative concentrations of CIC-C1q reactivity was similar among animals administered the vehicle control article or TNT009, with no evidence of a dose-related effect. Thus, no TNT009-related effects were noted on serum CIC-C1q levels. No change of levels of circulating immune complexes (CIC-C1q) was recorded maternal animals. However, the analysis of CIC-C1q in infants is inconclusive based on too low number of samples with measurable CIC-C1q.

Tissue cross-reactivity

A TCR study was performed with sutimlimab using a full panel normal tissues from 3 human donors. Sutimlimab showed an expected staining pattern in human tissue line with other complement proteins. There was no obvious cross-reactivity staining to un-intended target(s). Cytoplasmic staining represents no significant toxicologic risk since there is a limited ability of a therapeutic antibody to access the cytoplasmic compartment *in vivo*.

Ecotoxicity/environmental risk assessment

No ERA studies have been conducted. The applicant has submitted an ERA with a justification for the absences of studies since sutimlimab is recombinant monoclonal antibody and as such do not pose a risk to the environment. This is accepted since monoclonal antibodies such as sutimlimab are most likely catabolized to individual amino acids and/or small peptides by endogenous proteases and high molecular weight prevents intact urinary excretion. As such, excretion of active drug is not expected. For these reasons, exposure to concentrations of sutimlimab in the environment does not pose any concern.

Discussion on non-clinical aspects

Pharmacodynamics

Sutimlimab is a humanized IgG4 mAb that binds to and inhibits the classical complement pathway specific serine protease, complement component 1, s subcomponent (C1s).

Sutimlimab and/or TNT003 were demonstrated *in vitro* to inhibit the following:

- CA-mediated complement C3 fragment opsonization of human RBCs, subsequent erythrophagocytosis of fragment-opsonized RBCs, CA-mediated RBC hemolysis, and CA-mediated production of anaphylatoxins generated by the cleavage of complement C3a, C4a, and C5a
- Deposition of C1q, C3b, C4d, and C5b-9 on platelets in ITP patient samples
- Deposition of C3d at the dermal epidermal junction of normal human skin mediated by autoantibodies from patients with BP
- HLA antibody-mediated C3d deposition on HLA-coated microbeads or HLA-mismatched aortic endothelial cells and splenic lymphocytes.

Collectively, these results suggest that sutimlimab has the potential to inhibit both extravascular and intravascular hemolysis in CAD.

In vitro autoimmunity studies demonstrated that TNT003 does not inhibit C1q deposition on early apoptotic cells. Furthermore, TNT003 does not inhibit the desirable immunosuppressive effects of efferocytosis of EACs. These results suggest that sutimlimab has the potential to preserve C1q deposition and efferocytosis of EACs in patients with CP-mediated disorders, thus mitigating the risk of autoimmunity that is observed in individuals with genetic deficiencies of the CP.

Complement is required for clearance of pathogens such as *Neisseria meningitidis* and *Streptococcus pneumoniae*. An experiment was performed in whole blood, to which *N. meningitidis* was added, with or without anti-capsular antibodies to *N. meningitidis*. The classical pathway (CP) is inhibited by Ab TNT005, and the alternative pathway (AP) by α-Bb. These results imply that a functioning complement system is required for effective pathogen killing, since even in the presence of anti-capsular antibodies, inhibition of the complete system results in reduced killing. It appears that the CP plays the most important role, since inhibition of the AP has no effect on killing. However, when CP is inhibited, the AP does appear to take over but the presence of antibodies is required for effective killing. The conclusion

by the Applicant that inhibition of CP does not prevent killing of *N. meningitidis* by whole blood containing specific anti-meningococcal antibodies is endorsed.

Pharmacokinetics

The PK of sutimlimab is typical of most mAbs, with dose-dependent C_{max} values following the end of the infusion, followed by sustained exposure. In cynomolgus monkeys, sutimlimab profiles after IV administration exhibited a typically high C_{max} followed by rapid clearance at low doses (≤30 mg/kg) and a more sustained terminal exposure at higher doses with slower systemic clearance. Sutimlimab exposure parameters, C_{max} and AUC, were dose-proportional at relatively low doses (≤45 mg/kg), but at higher doses sutimlimab exhibited a greater than dose-proportional exposure (C_{max} and AUC). The $t_{1/2}$ of serum sutimlimab appears to be concentration dependent. At 30 mg/kg, the $t_{1/2}$ was approximately 18 to 25 hours. When the dose is doubled from 30 to 60 mg/kg, the mean $t_{1/2}$ increased to 50 hours.

Target-mediated elimination is believed to have a greater impact on the PK of sutimlimab at lower doses (≤30 mg/kg) than on that at higher doses (>30 mg/kg), where the concentration of sutimlimab exceeded that of circulating C1s and saturation of systemic target-mediated CL mechanisms appeared to occur. This observation occurs when sutimlimab concentrations are above 100 µg/mL. The apparent Vz of sutimlimab generally decreased with increasing dose and was consistent with low tissue distribution and primary presence in the systemic circulation.

Toxicology

The toxicity of sutimlimab has been tested in 5- and 26-weeks repeat-dose studies and an ePPND study in cynomolgus monkey at doses up to 180 mg/kg/week. Overall, sutimlimab was well-tolerated and no adverse effects or findings was observed in most of the parameters evaluated that also included immunogenicity, autoimmunity, and effects of levels of circulating immune complexes.

In the repeated toxicology studies, no signs of treatment related neoplastic proliferative lesions were found. In the 5 weeks study hyperplastic changes that involved the thyroid tissue and fibrotic changes at the infusion site were observed. However, the applicant claims that these lesions are not treatment-related since they were observed also in control animals and was related to the treatment procedure and not seen in the 26 weeks study. Further, in the 5- and 26 w repeated toxicology studies the applicant claim that no signs of impaired immune surveillance or suppression observed. However, as noted in the 26 weeks study testicle-, epididymis-, seminal vesicle- and prostate weights (% of total weight) with increased exposure to test article were observed. This may indicate neoplastic or hyperplastic changes in male reproduction organs. The Applicant argued that this is a sign of an overall indication of early sexual maturity. This is agreed but cannot be regarded as evidence that complementary inhibition by sutimlimab does not have the potential to increase testicular with/advance sexual development. However, based on the totality of data, it seems less likely that sutimlimab would enhance sexual development and is the cause of the increase in testicular weight; it seems more likely to be a cause of a heterogeneity in pubertal onset based on the age that the monkeys had during investigations.

No carcinogenicity studies were conducted. The applicant claims that there is no support of a causal mechanistic/target-related link between Cls inhibition and increased cancer risk based on 3 publications. For example, Wang et al. 2002 found a relationship between increased presence of various complement factor H molecules and hepatocellular carcinoma (HCC). The applicant did not consider this observation as toxicologically relevant to the question whether sutimlimab is pro-tumorigenic since H molecules are involved in the function of the alternative pathway of the complement system and not the classical pathway that to be targeted by sutimlimab. Sakai et al 1994 evaluated the tumorigenicity of BALB/c fibroblast A31 cells transfected with hamster complement C1s

cDNA. Non-transfected BALB fibroblast A31 cells do not produce C1s, while normal C1s production by transfected cells was observed. When the transfected cells were administered to BALB/c nu/nu mice, the C1s cDNA transfectants formed tumours whereas BALB/c A31 and A31 mice transfected with only the vector did not. Tumours derived from the C1s cDNA transfectant showed invasive growth.

Furthermore, the Applicant states that no publications showed that suppression of the classical complement system has the potential to increase the risk of tumour development in participants with complement disease.

In conclusion, the weight-of-evidence assessment of carcinogenic potential of sutimlimab that included a literature review of published literature regarding the inhibition of C1s of the classical complement pathway and its relationship to tumour development has been provided and is acceptable. The applicant's claim that the weight-of-evidence assessment of carcinogenic potential was done in line with the ICH S6 (R1) and that it showed a low cancerogenic risk of sutimlimab is accepted.

A fertility and early embryonic study were not performed. A detailed qualitative microscopic evaluation of the reproduction organs of males and females in the repeat-dose toxicity studies has been conducted. Due to sexual immaturity of male animals, examination of the spermatogenic cycle was not conducted. Therefore, effects on male fertility remain unknown for sutimlimab. This has been adequately reflected in the SmPC.

Although male reproduction organs have not been fully evaluated it seems likely that there is a low risk for sutimlimab related effects on reproductive function since 1) short term studies did not suggest (immediate) toxicity; 2) there is no evidence of a relationship between inhibition of complement and male and female sex hormones in the studies; 3) there is no clear evidence of sutimlimab-related enhancement of sexual maturity but rather the changes reflex heterogeneity in pubertal onset based on the age of the subjects in the study; and 4) a thorough literature review does not suggest that inhibition of complement would adversely affect reproductive capacity. In the ePPND study in cynomolgus monkeys, pregnancy loss occurred in all groups and stillbirths were noted for two maternal animals administered 60 mg/kg/week. The incidences of abortions and stillbirths in test article-treated groups were within the normal range based on historical control data and were considered not attributable to the test article.

Conclusion on non-clinical aspects

The pharmacology of sutimlimab was evaluated *in vitro* and *in vivo* in the general toxicology program. This program is considered sufficient. Single- and multiple dose pharmacokinetics has been evaluated in the cynomolgus monkey.

A limited toxicology program with sutimlimab has been evaluated in non-clinical studies in agreement with relevant guidelines. Overall, the toxicology program has shown that there is no major toxicological risk after sutimlimab administration. The section 5.3 of the summary of product characteristics (SmPC) reflects the preclinical safety data.

3. Clinical aspects

Introduction

GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Table 1 Tabular overview of clinical studies

Study number (study part)	Type of study	Treatment/ follow-up duration	Participants treated
Phase 1			
BIVV009-01 (Part A)	Safety, PK, PD in NHVs	One day (single dose)	48
BIVV009-01 (Part B)	Safety, PK, PD in NHVs	Four weeks (weekly dosing)	16
BIVV009-01 (Part C)	Safety, PK, PD including disease-related biomarkers in patients with complement-mediated disorders.	4 weeks/ follow-up for 4 weeks after the last dose until the end of study visit on Day 53	34 (10 with CAD)
BIVV009-01 (Part E)	Safety, PK, PD including disease-related biomarkers in patients with primary CAD.	>2 years/ 9 weeks follow-up after last study drug administration	4
TNT009-02	Safety, PK, PD in NHVs	36 days	24
BIVV009-05 (Part A)	PK in NHVs (single dose)	92 days	18
BIVV009-05 (Part B)	PK in NHVs (multi-dose)	141 days	12
Phase 3			
BIVV009-03 (Part A), (CARDINAL)	Efficacy, safety, PK, PD.	26 weeks/	24
BIVV009-03 (Part B), (CARDINAL)	Long-term safety, duration or maintenance of efficacy	2 years following LPO under Part A/ 9 weeks follow-up visit after last study drug administration	22
BIVV009-04 (Part A), (CADENZA)	Efficacy, safety, PK, PD.	6 months/	42
BIVV009-04 (Part B), (CADENZA)	Long-term safety, duration or maintenance of efficacy	1 year following LPO under Part A/9 weeks after last dose of study drug administration	39

Abbreviations: CAD = Cold Agglutinin Disease; LPO = last patient out; NHV = normal healthy volunteer

Clinical pharmacology

Pharmacokinetics

The clinical pharmacology database for sutimlimab (also called BIVV009; TNT009) is based on two phase-3 studies with sparse PK-sampling and 3 phase-1 studies with rich PK-sampling.

Methods

Quantification of sutimlimab in serum

A direct ELISA was developed to measure the free and partially bound sutimlimab (ie, sutimlimab with 1 or both binding sites available to interact with the target, C1s). The first version of this ELISA method (TN-1608/1609) detected sutimlimab in serum and was performed for study BIVV009-01 Parts A-C. The assay was further optimized with a switch to analysing sutimlimab in plasma to increase stability. This assay (TN-1702) was used for studies TNT009-02, BIVV009-05, BIVV009-01 (Part E), BIVV009-03, and BIVV009-04. Due to interference of endogenous C1s in the plasma matrix calibration standards were prepared in buffer. Accuracy and precision of the assay during the conduct of method validation was determined by evaluating the performance of the assay controls prepared in both assay buffer (Buffer QCs) and normal human plasma (Matrix QCs). The validated range is between 5-133 ng/ml.

Detection of anti-drug antibodies (ADA)

An electrochemiluminescence (ECL)-based bridging immunoassay was developed to detect anti-drug antibodies (ADAs) directed against sutimlimab. A 3-tiered approach was employed. The method was optimized in three steps to improve drug tolerance.

The third method (ABV0020) included both prior Melon Gel extraction and acid dissociation which led to an acceptable drug tolerance. This method was used for the two phase-3 studies as well as BIV009-01 part E. Screening and confirmatory cut-points were determined using 54 individual drug-naïve complement preserved human serum sample lots.

Given the overall low incidence of treatment-emergent anti-sutimlimab antibodies in the clinical study (4 subjects of 44 in the phase-3 studies) no assay for determining the neutralising potential of ADAs were developed. The effect of ADAs on sutimlimab PK and PD was assessed by comparing plasma concentration time profiles or PD-profiles of sutimlimab for each patient with treatment-emergent ADA to that of ADA negatives. Further, no subjects with confirmed treatment-emergent positive ADAs (treatment-boosted or treatment-induced) had treatment-emergent adverse events concerning hypersensitivity or anaphylactic reactions associated with sutimlimab.

Pharmacodynamic assays

Commercially available assays were validated for CP and AP activity measurement. Complement C4 and CH50 measurements were done by using commercially available IVD assays. For C1sC1INH, an exploratory research assay was used. C1q and free C1s measurements were completed using exploratory research assays. Validation reports have been provided for all methods (also for commercially available kits).

Non-compartment data analysis (NCA)

Standard non-compartment analysis was performed where rich sampling was applied.

Population pharmacokinetic analysis

The pharmacokinetic analysis using a population PK modelling approach was conducted in three steps as more data became available. An initial population PK analysis of sutimlimab was performed using data from two Phase 1 studies in healthy subjects and patients with CP-mediated diseases (study BIVV009-01 Parts A/B/C and study BIVV009-02), including CAD, to establish the base model (with limited covariate assessment) and to select the doses for BIVV009-03 and BIVV009-04 (study TNTH CSC 103, briefly described below). Additional studies that were subsequently completed (BIVV009-01 Part E, studies BIVV009-05 and BIVV009-03 Part A) were included in the population PK analysis in study POH0755 (report containing the final population PK model, described below), which was a continuation of the previous model development and covariate model development. As additional data became available from studies BIVV009-03 Part B and BIVV009 04 Part A population PK analysis was conducted using the maximum a priori (MAP) Bayesian approach (study POH0797), based on the previously established model in study POH0755 which was considered final after initial assessment of its ability to predict the phase 3 data. These analyses were based on prespecified plans.

POH0755

The main objectives of the analysis were to describe the population PK of sutimlimab and to explore demographic and laboratory values that may affect the PK of sutimlimab in patients with CAD. The secondary objective of the analysis was to assess the PK differences between Japanese and non-Japanese subjects. Dense PK data from 3 Phase 1 studies and sparse PK data from the Phase 3 study, totalling 154 subjects (including 34 CAD patients), were pooled for this analysis. Sutimlimab was administered as a 1-hour IV infusion as a single dose (0.3 to 100 mg/kg) or as repeated doses (30 to 75 mg/kg or 6.5 g [patients <75 kg]/7.5 g [patients ≥75 kg]), either once every week or 2 doses 1 week apart followed by Q2W doses.

The final population PK model for BIVV009 following intravenous administration is a 2-compartment disposition model with parallel linear and non-linear CL terms. Body weight was identified as a covariate on Vc and CL. Ethnicity (Japanese) was included as a covariate on Vc and Vmax. After including the body weight and Japanese subject covariates, the following covariates did not have an additional impact on the PK of sutimlimab: sex, race, age, albumin, hepatic function (alanine aminotransferase [ALT], aspartate aminotransferase [AST], bilirubin), renal function (creatinine clearance [CRCL], eGFR), and immunogenicity (presence/absence of ADAs).

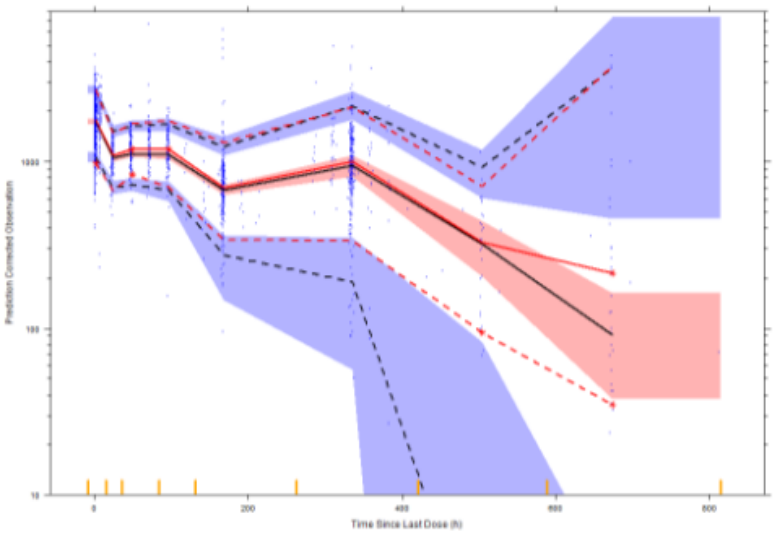
Table 2 Parameter estimates of the final population PK model for sutimlimab – study POH0755

	Estimate		Interindividual Variability		
Parameter (unit)	**Typical Value**	**RSE[0]**	**Typical Value**	**RSE[0]**	**Shrinkage[0]**
Clearance (CL, mL/h)	5.65	7.6%	34%	16%	35%
Effect of body weight on CL[0]	1.72	11%	—	—	—
Intercompartmental clearance (Q, mL/h)	19.7	7.1%	—	—	—
Central volume of distribution (Vc, mL)	3841	2.2%	21%	5.4%	25%
Effect of body weight on Vc[0]	0.52	18%	—	—	—
Japanese ethnicity effect on Vc	-29%	9.8%	—	—	—
Peripheral volume of distribution (Vp, mL)	1994	4.5%	55%	19%	5.2%
Maximal non-linear clearance (V_{max}, µg/hr)	9870	4.0%	20%	15%	23%
Japanese ethnicity effect on V_{max}	-30%	21%	—	—	—

sutimlimab concentration required for half-maximal non-linear clearance (Km, µg/mL)	8.7	29%	—	—	—
Residual variability					
BIVV009-03 study proportional residual error	27%	10%	—	—	3.9%
BIVV009-03 study additive residual error SD (µg/mL)	111	21%	—	—	3.9%
Non-BIVV009-03 studies proportional residual error	14%	4.4%	—	—	8.7%
Non-BIVV09-03 studies additive residual error SD (µg/mL)	5.7	8.1%	—	—	8.7%

Abbreviations: %CV = percent coefficient of variation, BSV = between-subject variability; CL = clearance; ND = not determined; Q = intercompartmental clearance; RSE = relative standard error, SD = standard deviation; SE = standard error; Vc = central volume; Vmax = rate of non-linear disposition; Vp = peripheral volume of distribution.
RSE of parameter estimate are calculated as 100 × (SE/typical value); RSE of BSV magnitude are presented on %CV scale and approximated as 100 × (SE/variance estimate)/2.
Shrinkage (%) is calculated as 100 × (1 – SD of post hocs/estimated variance).
Effect of body weight is relative to the median body weight of 71.85 kg; power coefficient presented.
Source: study POH0755, Table 8

Figure 2 pcVPC of the final population PK model for BIVV009



Abbreviations: h=hour; pcVPC=prediction-corrected visual predictive check; PK=pharmacokinetic.
Note: The blue circles represent prediction-corrected observed data, the red solid line represents the median of the prediction-corrected observed data, and the red dashed lines represent the 5th and 95th percentiles of the prediction-corrected observed data. The red stars represent observed values that lie outside of the 90% prediction interval. The black solid line represents the median of the prediction-corrected simulation data, and the black dashed lines represent the 5th and 95th percentiles of the prediction-corrected simulation data. The blue shaded areas represent the 90% prediction interval for the 5th and 95th percentiles of the predicted data, and the red shaded areas represent the 90% prediction interval for the median of the predicted data. The yellow vertical ticks on x-axis represent the edges of the bins used to group the data for calculation of the quartiles.
Source: PK figures – report 2019-10-18.R

Study POH0797

When phase 3 data from studies BIVV009-03 part B and BIVV009-04 part A became available a MAP Bayesian approach based on a previously developed model was selected to assess the PK of sutimlimab and to evaluate the predictions.

Absorption

Absorption data are not available since all studies administered sutimlimab as an IV infusion. No food effect study was conducted.

Bioequivalence

No human bioequivalence studies were performed to demonstrate comparability between the formulations/processes used during the clinical development program of sutimlimab, see quality part of AR for assessment of comparability.

Distribution

As typical for monoclonal antibodies, it is distributed primarily in the circulatory system as illustrated by the small volume of distribution, of 5.8 L (sum of central and peripheral volumes of distribution) based on population PK analysis. No protein-binding assays have been performed.

Elimination

The excretion and metabolic pathways of sutimlimab has not been investigated. As an IgG4 antibody, the biotransformation of sutimlimab is expected to be similar to endogenous IgG (degraded into small peptides and amino acids via catabolic pathways) and subject to similar elimination pathways. For a 147 kDa protein renal excretion is not anticipated.

Sutimlimab CL is governed by 2 parallel elimination pathways: a nonlinear, target mediated pathway predominating at low concentrations and a nonspecific, linear pathway predominating at higher concentrations. The half-life of sutimlimab is dependent on the plasma concentration. The elimination half-life of sutimlimab at steady-state based on the total clearance (linear and non-linear clearance) is 16 days.

Dose proportionality and time dependencies

Target-mediated drug disposition (TMDD) was apparent at single low doses, less than 30 mg/kg (~ 2 g), resulting in a greater than dose-proportional increase in sutimlimab exposure (AUC0-168 h) up to 30 mg/kg. Between doses of 60 and 100 mg/kg of sutimlimab TMDD was saturated with resulting dose proportional increases in exposure.

Steady state was achieved by week 7 after starting sutimlimab treatment, with accumulation ratio of 1.5-1.8.

Special populations

	Age 65-74 (Older subjects number /total number)	**Age 75-84 (Older subjects number /total number)**	**Age 85+ (Older subjects number /total number)**
PK Trials	**25/66**	**15/66**	**3/66**

Variations in renal and hepatic function or drug-metabolizing enzymes are not expected to affect the elimination of sutimlimab. No dedicated formal intrinsic factor PK studies has been conducted. Demographic factors and the effect of organ dysfunction was investigated in the population PK analysis. Body weight and ethnicity (Japanese versus non-Japanese) influenced the pharmacokinetics of sutimlimab. Lower exposure was observed in subjects with higher body weight and was considered clinically relevant. The effect of body weight on pharmacokinetics has been integrated in the

recommended dose regimen tiered by body weight. Although a higher exposure (44 % higher Cmax and >20% higher AUC) was observed in Japanese subjects compared to the non-Japanese subjects, the differences were not considered clinically significant.

Sutimlimab was not studied in children and is not intended for use in children.

Pharmacokinetic interaction studies

No dedicated drug-drug interaction studies were performed with sutimlimab. In clinical samples from the Cardinal study the levels of IL-6 and IL-10 were shown to be decreased by almost half by sutimlimab. This demonstrates that sutimlimab acts as an immunomodulator and affects cytokines known to affect CYP expression in CAD patients, e.g. CYP1A2, CYP2C9, CYP2C19, and CYP3A4.

Pharmacodynamics

Mechanism of action

Sutimlimab is a humanized monoclonal antibody (IgG4) of directed against human complement factor C1s, a serine protease, that together with sub-component q (C1q) and another serine protease, sub-component r (C1r), forms the C1 complex, the first component of the classical pathway of the complement system. It specifically binds to C1s of humans and non-human primates. It has no affinity for the related proteases of the lectin pathway, mannose-associated serine protease (MASP)-1 and MASP-2. Sutimlimab has shown disease-relevant inhibitory activity against classic complement pathway (CP) in a variety of human *in vitro* models of human disease (including cold CAD, bullous pemphigoid, and warm autoimmune haemolytic anaemia).

Primary and Secondary pharmacology

The clinical pharmacology development program of sutimlimab comprises of 3 clinical studies providing pharmacodynamic data on CP activity, dose selection and immunogenicity: a first-in-human SAD/MAD study in healthy subjects (BIVV009-01 parts A and B), and in patients with CP mediated disorders (part C), a phase 1 dose confirmation study in healthy subjects (BIVV009-02), and a SAD/MAD and a multiple dose study in healthy Japanese subjects (BIVV009 05). Additionally, PD results were collected in both phase 3 studies (BIVV009-03 and BIVV009-04) as detailed in the efficacy part of this report.

Classical complement pathway (CP) activity

Levels of CP activity, CH50, C1s (target of sutimlimab), C4 (first soluble cleavable substrate of C1s) measured, as well as levels of C1sC1INH to confirm the binding of sutimlimab. Further, C1q was measured in all studies to confirm that the non-enzymatic role of C1q is left intact by sutimlimab.

Study BIVV009-01, the first-in-human, prospective, double-blind, randomized, placebo-controlled study tested single dose of sutimlimab infusion over 1 hour escalating from 0.3 mg/kg to 100 mg/kg (Part A, 36 on sutimlimab and 12 on placebo), and multiple doses of 30 or 60 mg/kg (Part B) or placebo once weekly for 4 consecutive weeks in healthy volunteer. After a single dose of 30 mg/kg or higher, the inhibition of serum CP activity and the decrease of free C1s and C1sC1INH concentration reached a maximum effect. This inhibition was reversible as levels returned to baseline after 7 days, with the duration of inhibition increasing in a dose-dependent manner. Return to baseline was more prolonged with increasing dose. With multiple dosing with 30 and 60 mg/kg once weekly for 4 weeks similar findings were noted as seen in the SAD study with nearly complete inhibition of mean CP activity, C1s, and C1sC1INH concentration profiles. After discontinuation, a partial return to baseline was noted after 7 days with 30 mg/kg, while a nearly complete knockdown was observed over the entire study duration for the 60 mg/kg group. Total C4 levels were not affected and C1q changes from

baseline in 30 and 60 mg/kg groups were comparable to those seen in the placebo subjects, in whom little to no effect on CCP activity was seen.

Study BIVV009-02, a double-blind, randomized, placebo-controlled Phase 1 study (n = 24, randomized 3:1 for sutimlimab: placebo), evaluated multiple doses of sutimlimab at 75 mg/kg in healthy subjects on Days 1, 8, 22, and 36. The findings of the study confirmed the findings in the earlier MAD study BIVV009-01 (Part B). An inhibition of >90% of CP, CH50, C1s, and C1sC1INH activity was shown throughout the treatment period, and was maintained up to 2 weeks after the final dose on Day 36. A small and no clinically relevant effect has been observed on the C1q and C4 levels.

Study BIVV009-05 was a Phase 1 PK/PD study in 12 Japanese healthy subjects. Part A examined 3 different single doses (30, 60 and 100 mg/kg) of sutimlimab. Part B examined 2 different multiple doses of sutimlimab (6.5 g for body weight (BW) <75 kg and 7.5 g for BW ≥75 kg) on Days 1, 8, and 22. Also here, the CCP activity was immediately and effectively inhibited up to >90% at all dose levels in both Parts A and B. Dose-related differences in the duration of CP activity were observed, with increased doses resulting in longer durations of CP inhibition. C1q and C4 levels were only slightly affected, as also seen in the previous studies.

SAD/MAD evaluation in patients with complement-mediated disorders

Part C of the first-in-human study BIVV009-01 was a non-randomized multiple-dose study in 24 patients with complement-mediated disorders including CAD, WAIHA, BP, and active AMR in patients who had received a kidney transplant. Patients received a single dose of 10 mg/kg (day 0), followed by 4 weekly doses of 60 mg/kg (day 1, 8, 15, 22). Although there was a difference in baseline levels of CP activity across patient population, the mean CP activity and C1s concentrations displayed nearly complete inhibition over the entire profile across all patient populations and was maintained 3 weeks after the last weekly 60 mg/kg dose. The effects on the C1q levels were small and not clinically relevant. Important to note were the C4 levels in CAD patients. They were below the normal range (<0.18 g/L) at baseline. The C4 levels restored immediately after receiving the first weekly dose of 60 mg/kg, but then returned to the pre-treatment level 4 weeks after the last 60 mg/kg dose.

Sub-study E was a long-term extension study where four of the CAD-patients from sub-study C was followed. Some PD-data are presented as an interim analysis and presented in the efficacy part of this report.

Pharmacodynamics and Pharmacokinetics-Pharmacodynamics (PK/PD)

An updated analysis (POH0798) was conducted with the objectives to characterize and quantify the exposure-response relationship of sutimlimab and assess the impact of covariates on it by developing a PK-PD model for Hgb as the primary efficacy parameter, and to characterize the relationships between exposure and response, including graphical evaluation of PD markers bilirubin and C4. No discussion of analysis of exposure-safety was presented (see discussion).

The analysis was performed through:

- graphical exploration of biomarkers (Hgb, bilirubin, and C4), including an exploratory characterization of the exposure-response relationship between the maximum observed change in biomarker from baseline and maximum C_{min};

- development of a dynamic population PK-PD model for Hgb; and

- simulations to illustrate the PK-PD relationship of Hgb and to investigate the impact of PK covariates on the PK-PD relationship for Hgb.

CAD subjects from study BIVV009-01 part C were included in part E, and subjects from BIVV009-03 part A were included in BIVV009-03 part B, resulting in a total of 72 subjects included in the analysis. In total, 25% of the patients were males and 69.5% presented impaired renal function (based on CLCR), the proportion of patients who received placebo was around 28% (20 subjects from study BIVV009-04 part A). The subjects received either 5.5, 6.5 or 7.5 g of sutimlimab.

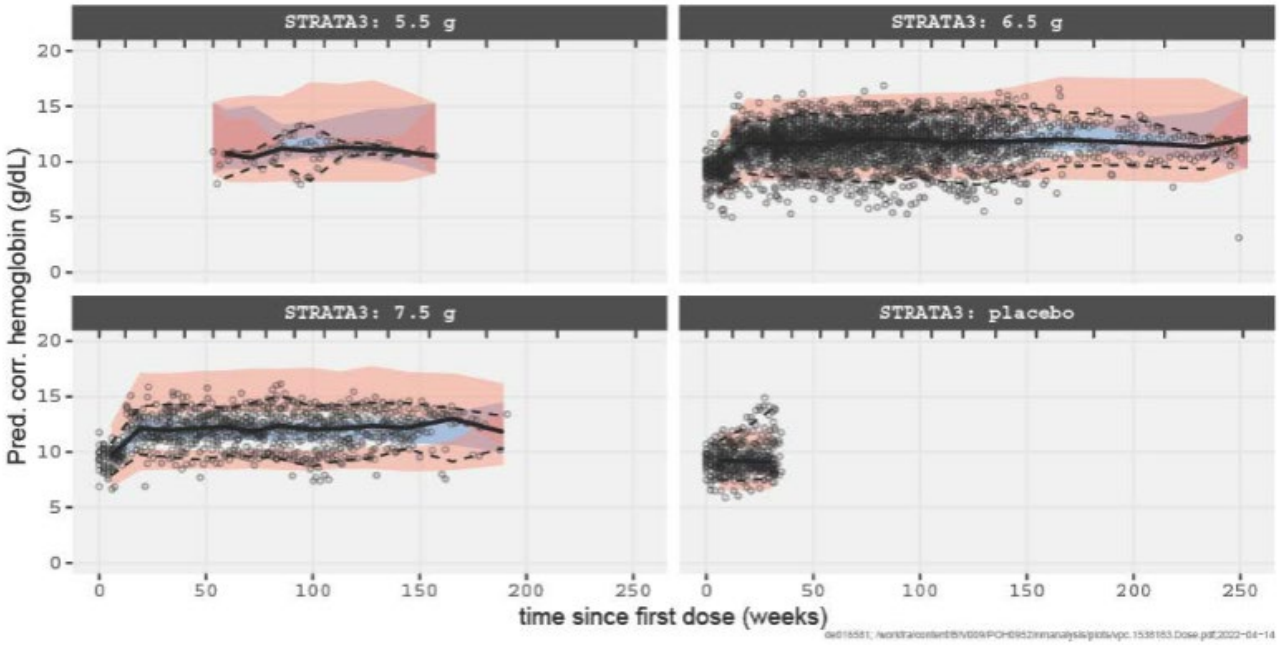
Hgb model

A dynamic model was developed by integrating a turnover model for Hgb (to capture the delay in PD effect in relation to plasma concentration) with an E_{max} model (to capture the drug effect) relating the Hgb-elevating effect of sutimlimab to its plasma exposure at time t. The PK component consisted of the final population PK model for sutimlimab. The individual PK parameters predicted from the PK model were used to inform the PD response. Selection of an indirect response model was supported by hysteresis plots for time-matched observed Hgb versus observed sutimlimab concentrations supporting the selection of an indirect response model. The current model does not contain a placebo effect, which is in line with the lack of time-dependent changes observed during the exploratory analysis.

Covariate analysis was performed at the level of the base model (combined structural and statistical model). PD parameters with identified interindividual variability (IIV) were further investigated. ADA and disease status were not taken into account, while blood transfusion was additionally included in the list of covariates to be tested. Among the known correlation of CLCR with body weight and age, there is also a correlation of baseline Hgb levels with CLCR and bilirubin. The parameters were estimated with an RSE < 50%. The magnitude of ETA shrinkage on the IIVs was ≤ 30% for all PD parameters with IIV terms. The adequacy of the model to describe the data in placebo patients supports the absence of a placebo model.

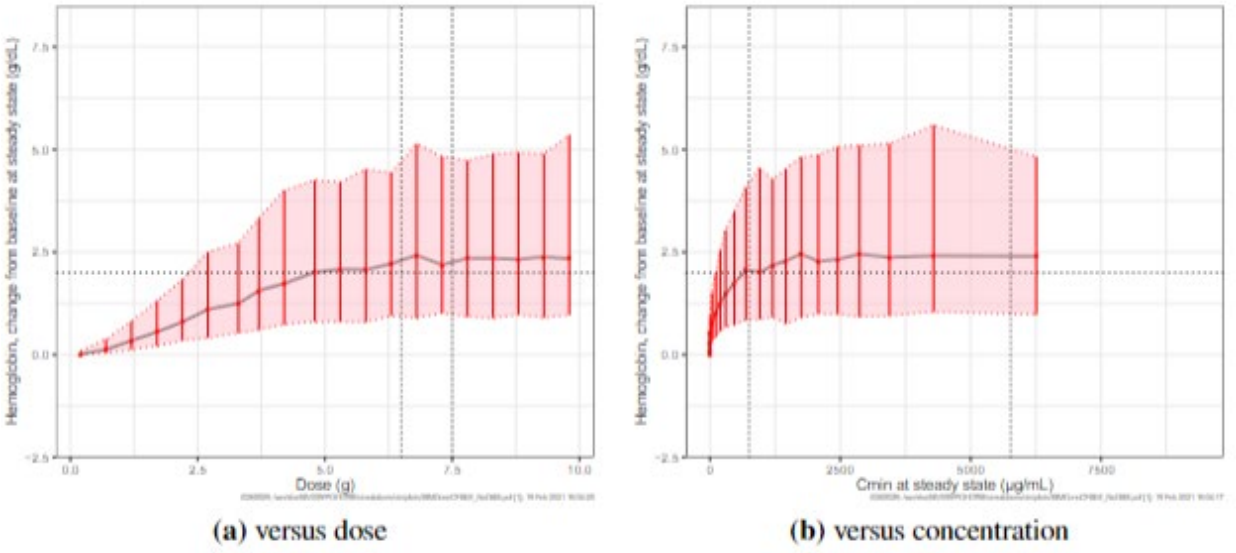
The model estimated the turnover time of 188 hours with a derived median k out of 0.0053 h−1, which corresponds to a half-life of 5.4 days. This half-life is lower than the lifetime of Hgb (~ 120 days), but reflects its higher degradation rate in CAD patients. The drug effect was estimated to have an E_{max} of 25% and the EC50 as 155 µg/mL, which is similar to the parameters obtained with the prior descriptive models. The additive residual unknown variability was 0.92 g/dL and reflects circadian variation of Hgb levels over the course of the study, which was not specifically accounted for in the model and probably at least partially explains the oscillations observed in some patients. After stepwise covariate modeling, only CLCR and blood transfusion, which explained 12.2% and 16.5% of the IIV in E_{base} and E_{max}, respectively, were kept in the model. Patients receiving at least one blood transfusion during the study showed a lowering of E_{max} of 40%. Solely in patients undergoing blood transfusion inter-individual variability was under-predicted by the model. This is probably because occurrence of transfusion was incorporated as a binominal covariate which did not consider neither the number of transfusions nor the time during treatment when transfusion occurred.

Figure 3 Prediction-corrected visual predictive check plot of model no. 1538183 (all data), stratified by dose. Dots represent observations. The solid line represents the 50th percentile (median) of the observations. The observed 5th and 95th percentiles are presented with dashed lines. The shaded areas represent the 90% confidence intervals around the 5th, 50th (median) and 95th percentiles of the simulations (n = 500 subproblem simulations)



Using the simulated steady state levels of sutimlimab concentrations and Hgb levels, the dose and exposure-response relationship were graphically visualized (Figure 4).

Figure 4 Simulated hemoglobin, change from baseline at steady state versus dose (a) and plasma concentration (b) after administration of sutimlimab. In (a), the vertical lines represent the 6.5 and 7.5 g doses of sutimlimab. In (b) each line represents the concentration-response relationship using the simulated steady state concentrations at various times between two doses. The vertical lines represent the minimum and the maximum simulated concentration following administration of 6.5 and 7.5 g doses of sutimlimab, respectively. Horizontal lines represent 2 g/dL hemoglobin change from baseline. The red lines and the segments represent the 90% prediction intervals around the median for each bin, the black line is the interpolation line. These simulations do not consider patients undergoing transfusion



(a) versus dose (b) versus concentration

Exploratory exposure-response modelling for Hgb, bilirubin and C4

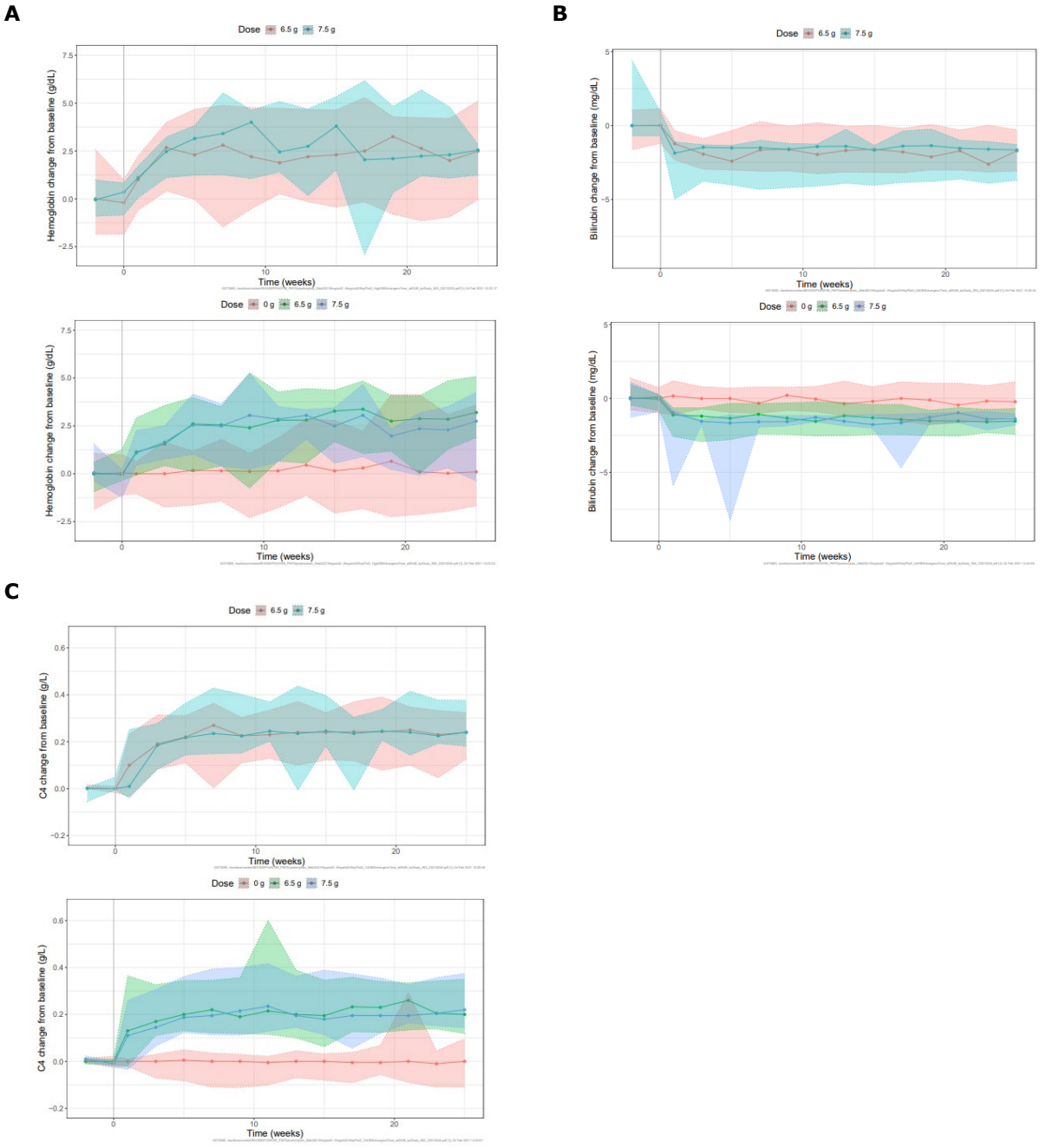
The characterization of the exposure-response relationship between the maximum observed change in biomarker from baseline and maximum C_{min} irrespective of time was performed using an E_{max} model with hill coefficient fixed to 1. For each biomarker, two models were run: one with and one without priors for EC_{min50}. The prior for EC_{min50} was defined to be the 90% CI for Hgb EC50 estimated in the population analysis.

Exploratory exposure-response relationship characterization was limited without priors due to low number of observations at lower concentrations. Therefore, Hgb EC50 confidence interval from population exposure-response analysis was used as prior to estimate parameters for exploratory exposure-response relationship of change in Hgb, bilirubin, and C4 from baseline. Because maximum change in biomarkers was used for this analysis, estimated E0 (baseline change in biomarker) was higher than zero for Hgb and C4 and lower than zero for bilirubin. Estimated E_{max} captured maximum observed effect on biomarker.

Graphical exploration of the data

The median (2.5 - 97.5%) data for biomarker levels (with correction for baseline) over time in studies 903 and 904 are presented in Figure 5. After baseline correction, effect on Hgb, C4 and bilirubin levels appear similar following 6.5 and 7.5 g of sutimlimab.

Figure 5. Median (2.5 - 97.5th percentiles) haemoglobin (A), bilirubin (B) and C4 (C) change from baseline over time by dose in CAD patients from BIVV009-03 study (excluded subject 3182301 treated with 1.079 g dose, upper panel) or BIVV009-04 study (lower panel)



Exposure-safety analysis

Adverse events categorized based on System Organ Class (SOC) guidelines were used for weight quartile plot. No clear trend was observed between the majority of adverse events and body weight.

Discussion on clinical pharmacology

Enjaymo is indicated for CAD, an orphan disease. The clinical pharmacology database for sutimlimab is thus rather limited but comprises all PK and PD data collected from 118 healthy subjects (96 on sutimlimab), including Japanese subjects and 72 patients with primary CAD. The distribution,

metabolism, and excretion characteristics of sutimlimab are mainly based on popPK model-estimated parameters. No dose adjustments for special populations are proposed in the SmPC and the PK-information is mainly descriptive.

Sutimlimab (also called BIVV009; TNT009), is a first-in-class, humanized IgG4 monoclonal antibody which is expressed by recombinant in CHO cells. No human bioequivalence studies were performed to demonstrate comparability between the formulations/processes used during the clinical development program of sutimlimab. Comparability has been shown *in vitro,* see discussion in quality section.

A direct ELISA was developed to measure the free and partially bound sutimlimab (ie, sutimlimab with 1 or both binding sites available to interact with the target, C1s) initially in serum but the method was further developed to detect sutimlimab in plasma (by a different CRO). The initial bioanalytical method (TN-1608/1609) used for study BIVV009-01 Parts A-C, that is the SAD and MAD in healthy volunteers as well as the MAD in patients with different complement-mediated disorder, was considered not fully validated. None of the provided validation-data indicated that the method was not appropriate, however, several aspects of the validation process described in the EMA guideline on bioanalytical method validation had not been evaluated resulting in an Other Concern atOC day 120. of the procedure. In the response to this question, the Applicant compared the serum and plasma concentrations using non-compartmental analysis and popPK analysis. There are limitations in the analysis but assessing the totality of data it can be agreed that the bioanalytical method is fit for the purpose of characterising the exposure in patients with CAD given doses ≥60 mg/kg. As the population PK results are supportive to the clinical data, the BIVV009-01 study Part A, B and C data can be included in the popPK model.

The second bioanalytical method (TN1702) detected sutimlimab in plasma, and in the validation process complement preserved plasma was used as matrix, however due to interference of endogenous C1s in this human matrix, calibration standards and some QC-samples were prepared in buffer. The calibration curve, prepared in buffer, gives information on total concentration of sutimlimab as all sutimlimab is unbound in buffer due to the absence of interference of endogenous C1s or other potentially interfering factors present in plasma. There are also QC-samples prepared in buffer which have been included in all analytical runs. However, some QCs (matrix-QCs) and study samples are in another matrix (plasma) and give information on partially bound and free sutimlimab. It is thus expected that matrix-QCs may not give the same result as their nominal concentration (i.e. what was spiked in the sample) as target is present in plasma. During the validation process, an "actual nominal concentration" is determined for the matrix-QCs, i.e. the concentration of partially bound or free sutimlimab. This is expected to differ more strongly at low concentrations, due to the binding to target. Then CV% is calculated as usual from the determined "actual nominal concentration". In the analysis of study samples, the actual nominal concentrations of matrix QCs are determined in each run, where n=6.

Also for TN17-02 there are deviations from the validation process described in the EMA guideline. Accuracy and precision were only successfully evaluated in 4 runs instead of 6. Selectivity and specificity were not evaluated using matrix-based LLOQ and ULOQ (although these levels were evaluated with buffer QCs) but with M-HQC (spiked to 100 ng/ml after MRD) and M-LQC1 (spiked to 20 ng/ml after MRD). This could be an issue defining LLOQ which is only evaluated with buffer-samples. In the clinical studies few samples were below the limit of quantification (BQL), in the popPK model these samples are set as missing which is considered appropriate (setting these to e.g. half LLOQ would have been more problematic in this case). An acceptable justification for not performing a parallelism investigation has been provided by the Applicant. Overall, it is considered that the Applicant has made attempts to address the issues with developing a bioanalytical method for sutimlimab and the method is sufficiently validated and appropriate for its purpose.

ADAs were detected by a 3-tier electrochemiluminescent (ECL) bridging immunoassay. Which has been optimized and revalidated 3 times (by different CROs) during the clinical program due to issues with drug tolerance and target interference. Only the last assay (ABV0020) used in clinical studies BIV009-01 (part E), BIV009-03 and 04 has shown an acceptable drug tolerance. Overall, this assay appears adequately validated, the assay is acceptably selective and sensitive, capable of detecting low levels antibodies at 5.5 ng/ml. As the assay used for the phase-3 trials is appropriately validated information regarding immunogenicity in the target population is considered acceptable. Given the low incidence of ADAs in the phase-3 trials and that no impact of ADAs on PK/PD has been detected, issues with the early assays are not further pursued. The low incidence of ADAs and the different analyses of the effect of ADAs on sutimlimab's PK, PD and safety also justifies that no Nab-assay has been developed.

The volume of distribution at steady state in central and peripheral compartments was approximately 5.8 L in patients with CAD (SmPC section 5.2).

Sutimlimab CL showed a steep initial decrease at doses less than 30 mg/kg (~total dose of 2000 mg or 2 g), before becoming relatively stable between 60 and 100 mg/kg, resulting in a greater than dose-proportional increase in sutimlimab exposure (AUC0-168 h) up to 30 mg/kg (single dose) and ~60 mg/kg (multiple dose). In the SmPC (section 5.2) it is claimed that sutimlimab concentrations above 100 μg/mL resulted in maximal CP inhibition. Non-clinical data indicate that complete CP inhibition occurs at sutimlimab levels above 20 μg/mL. The limit 100 μg/mL is chosen as the concentration where target mediated drug disposition (TMDD) is not predominant. As no dose adjustments are proposed based on drug monitoring (e.g. non-responders are not proposed to have drug levels determined and if shown low an increase in dose) the information is not of great importance.

Sutimlimab CL is governed by 2 parallel elimination pathways and the half-life of sutimlimab is dependent on the plasma concentration. The elimination half-life of sutimlimab at steady-state based on the total clearance (linear and non-linear clearance) is 16 days. In the range of observed sutimlimab concentrations achieved over the dosing interval at the therapeutic dose in Cardinal and Cadenza studies, non-linear clearance represents 36 % of total clearance while linear clearance represents 64 % of total clearance. The protein binding, excretion and metabolic pathways of sutimlimab has not been investigated. This is acceptable for an IgG antibody.

No dedicated studies have been conducted to investigate the pharmacokinetics of sutimlimab in special populations, which is considered acceptable for a monoclonal antibody. Special populations were evaluated as covariates in the popPK analysis, see discussion below.

No drug interaction studies have been performed. At Day 120 a discussion of how CAD as disease affects cytokine levels and if this will be altered by sutimlimab treatment leading to a potential for DDIs was requested. The Applicant has provided an article discussing *in vitro* data generated using a mouse version of sutimlimab. However, when searching PubMed another publication (Weitz IC et al. Blood, vol 136, 2020) was retrieved in which patient samples from the Cardinal study had been evaluated for IL-6 and IL-10 levels, showing a relevant decrease in cytokine levels by sutimlimab. A DDI study investigating the clinical relevance of this interaction mechanism would have been of interest. However, the SmPC section 4.5 has been updated to include a warning indicating potential for CYP/transporter mediated drug interaction (SmPC section 4.5).

Population PK

The pharmacokinetic analysis using a population PK modelling approach was conducted in three steps as more data became available. An initial population PK analysis of sutimlimab was performed using data from two Phase 1 studies in healthy subjects and patients with CP-mediated diseases (study BIVV009-01 Parts A/B/C and study BIVV009-02), including CAD, to establish the base model (with limited covariate assessment) and to select the doses for BIVV009-03 and BIVV009-04 (study TNTH

CSC 103). Additional studies that were subsequently completed (BIVV009-01 Part E, studies BIVV009-05 and BIVV009-03 Part A) were included in the population PK analysis in study POH0755, which was a continuation of the previous model development and covariate model development, and a final population PK model was developed based on these data. As additional data became available from studies BIVV009-03 Part B and BIVV009 04 Part-A population PK analysis was conducted using the maximum a priori (MAP) Bayesian approach (study POH0797). The methods for evaluation and qualification of models are acceptable. In the second round of assessment additional patient data from study 904 were included in the dataset, also evaluated using the maximum a priori (MAP) Bayesian approach (report POH0951).

The final population PK model for BIVV009 (study POH0755) following intravenous administration is a 2-compartment disposition model with parallel linear and non-linear CL terms. BSV terms are included on CL, Vc, Vp, and Vmax. Separate residual error models were employed for BIVV009-03 study and the other 3 studies (TNT009-01, TNT009-02, and BIVV009-05). Due to the small number of BLQ samples (7.6% of all post-dose PK observations), and the quality of the base model fit, the M3 method was not explored. Body weight was identified as a covariate on Vc and CL. Ethnicity (Japanese) was included as a covariate on Vc and V_{max}. After including the body weight and Japanese subject covariates, the following covariates did not have an additional impact on the PK of sutimlimab: sex, race, age, albumin, hepatic function (alanine aminotransferase [ALT], aspartate aminotransferase [AST], bilirubin), renal function (creatinine clearance [CRCL], eGFR), and immunogenicity (presence/absence of ADAs).

The main objective was to describe the PK in patients with CAD, however a pcVPC showing how well the model describes the observed concentration in patients with CAD has not been presented. Overall, the model appears to capture most of observed concentrations over time. The shrinkage on CL is very high, probably due to the estimation of a non-linear component of the elimination model resulting in a higher-than-expected uncertainty in the linear elimination parameter. The goodness-of-fit plots do not indicate any major model misspecifications.

When data from studies BIVV009-03 Part B and BIVV009 04 Part A became available, population PK analysis was conducted using the maximum a priori (MAP) Bayesian approach (study POH0797). However, the model used for this comparison included the covariate age on Vc (model 1538180), while the final model in report 0755 does not as this covariate was considered to not have high clinical impact and was removed. As the differences in model and model parameters are relatively small, the results are accepted. Goodness-of-fit plots stratified on study indicate that the model does not capture the C_{max} for study 904. However, overall, the model appears to capture the data. Separate residual error models were used for study BIVV009-03 due to the large difference in observed concentration between steady-state dosing (BIVV009-03) and single- or multiple-dose studies. With the additional data from the Phase 3 study 904, the applicant evaluated the model using MAP. The pcVPCs indicate that the model can adequately describe the Phase 3 data from study BIVV009-03 and BIVV009-04. However, the model overpredicts exposure in Japanese subjects, therefore, the model output and simulation should not be used to draw conclusions on exposure in this population. Therefore, a PK exposure metric derived directly from the observed data (i.e. non-model-based approach) is used to describe the increased exposures in Japanese subjects in the SmPC. It appears that transfusion has a relatively modest effect on predicted PK parameters. In addition, predicted C_{min} exposures are generally above 100 µg/mL. A simulation of the re-initiation of the dosing regimen as described in the SmPC was provided. Predicted concentration-time profiles in case a dose is missed is largely overlapping with the situation where doses are administered according to protocol. Also, no large increases in C_{max} concentrations are observed after re-initiation of the dosing schedule. This is considered acceptable.

Pharmacodynamics

The 3 clinical phase 1 studies provided PD data on CP activity, dose selection and immunogenicity. Additionally, PD results were collected in both phase 3 studies (CADENZA and CARDINAL trials).

Classical complement pathway (CP) activity

CP activity, CH50, C1s (target of sutimlimab), C4 (first soluble cleavable substrate of C1s) levels, as well as levels of C1sC1INH were measured to confirm the binding of sutimlimab. Further, to confirm that the non-enzymatic role of C1q is left intact by sutimlimab, C1q was measured in all studies.

Single doses (study BIVV009-01) of sutimlimab escalating from 0.3 mg/kg to 100 mg/kg showed that after 30 mg/kg or higher, inhibition of serum CP activity and the decrease of free C1s and C1sC1INH concentrations reached maximum effect. The duration of inhibition increased in a dose-dependent manner. This inhibition was reversible as levels returned to baseline after 7 days. Return to baseline was more prolonged as the dose level increased. After multiple doses of 30 and 60 mg/kg once weekly for 4 weeks similar findings were noted with nearly complete inhibition of mean CP activity, C1s, and C1sC1INH concentration profiles. After discontinuation, a partial return to baseline was noted after 7 days with 30 mg/kg, while a nearly complete knockdown was observed over the entire study duration for the 60 mg/kg dose. The effect was of nearly the same magnitude for both doses. Total C4 levels were not affected and also C1q changes from baseline in 30 and 60 mg/kg groups were comparable to those seen in the placebo subjects, in whom little to no effect on CP activity was seen. Multiple dosing of sutimlimab at 75 mg/kg in healthy subjects on Days 1, 8, 22, and 36 (Study BIVV009-02) confirmed the findings of study BIVV009-01 (Part B), showing an inhibition of >90% of CP, CH50, C1s, and C1sC1INH activity which was maintained up to 2 weeks after the final dose. In line with the mechanism of action of sutimlimab, a small and no clinically relevant effect has been observed on the C1q and C4 levels. Similar effects were noted with 3 different single doses (30, 60 and 100 mg/kg) and 2 different multiple doses of sutimlimab (6.5 g for body weight (BW) <75 kg and 7.5 g for BW ≥75 kg) on Days 1, 8, and 22 in Japanese healthy subjects (Study BIVV009-05).

SAD/MAD evaluation in patients with complement-mediated disorders

In patients with complement-mediated disorders including CAD, WAIHA, BP, and active AMR in patients who had received a kidney transplant (Part C of the first-in-human study BIVV009-01), a single dose of 10 mg/kg (day 0), followed by 4 weekly doses of 60 mg/kg, the mean CP activity and C1s concentrations displayed nearly complete inhibition over the entire profile across all patient populations, and was maintained 3 weeks after the last weekly 60 mg/kg dose. The effects on the C1q levels were small and not clinically relevant. Important to note that C4 levels in CAD patients were below the normal range (<0.18 g/L) at baseline but restored immediately after receiving the first weekly dose of 60 mg/kg, but then returned to the pre-treatment level 4 weeks after the last 60 mg/kg dose.

Of note, a thorough QT/QTc study was considered not needed, given the nature of the drug molecule, as this concerns a monoclonal antibody.

Relationship between plasma concentration and effect

Two exposure-response analyses were conducted as more data became available. An initial analysis (POH0756) was performed using data from Studies BIVV009-01 part C (also known as TNT009-01 part C) and BIVV009-03 Part A with the objectives to describe the exposure-efficacy response of BIVV009 with regards to Hgb and bilirubin level, and to explore the demographic and laboratory values that may affect the safety profile of BIVV009 therapy and model, if necessary. It was concluded that information on AEs were sparse and therefore no exposure-safety analysis was conducted. As additional data from studies BIVV009-01 part E, BIVV009-03 part B, and BIVV009-04 Part A became available an updated

analysis (POH0798) was conducted with the objectives to characterize and quantify the exposure-response relationship of sutimlimab and assess the impact of covariates on it by developing a PK-PD model for Hgb as the primary efficacy parameter, and to characterize the relationships between exposure and response, including graphical evaluation of PD markers bilirubin and C4. As the same data were included in the updated analysis as in the initial one, only results from the latter were presented in depth.

A dynamic population PK-PD model for Hgb was developed by linking the complete time profile of sutimlimab concentrations to the time-profiles of Hgb. The RSE was high for EC50 and on the impact of the covariates blood transfusion on E_{max} and baseline CRCL on E_{base} (baseline effect). It is also high on the estimates inter-individual variabilities, however, the introduction of covariates on E_{base} and E_{max} reduced the IIV of these parameters by 12.2% and 16.5%, respectively. The magnitude of ETA shrinkage on the IIVs was ≤ 30% for all PD parameters with IIV terms. In general, observations are randomly distributed around the identity line in the goodness-of-fit plots, however, it is noted that the low haemoglobin measures are not captured on a population level by the model (GOF only displayed for subjects receiving sutimlimab). This is also visible in the VPC where the lower prediction interval does not capture all observations over time. The model appears to adequately predict the median change in haemoglobin with and without treatment (i.e. change in haemoglobin over time with placebo treatment).

The applicant conducted an exploratory exposure-response modelling for the relationship between maximum observed change from baseline in Hbg, bilirubin and C4 and maximum C_{min} using an E_{max} model with hill coefficient fixed to 1. The uncertainty in EC50/IC50 is high for all biomarker models. The exploratory modelling exercise is of little value as the biomarker measure is detached from actual Cmin-value at time point of measurement and a conclusion of efficacy cannot be made based on these models. The figures of the observed biomarker measurements with correction for baseline versus time, stratified on study and doses do not indicate a major difference in efficacy between the doses on a population level. For study 903, the higher dose appears to result in slightly higher change from baseline initially for haemoglobin. However, in the 904 study it is noticed that the median for the 7.5 g dose, and the 2.5^{th} percentile, is lower at later time points. The trend is not clearly observed for the median bilirubin, or C4, however the lower percentiles appear to go lower for the 7.5 g group indicating a lower change from baseline for some subjects who received the higher dose. Exposure-safety analysis was conducted using all available data for Cardinal and Cadenza studies, with the adverse events plotted against predicted sutimlimab exposure quartiles for AUC and C_{max}. Each quartile includes 16-17 subjects. A trend is observed towards higher GI disorders with an increased C_{max}, and general disorders and administration site conditions for AUC and C_{max}. However, in general, there does not appear to a clear trend between the other adverse events and high exposure.

Conclusions on clinical pharmacology

The clinical results of the abovementioned clinical pharmacology programme is sufficient for the proposed dose range and regimen of 6,500 mg for patients weighing 39-<75 kg and 7,500 mg for patients weighing ≥75 kg. This dosing regimen demonstrated an appropriate effect on CP activity, and on anaemia and haemolysis markers (i.e. Hb and bilirubin). Further, both doses seemed generally well-tolerated with low immunogenicity.

Clinical efficacy

Table 3. List of Phase 1/3 studies contributing with data on efficacy for sutimlimab in CAD

Study number (study part)	Study objectives	Treatment/ follow-up duration	Patients treated
Phase 1			
BIVV009-01 (Part C)	Assessment of safety and tolerability of BIVV009 in patients. The secondary objectives included evaluating the pharmacodynamics of sutimlimab with respect to CP function and evaluate the effect of sutimlimab on disease-related biomarkers.	4 weeks/ follow-up for 4 weeks after the last dose until the end of study visit on Day 53	34 (10 with CAD)
BIVV009-01 (Part E)	Assessment of safety and tolerability of BIVV009 in patients. The secondary objectives included evaluating the pharmacodynamics of sutimlimab with respect to CP function and evaluate the effect of sutimlimab on disease-related biomarkers.	>2 years/ 9 weeks follow-up after last study drug administration	4
Phase 3			
BIVV009-03 (Part A), (CARDINAL)	To determine whether BIVV009 administration results in a ≥ 2 g/dL increase in hemoglobin levels or increases hemoglobin to ≥ 12 g/dL and obviates the need for blood transfusion during treatment in patients with CAD who have a recent history of transfusion.	26 weeks/	24
BIVV009-03 (Part B), (CARDINAL)	To evaluate the long-term safety, durability of response and tolerability of BIVV009 in patients with CAD	2 years following LPO under Part A/ 9 weeks follow-up visit after last study drug administration	22
BIVV009-04 (Part A), (CADENZA)	To determine whether BIVV009 administration results in a ≥1.5 g/dL increase in hgb level and avoidance of transfusion in patients with CAD without a recent history of blood transfusion.	6 months/	42
BIVV009-04 (Part B), (CADENZA)	To evaluate the long-term safety and tolerability of BIVV009 in patients with CAD. The secondary objective is to investigate the durability of response during long-term treatment with BIVV009 in patients with CAD.	1 year following LPO under Part A/9 weeks after last dose of study drug administration	39

Abbreviations: CAD = Cold Agglutinin Disease; CP = classical component pathway; hgb = hemoglobin; LPO = last patient out; QOL = quality of life

Dose-response studies

No dedicated dose response studies were conducted in patients.

The starting dose, 0.3 mg/kg, for first-in-human study BIVV009-01 Part A was chosen to result in sutimlimab exposure that would be 1/300 of the exposure at the no adverse effect level in the 28-day

toxicology study in nonhuman primates. Successively higher sutimlimab doses up to 100 mg/kg (BIVV009-01 Part A) or 60 mg/kg once weekly (BIVV009-01 Part B) were then tested in healthy subjects to exceed the concentrations that produced complete CP inhibition *in vitro* and to maintain above this level for increasing duration. Based on the extremely steep PK/PD relationship of sutimlimab observed at concentrations 15.5 µg/mL (concentration associated with 90% reduction of CP activity, concentration for 90% of effect [IC90]; report TNTH-CSC-103), and the rapid clearance due to TMDD observed at concentrations <100 µg/mL, 60 mg/kg once weekly was chosen for subsequent assessment in patients with CP-mediated disorders (study BIVV009-01 Part C) to maintain CP inhibition throughout the dosing interval. A tiered flat-dosing approach based on body weight cut-offs was proposed for Phase 3 with a dose of 6.5 g for subjects <75 kg and a dose of 7.5 g for subjects ≥75 kg. The weight cut-off of 75 kg was chosen based on the expected weight distribution in CAD patients. This body-weight tiered induction/maintenance dosing regimen was predicted to maintain target trough concentrations >100 µg/mL throughout the dosing period in approximately 94% of CAD subjects.

Main studies

BIVV009-04 (CADENZA) Part A

A Phase 3, randomised, double-blind, placebo-controlled study to assess the efficacy and safety of sutimlimab/BIVV009 in patients with primary cold agglutinin disease (CAD) without a recent history of blood transfusion.

A 6-week Screening/Observation period was followed by randomization 1:1 to sutimlimab or placebo through Week 25 for Part A. Following completion of dosing in the 6-month treatment period, patients could continue to receive sutimlimab during Part B (long-term study). Part A is completed. An interim analysis of Part B has been provided at the start of the procedure.

Methods

Study participants

Inclusion criteria

Among important inclusion criteria were:

Adult male and female patients ≥18 years of age at Screening.

Body weight of ≥39 kg at Screening.

Confirmed diagnosis of primary CAD based on the following criteria:

a) Chronic haemolysis
b) Polyspecific direct antiglobulin test (DAT) positive
c) Monospecific DAT strongly positive for C3d
d) Cold agglutinin titer ≥64 at 4°C
e) IgG DAT ≤1+, and
f) No overt malignant disease

- Haemoglobin level ≤10.0 g/dL.
- Bilirubin level above the normal reference range, including patients with Gilbert's Syndrome.
- Ferritin levels above the lower limit of normal. Concurrent treatment with iron supplementation was permitted if the patient had been on a stable dose during the previous 4 weeks.

- Presence of one or more of the following CAD-related signs or symptoms within 3 months of Screening:
    a) Symptomatic anaemia defined as:
        i. Fatigue
        ii. Weakness
        iii. Shortness of breath
        iv. Palpitations, fast heartbeat
        v. Light headedness and/or
        vi. Chest pain
    b) Acrocyanosis
    c) Raynaud's syndrome
    d) Haemoglobinuria
    e) Disabling circulatory symptoms, and/or
    f) Major adverse vascular event (including thrombosis)

- Bone marrow biopsy within 6 months of Screening with no overt evidence of lymphoproliferative disease or other haematological malignancy. An additional bone marrow biopsy was required if the prior bone marrow was deemed unsuitable for analysis by the Sponsor Documented vaccinations against encapsulated bacterial pathogens (*Neisseria meningitis*, including serogroup B *meningococcus*, *Haemophilus influenzae*, where available, and *Streptococcus pneumoniae*) within 5 years of enrolment or as specified.
- Willing to receive transfusions if they met the eligibility criteria during the study treatment period;
- If female: post-menopausal, surgically sterile, or established on and agreed to continue highly effective methods of birth control throughout the study and for 9 weeks following administration of the last dose of study drug.
- Males: surgically sterile for at least 90 days or when sexually-active with female partners of child-bearing potential agreed to use highly effective contraception from Day 0 until 9 weeks following administration of the last dose of study drug.

Exclusion criteria

Among important exclusion criteria were:

- Cold agglutinin syndrome secondary to infection, rheumatologic disease, or active hematologic malignancy.
- History of blood transfusion within 6 months of screening, or history of more than one blood transfusion within 12 months of screening.
- Clinically relevant infection of any kind within the month preceding enrolment (eg, active hepatitis C, pneumonia)
- Clinical diagnosis of system lupus erythematosus (SLE); or other autoimmune disorders with anti-nuclear antibodies at Screening. Anti-nuclear antibodies (ANA) of long-standing duration without associated clinical symptoms were adjudicated on a case-by-case basis.
- Positive hepatitis panel (including hepatitis B surface antigen and/or hepatitis C virus antibody) prior to or at Screening.
- Positive human immunodeficiency virus (HIV) antibody at Screening.
- Treatment with rituximab monotherapy within 3 months or rituximab combination therapies (eg, with bendamustine, fludarabine, ibrutinib, or cytotoxic drugs) within 6 months prior to enrolment.
- Concurrent treatment with corticosteroids other than a stable daily dose equivalent to ≤10 mg/day prednisone for previous 3 months.

- Erythropoietin deficiency. Concurrent treatment with erythropoietin was permitted if the patient was on a stable dose for the previous 3 months.
- Concurrent usage of iron supplementation unless the patient was on a stable dose for at least 4 weeks.
- Females who were pregnant, lactating, or, if having reproductive potential, were considered potentially unreliable with respect to contraceptive practice.

Patients could receive RBC 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.

Treatments

Study treatments
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
Batch numbers: 091E1, 091E2, 091E3, 091E4, 092C1, 092C2, 092E1, 092E2, 093E1, 093E2, 09620, 21919, 59619, 60819, 75019
Noninvestigational medicinal products: placebo
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
Batch number(s): 091E1, 091E2, 091E3, 091E4, 092E1, 092E2, 092C1, 092C2, 093E1, 093E2, 21919, 59619, 75019
Duration of treatment: 26 weeks in Part A
Duration of observation: 26 weeks in Part A

Prior and concomitant therapy

Treatment with rituximab monotherapy within 3 months of enrolment or rituximab combination therapies within 6 months of enrolment, and during the study, were prohibited. Concurrent administration of erythropoietin and/or a daily dose of corticosteroids (equivalent to ≤10 mg/day of prednisone) was acceptable provided the patient was on a stable dose during the previous 3 months; concurrent use of B12, folate, and iron supplementation was acceptable provided the patient was on a stable dose during the previous 4 weeks.

RBC transfusions were indicated if haemoglobin levels met either of the following criteria:

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

Objectives

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

Outcomes/endpoints

Primary endpoint: Rate of responders defined as patients who had a ≥1.5 g/dL increase in Hgb levels at the treatment assessment endpoint (TAT; defined as the mean value of Weeks 23, 25, and 26), did not receive a blood transfusion from Week 5 through Week 26 and did not receive treatment for CAD beyond what is permitted per protocol.

Key secondary endpoints: Change from baseline in Hgb at the TAT; Change from baseline in QOL, as assessed by the change in Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue scale scores at the TAT.

Additional secondary endpoints included changes from baseline in markers of haemolysis.

Sample size

Approximately 40 patients with primary CAD who did not have a recent history of transfusion were randomized. It was expected that few patients would meet the composite primary endpoint without treatment intervention. The proposed sample size was chosen to provide sufficient power to detect a 50% improvement in meeting primary endpoint criteria with sutimlimab treatment compared to placebo with a significance level of 0.05. A total of 40 patients (20 patients per group) would provide a statistical power of greater than 85% to detect a treatment difference of 50% for placebo response rates between the range of 15% to 40%. This calculation assumed a 2-sided 5%-level test comparing the response rates between the sutimlimab and placebo groups. A 50% improvement over placebo was considered clinically relevant.

Randomisation and blinding (masking)

On Day 0, patients were randomized with a ratio of 1:1 to sutimlimab or Placebo by a permuted block randomization with a fixed block size of 4. The randomization was performed by Pharm-Olam's Interactive Web Response System (IWRS). Sponsor personnel (except for those who provide drug supply) were blinded to the treatment assignment until the interim analysis (Part A DBL). There was no stratification at randomisation.

The study was double-blind. Sutimlimab or placebo doses for infusion were prepared by the pharmacist or qualified site staff in a blinded manner.

Statistical methods

Analysis populations

Full Analysis Set: The Full Analysis Set (FAS) and Intent-to-treat [ITT] population were synonymous and consisted of all randomized subjects who received at least 1 dose (including partial dose) of IMP. Analyses of efficacy were performed on the FAS.

Modified Full Analysis Set: Following the guidelines from FDA and EMA to assess any potential impact of COVID-19 on efficacy evaluation, a Modified Full Analysis Set (mFAS) was included. The mFAS population was a subset of the FAS and included patients from the FAS who did not miss any visits or discontinue early due to the COVID-19 pandemic.

Per-protocol Set: The Per-protocol (PP) Set was a as a subset of FAS and included patients in the FAS who did not have any important protocol deviations that impacted their efficacy assessments. Selected efficacy endpoints were analysed for the PP Population.

Safety Analysis Set: Patients who received at least 1 dose (including partial dose) of study drug were included in the Safety Analysis Set. Note that Safety Analysis Set is the same as FAS in this study.

PK Analysis Set: Patients who received at least 1 dose of study drug and had evaluable PK concentrations were included in PK Analysis Set.

PD Analysis Set: All subjects who received at least 1 dose of study drug and had at least one evaluable PD sample during Part A were included in the PD Analysis Set.

Analyses of Primary efficacy endpoint

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 as defined in Table 4. 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. 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 stratified by baseline haemoglobin (< median baseline haemoglobin versus ≥ median baseline haemoglobin) and geographic region (Japan/Australia, United States, Europe). In addition, the proportion of subjects who met each of the 3 response criteria as well as the number of transfusions by study period (before Week 5 and between Week 5 and Week 26) and by treatment arm were summarized.

Table 4. COVID-adjusted Composite Estimand

	COVID-adjusted Composite Estimand
Population	FAS
Response variable	To meet primary endpoint criteria, a patient had to fulfill all 3 of the following components: • 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
ICEs handling	• 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-19 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 model for repeated measures

Supplementary analyses

Four sensitivity, or rather supplementary, analyses of the primary endpoint were conducted and are listed below. The CMH test was used to estimate the p-values and 95% CIs for the sensitivity analyses.

• Sensitivity Analysis 1: Analysis included no adjustment for COVID-related intercurrent events.

• Sensitivity Analysis 2: mFAS analysis population included patients who did not miss visits or did not discontinue treatment early due to COVID.

• Sensitivity Analysis 3: Analysis included any patient who completed treatment through at least Week 23 and had at least 1 evaluable haemoglobin value from Week 23, 25, and 26.

• Sensitivity Analysis 4: PP population analysis excluded patients who had an important protocol deviation which could have potentially impacted the efficacy assessment.

Subgroup analyses

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 haemoglobin 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. For these analyses, if the sample size in a category was small, the cut-off may have been modified to adjust distribution. For these subgroups, the CMH odds ratio and 95% CI was summarized. Where possible, the CMH estimates were stratified by baseline haemoglobin and geographic region. The consistency of the odds ratio among these subgroups was evaluated using forest plots.

Analyses of Secondary efficacy endpoints

Key secondary endpoints were ranked ordered by clinical importance and a sequential closed testing procedure was performed to protect the type I error. When tested, a sequential closed procedure with alpha of 0.05 for each test was performed using the hypothetical estimand in this order: (1) mean change from baseline in haemoglobin at the treatment assessment timepoint in the sutimlimab versus placebo arms and (2) mean change from baseline in FACIT-Fatigue Score at treatment assessment timepoint in the sutimlimab versus placebo arms.

The change from baseline in Hgb at the treatment assessment timepoint was analysed for the FAS. The primary analysis will be performed according to the Hypothetical Estimand based on the MMRM model, while a sensitivity analysis will be done via De-facto Estimand. Similarly, COVID-specific sensitivity analyses will be performed according to the Modified Hypothetical Estimand and Modified De-facto Estimand in order to ascertain the results for subjects unaffected by the COVID pandemic.

Population	FAS	mFAS	FAS
Variable	Change from baseline at treatment assessment time point		
ICE handling	any value after transfusion and prohibited medication is considered missing	any value after transfusion and prohibited medication is considered missing	None
Treatment effect	Difference in mean change from baseline at TAT between BIVV009 and Placebo		

Mixed Model with Repeated Measures (MMRM) was used for the analysis of such endpoints at study visits (including the treatment assessment time points). The MMRM model will include the baseline value of the endpoint, visit, treatment, and treatment and visit interaction. A heterogeneous Toeplitz (TOEPH) covariance matrix within a subject will be used. For the endpoint at the treatment assessment timepoint (average of Week 23, 25, and 26), the estimate was calculated as the mean of MMRM estimates at Week 23, 25, and 26 visits.

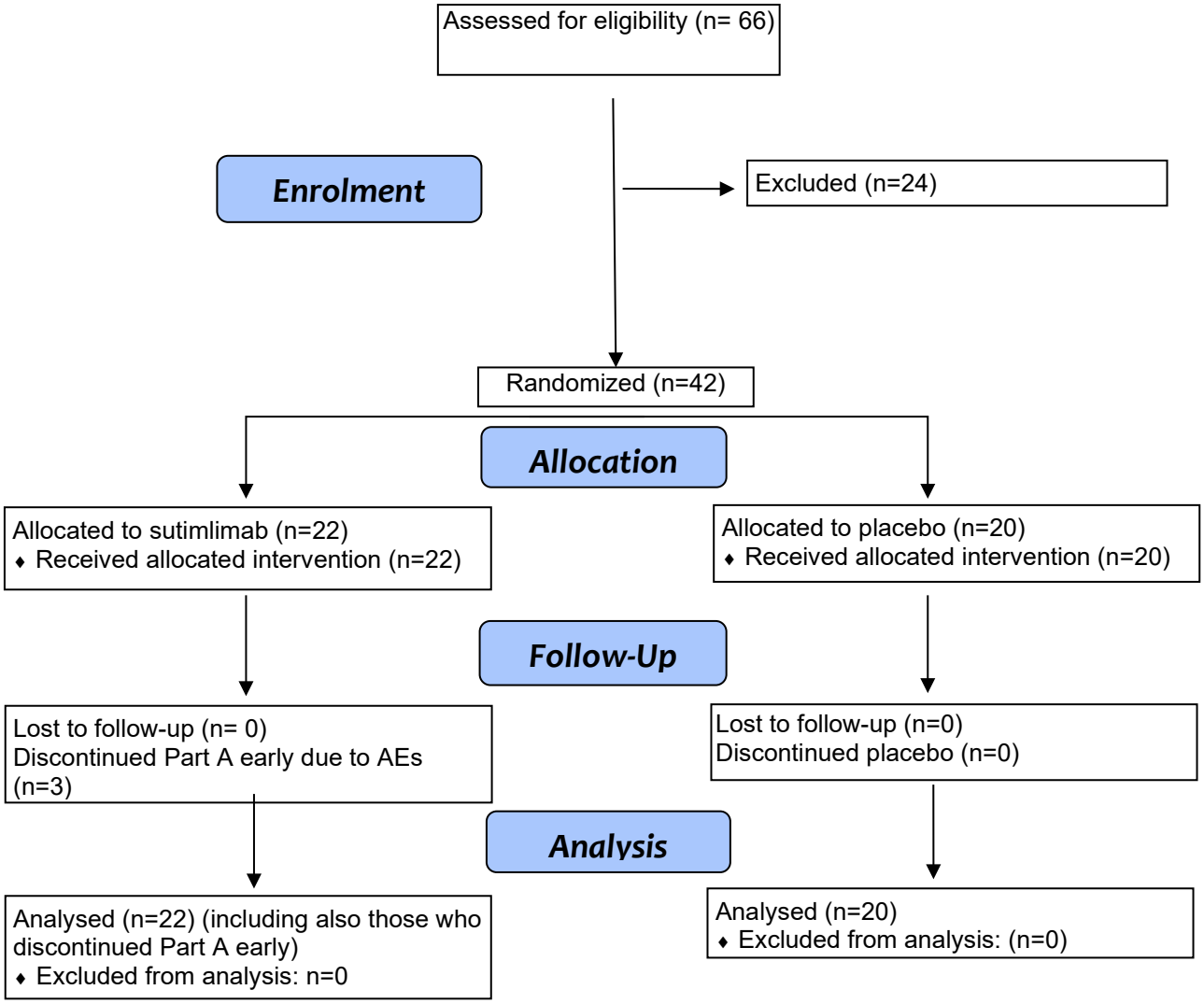
For either estimand, the mean change from baseline in Hgb at treatment assessment timepoint for both treatment arms, the estimated difference in change from baseline at TAT between BIVV009 and placebo, along with its 95% CI, was estimated by the MMRM model. The significance test for the treatment difference in Hgb at the treatment assessment timepoint was based on appropriate treatment contrast.

Additional sensitivity analysis based on multiple imputation was carried out for the Hypothetical Estimand to evaluate the appropriateness of the assumption of MAR. Specifically, multiple imputation was performed using a pattern-mixture model and the above MMRM model will be run on the imputed data. Non-monotone missing data will first be transformed to a monotone missing data structure. The control-based imputation method assumes subjects in the BIVV009 treatment arm who discontinued from the study or are missing Hgb values at the TAT will exhibit similar Hgb values to those subjects in the placebo arm (and subjects in the placebo arm will continue to exhibit those Hgb values). Thus, multiple imputation is performed using only information from the placebo arm.

The analyses for haemoglobin described above will also be performed for the FACIT-Fatigue score.

Results

Participant flow



Recruitment

Study Initiation Date (first patient enrolled): 06 March 2018; first dose 18 April 2018. Primary Completion Date: 29 September 2020 (Part A). Patients were enrolled at 27 sites in 13 countries. The

countries with the highest enrolment were Germany (10 patients), Japan (5 patients), and the United States (5 patients).

Conduct of the study

There were 5 global amendments and 6 country-specific amendments submitted to regulatory authorities, none of which are considered to affect the overall study integrity.

Major protocol deviations

Overall, 30/42 subjects reported major protocol deviations, most frequently related to receiving prohibited medication (27.3% sutimlimab and 20.0% placebo), IMP administration (13.6% and 30.0%), and study conduct (9.1% and 25.0%). Prohibited medications included rituximab monotherapy or rituximab combination therapies (eg, bendamustine, fludarabine, ibrutinib, or cytotoxic drugs). Most prohibited medication deviations were due to initiation of or dose modification of folate or iron *(stable dosing of such medications was allowed, CHMP's comment)*. Missed visits due to COVID-19 were not considered major protocol deviations. IMP administration deviations included missed crossover dose; missed loading dose; wrong filter used; dosing not done; missed Day 7 dose; missed dose; and 2 placebo group patients who each received a single dose of sutimlimab.

Baseline data

Table 5. BIVV009-04 Part A: Summary of demographics and baseline characteristics - FAS

	BIVV009 (N=22)	Placebo (N=20)	Total (N=42)
Age (years)			
Mean	65.3	68.2	66.7
SD	10.9	10.1	10.5
Median	64.0	69.0	66.0
Min ; Max	46 ; 88	51 ; 83	46 ; 88
<65	12 (54.5)	6 (30.0)	18 (42.9)
>=65	10 (45.5)	14 (70.0)	24 (57.1)
Sex			
Female	17 (77.3)	16 (80.0)	33 (78.6)
Male	5 (22.7)	4 (20.0)	9 (21.4)
Race			
Asian	5 (22.7)	2 (10.0)	7 (16.7)
White	0	4 (20.0)	4 (9.5)
Black or African American	0	0	0
American Indian or Alaska Native	0	0	0
Native Hawaiian or other Pacific Islander	0	0	0
Other	0	0	0
Not Collected	17 (77.3)	14 (70.0)	31 (73.8)
Other	0	0	0
Not Collected	17 (77.3)	14 (70.0)	31 (73.8)
Ethnicity			
Hispanic/Latino	0	1 (5.0)	1 (2.4)
Not Hispanic or Latino	5 (22.7)	5 (25.0)	10 (23.8)
Not Collected	17 (77.3)	14 (70.0)	31 (73.8)
Geographic location			
Europe	15 (68.2)	13 (65.0)	28 (66.7)
North America	3 (13.6)	3 (15.0)	6 (14.3)
Asia	3 (13.6)	2 (10.0)	5 (11.9)
Other	1 (4.5)	2 (10.0)	3 (7.1)
Height (cm)			

Mean	163.6	164.4	164.0
SD	11.9	7.5	9.9
Median	163.3	163.5	163.3
Min ; Max	138 ; 196	153 ; 178	138 ; 196
Weight (kg)			
Mean	66.8	64.9	65.9
SD	13.4	10.7	12.1
Median	67.2	63.3	65.3
Min ; Max	39 ; 100	48 ; 95	39 ; 100
<75	17 (77.3)	17 (85.0)	34 (81.0)
>=75	5 (22.7)	3 (15.0)	8 (19.0)
BMI (kg/m^2)			
Mean	24.8	24.0	24.4
SD	3.1	3.5	3.3
Median	25.2	23.2	23.9
Min ; Max	19 ; 30	18 ; 32	18 ; 32

NOTE: Percentages are based on the number of subjects in each treatment arm and total of the Full Analysis Set.

Race and ethnicity were not reported for 31 patients due to local laws.

At baseline mean haemoglobin (SD) was 9.15 (1.05) g/dL and 9.33 (1.04) g/dL in the sutimlimab and placebo groups, respectively; mean total bilirubin (SD) was 41.175 (27.266) µmol/L and 35.778 (11.822) µmol/L, respectively; mean LDH (SD) was 421.500 (194.702) U/L and 380.800 (243.111) U/L, respectively; haptoglobin (SD) was 0.200 (0.000) g/L and 0.207 (0.031) g/L (values <0.2 g/L were imputed as 0.2 g/L); and absolute reticulocytes were 159.022 × 109/L (69.636) and 145.022 × 109/L (46.046), respectively. Mean (SD) FACIT-Fatigue score at baseline was 31.673 (12.802) and 32.988 (10.946) in the sutimlimab and placebo groups, respectively.

No patient in either group received a transfusion within the last 6 months prior to screening. In the period between 6 to 12 months prior to screening, 19 (86.4%) and 20 (100%) patients in the sutimlimab and placebo groups, respectively, received no transfusions. For the 3 patients in the sutimlimab group who had received prior transfusions, a mean of 1.5 units (range 1 to 2) were transfused.

Medical history

In total, 5/42 (2 in the sutimlimab group and 3 in the placebo group) had any hospitalisation related to CAD within the last 2 years. A haematological malignancy within the last 5 years was reported in 8/42 patients (4 in each treatment group), all relating to lymphoproliferative disorder/lymphoma. None of the study subjects had any thromboembolic event within the last year; 4/42 (2 in each treatment group) had any previous thromboembolic event.

More patients in the sutimlimab group had a history of low-grade/indolent lymphoid malignancy (8/22 [36.4%] sutimlimab versus 2/20 [10.0%] placebo), with bone marrow involvement in 5 patients in the sutimlimab group and 2 patients in the placebo group. A history of other hematologic process was more prevalent in the placebo group (1 [4.5%] sutimlimab and 5 [25.0%] placebo). Of 39 patients who consented to testing for Gilbert's syndrome, none were positive and 1 test result was declared unknown.

Baseline CAD characteristics

All patients reported CAD-related anaemia symptom(s) and/or specific complications of CAD within 3 months prior to screening.

Fatigue was reported by 38/42 at day -42 and 32/42 at baseline. Weakness was reported by 23/42 at day -42 and 24/42 at baseline. Shortness of breath was reported by 24/42 at day -42 and 23/42 at baseline. Palpitations/fast heartbeat was reported by 17/42 at day -42 and 10/42 at baseline. Light-headedness/presyncope was reported by 11/42 at day -42 and 5/42 at baseline. Chest pain was reported by 5/42 at day -42 and 4/42 at baseline. Acrocyanosis was reported by 21/42 at day -42 and 13/42 at baseline. Raynaud's syndrome was reported by 13/42 at day -42 and 8/42 at baseline. Haemoglobinuria was reported by 13/42 at day -42 and 10/42 at baseline. Disabling circulatory symptoms was reported by 5/42 at day -42 and 3/42 at baseline. Major adverse vascular event including thrombosis was reported by 2/42 at day -42 and 1/42 at baseline.

Prior and/or concomitant medication

A total of 31 (73.8%) patients had received prior CAD therapy within the last 5 years, including single agent therapy with rituximab (21, 50.0%), corticosteroids (20, 47.6%), combination regimen that may have included rituximab (6, 14.3%), or other chemotherapy (6, 14.3%). Prior CAD therapy was similar in the sutimlimab and placebo groups.

All of the patients received at least 1 concomitant medication during the study. The most frequently used concomitant medications were anti-anaemic preparations (81.8% sutimlimab and 80.0% placebo), vaccines (68.2% and 30.0%), analgesics (36.4% and 35.0%), drugs for acid (reflux) related disorders (36.4% and 35.0%), antibacterials for systemic use (27.3% and 40.0%), antithrombotic agents (22.7% and 30.0%), and mineral supplements (0% and 50.0%). One patient in the sutimlimab group received a prohibited CAD medication (rituximab). This patient discontinued study treatment prematurely due to an AE and started rituximab treatment during the 9-week post-treatment follow up period.

In the previous 5 years or during the study, all patients received at least one meningococcal (conjugate) vaccine and at least one *Streptococcus pneumoniae* vaccine. Nineteen (86.4%) and 18 (90.0%) patients in the sutimlimab and placebo groups, respectively, received at least one *haemophilus influenzae* vaccination in the previous 5 years or during the study; this is consistent with global variations in vaccination guidelines for patients with complement deficiency.

Measurement of treatment compliance

Twenty-two (100%) and 19 (95.0%) of patients in the sutimlimab and placebo groups, respectively, were ≥80% compliant and 21 (95.5%) and 17 (85.0%), respectively were 100% compliant. Ten (45.5%) patients in the sutimlimab group and 8 (40.0%) patients in the placebo group received at least 1 dose out of window. In the sutimlimab group, 1 (4.5%) patient missed 1 dose at Week 7 due to COVID-19. In the placebo group, 1 (5.0%) patient missed 2 doses at Weeks 3 and 5) and 1 (5.0%) patient missed doses at Weeks 7, 9, 11, 13, 15, 17, 19, and 21 due to COVID-19. No patient received a partial dose.

Numbers analysed

Table 6. Study BIVV009-04 Part A: Summary of disposition - All subjects

	Treatment Arm		
	BIVV009 (N=22)	Placebo (N=20)	Total (N=42)
Number of subjects			
Screened			66
Safety Analysis Set (a)	22 (100)	20 (100)	42 (100)
Full Analysis Set (b)	22 (100)	20 (100)	42 (100)
Modified Full Analysis Set (c)	21 (95.5)	18 (90.0)	39 (92.9)
Per-protocol Set (d)	20 (90.9)	19 (95.0)	39 (92.9)
PK Analysis Set (e)	22 (100)	20 (100)	42 (100)
PD Analysis Set (f)	22 (100)	20 (100)	42 (100)
Missing at least 1 visit due to COVID-19	1 (4.5)	2 (10.0)	3 (7.1)
Completion status (g)			
Completed Part A	19 (86.4)	20 (100)	39 (92.9)
Discontinued Part A early	3 (13.6)	0	3 (7.1)
Adverse event	3 (13.6)	0	3 (7.1)
Lost to follow-up	0	0	0
Consent withdrawn	0	0	0
Investigator decision	0	0	0
Death	0	0	0
Lack of efficacy	0	0	0
COVID-19	0	0	0
Other	0	0	0
Continued into Part B	19 (86.4)	20 (100)	39 (92.9)

NOTE: Percentages are based on the number of subjects in each treatment arm and total.
(a) Safety Analysis Set is defined as all subjects who received at least 1 dose (including partial dose) of study drug.
(b) Full Analysis Set (FAS) is defined as all subjects who received at least 1 dose (including partial dose) of study drug.
(c) Modified Full Analysis Set is defined as a subset of FAS who did not miss any visits or discontinue early due to the COVID-19 pandemic.
(d) Per-protocol Set is defined as a subset of FAS who did not have any important protocol deviations impacting their efficacy assessments. Important protocol deviations are adjudicated.
(e) PK Analysis Set is defined as all subjects who received at least 1 dose of study drug and have evaluable PK concentrations.
(f) PD Analysis Set is defined as all subjects who received at least 1 dose of study drug and have at least 1 evaluable PD sample.
(g) Completed Part A means subjects did not discontinue prior to the Week 26 Visit in Part A. Discontinued Part A early means subjects terminated participation in Part A prematurely for any reason.
PGM=DEVOPS/BIVV009/BIVV009_04/CSR_A/REPORT/PGM/t1_disposition.sas
OUT=REPORT/OUTPUT/t1_disposition_i.rtf (24NOV2020 17:54)

Outcomes and estimation

Primary efficacy endpoint(s)

Table 7. BIVV009-04 Part A: Summary of primary endpoint: treatment response and components - Composite estimand - FAS

	BIVV009 (N=22)	Placebo (N=20)
Subjects with Hgb increased >=1.5 g/dL at treatment assessment timepoint (a)		
Yes	16 (72.7)	3 (15.0)
No	3 (13.6)	17 (85.0)
Unknown	3 (13.6)	0
Subjects free of transfusion during Week 5 to Week 26 (b)		
Yes	18 (81.8)	16 (80.0)
No	1 (4.5)	4 (20.0)
Unknown	3 (13.6)	0

Subjects receiving no protocol-prohibited CAD medications during Week 5 toWeek 26 (b)		
Yes	19 (86.4)	20 (100)
No	1 (4.5)	0
Unknown	2 (9.1)	0
Primary endpoint		
Responder rate	16 (72.7)	3 (15.0)
95% CI for responder rate (c)	(49.8, 89.3)	(3.2, 37.9)
Stratified CMH test (d)		
Odds Ratio (BIVV009 vs Placebo) (95% CI)	15.94 (2.88, 88.04)	
P-value	<0.001	

NOTE: 1: Percentages are based on the number of subjects in each treatment arm and total of the Full Analysis Set.2: Protocol prohibited CAD medications are medically adjudicated.
The unknown status is defined as missing Hgb value at all visits of Week 23, 25 and 26.
Subjects who discontinued prior to Week 23 without an event are considered unknown.
95% CI is calculated using the Clopper-Pearson exact method.
Stratified by baseline haemoglobin (< median vs >=median) and geographic region (Asia/Other, North America, and Europe).
Abbreviation: Hgb = haemoglobin; CI = confidence interval; CMH = Cochran-Mantel-Haenszel.

Patients who discontinued before Week 23 were to have prohibited medication and transfusion status "unknown". In the sutimlimab group, 2 of the 3 patients who discontinued before Week 23 had "unknown" prohibited medication status. The third patient, who discontinued due to a TESAE of blood IgM increased, received rituximab.

Transfusion status is summarized below from Weeks 1 to 5 and Weeks 5 to 26, including patients who discontinued before the TAT.

Table 8. BIVV009-04 Part A: Summary of number of transfusions and units by study period (FAS)

	During the first 5 Weeks		Week 5 to Week 26	
	BIVV009 (N=22)	**Placebo (N=20)**	**BIVV009 (N=22)**	**Placebo (N=20)**
Number of transfusions				
0	21 (95.5)	18 (90.0)	21 (95.5)	16 (80.0)
1	1 (4.5)	1 (5.0)	1 (4.5)	2 (10.0)
2	0	1 (5.0)	0	0
3	0	0	0	1 (5.0)
4	0	0	0	1 (5.0)
5	0	0	0	0
>5	0	0	0	0
Total units transfused	1	2	1	4
Mean	2.0	3.0	2.0	4.3
SD	NC	1.4	NC	2.6
Median	2.0	3.0	2.0	4.0
Min ; Max	2 ; 2	2 ; 4	2 ; 2	2 ; 7

NOTE: 1: Percentages are based on the number of subjects in each treatment arm of the full analysis set. (a) Number of subjects who had at least one transfusion. NC = Not calculated

Among the 19 patients receiving sutimlimab that completed Part A, 3 did not meet the primary endpoint criteria. These 3 did not achieve the required ≥1.5 g/dL increase in haemoglobin from baseline to TAT and 1 of them received a transfusion. However, 2 of these 3 patients had an increase in haemoglobin of at ≥1.5 g/dL over baseline on at least one occasion that was not associated with a transfusion and also showed either a consistently or sporadically normalized bilirubin with the level above ULN at TAT. The third patient also demonstrated improvement in haemolysis but only achieved a maximum increase in haemoglobin of 1.1 g/dL on one occasion during Part A.

An additional 3 patients were excluded from the primary endpoint analysis because they discontinued early due to TEAEs, including one patient who also received a prohibited CAD medication. Two of the patients who discontinued at Week 5 and Week 7, respectively, had achieved a ≥1.5 g/dL increase in haemoglobin and normalized bilirubin from Day 0 to the last dose of sutimlimab received. The third patient had a 1.2 g/dL increase in haemoglobin and a >50% reduction bilirubin from Day 0 to the last dose of sutimlimab at Week 5 and received a prohibited CAD medication after discontinuation from study treatment.

Secondary efficacy endpoints

Key secondary endpoints

The key secondary endpoints were tested using a sequential closed procedure with alpha of 0.05 for each test with the hypothetical estimand. The first analysis compared the mean change in haemoglobin from baseline to TAT for sutimlimab versus placebo. Because this was significant, the comparison was further performed with mean change from baseline in FACIT-Fatigue score at the treatment assessment timepoint.

Mean change from baseline in haemoglobin at TAT

The LS mean changes from baseline in haemoglobin to TAT were 2.66 g/dL (95% CI: 2.09 to 3.22) and 0.09 g/dL (95% CI: -0.50 to 0.68) for sutimlimab and placebo, respectively, estimated from a mixed model for repeated measures (MMRM) model using the FAS. The LS mean difference in haemoglobin between sutimlimab and placebo from baseline to the TAT was 2.56 g/dL (p<0.001; 95% CI: 1.75 to 3.38). Based on the results, there was a statistically significant difference in treatment effect on haemoglobin increase in favour of sutimlimab as compared to placebo.

Table 9. BIVV009-04 Part A: Summary of change from baseline in haemoglobin (g/dL) at TAT - Hypothetical estimand - Full Analysis Set

	Treatment Arm	
	BIVV009 (N=22)	Placebo (N=20)
Treatment Assessment Timepoint under MMRM (a)		
LS Mean change from baseline	2.66	0.09
SE	0.281	0.295
95% CI of LS Mean	2.09, 3.22	-0.50, 0.68
LS mean difference with placebo	2.56	
SE of mean difference with placebo	0.408	
95% CI for LS mean difference with placebo	1.75, 3.38	
P-value	<0.001	

NOTE: 1: Hypothetical estimand excludes any value after transfusion or prohibited medication use after Week 5.
2: Protocol prohibited CAD medications are medically adjudicated.
(a) Mixed Model for Repeated Measures (MMRM) using TOEPH covariance matrix is used with change from baseline as the dependent variable and baseline value and visits as independent variables.
Abbreviation: TOEPH = Heterogeneous Toeplitz; MMRM = mixed model for repeated measures; LS = least squares; SE = standard error.
PGM=DEVOPS/BIVV009/BIVV009_04/CSR_A/REPORT/PGM/t30_eff_sec_chg_hgb_at_tap_hypo.sas
OUT=REPORT/OUTPUT/t30_eff_sec_chg_hgb_at_tap_hypo_i.rtf (24NOV2020 18:00)

Mean change from baseline in the FACIT-Fatigue scale at TAT

The LS mean change in FACIT-Fatigue score at the TAT showed an increase of 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, estimated from an MMRM model using the Full Analysis Set. The LS mean difference in FACIT-Fatigue score between sutimlimab and placebo from baseline to TAT was 8.93 points (p<0.001; 95% CI: 4.0 to 13.85).

Table 10. BIVV009-04 Part A: Summary of change from baseline in FACIT-Fatigue score at TAT - Hypothetical Estimand - Full Analysis Set

	Treatment Arm	
	BIVV009 (N=22)	**Placebo (N=20)**
Treatment Assessment Timepoint under MMRM (a)		
LS Mean change from baseline	10.83	1.91
SE	1.685	1.771
95% CI of LS Mean	7.45, 14.22	-1.65, 5.46
LS mean difference with placebo	8.93	
SE of mean difference with placebo	2.450	
95% CI for LS mean difference with placebo	4.00, 13.85	
P-value	<0.001	

NOTE: 1: Hypothetical estimand excludes any value after transfusion or prohibited medication use after Week 5.
2: Protocol prohibited CAD medications are medically adjudicated.
(a) Mixed Model for Repeated Measures (MMRM) using TOEPH covariance matrix is used with change from baseline as the dependent variable and baseline value and visits as independent variables.
Abbreviation: TOEPH = Heterogeneous Toeplitz; MMRM = mixed model for repeated measures; LS = least squares; SE = standard error.
PGM=DEVOPS/BIVV009/BIVV009_04/CSR_A/REPORT/PGM/t34_eff_sec_chg_fac_at_tap_hypo.sas
OUT=REPORT/OUTPUT/t34_eff_sec_chg_fac_at_tap_hypo_i.rtf (24NOV2020 18:00)

Additional analyses of key secondary endpoints:

Haemoglobin

Additional analyses of mean change in haemoglobin at TAT

The *de-facto* and modified hypothetical estimand analyses of mean change in haemoglobin at the TAT (LS mean difference versus placebo 2.45 [p<0.001] and 2.56 [p<0.001], respectively) were consistent with the hypothetical estimand analysis (LS mean difference versus placebo 2.56 [p<0.001]).

Summary of change in haemoglobin by visit

Figure 6. BIVV009-04. Part A: Plot of mean haemoglobin (g/dL) (+/- SE) by visit - Observed - Full Analysis Set

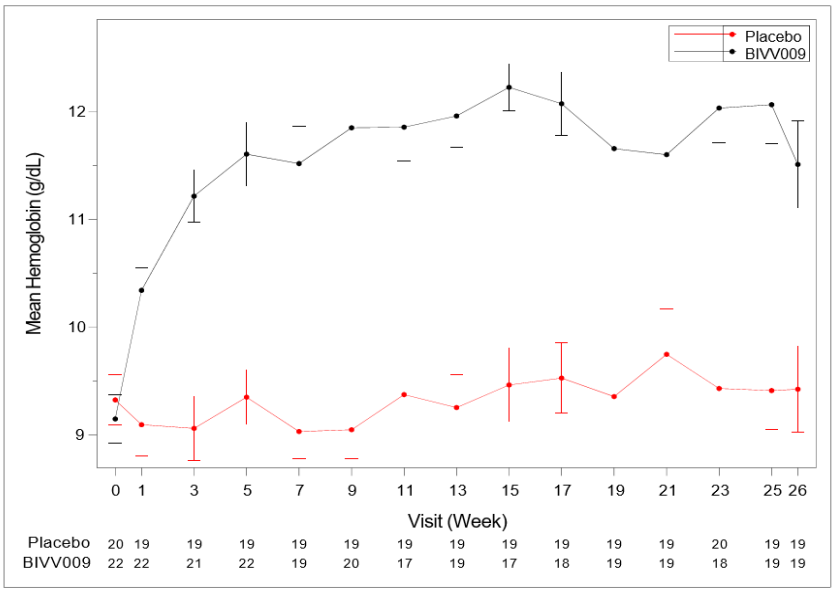


Table 11. BIVV009-04 Part A: Summary of mean change from baseline in haemoglobin by pre-specified threshold - Full Analysis Set

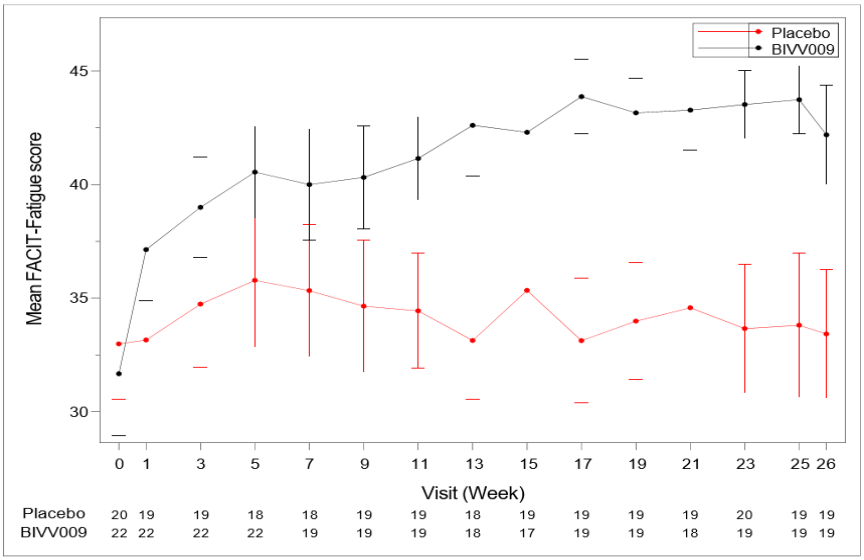
	Treatment Arm	
	BIVV009 (N=22)	**Placebo (N=20)**
Number of subjects with mean change from baseline in hemoglobin at treatment assessment timepoint		
>=1 g/dL	17 (77.3)	4 (20.0)
>=1.5 g/dL	16 (72.7)	3 (15.0)
>=2 g/dL	16 (72.7)	2 (10.0)
>=3 g/dL	6 (27.3)	1 (5.0)

NOTE: Percentages are based on the number of subjects in each treatment arm of the Full Analysis Set.
PGM=DEVOPS/BIVV009/BIVV009_04/CSR_A/REPORT/PGM/t37_lb_hgb_chg_complfl.sas
OUT=REPORT/OUTPUT/t37_lb_hgb_chg_complfl_x.rtf (24NOV2020 18:00)

FACIT-Fatigue

The *de-facto* and modified hypothetical estimand analyses of mean change in FACIT-Fatigue at the TAT (LS mean difference versus placebo 10.13 [p<0.001] and LS mean difference 11.33 [p<0.001], respectively) were consistent with the hypothetical estimand analysis (LS mean difference versus placebo 8.93 [p<0.001]).

Figure 7. BIVV009-04 Part A: Plot of mean FACIT-Fatigue score by visit - Observed - Full Analysis Set



Additional secondary endpoints

*Mean change in **bilirubin***

Normal range: 5.1 to 20.5 µmol/L. Among 17 patients in the sutimlimab group with baseline and TAT bilirubin values, the mean was 34.253 µmol/L (1.67-fold ULN) at baseline and 12.124 µmol/L (0.59-fold ULN) at the TAT, a decrease of 22.129 (SD 10.468) µmol/L. Among 18 patients in the placebo group with baseline and TAT bilirubin values, the mean was 35.778 µmol/L (1.75-fold ULN) at baseline and 33.949 µmol/L (1.65-fold ULN) at the TAT, a decrease of 1.829 (SD 13.894) µmol/L.

The mean bilirubin value in the sutimlimab group fell within the normal range, (ie, below ULN of 20.5 µmol/L) at the first post-baseline assessment (Week 1) and continued to decrease until Week 7 after which it remained relatively stable through the TAT.

*Mean change in **lactate dehydrogenase (LDH)***

Normal range: 120 to 246 U/L. Among 19 patients in the sutimlimab group with LDH data at both baseline and TAT, the baseline mean was 420.368 U/L (1.7 x ULN) and the mean at TAT was 269.535 U/L (1.1 x ULN), a decrease of 150.833 U/L (SD 160.824). Among 20 patients in the placebo group with LDH data at both baseline and TAT, the baseline mean was 380.800 U/L (1.5 x ULN) and the mean at TAT was 388.400 (1.6 x ULN), an increase of 7.600 U/L (SD 212.690). At baseline 12 (54.5%) and 13 (65.0%) patients in the sutimlimab and placebo groups, respectively, had LDH values ≤1.5 x ULN, and at the TAT, 18 (94.7%) and 14 (70.0%) patients, respectively, had LDH values ≤1.5 x ULN.

The mean decreases in LDH were observed in the sutimlimab group beginning at Week 9 that continued through Week 15 and were maintained until Week 26. In the placebo group, small fluctuations in LDH values were observed, with no overall reduction observed. Reductions in LDH observed in the sutimlimab group suggest a reduction in complement-mediated intravascular haemolysis.

*Incidence of solicited **symptomatic anaemia** at end of treatment*

In the sutimlimab group, the incidence of anaemia symptoms decreased from baseline to Week 26 for all individual components: fatigue (from 77.3% to 31.6%); weakness (from 63.6% to 5.3%), shortness of breath (from 50% to 5.3%); palpitations (from 27.3% to 0%); lightheadedness (from

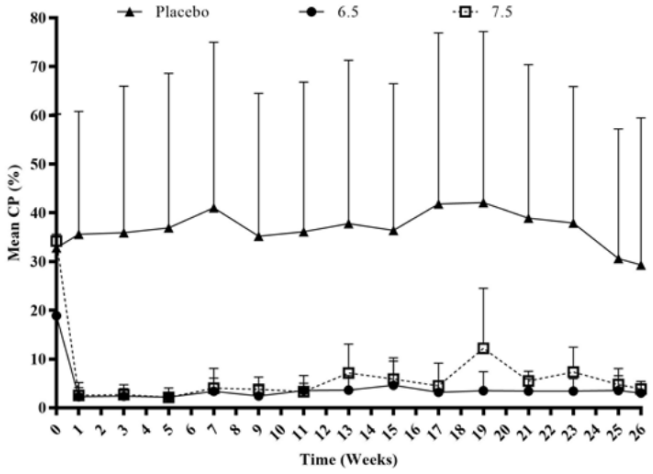
13.6% to 5.3%); and chest pain (13.6% to 0%). In the placebo group, the incidence of anaemia symptoms decreased from baseline to Week 26 for weakness (from 50.0% to 31.6%) and shortness of breath (from 60.0% to 36.8%) and remained relatively stable for the remaining components including fatigue (from 75.0% to 68.4%); lightheadedness (from 10.0% to 15.8%); palpitations (from 20.0% to 15.8%); and chest pain (from 5.0% to 5.3%).

Pharmacodynamic results

Classical pathway activity

Mean ± SD CP (group) activity at baseline was 18.847% ±16.651 (6.5 g sutimlimab), 34.300% ±26.073% (7.5 g sutimlimab), and 32.761% ±27.361% (placebo), which was low due to the nature of the disease. After the first dose of sutimlimab, the mean ± SD CP activity decreased to 0.794% ±0.837% (6.5 g) and 0.820% ±0.847% (7.5 g) in the sutimlimab group, whereas the level remained comparable to baseline in the placebo group (33.126% ±26.787%).

Figure 8. BIVV009-04 Part A: Mean CP (+SD) activity (predose) by visit - Observed - PD Analysis Set



Abbreviation: SD = standard deviation
PGM=DEVOPS/BIVV009/BIVV009_04/CSR_A/REPORT/PGM/f_mean_cp_byvisit.sas
OUT=REPORT/OUTPUT/f_mean_cp_byvisit_x.rtf (04FEB2021 15:03)

CH50

The CH50 normal range in serum is between 31.6 and 57.6 U/mL. Mean ± SD CH50 levels were 12.529 ±13.721 U/mL (6.5 g), 22.200 ±20.303 U/mL (7.5 g), and 20.750 ±19.936 U/mL (placebo) at baseline. The low CH50 values at baseline indicate low level of total complement activity, which is consistent with consumption of CP components due to ongoing overactivation of the CP by the auto-antibodies causing the disease. After the first dose of sutimlimab and throughout the treatment period, the mean value of CH50 for the 6.5 g and 7.5 g sutimlimab dose groups was below limit of quantification, whereas the mean ± SD values and in placebo group ranged from 15.889 ±17.435 to 23.889 ±20.355 U/mL.

Total C4

The SI reference range for serum C4 is 0.18 to 0.45 g/L. Blockade of C1s by sutimlimab increased circulating levels of C4 several-fold in patients, providing an in vivo readout of sutimlimab activity. The mean ± SD pre-treatment value, 0.051 ±0.044 g/L (6.5 g sutimlimab) and 0.082 ±0.065 g/L (7.5 g sutimlimab), was quickly restored to normal range. Mean ± SD predose C4 levels 1 week after the first dose were 0.227 ±0.061 g/L (6.5 g) and 0.262 ±0.069 g/L (7.5 g). These values remained within

normal range throughout 26 weeks of treatment. The mean ± SD C4 levels were unchanged, remaining low in the placebo group from baseline (0.071 ±0.070 g/L) throughout the treatment period (0.058 ±0.055 to 0.081 ±0.080 g/L).

C1q

C1q levels generally remained unchanged through the treatment period. The mean ± SD values at baseline were 78499.779 ±20816.769 ng/mL (6.5 g sutimlimab), 81971.412 ±11046.165 ng/mL (7.5 g sutimlimab), and 76653.634 ±26819.620 ng/mL (placebo), and at Week 26 predose values were 72226.034 ±19300.232 ng/mL (6.5 g sutimlimab), 71780.029 ±13571.965 ng/mL (7.5 g sutimlimab), and 68961.527 ±27837.948 ng/mL (placebo). Sutimlimab did not alter levels of C1q, indicating that the C1q-mediated pro-phagocytic "housekeeping" functions of the complement system, including removal of apoptotic cells, were not impacted.

C1s

Total C1s levels were measured in this study by a LC-MS/MS assay, in contrast to the free C1s quantitation from previous Phase 1 studies. The pre-treatment mean ± SD values were 39.144 ±10.845 µg/mL (6.5 g), 40.180 ±2.278 µg/mL (7.5 g), and 37.957 ±11.800 µg/mL (placebo). At Week 26, mean ± SD values in the sutimlimab groups increased to 53.467 ±14.395 µg/mL (6.5 g) and 55.300 ±4.844 µg/mL (7.5 g) µg/mL, whereas the mean level in the placebo group was decreased relative to baseline (31.788 ±10.577 µg/mL). The C1s data support that sutimlimab slowed the clearance of the drug target. The accumulation of drug target due to mAb presence has been observed with a number of therapeutic antibodies including C5 inhibitors.

Ancillary analyses

Sensitivity analyses

To evaluate the robustness of the primary analysis results, 3 sensitivity analyses were performed with different analysis populations. Consistent with the primary analysis, all 3 of the sensitivity analyses were statistically significant with odds ratios of 13.69 (p=0.001), 24.82 (p<0.001), and 14.93 (p<0.001), respectively.

Table 12. BIVV009-04 Summary of primary endpoint sensitivity analyses

Analysis	Estimand	Analysis population in estimand	Patients Meeting Primary Response Criteria n/N (%) BIVV009	Patients Meeting Primary Response Criteria n/N (%) Placebo	Odds ratio for BIVV009 versus placebo (95% CI) [a]	p-value
Sensitivity analysis 1	Modified composite	Patients in the FAS who did not miss visits or discontinue early due to COVID-19 (Modified FAS)	15/21 (71.4%)	3/18 (16.7%)	13.69 (2.43, 77.03)	0.001
Sensitivity analysis 2	Completer	All patients in the FAS who completed treatment at least through Week 23 and have at least 1 evaluable Hgb from Week 23, 25, and 26 (Completer Set)	16/19 (84.2%)	3/20 (15.0%)	24.82 (3.75, 164.42)	<0.001
Sensitivity analysis 3	Per-protocol	All patients in the FAS who did not have any important protocol deviations (Per-protocol Set)	15/20 (75.0%)	3/19 (15.8%)	14.93 (2.81, 79.29)	<0.001

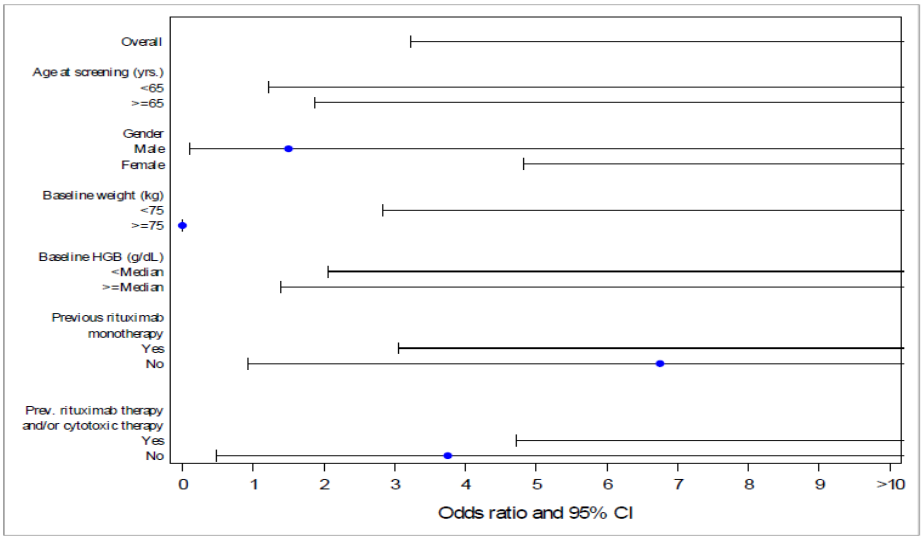
COVID=coronavirus disease; FAS=Full Analysis Set; Hgb=hemoglobin
a Stratified by baseline hemoglobin (< median vs >=median) and geographic region (Asia/Other, North America, and Europe).
Source: 16-2-6-eff-response-data [16.2.6.4], [16.2.6.5], [16.2.6.6]

Subgroup analyses

The robustness of sutimlimab's treatment effect has been evaluated in subgroup analysis. All the odds ratios in the subgroups with the exception of baseline weight ≥75kg are greater than 1, suggesting a consistent treatment effect in favour of sutimlimab over placebo. In particular, among patients who were previously treated with rituximab, 10 out of 12 patients in the sutimlimab arm met the primary composite response criteria and 1 out of 13 patients in the placebo arm met this criterion. The odds ratio for sutimlimab compared with placebo is 60.00 (95% CI: 4.72 to 763.01). There were no

responders among patients in the placebo group within the baseline weight ≥75 kg subgroup; thus, it was not possible to estimate the odds ratio for this subgroup. However, among patients with a body weight of 75 kg or more, there were 3/5 (60%; 95% CI 14.7%, 94.7%) responders; among those with a body weight < 75 kg, there were 13/17 (76.5%; 95% CI 50.1%, 93.2%) responders.

Figure 9. BIVV009-04 Part A: Forest plot of difference in treatment response and 95% CI by subgroups Composite estimand



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OUT=REPORT/OUTPUT/f1_eff_pri_subgrp_compest_forest_i.rtf (24NOV2020 18:59)

Post hoc sensitivity analyses

Three post hoc sensitivity analyses were performed for the primary endpoint and the following secondary endpoints, mean changes in haemoglobin and FACIT-Fatigue from baseline to TAT without the 2 patients in the placebo group who inadvertently received a single dose of sutimlimab. The results of the analyses were consistent with the primary and main secondary endpoint analyses including these 2 patients.

BIVV009-04 Part B

Open-label, multicenter extension study enrolling patients who completed Part A of study BIVV009-04. The primary objective of Part B is to evaluate the long-term safety and tolerability of sutimlimab in patients with primary CAD. The secondary objective is to investigate the durability of response during long-term treatment. Treatment/follow-up duration: 1 year following last patient out under Part A with 9 weeks follow-up visit after last study drug administration.

Beyond the permitted concomitant medications, study drug, and transfusions (*same criteria as for Part A)*, patients were not supposed to receive other therapies for the treatment of CAD while enrolled. Samples for safety and efficacy measures were collected every 2 weeks; PK and PD samples as well as antidrug antibodies were collected approximately every 3 months.

Efficacy endpoints included the following parameters of disease activity: • Haemoglobin • Bilirubin (total) • QOL assessments (FACIT-fatigue, EQ-5D-5L, SF-12, PGIS, and PGIC) • LDH • Transfusion requirements • Haptoglobin • Total healthcare resource utilization at EOT • Satisfaction with home infusion after first home infusion and after fourth home infusion will be assessed in patients with home infusion.

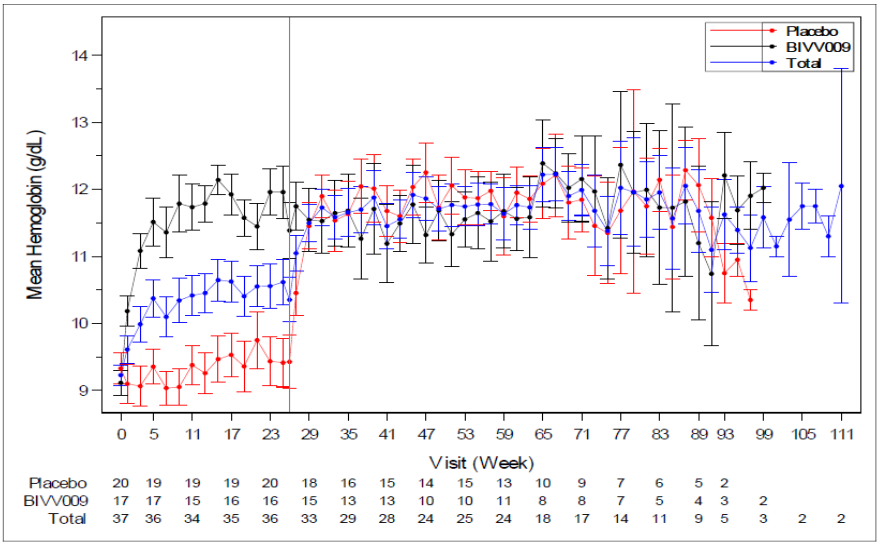
Results

Interim results based on a cut-off date of 29 September 2020 have been provided. A total of 37 patients enrolled from Part A (17 from the sutimlimab group and 20 from the placebo group). As of the cut-off date, 33 (89.2%) patients were ongoing in Part B, including 15 and 18 from the ex-sutimlimab and ex-placebo groups, respectively. Two (11.8%) from the ex sutimlimab and 2 (10.0%) from the ex-placebo group discontinued Part B early, three due to lack of efficacy and one due to withdrawal of consent. In median, patients received 45.1 weeks of sutimlimab treatment during part B and 14 (37.8%) patients received at least 52 weeks of sutimlimab treatment during Part B. For combined Parts A and B, median duration of sutimlimab treatment was 67.98 weeks (range 28.3 to 123.1) for the ex-sutimlimab group and 41.67 weeks (range 3.0 to 86.0) for the ex-placebo group as of the cut-off date.

Change in haemoglobin levels

Mean increases in haemoglobin observed for patients who switched from placebo in Part A to open-label sutimlimab in Part B were similar to those observed for sutimlimab-treated patients upon initiation of Part A. Beginning at Week 29 (third week in Part B) the mean level of haemoglobin in the ex-placebo group reached the level observed in ex sutimlimab group, and was maintained at comparable level for both groups in Part B through the cut-off date.

Figure 10. Plot of mean haemoglobin (g/dL) (+/- SE) by visit - Full Analysis Set (BIVV009-04 Parts A and B)

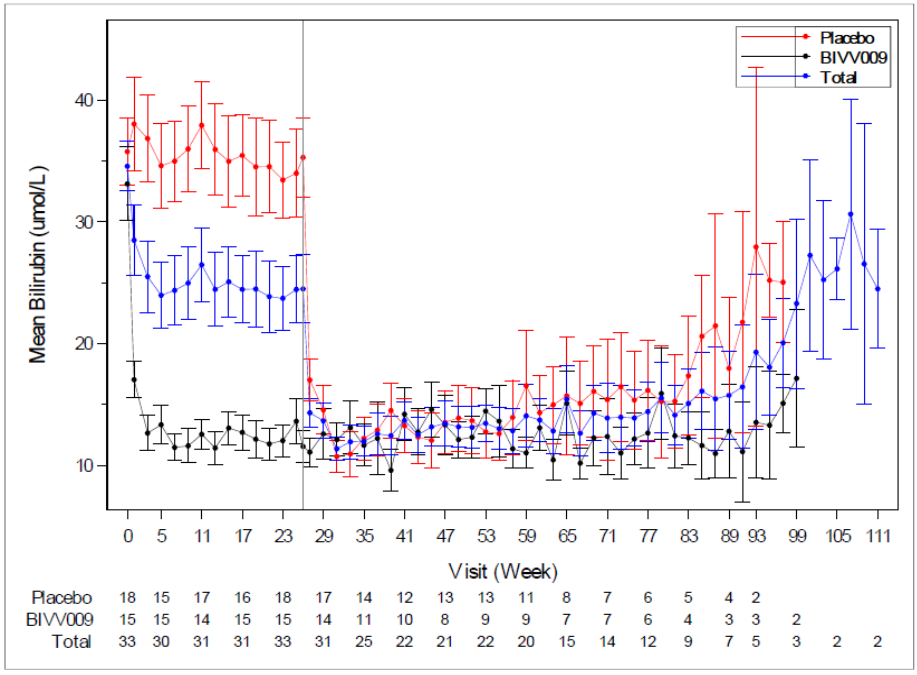


NOTE: Data cutoff date for BIVV009-04 is 29 September 2020. Abbreviation: SE = standard error. Only data based on n >=2 are presented at each visit.
PGM=DEVOPS/BIVV009/BIVV009_04/INTERIM_B_2020/REPORT/PGM/f1_mean_hgb_byvisit.sas
OUT=REPORT/OUTPUT/f1_mean_hgb_byvisit_i.rtf (01DEC2020 19:15)

Change in bilirubin levels

Mean decreases in bilirubin observed for patients who switched from placebo in Part A to open-label sutimlimab were similar to those observed for sutimlimab-treated patients upon initiation of Part A. At Week 27, after first dose of open-label sutimlimab, mean decrease in bilirubin in the ex-placebo group was almost as high as in the ex sutimlimab group. The mean decreases in bilirubin were overall maintained in Part B through the cut-off date.

Figure 11. Plot of mean bilirubin (umol/L) (+/- SE) by visit (excluding subjects with positive or unknown Gilbert's syndrome) - Full Analysis Set (BIVV009-04 Parts A and B)



NOTE: Data cutoff date for BIVV009-04 Part B is 29 September 2020. Laboratory results reported as <x are considered as x for this summary. Abbreviation: SE = standard error. Only data based on n >=2 are presented at each visit.
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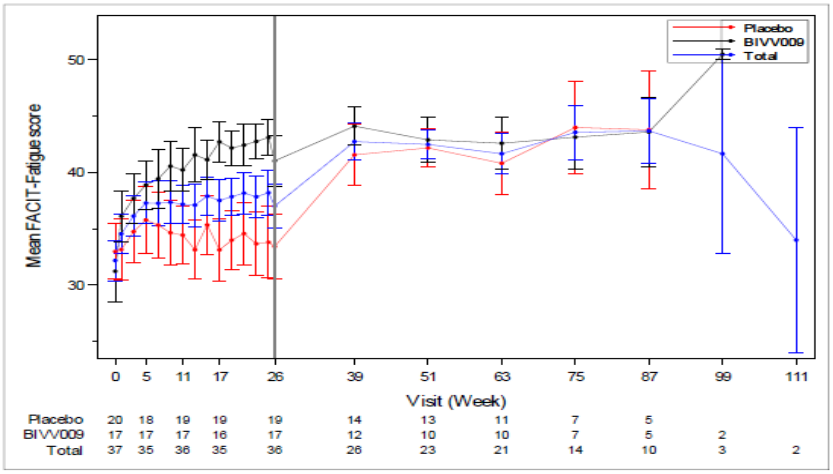
OUT=REPORT/OUTPUT/f3_mean_bili_byvisit_excl_gilb_i.rtf (01DEC2020 19:15)

Change in FACIT-F

Figure 12. Plot of mean FACIT-Fatigue score by visit (+/- SE) - Full Analysis Set (BIVV009-04 Parts A and B)



NOTE: Data cutoff date for BIVV009-04 is 29 September 2020. Abbreviation: SE = standard error. Only data based on n >=2 are presented at each visit.
PGM=DEVOPS/BIVV009/BIVV009_04/INTERIM_B_2020/REPORT/PGM/f2_mean_facit_byvisit.sas
OUT=REPORT/OUTPUT/f2_mean_facit_byvisit_i.rtf (01DEC2020 19:15)

Change in LDH

At Week 26 (end of Part A), the mean change in LDH was -141 U/L in the sutimlimab arm and 26 U/L in the placebo arm. In the ex-sutimlimab arm, who continued with sutimlimab during part B, considerable fluctuations in LDH are noted. The mean and median LDH at week 26 was 285 U/L and

221 U/L respectively based on those 17 subjects who continued into part B. During part B (including data based on N>/=2), mean LDH varied from 218 U/L (week 89) to 488 U/L (week 37). In the ex-placebo group who switched to sutimlimab during part B, there was no or little effect on LDH, again however with some fluctuations. Mean and median LDH at week 26 was 418 and 317 U/L respectively (N = 18). During part B (including data based on N>/=2), mean LDH varied from 296 U/L (week 45) to 584 U/L (week 93).

Change in haptoglobin

The mean baseline value of haptoglobin for the combined group was 0.20 g/L. Of note, haptoglobin levels <0.2 g/L were imputed as 0.2 g/L. At Week 26 (end of Part A) the mean increase was 0.32 g/L in the sutimlimab arm and 0.05 g/L in the placebo arm. For the remainder of Part B, prior to data cut-off, the summary of changes from baseline in haptoglobin by visit showed an increase of variable extent at different time points.

Transfusions

In Part B prior 7 patients received a minimum of 1 transfusion (range of 1.0 to 27.0 transfusions per patient), including 2 patients, who were free of transfusions during Part A and received a transfusion during Part B.

BIVV009-03 (CARDINAL) Part A

"Cardinal": A Phase 3 open-label, single-arm multicentre study to assess the efficacy, safety and tolerability of sutimlimab in patients with primary cold agglutinin disease who have a recent history of blood transfusion (Part A). Part B was ongoing at the time of submission and will evaluate the long-term safety, tolerability and durability of response of sutimlimab in patients with CAD. For Part A, diagnosis and eligibility was confirmed during a 6-week screening/observation period, followed by a 26-week treatment period.

Methods

Study Participants

Inclusion criteria

Among important inclusion criteria were:

- Adult male and female patients ≥18 years of age at Screening.
- Body weight of ≥39 kg at Screening.
- Confirmed diagnosis of primary CAD based on the following criteria:
    - Chronic haemolysis
    - Polyspecific direct antiglobulin test (DAT) positive
    - Monospecific DAT strongly positive for C3d
    - Cold agglutinin titre ≥64 at 4°C
    - IgG DAT ≤1+
    - No overt malignant disease
- History of at least 1 documented blood transfusion within 6 months of enrolment.
- Haemoglobin level ≤10.0 g/dL.
- Bilirubin level above the normal reference range, including patients with Gilbert's syndrome
- Ferritin levels above the lower limit of normal. Concurrent treatment with iron supplementation was permitted if the patient had been on a stable dose during the previous 4 weeks.

- Presence of 1 or more of the following CAD-related signs or symptoms within 3 months of Screening:
    - Symptomatic anaemia, defined as:
        - Fatigue
        - Weakness
        - Shortness of breath
        - Palpitations or fast heartbeat
        - Light headedness, and/or
        - Chest pain
    - Acrocyanosis
    - Raynaud's syndrome
    - Haemoglobinuria
    - Disabling circulatory symptoms
    - Major adverse vascular event (including thrombosis)
- Bone marrow biopsy within 6 months of Screening, with no overt evidence of lymphoproliferative disease or other haematological malignancy. An additional bone marrow biopsy was required if the prior bone marrow was deemed unsuitable for analysis by the Sponsor.
- Documented vaccinations against encapsulated bacterial pathogens (eg, Neisseria meningitidis, including serogroup B meningococcus, where available; Haemophilus influenzae, and Streptococcus pneumoniae) within 5 years of enrolment or as specified in the protocol.
- If female, must be post-menopausal, surgically sterile, or be established on (≥3 months prior to Screening) and agree to continue to use the same highly effective methods of birth control throughout the study and for 9 weeks following administration of the last dose of study drug. 13. Males must be surgically sterile for at least 90 days or, when sexually active with female partners of childbearing potential, will agree to use highly effective contraception from Day 0 until 9 weeks following administration of the last dose of study drug.

Exclusion criteria

Among important exclusion criteria were:

Cold agglutinin syndrome secondary to infection, rheumatologic disease, or active hematologic malignancy.

Clinically relevant infection of any kind within the month preceding enrolment (eg, active hepatitis C, or pneumonia).

Clinical diagnosis of SLE or other autoimmune disorders with anti-nuclear antibodies atScreening. *Anti-nuclear antibodies of long-standing duration without associated clinicalsymptoms were adjudicated on a case-by-case basis during the Confirmatory Review of Patient Eligibility*

Positive hepatitis panel (including hepatitis B surface antigen and/or hepatitis C virusantibody) prior to or at Screening.

Positive human immunodeficiency virus (HIV) antibody at Screening.

Treatment with rituximab monotherapy within 3 months or rituximab combinationtherapies (eg, with bendamustine, fludarabine, ibrutinib, or cytotoxic drugs) within 6 months prior to enrolment.

Concurrent treatment with corticosteroids other than a stable daily dose equivalent to ≤10 mg/day prednisone for the previous 3 months.

Erythropoietin deficiency. Concurrent treatment with erythropoietin was permitted if thepatient had been on a stable dose for the previous 3 months.

Concurrent usage of iron supplementation, unless the patient had been on a stable dose forat least 4 weeks.

Females who were pregnant, lactating, or, if having reproductive potential, considered potentially unreliable with respect to contraceptive practice.

Treatments

Patients received fixed doses of sutimlimab via approximately 60 minutes IV infusion of either 6.5 g (if <75 kg) or 7.5 g (if ≥75 kg) on Day 0, Day 7, and every 14 days thereafter through Week 25. Patients with underlying cardiopulmonary disease could receive a 2-hour infusion. Patients who missed a dose (ie, outside the dosing window or >17 days since the last dose) were to receive an additional loading dose.

Other treatments

Treatment with rituximab monotherapy within 3 months of enrolment or rituximab combination therapies (e.g., with bendamustine, fludarabine, ibrutinib, or cytotoxic drugs) were prohibited within 6 months of enrolment as well as during the study.

During Part A, patients were not to take any prescription or over-the-counter medications/products until completion of the follow-up assessments, unless prescribed by the Investigator or another physician for the treatment of an AE. Concurrent administration of erythropoietin and/or a daily dose of corticosteroids (equivalent to ≤10 mg/day of prednisone) was acceptable, provided the patient had been on a stable dose during the previous 3 months. Concurrent use of vitamin B12, folate, and iron supplementation was acceptable, provided the patient had been on a stable dose during the previous 4 weeks.

Patients who met the transfusion criteria during the 6-month treatment period were to receive a RBC transfusion.

Transfusion criteria

• The haemoglobin level was <9 g/dL, and the patient was symptomatic.

• The haemoglobin level was <7 g/dL, and the patient was asymptomatic.

Objectives

The primary objective of Part A was to determine whether sutimlimab administration resulted in a ≥2 g/dL increase in haemoglobin levels or increases haemoglobin 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.

Outcomes/endpoints

Primary efficacy endpoint

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 haemoglobin level must have met either of the following criteria:

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

For analysis of primary efficacy endpoint, see Statistical methods below.

Secondary efficacy endpoints

The secondary efficacy endpoints for Part A were:

- 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 haemoglobin at the treatment assessment endpoint.

Sample size

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

Randomisation and blinding (masking)

N/A (open-label study)

Statistical methods

For the purposes of regulatory submission, an interim analysis of safety and efficacy data will be performed for Part A after all patients have completed Part A. Parts A and B will have separate database locks to enable submission of the BLA/MAA following completion of Part A.

Analysis populations

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.

The **Per-Protocol (PP)** population was defined as a subset of FAS who did not have any important protocol deviations impacting their efficacy assessments. Selected efficacy endpoints were analyzed for the PP population.

Patients who received at least 1 dose (including partial dose) of study drug were included in the **Safety Analysis Set**. Note that the Safety Analysis Set was the same as the FAS in this study.

Patients who received at least 1 dose of study drug and had at least 1 evaluable sample for baseline and PK concentrations were included in **PK Analysis Set**.

All patients who received at least 1 dose of study drug and had at least 1 evaluable sample for baseline and PD analyses during Part A were included in the **PD analysis set**.

Analyses of efficacy endpoints

Each patient in the FAS population was classified as meeting the criteria of the primary endpoint (responder) or not meeting the criteria of the primary endpoint (non-responder) and the 95% CI for the proportion of responders was calculated using Clopper-Pearson exact method.

Primary endpoint criteria: A patient was considered a responder in Part A 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 is permitted per protocol. Additionally, the patient's haemoglobin level must have met either of the following criteria:

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

Any patient withdrawing from the study prior to the Week 23 visit was considered a nonresponder. To assess the hematology component of response, the mean of the nonmissing haemoglobin 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 nonresponder. With the determination that a response rate ≤30% was 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.

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

All secondary efficacy endpoints (change from baseline in haemoglobin, 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 where any post-baseline value after transfusion and prohibited medication (from Week 5 to Week 26) is considered missing and the De-facto Estimand where all available data is used, respectively. Additional sensitivity analyses were carried out using multiple imputations.

Results

Participant flow

Table 13 Part A; summary of disposition – All subjects

	Dose cohort		
	6.5g (N=17)	7.5g (N=7)	Total (N=24)
Number of subjects			
Screened			42
Safety Analysis Set (a)	17 (100.0%)	7 (100.0%)	24 (100.0%)
Full Analysis Set (b)	17 (100.0%)	7 (100.0%)	24 (100.0%)
Per-protocol Set (c)	16 (94.1%)	6 (85.7%)	22 (91.7%)
PK Analysis Set (d)	17 (100.0%)	7 (100.0%)	24 (100.0%)
PD Analysis Set (e)	17 (100.0%)	7 (100.0%)	24 (100.0%)
Completion status			
Completed Part A (f)	16 (94.1%)	6 (85.7%)	22 (91.7%)
Discontinued Part A early (g)	1 (5.9%)	1 (14.3%)	2 (8.3%)
Adverse event (h)	1 (5.9%)	0	1 (4.2%)
Lost to follow up	0	0	0
Consent withdrawn	0	0	0
Investigator decision	0	0	0
Death	0	1 (14.3%)	1 (4.2%)
	Dose cohort		
	6.5g (N=17)	7.5g (N=7)	Total (N=24)
Lack of efficacy	0	0	0
Other	0	0	0
Continued into Part B	16 (94.1%)	6 (85.7%)	22 (91.7%)

NOTE: Percentages are based on the number of subjects in each dose cohort (or total) of the Safety Analysis Set.
(a) Safety Analysis Set is defined as all subjects who received at least 1 dose (including partial dose) of study drug.
(b) Full Analysis Set (FAS) is defined as all subjects who received at least 1 dose (including partial dose) of study drug.
(c) Per-protocol Set is defined as a subset of FAS who do not have any important protocol deviations impacting their efficacy assessments. Important protocol deviations are adjudicated.
(d) PK Analysis Set is defined as all subjects who received at least 1 dose of study drug and have evaluable PK concentrations.
(e) PD Analysis Set is defined as all subjects who received at least 1 dose of study drug and have at least 1 evaluable PD sample.
(f) Completed Part A means subjects did not discontinue prior to the Week 26 Visit in Part A.
(g) Discontinued Part A early means subjects terminated participation in Part A prematurely for any reason.
(h) Both treatment emergent or non-treatment emergent adverse events are included.

Recruitment

Study Initiation Date (first patient enrolled): 5 March 2018. Study Completion Date (last patient completed): 11 July 2019 (Part A). A total of 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.

Conduct of the study

There were 5 global amendments and 5 country-specific amendments. Overall, the study amendments are not considered to affect the study integrity.

Baseline data

Table 14 BIVV009-03 Part A: Summary of demographics and baseline characteristics (FAS)

	Dose cohort		
	6.5 g (N=17)	**7.5 g (N=7)**	**Total (N=24)**
Age (years)			
n	17	7	24
Mean	71.8	70.1	71.3
SD	9.05	6.01	8.18
Median	72.0	70.0	71.5
Min, Max	55, 85	63, 77	55, 85
<65	3 (17.6%)	2 (28.6%)	5 (20.8%)
>=65	14 (82.4%)	5 (71.4%)	19 (79.2%)
Sex			
n	17	7	24
Female	11 (64.7%)	4 (57.1%)	15 (62.5%)
Male	6 (35.3%)	3 (42.9%)	9 (37.5%)
Race			
n	17	7	24
Asian	3 (17.6%)	0	3 (12.5%)
White	2 (11.8%)	1 (14.3%)	3 (12.5%)
Black or African American	0	0	0
American Indian or Alaska Native	0	0	0
Native Hawaiian or other Pacific Islander	0	0	0
Other	0	0	0
Not collected	12 (70.6%)	6 (85.7%)	18 (75.0%)
Ethnicity			
n	17	7	24
Hispanic/Latino	0	0	0
Not Hispanic or Latino	5 (29.4%)	1 (14.3%)	6 (25.0%)
Not collected	12 (70.6%)	6 (85.7%)	18 (75.0%)
Geographic Location (a)			
n	17	7	24
Europe	12 (70.6%)	5 (71.4%)	17 (70.8%)
North America	2 (11.8%)	1 (14.3%)	3 (12.5%)
Asia	3 (17.6%)	0	3 (12.5%)
Other	0	1 (14.3%)	1 (4.2%)
Height (cm) (b)			
n	17	7	24
Mean	163.5	172.7	166.2
SD	8.53	9.50	9.61
Median	164.0	169.0	166.5
Min, Max	146, 175	164, 187	146, 187
Weight (kg) (b)			
n	17	7	24
Mean	60.2	86.1	67.8
SD	9.55	12.46	15.78
Median	61.0	82.5	66.5
Min, Max	40, 72	76, 112	40, 112

<75	17 (100.0%)	0	17 (70.8%)
>=75	0	7 (100.0%)	7 (29.2%)
BMI (kg/m^2)			
n	17	7	24
Mean	22.455	28.911	24.338
SD	2.8614	3.4265	4.2124
Median	22.860	28.890	23.685
Min, Max	17.31, 25.96	23.46, 33.06	17.31, 33.06

NOTE: 1: Age = year of informed consent – year of birth.

2: Percentages are based on the number of subjects with non-missing data in each dose cohort (or total) of the Full Analysis Set.3: Baseline is defined as the last non-missing value prior to the first administration of study drug.

(a) Europe includes France, Germany, Italy, Norway and the United Kingdom. North America includes the United States. Asia includes Japan. Other includes Australia.

(b) Height and Weight at Baseline

PGM=t-dm-bl-char.sas OUT=/sasdata/bivv009/bivv009-03/csr_a/dev/t-dm-bl-char_i.rtf (14OCT2019 15:44)

Baseline disease characteristics

Of the 24 subjects in the FAS, 16 (66.7%) had any hospitalization related to CAD within the last 2 years. None had a prior haematological malignancy and 8/24 subjects had a prior thromboembolic event, primarily venous (5 events of pulmonary embolism, 2 of deep vein thrombosis).

At baseline, median haemoglobin was 8.65 g/dL (range 4.9 to 11.1; normal range determined by local laboratory at site), bilirubin was 45.85 µmol/L (range 16.1 to 112.4; normal range 5.1 to 20.5), LDH was 325 U/L (range 160 to 1040; normal range 120 to 246), haptoglobin was 0.2 g/L (range 0.2 to 1.6; normal range 0.4 to 2.4 [note that values <0.2 g/L were imputed as 0.2 g/L]); and absolute reticulocytes were 115.7 × 109/L (range 27.7 to 301.0; normal range determined by local laboratory). A total of 15 (62.5%) patients had received prior CAD therapy within the last 5 years, including corticosteroids (10/24), single agent therapy with rituximab (12/24) or ibrutinib (1/24), combinations regimens (6/24, most frequently bendamustine/rituximab), or other chemotherapy (5/24). One patient had been treated with plasmapheresis.

Fatigue was reported by 22/22 who had data available at day -42 and 18/24 at baseline. **Weakness** was reported by 18/22 at day -42 and 15/24 at baseline. **Shortness of breath** was reported by 17/22 at day -42 and 13/24 at baseline. **Palpitations/fast heartbeat** was reported by 11/22 at day -42 and 7/24 at baseline. **Light-headedness/presyncope** was reported by 3/22 at day -42 and 0/24 at baseline. **Chest pain** was reported by 3/22 at day -42 and 0/24 at baseline. **Acrocyanosis** was reported by 5/22 at day -42 and 3/24 at baseline. **Raynaud's syndrome** was reported by 3/22 at day -42 and 1/24 at baseline. **Haemoglobinuria** was reported by 8/22 at day -42 and 5/24 at baseline. **Disabling circulatory symptoms** was reported by 0/22 at day -42 and 2/24 at baseline. **Major adverse vascular event** including thrombosis was reported by 3/22 at day -42 and 0/24 at baseline.

<u>Transfusion history prior to and during screening</u>

Table 15. BIVV009-03 Part A: Summary of transfusion history - Full Analysis Set

	Dose cohort		
	6.5g (N=17)	7.5g (N=7)	Total (N=24)
Within the last 1 year			
Number of transfusions			
n	17	7	24
Mean	4.3	6.0	4.8
SD	5.53	7.87	6.17
Median	2.0	2.0	2.0
Min, Max	1, 21	1, 23	1, 23
0	0	0	0
1-2	10 (58.8%)	4 (57.1%)	14 (58.3%)
3-4	3 (17.6%)	0	3 (12.5%)
>4	4 (23.5%)	3 (42.9%)	7 (29.2%)
Total volume transfused (unit)			
n (a)	17	7	24
Mean	7.8	11.9	9.0
SD	11.22	14.51	12.08
Median	3.0	8.0	3.5
Min, Max	1, 42	2, 43	1, 43
Within the last 6 months			
Number of transfusions			
n	17	7	24
Mean	3.0	3.7	3.2
SD	4.33	3.15	3.97
Median	1.0	2.0	2.0
Min, Max	1, 19	1, 9	1, 19
0	0	0	0
1-2	11 (64.7%)	4 (57.1%)	15 (62.5%)
3-4	4 (23.5%)	1 (14.3%)	5 (20.8%)
>4	2 (11.8%)	2 (28.6%)	4 (16.7%)
Total volume transfused (unit)			
n (a)	17	7	24
Mean	5.4	7.9	6.1
SD	8.72	6.23	8.02
Median	2.0	8.0	3.0
Min, Max	1, 38	2, 18	1, 38

NOTE: Percentages are based on the number of subjects in each dose cohort (or total) of the Full Analysis Set.
(a) Number of subjects who had at least one transfusion.
PGM=t-sum-trf-hist.sas OUT=/sasdata/bivv009/bivv009-03/csr_a/dev/t-sum-trf-hist_i.rtf (14OCT2019 15:45)

Table 16. BIVV009-03 Part A: Summary of transfusions during screening period - Full Analysis Set

	Dose cohort		
	6.5g (N=17)	7.5g (N=7)	Total (N=24)
During screening period			
Number of transfusions			
n	17	7	24
Mean	1.4	2.3	1.7
SD	1.37	3.59	2.20
Median	1.0	0.0	1.0
Min, Max	0, 4	0, 8	0, 8
0	5 (29.4%)	4 (57.1%)	9 (37.5%)
1-2	8 (47.1%)	1 (14.3%)	9 (37.5%)
3-4	4 (23.5%)	0	4 (16.7%)
>4	0	2 (28.6%)	2 (8.3%)
Total volume transfused (unit)			
n (a)	12	3	15
Mean	3.8	9.0	4.8
SD	2.18	6.24	3.75
Median	3.0	11.0	4.0
Min, Max	2, 8	2, 14	2, 14

NOTE: Percentages are based on the number of subjects in each dose cohort (or total) of the Full Analysis Set.
(a) Number of subjects who had at least one transfusion.
PGM=t-sum-trf-scr.sas OUT=/sasdata/bivv009/bivv009-03/csr_a/dev/t-sum-trf-scr_i.rtf (14OCT2019 15:45)

Concomitant medication

The most frequently used concomitant medications were antianemic preparations (15 patients, 62.5%), drugs for acid related disorders (15, 62.5%), antithrombotic agents (14, 58.3%), analgesics (12, 50.0%), antibacterials for systemic use (9, 37.5%), vaccines (7, 29.2%), vitamins (7, 29.2%),

agents acting on the renin-angiotensin system (6, 25.0%), beta blocking agents (6, 25.0%), corticosteroids for systemic use (6, 25.0%), and diuretics (6, 25.0%). All patients had received at least one meningococcal (conjugate) vaccine, and at least one streptococcus pneumoniae vaccine in the previous 5 years or during the study. Twenty of 24 patients received at least one haemophilus influenzae vaccination in the previous 5 years or during the study; this is consistent with global variations in vaccination guidelines for patients with complement deficiency.

Numbers analysed

The FAS corresponds to the ITT and the SAS with all 24 subjects. The FAS was used for the analyses below unless otherwise stated. The Per Protocol set includes 22/24 subjects. Two subjects discontinued early: one due to adverse event and one due to death.

Outcomes and estimation

Primary efficacy endpoint: The study met the primary endpoint. Of the 24 patients in the FAS, 13 patients met the composite primary endpoint criteria and the lower bound of the response rate was >30% (54.2%, 95% CI: 32.8% to 74.4%).

Table 17. BIVV009-03 Part A: Summary of primary endpoint: treatment response - Composite estimand – Full Analysis Set

	BIVV009 (N=24)
Number of subjects responded	
Yes	13 (54.2%)
No	11 (45.8%)
95% CI for responder proportion (a)	(32.8%, 74.4%)

NOTE 1: Percentages are based on the number of subjects in the Full Analysis Set.
2: Subjects with missing response are considered as non-responders.
(a) 95% CI is calculated using the Clopper-Pearson exact method.
Abbreviation: CI = confidence interval.
PGM=t-eff-pri-trt-resp-comp-est.sas OUT=/sasdata/bivv009/bivv009-03/csr_a/dev/t-eff-pri-trt-resp-comp-est_i.rtf (14OCT2019 15:44)

Table 18. BIVV009-03 Part A: Summary of primary endpoint: components of treatment response - Full Analysis Set

Components	BIVV009 (N=24)
Subjects with either Hgb >=12 g/dL or increased >=2 g/dL from baseline at treatment assessment timepoint (a)	
Yes	15 (62.5%)
No	7 (29.2%)
Unknown	2 (8.3%)
Subjects with Hgb >=12 g/dL at treatment assessment timepoint (a)	
Yes	9 (37.5%)
No	13 (54.2%)
Unknown	2 (8.3%)
Subjects with Hgb increased >=2 g/dL from baseline at treatment assessment timepoint (a)	
Yes	15 (62.5%)
No	7 (29.2%)
Unknown	2 (8.3%)

Subjects free of transfusions during Week 5 to Week 26 (EOT) (b)	
Yes	17 (70.8%)
No	6 (25.0%)
Unknown	1 (4.2%)
Subjects receiving no protocol prohibited CAD medications during Week 5 to Week 26 (EOT) (b)	
Yes	22 (91.7%)
No	0
Unknown	2 (8.3%)
Primary endpoint (c)	
Responder	13 (54.2%)
Non-responder	10 (41.7%)
Missing	1 (4.2%)

NOTE 1: Percentages are based on the number of subjects in the Full Analysis Set.
2: Baseline is defined as the last non-missing value prior to the first administration of study drug.
3: The treatment assessment timepoint is defined as the average of the values from the Week 23, 25, and 26 visits. In the case of any missing value at any of those visits, it will be calculated as the average of the available values, unless no value is available from all three visits.
4: Protocol prohibited CAD medications are medically adjudicated.
(a) The unknown status is defined as missing Hgb value at all visits of Week 23, 25 and 26.
(b) Subjects who discontinued prior to Week 23 are considered unknown.
(c) 'Responder' if a subject meets all three components; 'Non-responder' if a subject is known to fail any components; 'Missing' if otherwise.
Abbreviation: Hgb = hemoglobin; EOT = End of treatment.
PGM=t-eff-pri-trt-response.sas OUT=/sasdata/bivv009/bivv009-03/csr_a/dev/t-eff-pri-trt-response_i.rtf (14OCT2019 15:44)

Eleven patients did not meet the primary efficacy endpoint:

- Six patients had some evidence of a response. Of these, 4 patients had an increase in Hb level ≥1 g/dL; 1 patient had an increase in Hb level ≥2 g/dL with Hb level ≥12 g/dL at the treatment assessment endpoint (TAE) with no transfusion beyond Week 15. The sixth patient had a change in Hb level from 11.0 g/dL to 11.83 g/dL at the TAE in the absence of transfusions. 4 of the 6 patients experienced normalization of their bilirubin levels that correlated with improvements in Hb levels. The reasons for not meeting the criteria for the primary endpoint in these 6 patients included transient decreases in haemolytic anaemia during Weeks 5 to 26 due to missed doses, intercurrent infection/inflammation, and variability in Hb levels with lower levels at the end of Part A.
- Two patients discontinued early: 1 patient discontinued after 2 doses due to an unrelated fatal malignancy and gastrointestinal bleeding; the other patient discontinued after 6 doses due to a pre-treatment AE, had improvement in Hb and bilirubin at Week 3, but the next dose was delayed beyond 17 days, Hb decreased, and the patient received 2 transfusions.
- Three patients did not have a response. This was determined based on decreases in Hb, bilirubin levels that did not normalize, and/or little or minimal improvement on the FACIT-Fatigue.

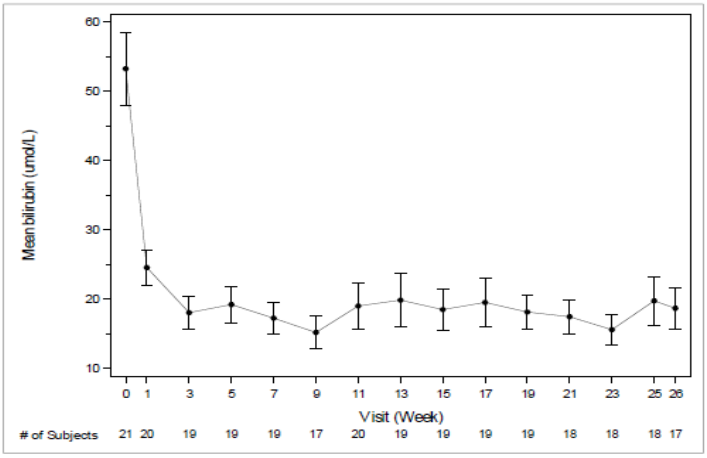
Of the 11 patients who did not meet the pre-defined criteria of the primary endpoint, all except the 2 patients who discontinued treatment Part A elected to continue sutimlimab treatment in Part B.

Secondary efficacy endpoints

In the model for hypothetical estimand which was used to assess change from baseline at the TAE, if a subject had a transfusion or received protocol prohibited medication after Week 5, their values (for the study endpoint) after the transfusion or receipt of protocol prohibited medication were considered missing, but all other available data were used in the MMRM model.

Mean change from baseline in bilirubin levels

Figure 13. BIVV009-03 Part A: Plot of mean bilirubin (umol/L) (+/- SE) by visit (excluding subjects with Gilbert's syndrome)- Observed



Note 1: Baseline (Week 0) is defined as the last non-missing value prior to the first administration of study drug.
2: Summaries are based on the Full Analysis Set excluding subjects with Gilbert's syndrome (or subjects with unknown Gilbert's syndrome test results).
Abbreviation: SE = Standard error.
PGM=f-mean-bili-byvisit-excl-gilb.sas OUT=/sasdata/bivv009/bivv009-03/csr_a/dev/f-mean-bili-byvisit-excl-gilb_i.rtf (14OCT2019 15:42)

Mean change from baseline in FACIT-F score

Among 17 patients with evaluable baseline and treatment assessment endpoint (TAE) FACIT-fatigue values, the mean score was 31.24 at baseline and 44.26 at the TAE, a mean increase of 13.03 points.

Mean change from baseline in lactate dehydrogenase

The normal range for LDH was 120-246 U/L. Among 17 patients with evaluable baseline and TAE LDH values, the mean LDH was 424.06 U/L (1.7-fold ULN) at baseline and 301.91 U/L (1.2-fold ULN) at the TAE.

Transfusions received before and after initiating sutimlimab treatment

The 24 subjects had at least one, in mean 3.2, RBC transfusions (median 2.0, range 1 to 19) during the prior 6 months. During the 6-week screening period, patients had a mean of 1.7 transfusions (median 1.0, range 0 to 8). Fifteen of the 24 patients had at least 1 transfusion.

During the first 5 weeks of sutimlimab treatment, patients had a mean of 0.3 transfusions (median 0, range 0 to 2). Five of 24 patients had at least 1 transfusion and 4 of the 5 patients had a transfusion after the first 5 weeks. Between Weeks 5 and 26, patients had a mean of 0.9 transfusions (median 0, range 0 to 13). Six of 23 patients had at least 1 transfusion.

Mean change from baseline in haemoglobin levels

Among 17 patients with evaluable baseline and treatment assessment endpoint (TAE) haemoglobin values, mean haemoglobin was 8.45 g/dL at baseline and 11.63 g/dL at the TAE. The LS mean change at the TAE was an increase of 2.60 g/dL (95% CI: 0.74 to 4.46). Mean increases in haemoglobin were observed beginning at Week 1, with a maximum increase observed at Week 7.

Haemoglobin levels after missed doses

Ten patients had dosing intervals exceeding 17 days and 6 of the patients had evidence of rebound anaemia. Four of the 6 patients had 1 occurrence of a >17-day interval between doses, including three patients who required a transfusion and one patient who had a decrease in haemoglobin level, but no transfusion. The other 2 patients each had 2 occurrences of >17-day intervals; one patient had

transfusions for both occurrences and another patient had 1 occurrence with reduced haemoglobin level and no transfusion and 1 requiring a transfusion.

Exploratory endpoints:

Quality of Life

*Mean change from baseline in **EQ-5D-5L index score***

Table 19. Summary of EQ-5D index score and change from baseline – FAS

Visit Index scores	Actual result	Change from baseline
Baseline		
n	23	
Mean	0.701	
SD	0.2330	
Median	0.768	
Min, Max	-0.03, 1.00	
Week 26		
n	16	16
Baseline mean	0.718	
Baseline median	0.790	
Mean	0.792	0.074
SD	0.1761	0.1846
Median	0.805	0.049
Min, Max	0.35, 1.00	-0.21, 0.43

NOTE: 1: Baseline is defined as the last non-missing value prior to the first administration of study drug.
2: EQ-5D index scores are calculated by applying a crosswalk link function to the individual subject responses to the EQ-5D-5L descriptive system.
PGM=t-qs-sum-index.sas OUT=/sasdata/bivv009/bivv009-03/csr_a/dev/t-qs-sum-index_i.rtf (14OCT2019 15:45)

*Mean change from baseline in **EQ-5D-5L visual analogue scale***

Table 20. Summary of EQ-5D-5L VAS and change from baseline - FAS

Visit VAS scores	Actual result	Change from baseline
Baseline		
n	23	
Mean	61.96	
SD	14.674	
Median	60.00	
Min, Max	25.0, 80.0	
Week 26		
n	16	16
Baseline mean	63.13	
Baseline median	60.00	
Mean	79.88	16.75
SD	14.431	16.902
Median	82.50	15.00
Min, Max	45.0, 98.0	-10.0, 45.0

NOTE: 1: Baseline is defined as the last non-missing value prior to the first administration of study drug.
2: The visual analogue scale records a response from 0-100 indicating a subject's overall self-rated health state. Lower scores indicate worse health states.
PGM=t-qs-sum-vas.sas OUT=/sasdata/bivv009/bivv009-03/csr_a/dev/t-qs-sum-vas_i.rtf (14OCT2019 15:45)

*Mean change from baseline in **SF-12***

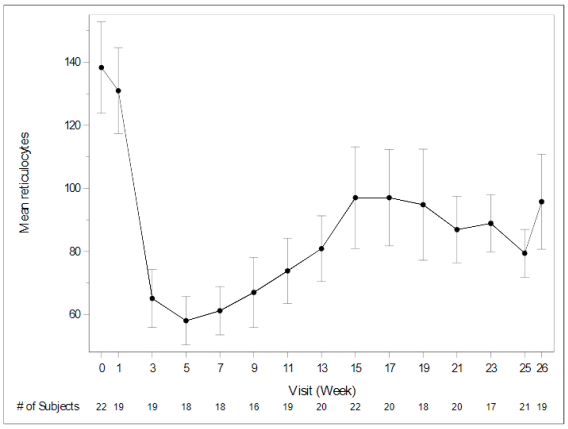
Increases in mean physical and mental component scores were observed at Week 26 (5.37 and 4.37 points, respectively). Increases in mean in SF-12 subscale scores at Week 26 for general health (5.47 points), physical functioning (6.39 points), role physical (7.14 points), and vitality (12.91 points) were observed at Week 26; other subscale scores were similar to baseline during the treatment period.

Changes in haptoglobin and reticulocyte levels

Haptoglobin: The normal range for haptoglobin was 0.4-2.4 g/L. Values <0.2 g/L were imputed as 0.2 g/L. Twenty-two patients had non-detectable haptoglobin levels (<0.2 g/L) at baseline. At Week 26, 4 of 22 patients had detectable levels at Week 26, while 15 patients still had non-detectable levels and data were missing for 3 patients. Sixteen patients had at least one detectable value through Week 26.

Reticulocytes: Among 17 patients with evaluable baseline and Week 26 absolute reticulocyte values, mean reticulocyte counts decreased by 54.92 × 109/L between baseline and Week 26. After an initial decrease in reticulocyte count was observed from Weeks 1 to 5, renormalization of absolute reticulocyte counts were observed through Week 15 to levels lower than baseline that were generally maintained through the Week 26 and appropriate for the corresponding mean haemoglobin.

Figure 14. BIVV009-03 Part A: Plot of mean reticulocytes (10^9/L) (+/- SE) by visit - Observed



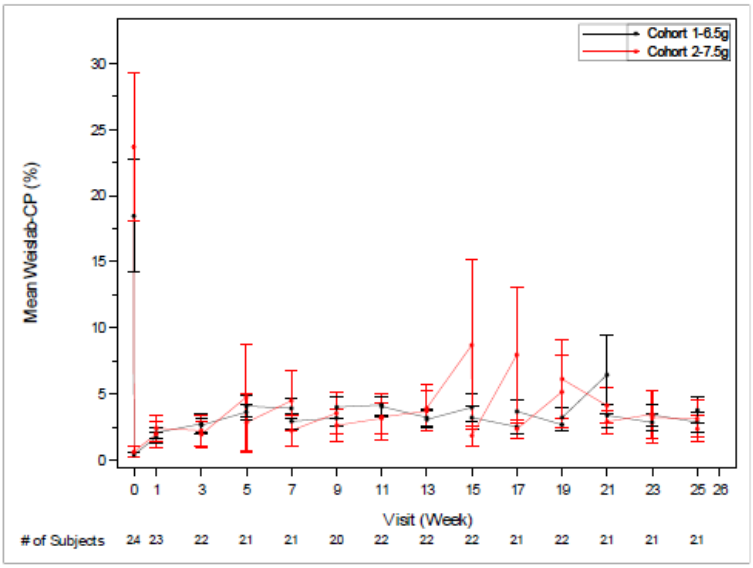
Note 1: Baseline (Week 0) is defined as the last non-missing value prior to the first administration of study drug.
Abbreviation: SE = Standard error.
PGM=f-mean-reti-byvisit.sas OUT=/sasdata/bivv009/bivv009-03/csr_a/dev/f-mean-reti-byvisit_i.rtf (14OCT2019 15:43)

Pharmacodynamic results

Classical pathway activity

The CP activities in CAD patients were low during screening and baseline, which is consistent with the nature of the disease, and supported by the suppressed levels of C4 observed in these patients prior to treatment. At baseline, the mean ± SD CP activity overall was 19.97 ± 16.69%. After the first dose of sutimlimab, the mean CP activity decreased to 0.50% ± 0.876%, which was consistent with what was observed in Phase 1 studies. The near complete inhibition of CP was sustained throughout the treatment period.

Figure 15. BIVV009-03 Part A: Plot of mean (+/-SE) Wieslab-CP (%) over time - PD Analysis Set



NOTE: Samples below the limit of quantification (BLQ) are set to zero
PGM=f-pd-cp-mean.sas OUT=/sasdata/bivv009/bivv009-03/csr_a/dev/f-pd-cp-mean_i.rtf (14OCT2019 18:50)

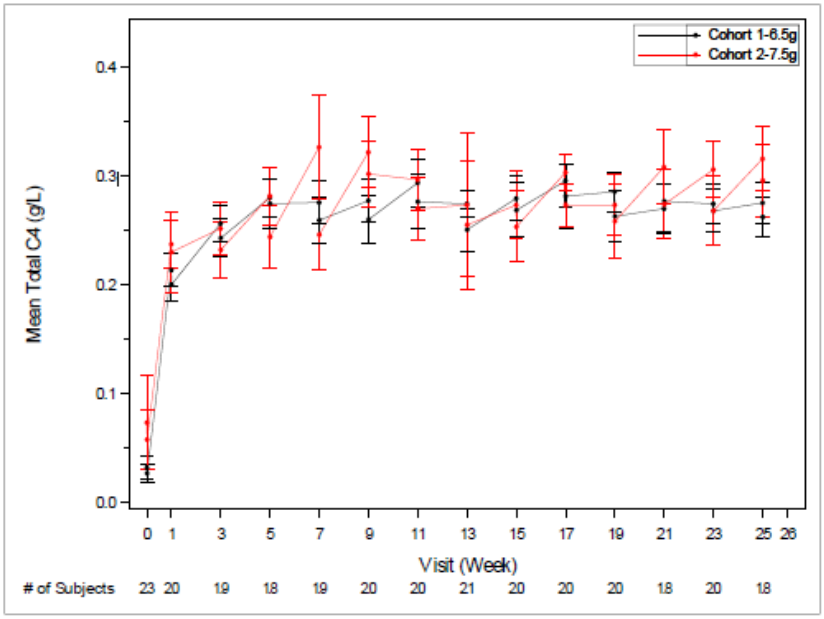
CH50

Only 11 patients had quantifiable CH50 levels at baseline (pre-treatment), of which 1 patient had quantifiable levels after the first dose of sutimlimab. The low unquantifiable CH50 levels of the remaining patients at baseline was consistent with consumption of CP components due to ongoing increased activation of the CP by the disease. In the context of the increased C4 seen after sutimlimab treatment, the data indicate that sutimlimab effectively inhibited CP activity.

Total C4

Baseline levels of C4, the first substrate cleaved following activation of C1s, were low in patients with CAD, owing to cold agglutinin–mediated classical pathway consumption. Blockade of C1s by sutimlimab increased circulating levels of C4 several-fold in patients, providing an in vivo readout of sutimlimab activity. The data showed that the mean pre-treatment value, 0.04 g/L, was quickly restored to normal range, 0.22 g/L after the first dose of sutimlimab (SI reference range 0.18- 0.45 g/L). The C4 levels remained in the normal range throughout the treatment period.

Figure 16. BIVV009-03 Part A: Plot of mean (+/-SE) total C4 (g/L) over time - PD Analysis Set



NOTE: Samples below the limit of quantification (BLQ) are set to zero
PGM=f-pd-c4-mean.sas OUT=/sasdata/bivv009/bivv009-03/csr_a/dev/f-pd-c4-mean_i.rtf (14OCT2019 18:50)

C1q

C1q levels generally remained unchanged through the treatment period with the mean ± SE at baseline 84956 ± 35723 ng/mL and 77886 ± 28302 ng/mL predose at Week 25. Sutimlimab did not alter levels of C1q, indicating that the role of C1q in the pro-phagocytic "housekeeping" functions of the complement system, including removal of apoptotic cells, were not impacted.

C1s

Total C1s levels were measured in this study, in contrast to the free C1s quantitation from previous Phase 1 studies. The pre-treatment mean ± SD, 44.23 ± 12.94 µg/mL, increased slightly to 55.15 ± 20.96 µg/mL at Week 25. The accumulation of target due to mAb on-board has been observed with therapeutic antibodies including C5 inhibitors. The C1s data support that sutimlimab slowed the clearance of the target.

Ancillary analyses

Sensitivity analyses

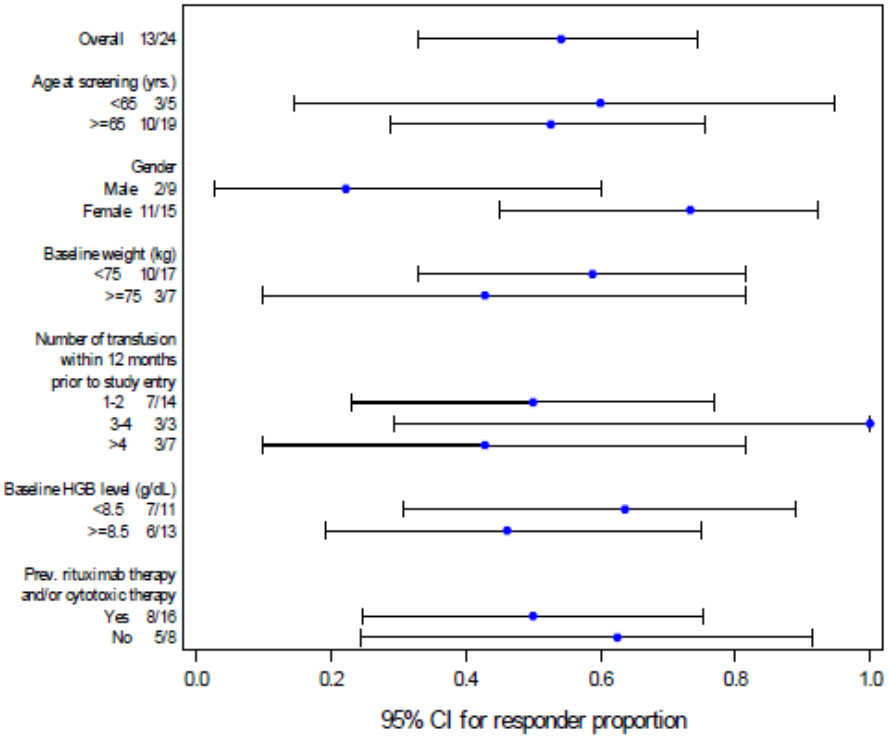
The robustness of the results was tested in 3 sensitivity analyses, which all supported the results of the primary endpoint. Consistent with the primary analysis, the lower bound of the 95% CI for the response rate was >30% in these analyses.

- Sensitivity analysis 1: In this analysis, where normalization of haemoglobin was considered a value of ≥LLN instead of ≥12 g/dL, the response rate was 58.3%, (95% CI: 36.6% to 77.9%).
- Sensitivity analysis 2: In this analysis, patients in the FAS were included if they completed treatment at least through Week 23 and had at least 1 evaluable haemoglobin value from Week 23, 25, and 26. The response rate was 59.1%, (95% CI: 36.4% to 79.3%).

- Sensitivity analysis 3: In this analysis, including patients in the PP, ie, those who did not have important protocol deviations impacting efficacy assessments, the response rate was 59.1% (95% CI: 36.4% to 79.3%).

Subgroup analyses

Figure 17. BIVV009-03 Part A: Forest plot of treatment response and 95% CI by subgroups – Composite estimand



PGM=f-eff-pri-subgrp-comp-est-forest.sas OUT=/sasdata/bivv009/bivv009-03/csr a/dev/f-eff-pri-subgrp-comp-est-forest i.rtf (14OCT2019 15:42)

BIVV009-03 Part B

Long-term extension, open-label study to assess the safety and durability of response of sutimlimab in patients with CAD who had a recent history of blood transfusions and had completed Part A of the study. IV sutimlimab doses of 6.5 g (if <75 kg) or 7.5 g (if ≥75 kg) were administered every 14 days during Part B. Treatment/follow-up duration: 2 years following last patient out under Part A with 9 weeks follow-up visit after last study drug administration.

The primary objective was to evaluate the long-term safety and tolerability of sutimlimab in CAD. The secondary objective of Part B was to investigate the durability of response during long-term treatment with sutimlimab in CAD. Exploratory objectives pertained to home infusions (not implemented) and evaluation of immunogenicity of sutimlimab. Beyond the permitted concomitant medications, study drug, and transfusions (*same criteria as for Part A)*, patients were not supposed to receive other therapies for the treatment of CAD while enrolled.

For patients who had completed Part A, haematology panel and clinical chemistry panel (including markers of haemolysis); recording of concomitant medications/procedures including transfusions was performed every 2 weeks. In addition, the following procedures of interest for efficacy were performed every 3 months: QoL assessments: FACIT-Fatigue, EQ-5D-5L, SF-12, PGIC/PGIS (every 6 months); PK and PD sampling. No PK or PD results have been provided with the interim report.

Results

Interim results based on a cut-off date of 29 September 2020 have been provided.

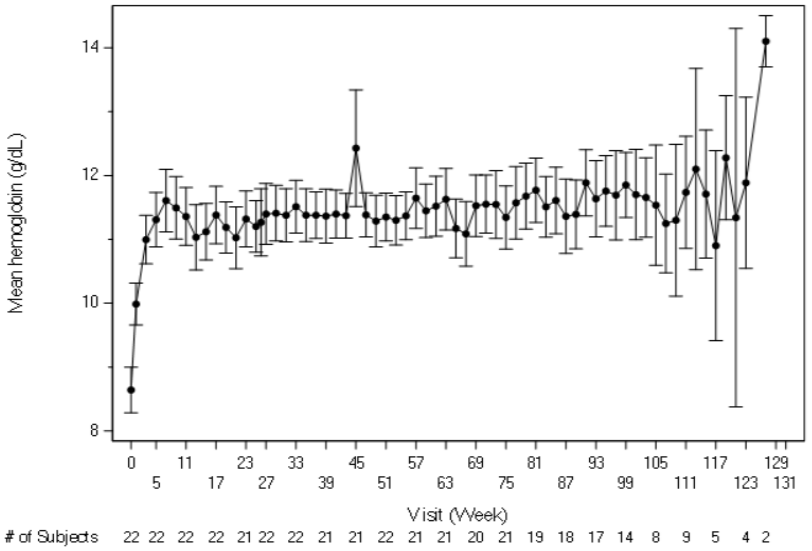
Of the 22 patients who completed Part A of the study, all enrolled into Part B. As of the interim cut-off, 21 patients were ongoing, and 1 patient discontinued treatment due to AEs of dyspepsia, cyanosis (reported by the Investigator as acrocyanosis), dysphagia, and erosive gastritis. The study population had a median age of 71.5 years, and most patients (81.8%) were ≥65 years. Most patients (68.2%) were from Europe, and most (68.2%) were female. In Part B, patients received a median of 77.6 weeks (range 27.9 to 107.9 weeks) of sutimlimab and a median of 38.0 administered doses of sutimlimab.

Thirteen (59.1%) patients had at least 1 major protocol deviation, mostly prohibited medications (8 [36.4%] patients); and investigational product, study conduct, visit procedures and subject safety (3 [13.6%] patients each). Major deviations within the prohibited medications subcategory concerned use of protocol-forbidden medication or increase in dose of a medication that was allowed to be given at stable dose.

Change in haemoglobin levels

Mean haemoglobin levels were maintained at ≥11 g/dL throughout Part B. However, six patients received transfusion during Part B.

Figure 18. Plot of mean haemoglobin (g/dL) (+/- SE) by visit – Full Analysis Set – BIVV009-03 Part A/B

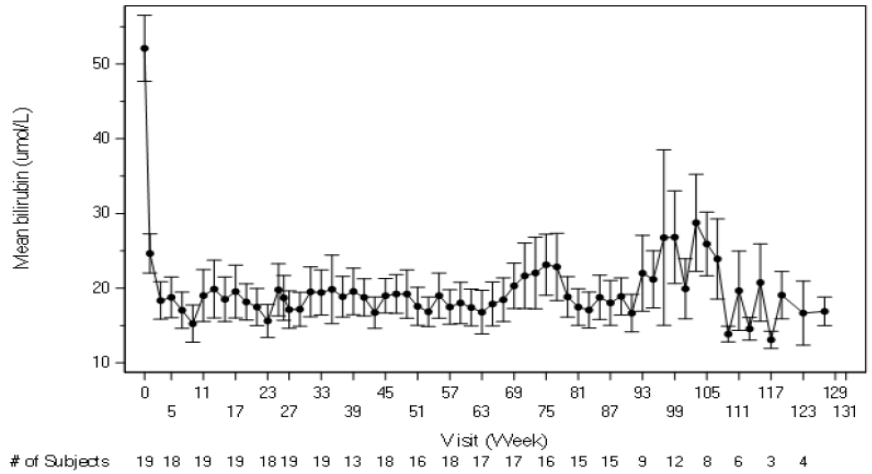


NOTE: 1: Week 0 is the baseline. Baseline is defined as the last non-missing value prior to the first administration of study drug in Part A. Only data based on n>=2 are presented at each visit.
Abbreviation: SE = standard error
Data cutoff date is 29 September 2020.
PGM=f1_mean_hgb_byvisit_comb.sas
OUT=/home/I0402046/wise/DEVOPS/BIVV009/BIVV009_03/INTERIM_B_2020/REPORT/OUTPUT/f1_mean_hgb_byvisit_comb_i.rtf (12NOV2020 20:57)

Change in bilirubin levels

Mean decreases in bilirubin were maintained during Part B.

Figure 19. Plot of mean total bilirubin (µmol/L) (+/- SE) by visit (excluding subjects with Gilbert's syndrome) – Full Analysis Set (BIVV009-03 Part A/B)



NOTE: 1: Summaries are based on the Full Analysis Set excluding subjects with Gilbert's syndrome (or subjects with unknown Gilbert's syndrome test results).
2: Week 0 is the baseline. Baseline is defined as the last non-missing value prior to the first administration of study drug in Part A.
Only data based on n>=2 are presented at each visit.
Abbreviation: SE = standard error
Data cutoff date is 29 September 2020.
PGM=f2_mean_bili_byvisit_exgilb_comb.sas
OUT=/home/I0402046/wise/DEVOPS/BIVV009/BIVV009_03/INTERIM_B_2020/REPORT/OUTPUT/f2_mean_bili_byvisit_exgilb_comb_i.rtf (17NOV2020 20:28)

Change in FACIT-F

Higher FACIT-Fatigue subscale scores denote better QoL. Score ranges from 0-52. At baseline, mean and median FACIT-F scores were 32.43 and 38.00 for the 21 patients participating in part B with these data available; min-max were 14.0-47.0. At week 39, mean and median FACIT-F scores were 40.79 and 45.00 (based on 19 subjects); min-max were 5.0-52.0. At week 87, mean and median FACIT-F scores were 41.28 and 43.50 (based on 18 subjects); min-max were 6.0-52.0. Similar levels of FACIT-F scores are reported at week 99 and week 111 but with a decreasing number of subjects (12 and 8 respectively).

Change in LDH

The normal range for LDH was 120-246 U/L. The mean change from baseline was -111.6 UL (range -863.0, 449.0) at Week 27 (n=22), -49.3 UL (range -495.0; 254.0) at Week 39 (n=15), and -4.50 UL (range -301.0; 118.0) at Week 99 (n=14).

RBC transfusions

Table 21. BIVV009-03 Part A/B: Summary of number of transfusions and units by study period - FAS

	Within the first 5 weeks of Part A (N=22)	Week 5 to 26 of Part A (N=22)	Part B Study Period (N=22)
Number of transfusions			
n	22	22	22
Mean	0.23	0.86	2.00
SD	0.53	2.80	4.64
Median	0.00	0.00	0.00
Min ; Max	0.0 ; 2.0	0.0 ; 13.0	0.0 ; 19.0
0	18 (81.8)	17 (77.3)	16 (72.7)
1	3 (13.6)	3 (13.6)	1 (4.5)
2	1 (4.5)	0	1 (4.5)
3	0	1 (4.5)	0
4	0	0	0
>4	0	1 (4.5)	4 (18.2)
Total units transfused			
n	4	5	6
Mean	2.50	6.20	13.17
SD	0.58	9.42	11.03
Median	2.50	2.00	11.00
Min ; Max	2.0 ; 3.0	1.0 ; 23.0	2.0 ; 32.0
Annualized number of transfusions (a)			
n	22	22	22
Mean	2.31	2.09	1.54
SD	5.42	6.70	3.58
Median	0.00	0.00	0.00
Min ; Max	0.0 ; 20.9	0.0 ; 31.0	0.0 ; 12.7
0	18 (81.8)	17 (77.3)	16 (72.7)
>0-1	0	0	1 (4.5)
>1-2	0	0	1 (4.5)
>2-3	0	3 (13.6)	1 (4.5)
>3-4	0	0	0
>4	4 (18.2)	2 (9.1)	3 (13.6)
Annualized transfusion units (a)			
n	4	5	6
Mean	25.18	14.92	10.03
SD	5.74	22.43	8.42
Median	24.56	4.97	8.15
Min ; Max	20.3 ; 31.3	2.5 ; 54.9	1.6 ; 21.4

NOTE: Percentages are based on the number of subjects in the Full Analysis Set.
(a) Annualized values are calculated as follows: (Number of events during the Study Period)/(Number of days during the Study Period) x 365.25
Data cutoff date is 29 September 2020.
PGM=DEVOPS/BIVV009/BIVV009_03/INTERIM_B_2020/REPORT/PGM/t16_sum_trf_comb.sas OUT=REPORT/OUTPUT/t16_sum_trf_comb_x.rtf (29JUL2021 19:16)
159/273

Summary of main efficacy results

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 22. Summary of efficacy for trial BIVV009-04 (EFC16216) CADENZA

Title: 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 identifier	BIVV009-04 (EFC16216) EudraCT #2017-003539-12

Design	Randomized, double-blind, placebo-controlled, multicenter phase 3 study in patients with primary cold agglutinin disease (CAD) without a recent history of blood transfusion. Randomized patients were receiving study drug (BIVV009 [sutimlimab] or placebo) and were undergoing safety and efficacy assessments for 6 months (26 weeks) during Part A. Following completion of the initial 6-month treatment period (Part A), patients rolled into the open-label long-term safety and durability of response extension phase (Part B) during which they were receiving open-label sutimlimab.	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	6 months (26 weeks) 6 weeks 1 year after last patient out of Part A
Hypothesis	Superiority of sutimlimab compared with placebo	
Treatments groups	sutimlimab	6.5 gram of sutimlimab (for patients <75 kg) or 7.5 gram of sutimlimab (for patients ≥75 kg) diluted with saline to a total volume of 500 mL was administer through intravenous infusion at baseline (D0), at Week 1 and every 14 days thereafter during Part A, and every 2 weeks during Part B 22 patients randomized
	Placebo	Placebo solution of volume corresponding to that of sutimlimab for patients <75 kg or for patients ≥75 kg diluted with saline to a total volume of 500 mL was administer through intravenous infusion at baseline (D0), at Week 1 and every 14 days thereafter during Part A, and every 2 weeks during Part B 20 patients randomized
Endpoints and definitions	Primary endpoint	Rate of responders defined as patients who had a ≥1.5 g/dL increase in Hgb levels at the treatment assessment endpoint (TAT; defined as the mean value of Weeks 23, 25, and 26), did not receive a blood transfusion from Week 5 through Week 26 and did not receive treatment for CAD beyond what is permitted per protocol.
	Secondary endpoint (key)	Change from baseline in Hgb at the TAT
	Secondary endpoint (key)	Change from baseline in QOL, as assessed by the change in Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue scale scores at the TAT
	Secondary endpoint	Change from baseline in bilirubin at the TAT
	Secondary endpoint	Change from baseline in lactate dehydrogenase (LDH) at the TAT
	Secondary endpoint	Incidence of solicited symptomatic anaemia at EOT
Database lock	Part A DBL: 12-NOV-2020	
Results and Analysis		
Analysis description	**Primary Analysis**	
Analysis population and time point description	The analysis of the primary endpoint was conducted on the COVID-adjusted Composite estimand. The COVID-adjusted Composite estimand consists of a subset of FAS (all randomized subjects who received at least 1 dose [including partial dose] of study drug) who did not miss any visits or discontinue early due to the COVID-19 pandemic. The odds ratio of the proportion of responders between groups along with a 95% confidence interval (CI) for the odds ratio was calculated using the Cochran-Mantel Haenszel test. As the primary analysis reached statistical significance, the key secondary endpoints, i.e. change from baseline in hemoglobin and FACIT-Fatigue Score at TAT, were tested in above order using the hypothetical estimand and a sequential closed procedure with alpha of 0.05 for each test.	

Descriptive statistics and estimate variability	Treatment group	sutimlimab	placebo
	Number of subjects	22	20
	Primary endpoint: - rate of responders (%) - (95% CI for responder rate) - Odds ratio (sutimlimab vs placebo) (95% CI) - P value	72.7 (49.8, 89.3) 15.94 (2.88, 88.04) <0.001	15 (3.2, 37.9)
	- change from baseline in Hgb at the TAT (LS Mean change at TAT under MMRM) - 95% CI of LS Mean - LS mean difference with placebo -P-value	2.66 2.09, 3.22 2.56 <0.001	0.09 -0.50, 0.68
	- change from baseline in FACIT-Fatigue scale scores at the TAT (LS Mean change at TAT under MMRM) - 95% CI of LS Mean - LS mean difference with placebo -P-value	10.83 7.45, 14.22 8.93 <0.001	1.91 -1.65, 5.46
	Change from baseline in bilirubin (umol/L) (mean)	-22.1	-1.8
	Change from baseline in LDH (U/L) (mean)	-150.8	7.6
Notes	The primary analysis of the primary endpoint involved the composite estimand, for which any missing response for a component of the primary efficacy endpoint rendered the patient a non-responder. If a patient had a COVID-related infusion gap (defined as 2 consecutive missed infusions due to COVID-19), 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 responder derivation. Since none of the patients with COVID-19-related infusion gaps received a transfusion or prohibited medication, the patients included in the COVID-19-adjusted composite estimand were the same as the patients in the composite estimand as defined in the SAP. The change from baseline in bilirubin at the TAT was analyzed for FAS excluding subjects with Gilbert's syndrome either confirmed or not ruled out.		

Table 23. Summary of efficacy for trial BIVV009-03 (EFC16215) CARDINAL

Title: 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 identifier	BIVV009-03 (EFC16215) EudraCT #2017-003538-10
Design	Open-label, single-arm, multicenter phase 3 study in patients with primary cold agglutinin disease (CAD) who had a recent history of blood transfusion. Enrolled patients were receiving BIVV009 (sutimlimab) and were undergoing safety and efficacy assessments for 6 months (26 weeks) during Part A. Following completion of Part A, patients rolled into the long-term safety and durability of response extension phase (Part B) where they continued to receive study drug.

	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	6 months (26 weeks) 6 weeks 2 years after last patient out of Part A
Hypothesis	Patients treated with sutimlimab achieve a response rate greater than 30%	
Treatments groups	sutimlimab	6.5 gram of sutimlimab (for patients <75 kg) or 7.5 gram of sutimlimab (for patients ≥75 kg) diluted with saline to a total volume of 500 mL was administer through intravenous infusion at baseline (D0), at Week 1 and every 14 days thereafter during Part A, and every 2 weeks during Part B 24 patients enrolled
Endpoints and definitions	Primary endpoint	Proportion of responders defined as patients who did not receive a blood transfusion from Week 5 through Week 26, did not receive treatment for CAD beyond what is permitted per protocol and had a ≥2 g/dL increase from baseline in Hgb levels or increases Hgb to ≥12 g/dL at the treatment assessment endpoint (TAT; defined as the mean value of Weeks 23, 25, and 26).
	Secondary endpoint	Change from baseline in bilirubin at the TAT
	Secondary endpoint	Change from baseline in QOL, as assessed by the change in Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue scale scores at the TAT
	Secondary endpoint	Change from baseline in lactate dehydrogenase (LDH) at the TAT
	Secondary endpoint	Number of transfusions after the first 5 weeks of study drug administration
	Secondary endpoint	Change from baseline in Hgb at the TAT
Database lock	Part A DBL: 28-AUG-2019	

Results and Analysis

Analysis description	**Primary Analysis**	
Analysis population and time point description	The analysis of the primary endpoint was conducted on the Full Analysis Set (FAS) consisting of all patients who received at least one dose of study drug. 95% CI was calculated using the Clopper-Pearson exact method. Secondary endpoints were analyzed using descriptive statistics, frequency, percentage, and CIs as appropriate. Change from baseline for continuous parameters was analyzed using the Mixed Model for Repeated Measures (MMRM) at the TAT.	
Descriptive statistics and estimate variability	Treatment group	sutimlimab
	Number of subjects	24
	Primary endpoint: rate of responders (%) (95% CI for responder proportion)	54 (32.8, 74.4)
	Change from baseline in bilirubin (umol/L) (LS Mean change at TAT under MMRM)	-38.18
	Change from baseline in FACIT-Fatigue scale scores (LS Mean change at TAT under MMRM)	10.85

	Change from baseline in LDH (U/L) (LS Mean change at TAT under MMRM)	-126.95
	Mean number of transfusions after Week 5	0.9
	Change from baseline in Hgb (g/dL) (LS Mean change at TAT under MMRM)	2.6
Notes	The primary analysis of the primary endpoint involved the composite estimand, for which any missing response for a component of the primary efficacy endpoint rendered the patient a non-responder. Patients treated with sutimlimab achieved a response rate greater than 30% as the lower bound of the response was >30%. The change from baseline in bilirubin at the TAT was analyzed for FAS excluding subjects with Gilbert's syndrome either confirmed or not ruled out.	

Clinical studies in special populations

Of the total number of patients included (76), 31 were 65-74 years of age, 17 were 75-85 and 3 were 85 years of age or older.

	Age 65-74 (Older subjects number /total number)	**Age 75-84 (Older subjects number /total number)**	**Age 85+ (Older subjects number /total number)**
Cardinal and Candenza	**25/66**	**15/66**	**3/66**

In vitro biomarker test for patient selection for efficacy

N/A

Analysis performed across trials (pooled analyses and meta-analysis)

N/A

Supportive study(ies)

Study BIVV009-01 Part C addressed safety and tolerability of sutimlimab; secondary objectives included pharmacodynamics of sutimlimab with respect to CP function and disease-related biomarkers; see section 2 above. Study BIVV009-01 Part E is a long-term follow-up from the phase 1 study.

Methods

Study BIVV009-01 Part E

Study BIVV009-01 Part E enrolled patients with a history of CAD who had previously been treated with sutimlimab in a sutimlimab clinical trial or NPP with evidence of treatment response. Sutimlimab 5.5 g to 7.5 g doses were administered IV at week 0, week 1, and every 2 weeks thereafter. Under Version 13.0 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 haemolysis (rapid fall in haemoglobin ≥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 is permitted. Duration of treatment: Indefinite (ongoing, long-term treatment continuation study). Duration of observation: Up to 30 days after the last dose of study medication.

The primary objective of Part E was to evaluate the safety. No efficacy endpoint was designated. Exploratory PD endpoints included disease-related biomarkers: cold agglutinin titre; haptoglobin and routine clinical lab parameters of haemolysis (haemoglobin, haematocrit, reticulocyte count, LDH, bilirubin), and specific LDH isoforms.

Results

Change in haemoglobin levels

At baseline, haemoglobin values were below LLN for all 4 patients, with a median baseline value of 8.25 g/dL (range, 7.7 to 9.6 g/dL). At Day 7, median increase in haemoglobin over baseline was 1.30 g/dL (range, 0.1 to 1.9 g/dL). By Week 3 of treatment, an increase from baseline in haemoglobin could be observed for all 4 patients, with a median increase of 2.20 g/dL (range, 1.3 to 3.8 g/dL). By Week 7, the median increase in haemoglobin over baseline was 2.65 g/dL (range, 2.4 to 4.5 g/dL), and haemoglobin values for 3 patients were in the normal range (>12 g/dL). With the exception of declines in haemoglobin observed in the fourth patient prior to being discontinued from the study due to an AE, patients' improvements in haemoglobin stabilized after 5 weeks of treatment. Accordingly, mean improvements over baseline haemoglobin by at least 2 g/dL were observed through the study.

Change in bilirubin levels

During the first 2 weeks of treatment, bilirubin concentrations dropped rapidly in all 4 patients, with 3 of the patients attaining normal bilirubin values by Day 7. These 3 patients maintained normal bilirubin levels from Day 7 up to the cut-off date, whereas the levels of the fourth patient appeared to become more variable prior to discontinuing from the study.

Change in LDH

In BIVV009-01 Part E, over the first 3 weeks of treatment, LDH levels dropped rapidly in all 4 patients. By Week 3, mean decreases in LDH of -215.7 ±53.59 U/L (range, -251 to 154) were observed. In 3 patients, LDH levels appeared to stabilize below baseline levels, with values for individual patients frequently falling below the upper limit of normal, 250 U/L. Levels of LDH in the fourth patient appeared to become more variable but remained below baseline until the patient discontinued from the study.

Discussion on clinical efficacy

Design and conduct of clinical studies

Efficacy assessment of sutimlimab in primary CAD relies on two phase 3 studies, addressing slightly different populations (transfusion-free in the controlled BIVV009-04 study vs recently transfused in the open-label single-arm BIVV009-03 study). Both studies utilised the posology intended for marketing. CAD is rare, which is reflected by the small study sizes (22 and 24 sutimlimab-treated patients, respectively). Both studies have completed the main periods (Part A) of six months; long-term extension studies (Part B) are now completed.

The randomised placebo-controlled design of BIVV009-04 Part A is considered to provide more robust data. Although the number of patients studied in a controlled setting is limited, the study design is overall found adequate, with 22 sutimlimab treated subjects and 20 subjects receiving placebo,

followed for a 6-month main study period. Study BIVV009-03 is considered to further support efficacy albeit less conclusively due to the open-label single-arm study design.

In general, the inclusion and exclusion criteria are acceptable. The study population selected is reflective of the target population indicated for treatment of haemolytic anaemia with (primary) CAD. Key eligibility criteria for study BIVV009-04 were a baseline haemoglobin (Hb) level ≤10 g/dL, active haemolysis with a bilirubin level above the normal reference range, exclusion of patients with a history of blood transfusion within 6 months of screening, or history of more than one blood transfusion within 12 months of screening. The inclusion and exclusion criteria for study BIVV009-03 are generally in line with those of the study BIVV009-04, though with the exception that a transfusion history of ≥1 blood transfusions within 6 months of enrolment was allowed and was acceptable. Both phase 3 studies included adults only, which is reasonable given that CAD occurs almost exclusively in higher age groups. A strength of both studies is that secondary CAS was to be excluded by a specific exclusion criterion as well as through bone marrow biopsies. The threshold for transfusion dependence set for study BIVV009-03 is considered rather low with at least 1 documented blood transfusion within 6 months of enrolment, implying that the burden of disease could differ between subjects; some patients may warrant transfusion only in relation to transient deterioration due to e.g., infectious disease, but may otherwise not require treatment, whereas others warrant regular RBC transfusions. Nevertheless, both studies aimed at including patients with symptomatic disease and moderate to severe haemolytic anaemia (Hb <10 g/dL).

There is currently no approved specific therapy in primary CAD although therapy to reduce antibody production in patients with symptomatic disease is widespread, primarily through rituximab-containing regimens. Other standard of care includes RBC transfusions and plasmapheresis. In both the phase 3 sutimlimab studies, specific therapy to reduce antibody production was prohibited; thus, there are no efficacy data on sutimlimab in combination or in comparison with therapy to reduce antibody production in CAD like retuximab, including plasmapheresis which was not allowed.

Both studies started with a 6-week observation/screening period, during which RBC transfusions were allowed; RBC transfusions were also indicated during the main periods of the studies if patients had a Hb <9 g/dl and were symptomatic, or Hb <7 g/dl regardless of symptoms. They decision on a need for transfusion was taken at the investigator's discretion without applying any standardised criteria.

Endpoints

For both phase 3 studies, the primary endpoint was the responder rate, with slightly different definitions of a responder:

In study BIVV009-04, a responder was to meet all of the following 3 components: Hb increase ≥1.5 g/dL from baseline, no RBC transfusion week 5-26 and no prohibited CAD treatment week 5-26. The Hb increase was defined from baseline (last value before first dose of sutimlimab) to the mean value from Weeks 23, 25, and 26. The secondary endpoints pertained to laboratory parameters related to haemolysis and anaemia, effect on CAD-related complications and QoL assessments.

For study BIVV009-03, a responder was to be free from blood transfusion and non-permitted CAD treatment from Week 5 through Week 26 and not having received treatment for CAD beyond what was permitted per protocol, with either Hb ≥12 g/dL at the treatment assessment endpoint (mean value from Weeks 23, 25, and 26) or increased by ≥2 g/dL from baseline. Secondary endpoints included markers of haemolysis, QoL assessments and number of transfusions.

The primary endpoints in both studies are considered appropriate and are overall in line with the Protocol Assistance given. To assess the effect of sutimlimab, it is reasonable to have Hb levels in absence of RBC transfusions and/or specific CAD treatment which could otherwise have increased the Hb value. An increase in Hb of 1.5-2 g/dl or reaching Hb ≥12 g/dL could be clinically relevant per se,

as RBC transfusions could be given based on Hb level only but is further strengthened by the secondary endpoints related to an effect on markers of haemolysis and more symptom-oriented secondary endpoints, especially from the controlled study BIVV009-04. It is unlikely that a patient with primary CAD would spontaneously improve at least 1.5 g/dl in Hb levels, if no blood transfusions or other specific CAD treatment were given, unless enrolled during a period of deterioration or haemolytic crisis. Some improvement is noted during the screening period in both studies. Since worsening of symptoms could be triggered by minor exogenous factors, recruiting patients with stable disease may be unfeasible; however, this highlights that some patients improve spontaneously and thus that the treatment needs may vary over time. The Applicant was asked to discuss to what extent the variable course of symptomatic disease may impact the efficacy assessments, and whether treatment with sutimlimab is intended to be continuous or could be intermittent, during periods of deterioration only.

The Applicant commented on the choice for continuous rather than episodic treatment and argued that episodic treatment would not be in line with the posology as studied in the phase 3 CADENZA and CARDINAL trials and the primary mechanism of haemolysis. This is now reflected in Section 4.2 of the SmPC. Notwithstanding, it remains uncertain if episodic treatment would be the most beneficial treatment strategy in patients with controlled haemolysis (i.e. without anaemia). Some patients will need continuous treatment whereas other might be anaemic only periodically, this is nevertheless captured by the indication wording (stating haemolytic anaemia) in combination with the recommendations to apply continuous treatment.

The difference in study populations between the 2 phase 3 trials led to a difference in primary endpoints. A response in the CARDINAL trial was defined as a higher increase in Hb (≥(>2g/dL from baseline or ≥12 g/dL at TAT) as compared to the CADENZA trial, in which a response was defined as an increase of > 1.5 g/dL in Hb from baseline. However, a post-hoc analysis using the primary endpoint of an increase of >1.5 g/dL as response definition showed no differences in outcomes between studies.

Statistics

The sample size for study BIVV009-04 was estimated to be approximately 40 patients (20 in each treatment arm), which is limited but acceptable as this concerns an orphan disease. This was based on a treatment difference of 50% for placebo response rates between the range of 15% to 40% and a statistical power of greater than 85%.

The primary efficacy analysis for study BIVV009-04 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 as defined in Table 7. 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. 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 haemoglobin (< median baseline haemoglobin versus ≥ median baseline haemoglobin) 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 haemoglobin. In addition, the proportion of subjects who met each of the 3 response criteria as well as the number of transfusions by study period (before Week 5 and between Week 5 and Week 26) and by treatment arm were summarized. The FAS set consisting of all randomized subjects who received at least 1 dose (including partial dose) of IMP was used for the primary analysis. The definition of FAS analysis sets does not include all randomised subjects that is the basis for the intention to treat since it requires at least one dose of randomised treatment. There are no patients that were randomised but did not receive treatment, hence no additional analyses will be needed due to the definition excluding subjects not treated.

The primary estimand is defined to account for missing visits and treatments due to the COVID pandemic. Patients having 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. In addition, data for missing haemoglobin assessments were imputed prior to determining whether the haemoglobin level would be determined as failure or not. It is stated that none of these decision rules were fulfilled, leading to the primary COVID-adjusted estimand and the original estimand resulting in the same analysis.

For the primary endpoint, responder, handling of missing data is incorporated by the defined intercurrent events and the handling of those. Patients who discontinued the study early were considered non-responders. Patients with no Hb data at weeks 23, 25 and 26 for reasons other than Covid were also considered non-responders. The supplementary analyses planned includes the originally planned analysis and analyses using mFAS and PP.

For the secondary endpoints, change from baseline, the primary estimand is a hypothetical estimand where data after intercurrent events (ICE) are treated as missing and implicitly imputed using the MMRM model under the assumption of missing at random. Sensitivity analyses are planned using a pattern-mixture model with a control-based imputation strategy. Supplementary analyses for the secondary endpoints were planned, applying a treatment policy approach where all available data is used, and missing data is imputed by the MMRM model.

It is considered that the planned primary, sensitivity and supplementary analyses cover the exploration of impact of COVID, other ICE and missing data and allow for interpretation of the robustness of the results.

The study report mentioned one blinded interim analysis performed before Part A had completed. According to the SAP, an interim safety and efficacy analysis was to be performed for Part A after all patients had completed Part A and the data had been cleaned (Part A analysis). The applicant clarified that a blinded interim analysis was carried out to support a biologics license application (BLA) for the FDA based on a data cut off of 29 September 2020. This corresponds to the date for last patient out in part A and, hence, the results of the analysis have not influenced the conduct of Part A. Parts A and B were to have separate database locks to enable MAA submission following completion of Part A. Additional analyses of Part B data will be defined in a separate Part B SAP. Changes to the analysis plan with regard to COVID-related events was only documented in the SAP v.2. From the now provided SAP v1.0 it was clarified that the amendments pertained to any impact of the COVID-19 pandemic on the efficacy evaluation and the introduction of a modified FAS. The SAP v1.0 was issued on the same date as amendment 7; 07-Jul-2020. This is late during the conduct of Part A which completed in September 2020. However, as there were no patients affected by COVID-related infusion gaps this is not considered an issue for interpretation of the study results. Database lock and unblinding of part A was clarified to had both occurred on 11 Nov 2020. Sponsor personnel (except for those who provide drug supply) were blinded to the treatment assignment until the interim analysis (Part A DBL). Of note, last participant completed Part A on 29 September 2020, hence, prior to the unblinding. The Applicant adequately provided the estimand definition and attributes for the primary analysis as requested and further explained the differences between the COVID-adjusted composite estimand and the composite estimand.

The sample size for study BIVV009-03 of approximately 20 patients was based on a successful estimated responder rate of 66% with a minimum of 30%. For the trial to be successful the 95% lower bound CI for the response rate should exclude 30%.

Regarding the statistical methods of the study, for the primary analysis of the primary endpoint, a composite estimand was used while patients with missing values were considered as non-responders.

This leads to a conservative effect estimate and is considered acceptable as it is supplemented with sensitivity analyses that explore the impact of missing data. The analysis of the secondary endpoints is considered acceptable. However, the study is uncontrolled. Therefore, seasonal factors could have impacted the data, especially with the more subjective endpoints, such as the QoL questionnaire, since the patients experience more symptoms of the disease by cold temperatures. Further, this may have affected the assessment of disease burden and patient wellbeing.

Efficacy data and additional analyses

Primary endpoints

In the controlled study BIVV009-04, there were 16/22 or 72.7% (95% CI 49.8-89.3) and 3/20 or 15% (95% CI 3.2-37.9) responders in the sutimlimab and placebo group, respectively, who met all 3 of the components in the composite primary efficacy endpoint (Hb increase at least 1.5 g/dl from baseline; no blood transfusions during week 5-26 and no non-permitted CAD treatment during week 5-26). The difference was statistically significant (odds ratio of 15.94 [95% CI: 2.88 to 88.04; p<0.001]). There was no difference in proportion of subjects free from transfusions or CAD-specific therapy between the treatment groups; this could be expected given that patients recruited were free from transfusions during the previous six months at baseline and that CAD-specific therapy was prohibited.

In study BIVV009-03, the primary efficacy endpoint was met in 13/24 (54%) of subjects who fulfilled the 'responder' criteria with no blood transfusion from Week 5 through Week 26, no other treatment for CAD and Hb level ≥12 g/dL at TAT or increased by ≥2 g/dL from baseline. No subject received a different CAD specific therapy during Part A (for two subjects, however, was this unknown).

Taken together, the primary endpoints in both phase 3 studies are considered to support that sutimlimab provides an increase in Hb of clear clinical relevance in a symptomatic CAD population with moderate to severe anaemia at baseline. With regard to need for transfusions, the decision was left at the investigator's discretion according to clinical practice and thus transfusion was not conducted strictly according to the criteria set at baseline. The overall results for this parameter were nevertheless well in line with the change in Hb levels and the overall efficacy results is not deemed sensitive to variation in factors triggering the transfusion decision for included subjects.

Secondary endpoints

The primary efficacy endpoint results are supported by the secondary efficacy endpoints from both studies, with an increase in Hb levels, a decrease in markers of haemolysis and an increase in QoL measures such as the FACIT-Fatigue score. In study BIVV009-04, the LS mean change from baseline in haemoglobin at treatment assessment timepoint was 2.66 g/dL (95% CI: 2.09 to 3.22) and 0.09 g/dL (95% CI: -0.50 to 0.68) for sutimlimab and placebo, respectively. The LS mean difference was 2.56 g/dL (p<0.001; 95% CI: 1.75 to 3.38). Over a quarter (27%) of the patients had a mean Hb increase >3 g/dL. There appears to be a rapid increase in mean Hb in the sutimlimab groups with sustained levels throughout the 26 weeks of the study. Despite the increase, the mean values appear to fluctuate around the lower limit of normal range in Hb. Thus, it appears that despite having a clear effect of treatment, a large proportion of patients do not have their Hb levels fully restored.

For markers of haemolysis, there was a clear and rapid decrease in bilirubin and a decrease, albeit of a smaller magnitude than bilirubin, for LDH in study BIVV009-04; there was no decrease for any of these markers in the placebo group. In study BIVV009-03**,** mean bilirubin levels decreased substantially at the week 1 measurement and remained low throughout the 26 weeks; however, for LDH, despite a decrease, mean values remained above the upper limit of normal throughout Part A. Despite the mean increase in Hb and the mean decrease in bilirubin in the study population, a minority of patients (9/24) reached at least 12 g/dl; this is likely due to ongoing haemolysis given that the majority of subjects continued to have non-detectable levels of haptoglobin at week 26.

The LS mean change in FACIT-Fatigue score in study BIVV009-04 showed an increase of 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. Similar, in study BIVV009-03, there was a mean increase of 13.03 points in the FACIT-Fatigue score (based on data from 17 subjects) during the main study part. It is agreed with the Applicant that the increases in the sutimlimab groups could be considered clinically relevant.

In study BIVV009-03, 17/24 or 71% received no transfusions during week 5-26. Although all subjects included were mandated to have received at least one RBC transfusion during the 6 months before study entry, a large proportion of subjects had a low need of transfusions before study entry but were given relatively many RBC transfusions during the 6-week screening period before starting sutimlimab treatment. Nevertheless, the large proportion of transfusion-free subjects during the main period is considered to support efficacy of sutimlimab and is in line with the increase in Hb levels.

Protocol deviations

In study BIVV009-04, major protocol deviations were reported in 16/20 or 80% of subjects in the placebo group and 14/22 or 64% in the sutimlimab group. Use of prohibited medication was the most frequently reported major deviation and was reported in 6/22 subjects in the sutimlimab group and 4/20 in the placebo group, followed by deviations relating to dosing or administering investigational product and study conduct. One patient in each group had a deviation relating to the primary efficacy endpoint and in both cases, this concerned missing ≥2 consecutive or 3 intermittent doses. For study BIVV009-04 Part B, there were 8/37 or 21.6% who received prohibited medication. There were no major protocol deviations relating to prohibited medication in study BIVV009-03 Part A, however, in the extension part of study BIVV009-03 (Part B), there were 8/22 or 36% of patients who had use of prohibited medication reported as a major protocol deviation. Since the type of prohibited medication (which includes CAD specific products as well as dose changes of more general anaemic treatments such as folate and iron) could impact the efficacy assessment, the MAH was asked to clarify the use of prohibited medication in both study BIVV009-03 and BIVV009-04. The applicant has provided summaries of concomitant prohibited medication and sensitivity analyses as requested. The estimated treatment effects are considered robust.

PD endpoints

For both phase 3 studies, the pharmacodynamic assessments including mean CP, total C4, C1q and C1s support that the classical complement pathway was inhibited with restoration of complement components but without an impact on the C1q levels. The utility of CH50 levels is less clear; these levels are expected to be low due to consumption with ongoing complement activity at baseline, and then be low with inhibited classical pathway activity during sutimlimab treatment. There are no consistent findings in the PD measurements that support any differences between those who received 6.5 g and 7.5 g sutimlimab respectively.

Non-responders

In study BIVV009-04, 6/22 patients in the sutimlimab group were non-responders, three of whom discontinued early due to TEAEs. For the remaining three subjects, some improvements in haemoglobin levels and/or bilirubin are described; one however had RBC transfusion and the two others did not reach the haemoglobin level threshold. For study BIVV009-03, 11/24 subjects were non-responders. Some improvement in Hb and/or bilirubin was reported in six; two discontinued early and three patients had decreases in Hb/no normalisation of bilirubin/no change in FACIT-Fatigue.

Long-term efficacy

In line with the previous CHMP Protocol Assistance, maintenance of any initial effect over at least 12 months should be demonstrated. Interim analysis of extension parts ('Part B') of both phase 3 studies have been provided.

The BIVV009-04 Part B was an open-label extension study for patients who continued on study drug for 1 year after last patient completed Part A to evaluate the long-term safety and tolerability and to investigate the durability of response during long-term treatment with sutimlimab in patients with primary CAD. Patients who qualified for the study immediately rolled over from part A into part B by receiving a cross-over loading dose, in a blinded manner, at the Week 26 visit. Regarding study disposition and baseline data, a total of 37 patients enrolled from Part A, 17 from the sutimlimab group and 20 from the placebo group in Part B. 39 patients completed Part A, therefore, 2 patients did not enter Part B. Of the 37 enrolled patients, 4 discontinued earlier in part B due to lack of efficacy (n=3) and withdraw consent (n=1). As of the cut-off date, median exposure of sutimlimab was 45 weeks in Part B and 68 weeks in Part A and B. Thus, the presented Part B data as of the cut-off date includes data from 15 patients from the sutimlimab group and 18 from the ex-placebo group in part A (switched to open-label sutimlimab at week 26). There was a clear and rapid increase in Hb levels and decrease in bilirubin levels among previous placebo-subjects from part A who switched to sutimlimab in part B. This effect appears to be maintained during part B, however, late during phase B, mean levels are more fluctuating for Hb and levels appear to increase for bilirubin. This is based on very few subjects and thus entails a greater uncertainty. The Applicant presented an updated analysis of Hb and haemolysis parameters from Part B and presented the number of patients who have been followed for at least 52 weeks of sutimlimab treatment. It was confirmed that the effect on haemoglobin and bilirubin was retained throughout the study.

Similar to Hb and bilirubin, a clear and rapid change in FACIT-Fatigue score is noted for those in the previous placebo group during part A who were switched to open-label sutimlimab for part B, from a mean below 35 at week 26 to a mean above 40 at week 39. There are too few subjects included beyond week 87 for any meaningful conclusions but until week 87, the higher mean FACIT Fatigue score was maintained.

For LDH, the decrease during part A in the sutimlimab group appears not to have been fully maintained during part B, and interestingly, there appeared to be no clear reduction in LDH during part B among those who switched from placebo to sutimlimab. The Applicant was asked to present updated part B data on LDH and haptoglobin, including separate graphs plotting mean LDH levels and mean haptoglobin values respectively during part B.

For BIVV009-03 Part B, data from 21 subjects have been presented with the interim report, with a median treatment time of 77.6 weeks. Mean Hb and bilirubin levels appear to be maintained during part B. FACIT-Fatigue mean, and median, scores remained stable and increased as compared to baseline. It is however noted that a large number of patients (8/22) received a prohibited medication during part B, and that 6/22 required RBC transfusions. Further, for LDH, there was a clear decrease from baseline at week 27 at -111.6 U/L (range -863.0, 449.0; N = 22) but at week 99, the mean values were similar as to baseline at -4.50 U/L (range -301.0; 118.0; N = 14). The Applicant was asked to present updated data on parameters relevant for efficacy from BIVV009-03 Part B including a clear presentation of how many subjects have been treated with sutimlimab for at least 52 weeks.

The data are provided as requested. In study BIVV009-03 > 90% of participants followed after 52 weeks. In BIVV009-04, 35 (90%) participants were followed >52 weeks.

Further, the LDH findings, that are in line with study BIVV009-04, were addressed, including whether this could indicate a return of haemolysis due to loss of efficacy. The applicant presented the final

study reports for both studies BIVV009-03 and BIVV009-04. The pattern of responses seen is generally retained over time and the patients treated with placebo in BIVV009-04 part A caught up with the patient is the active arm. The data presented in the final reports are overall consistent with data presented with the interim reports.

Generalisability

Both phase 3 studies included patients with primary CAD who had moderate to severe haemolytic anaemia based on Hb < 10 g/dL and increased haemolytic markers. Thus, all efficacy data pertains to such patients. It is thus deemed appropriate to restrict the indication to patients with haemolytic anaemia (not all patients with haemolysis). As could be expected given the requirement to have a recent RBC transfusion, the population in study BIVV009-03 appears to have a more severe primary CAD as compared to study BIVV009-04; the majority of subjects (16/24) in study BIVV009-03 had been hospitalised due to CAD within the last 2 years. Based on Hb levels at baseline, however, both studies appear to have included a rather wide range of CAD severity. Only a relatively small proportion of patients had previously been treated with a specific antibody reducing regimen; however, it is recognised that these regimens are not approved for CAD.

Given the low number of subjects, subgroup analyses are expected to be of limited value. No clear difference in effect across age, weight, previous number of transfusions, baseline Hb level or previous specific antibody reducing regimens are noted.

Conclusions on clinical efficacy

The data from the two pivotal phase 3 studies, especially from controlled trial BIVV009-04, in adults with primary CAD and moderate to severe haemolytic anaemia are considered to support a clear and clinically relevant increase in Hb and a decrease in haemolytic markers. Controlled data further support an improvement in symptoms and quality of life.

Clinical safety

Safety data provided by the applicant in the dossier were collected from:

Study BIVV009-01 has four parts:

Part A: A Phase 1, double-blind, randomized, placebo-controlled FIH single-ascending dose (SAD) study in NHVs.

Part B: A Phase 1, double-blind, randomized, placebo-controlled FIH multiple-ascending dose (MAD) study in NHVs.

Part C: A Phase 1, open-label, multiple-dose study in patients with CMDs, including CAD, BP, WAIHA, and AMR indications.

Part E is a Phase 1, non-randomized open label multiple-dose study in patients with CAD previously treated with sutimlimab within the scope of a sutimlimab clinical trial or named patient program (NPP).

Study TNT009-02: is a Phase 1, double-blind, randomized, placebo-controlled, multiple-dose study in NHVs to evaluate the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of multiple doses of sutimlimab.

Study BIVV009-05: is a Phase 1, open-label, single and multiple-dose study designed to evaluate the safety, tolerability, and PK/PD of sutimlimab in healthy Japanese volunteers.

Study BIVV009-201: has two parts:

Part A: is a Phase 1, open-label, multiple-dose study of sutimlimab in patients who have chronic ITP

Part B: A Phase 1, open-label long-term treatment for patients who benefited from sutimlimab in Part A.

Study BIVV009-03 (CARDINAL) has two parts:

Part A: is a pivotal Phase 3, open-label, single-arm study designed to evaluate the efficacy, safety, and tolerability of sutimlimab in patients with primary CAD who had a recent history of blood transfusion (defined as at least 1 transfusion during the 6 months prior to enrolment).

Part B: A Phase 3, open-label extension in patients with primary CAD who completed BIVV009-03 Part A.

Study BIVV009-04 (CADENZA) has two parts:

Part A: is a Phase 3, supportive randomized, double-blind, placebo-controlled study designed to evaluate the efficacy and safety of sutimlimab in symptomatic patients with primary CAD who did not have a recent history of blood transfusion (i.e., ≤ 1 transfusion during the previous year and no transfusion during the 6 months prior to enrolment).

Part B: is a Phase 3, open-label extension in patients with primary CAD who completed BIVV009-04 Part A.

The applicant has provided the final Clinical Study Reports (CSRs) for completed BIVV009-01E (duration of study was 2.5 years), BIVV009-03 Part B (duration of study was 2 years) and BIVV009-04 Part B study (duration of study was 1 year) along with RMPan updated risk management plan (RMP) and Cadence registry protocol. The Applicant has also presented an integrated safety analysis with CAD patients obtained from studies BIVV009-03 and BIVV009-04 that includes 66 patients out of the total 76 CAD patients.

Supportive safety data are available from other phase 1 studies in other CMD patients or in healthy volunteers.

Patient exposure

Table 24. Pools for safety analysis

Population	Study	Dose regimens	Pooled Groups for Integrated Analysis
CAD patients	Study BIVV009-01 Part C (CAD)	First dose (10 mg/kg) and subsequent weekly dosing × 4 (60 mg/kg)	• BIVV009-01 C (CAD) & E • BIVV009-03 • BIVV009-04 • Sutimlimab treatment (BIVV009 Parts A & B combined) • Total Sutimlimab (CAD) (all BIVV009 in any given study or study part combined) • For Section 3.1 AEs, the data are presented as integrated safety data from Studies BIVV009-03 (Parts A and B) and BIVV009-04 (Parts A and B); and individual study data from Studies BIVV009-01 Parts C and E, BIVV009-03 Parts A and B, and BIVV009-04 Parts A and B
	Study BIVV009-01 Part E	Phase 3 dosing regimen[a]	
	Study BIVV009-03 Parts A and B	Phase 3 dosing regimen[a]	
	Study BIVV009-04 Parts A and B	Placebo (Part A only) Phase 3 dosing regimen[a]	
NHV	Study BIVV009-01 Parts A and B	Placebo Single Sutimlimab Dose: 0.3 – 100 mg/kg Multiple Sutimlimab Doses: Weekly dosing × 4 (30 or 60 mg/kg)	• Placebo • Sutimlimab Single dose • Sutimlimab Multiple doses • Total Sutimlimab (NHV) (Sutimlimab Single dose and Sutimlimab Multiple doses combined)
	Study BIVV009-02 (TNT009-02)	Placebo Multiple Doses: 75 mg/kg × 4	
	Study BIVV009-05 Part A and B	Single Dose: 30 mg/kg, 60 mg/kg, or 100 mg/kg Multiple Doses: 6.5 g (for subjects who weigh less than 75 kg) or 7.5 g (for subjects who weight 75 kg or more) on Study Days 1, 8, and 22	
Other CMD patients	BIVV009-01 Part C (WAIHA/BP/AMR)	First dose (10 mg/kg) and subsequent weekly dosing × 4 (60 mg/kg)	• WAIHA • BP • AMR • ITP
	BIVV009-201 ITP Parts A and B	5.5 g or Phase 3 dosing regimen[a]	

Abbreviations: AE = adverse event, AMR = antibody-mediated rejection, BP = bullous pemphigoid, CAD = cold agglutinin disease, CMD = complement-mediated disorders, ITP = immune thrombocytopenia purpura, NHV = normal healthy volunteer, WAIH = warm autoimmune hemolytic anemia.

a Subjects who weigh <75 kg will receive fixed doses of 6.5 grams of sutimlimab and subjects who weigh ≥75 kg will receive fixed doses of 7.5 grams of sutimlimab on Study Day 0, Week 1, and every 2 weeks thereafter until the last visit at which study drug is administered.

Duration of treatment and dose

CAD patients

Overall, the median duration of exposure to sutimlimab among the 76 CAD patients exposed to sutimlimab was 114.50 (Range: 3.1 – 177.3) weeks with the majority of patients (42 of 76 [55.3%] patients) exposed to sutimlimab ≥105 weeks. The total subject-years of exposure to sutimlimab was

146.9 years, with a median number of sutimlimab administrations of 56.0 (Range: 2 - 89) and median total dose of sutimlimab of 380.25 g (Range: 13.9 – 667.5 g).

NHV

The median duration of exposure to sutimlimab among the 96 NHVs exposed to sutimlimab in was 2.14 (Range: 2.1 – 7.1) weeks with all subjects exposed to sutimlimab for ≥1 week. The total subject-years of exposure to sutimlimab was 6.8 years, with a median number of sutimlimab administrations of 1.0 (Range: 1 - 4) and median total dose of sutimlimab of 5.8 g (Range: 0.02 – 32.5 g).

Other CMD patients

The median duration of exposure to sutimlimab for the 4 patients with WAIHA in study BIVV009-01 Part C was 2.29 (Range: 2.3 – 5.3) weeks, BP was 5.29 (Range: 5.1 – 5.4) weeks AMR was 5.29 (Range: 5.3 – 5.3) weeks and 43.36 (Range: 3.1 – 130.3) weeks for ITP patients.

The total subject years of exposure for WAIHA patients was 0.2 years, BP 1.0 year, AMR 1.0 year and 12.8 years for ITP.

The median number of sutimlimab administrations for WAIHA patients were 2.0 (Range: 2 – 5), BP 5.0 (Range: 5 – 5), AMR 5.0 (Range: 5 – 5) and ITP 17.5 (Range: 2 – 64).

The median total dose of sutimlimab for WAIHA patients was 5.65 g (Range: 5.1 – 24.2 g), BP 18.76 g (Range: 15.5 – 24.5 g), AMR 20.46 g (Range: 12.9 – 24.3 g) and ITP 119.75 g (Range: 11.0 – 462.5 g).

Demographics

Overall, for CAD patients the mean age at baseline was 68.4 (Range: 46-88), NHV 35.1 (range 19-59) and other CMD patients: WAIHA: 61.0 (Range: 53- 75), BP 73.8 (Range: 47 - 88), AMR 54.5 (Range: 36 – 77) and ITP 44.4 (Range: 27 - 65) years.

In CAD patients at baseline, the majority were female 56 of 76 [73.7%], in NHV the majority were male (70.8%), in other CMD patients: in WAIHA and BP equally male or female (50%), in BP the majority were male (60.0%) and in ITP the majority were female (75.0%).

For details on demographics, see efficacy part.

Within the six studies included in the integrated analyses, 208 patients (76 with CAD, 36 patients with other CMDs, and 96 NHVs) were exposed to sutimlimab. Of the 76 patients with CAD, 20 were exposed to placebo in BIVV009-04 Part A and then sutimlimab in BIVV009-04 Part B. An additional 22 NHVs were exposed to placebo

The demographic profile of subjects across all 6 clinical trials is generally considered representative for CAD patients, although ethnicity has not been collected, it was however noted that studies were mostly performed in Europe and North America. The average age throughout the studies is deemed representative of CAD-patients since a median age of diagnosis in the late 60s to early 70s is common.

It is also noted that a majority of patients were female (74% vs 26%) across all studies which could at least partly reflect the higher prevalence in females reported.

Adverse events

Total safety population

Table 25. Overall summary of treatment-emergent adverse events (CAD)

	Study		
	BIVV009-03 (N=24)	**BIVV009-04 (a) (N=42)**	**Total (a) (N=66)**
Total number of TEAEs	519	553	1072
Number of subjects with at least 1 TEAE	24 (100.0%)	40 (95.2%)	64 (97.0%)
Number of subjects with at least 1 related TEAE (b)	14 (58.3%)	22 (52.4%)	36 (54.5%)
Number of subjects with at least 1 CTCAE Grade >=3 TEAE	17 (70.8%)	14 (33.3%)	31 (47.0%)
Number of subjects with at least 1 CTCAE Grade >=3 TEAE infection	9 (37.5%)	4 (9.5%)	13 (19.7%)
Total number of TEAE thromboembolic events	2	3	5
Number of subjects with at least 1 TEAE thromboembolic event	2 (8.3%)	3 (7.1%)	5 (7.6%)
Total number of TESAEs	53	15	68
Number of subjects with at least 1 TESAE	15 (62.5%)	10 (23.8%)	25 (37.9%)
Number of subjects with at least 1 related TESAE (b)	2 (8.3%)	2 (4.8%)	4 (6.1%)
Number of Subjects with at least 1 TESAE infection	8 (33.3%)	2 (4.8%)	10 (15.2%)
Total number of TEAE within 24 hours of start of infusion	11	50	61
Number of subjects with at least 1 TEAE within 24 hours of start of infusion	9 (37.5%)	26 (61.9%)	35 (53.0%)
Total number of TESAE within 24 hours of start of infusion	1	2	3
Number of subjects with at least 1 TESAE within 24 hours of start of infusion	1 (4.2%)	2 (4.8%)	3 (4.5%)
Number of subjects who discontinued study drug and/or withdraw from the study due to TEAE	4 (16.7%)	3 (7.1%)	7 (10.6%)
Number of deaths	3 (12.5%)	1 (2.4%)	4 (6.1%)

1: Abbreviations: CAD=cold agglutinin disease, TEAE=treatment-emergent adverse event, TESAE=treatment-emergent serious adverse event, CTCAE=common terminology criteria for Adverse events.
2: Percentages are based on number of subjects in the Safety Analysis Set. AEs with missing severity assessment are included in CTCAE Grade >=3.
3: Events are coded using MedDRA Version 24.1 . TEAE infections are identified as TEAEs within the system organ class of Infections and Infestations.
4: Thromboembolic events are medically adjudicated.
(a) Including TEAEs which occurred during or after the first dose of BIVV009. Not including TEAEs which occurred during or after the first dose of placebo and up until the first infusion of BIVV009.
(b) Related includes causality categories with "Possible", "Probable", and "Related". AEs with missing relationship are included in Related.

In CAD patients, a majority of 64 out of 66 experienced at least 1 TEAE for a total of 1072 TEAEs and 36 patients experienced at least 1 TEAE assessed as related to sutimlimab.

The most frequently reported TEAEs by SOC were infections and infestations 74%, gastrointestinal disorders 68%, general disorders and administration site conditions 64%, musculoskeletal and connective tissue disorders 53%, vascular disorders 52% and skin, subcutaneous tissue disorders 50%, blood a lymphatic system disorders 49% and nervous system disorders 47%. The most frequently reported TEAEs by PT were anaemia 29%, fatigue 28%, arthralgia 26%, hypertension 24%, diarrhoea 23%, headache 22% nasopharyngitis and cyanosis 20%, and nausea 18%.

In NHVs, NHVs experienced at least 1 TEAE for a total of 47 TEAEs and 11 experienced at least 1 TEAE assessed as related to sutimlimab

In other CMD patients, a majority of patients experienced 1 TEAE across all subgroups. However, only two patients in the BP group and one patient in the ITP group experienced TEAEs that were assessed as related to sutimlimab. The applicant has satisfactorily clarified how the data presentation was performed.

Placebo-controlled data

Overall, all except 1 patient in the sutimlimab group had at least 1 TEAE (sutimlimab 95.5% and placebo 100%), but a greater number of TEAEs were reported in the sutimlimab group than in the placebo group (146 versus 90 events). The incidence of related TEAEs was higher in the sutimlimab group than in the placebo group TEAEs (8 [36.4%] versus 4 [20.0%]), Grade ≥3 TEAEs (22.7% versus 15.0%), TESAEs (3 [13.6%] versus 1 [5.0%]), and TEAEs within 24 hours of start of infusion (11 [50.0%] versus 7 [35.0%]). Three (13.6%) patients in the sutimlimab group and no patient in the placebo group discontinued treatment due to a TEAE. There were no deaths. The incidences were generally similar in the sutimlimab and placebo groups for Grade ≥3 infections (2 [9.1%] and 1 [5.0%]), TESAEs of infection (1 [4.5%] and 1 [5.0%]), related TESAEs (1 [4.5%] and 0%) and thromboembolic events (1 [4.5%] and 0%).

Treatment-emergent AEs were reported most frequently (>20% of patients in either group) in the SOCs blood and lymphatic system disorders, gastrointestinal disorders, general disorders and administration site conditions, infections and infestations, injury, poisoning and procedural complications, musculoskeletal and connective tissue disorders, nervous system disorders, skin and subcutaneous tissue disorders, and vascular disorders.

Treatment-emergent AEs (by PT) reported more frequently in patients 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 (all PTs corresponded to investigator term acrocyanosis) (3 [13.6%] and 0%), constipation (2 [9.1%] and 0%), insomnia 2 [9.1%] and 0%), rash (2 [9.1%] and 0%) and vaccination complication (2 [9.1%] and 0%).

Treatment-emergent AEs (by PT) reported less frequently in the sutimlimab group than in the placebo group (≥2 patient difference in incidence) were anaemia (2 [9.1%] sutimlimab and 4 [20.0%] placebo), diarrhoea (2 [9.1%] and 4 [20.0%]), upper respiratory tract infection (1 [4.5%] and 3 [15.0%]), haemolysis (0% and 2 [10.0%]), sciatica (0% and 2 [10.0%]), and vomiting (0% and 2 [10.0%]).

Adverse drug reaction table:

The applicant provided an updated ADR table from the integrated safety data from the 2 completed Phase 3 clinical studies, BIVV009-03 Part A and Part B and BIVV009-04 Part A and Part B. A modified Bradford Hill causality framework was applied, supported by using the WHO UMC Causality assessment and Threshold Criteria on TEAEs for the cut off criteria to identify the ADRs.

Overall, in BIVV009-04 Part A, there were a greater number of TEAE reported in the sutimlimab group than in the placebo group (146 vs 90 events). The incidence of related TEAEs was higher in the sutimlimab group than in the placebo group 36% vs 20%, Grade≥3 TEAE 23% vs 15%, TESAEs 14% vs 5% and TEAEs within 24 hours of start of infusion 50% vs 35%.

The most frequently TEAEs reported by SOC compared to placebo were gastrointestinal disorders 50% vs 35%, vascular disorders 41% vs 0%, general disorders and administration site conditions 41% vs 35%, skin and subcutaneous tissue disorders 32% vs 20% and nervous system disorders 32% vs 25%. Of these the imbalance in vascular disorders is the most striking finding with zero cases in the placebo group and almost half of the patients in the test group affected. The events were hypertension, Raynaud's phenomenon and cyanosis.

Adverse events of special interest

Thromboembolic events

In CAD patients, thromboembolic events, 5 (7.6%) patients experienced a total of 5 TEAEs of a thromboembolic event which included cerebral venous sinus thrombosis (n=1), device-related thrombosis (n=1), peripheral artery thrombosis (n=1), transient ischemic attack (n=1), and deep vein thrombosis (n=1). In BIVV009-03 Part B, one patient had reported a serious thromboembolic event of peripheral artery thrombosis and one patient had a nonserious thromboembolic event of device-related thrombosis. Both events were assessed by the Investigator as unrelated to sutimlimab. In BIVV009-04, three patients experienced treatment-emergent thromboembolic events (cerebral venous thrombosis, deep vein thrombosis and transient ischemic attack). The event of cerebral venous thrombosis was assessed as related to treatment.

In other CMD patients, no thromboembolic events were observed.

Treatment-emergent adverse events with onset within 24 hours of infusion

In CAD patients, 35 of 66 (53.0%) patients with CAD experienced a total of 61 TEAEs within 24 hours of infusion. The most frequently reported TEAEs that occurred within 24 hours of the start of infusion of sutimlimab by PT were infusion-related reaction 6%, and hypertension and nausea 5%.

The most common TEAEs by SOC that occurred within 24 hours were general disorders and administration site conditions, gastrointestinal disorders and injury, poisoning and procedural complications, vascular disorders, skin and subcutaneous tissue disorders, and nervous system disorders, musculoskeletal and connective tissue disorders, and infections and infestations.

A total of 23 patients with CAD were exposed to at least 1 undiluted infusion of sutimlimab in study BIVV009-04 Part B and 43.5 3% experienced at least 1 TEAE for a total of 24 TEAEs within 24 hours of infusion. None of these patients discontinued from the study.

Treatment-emergent adverse events by time of onset

CAD patients

Overall, among the 66 patients with CAD, the number of patients with at least 1 TEAE within a given time interval (<6 months, 6 to <12 months, 12 to <18 months, 18 to <24 months, 24 to <30 months, 30 to <36 months, 36 to <42 months, and ≥42 months) ranged from 1 to 55 patients with a varying incidence based on the number of patients followed within a given interval.

The events of anaemia appeared to be evenly distributed over time through all time intervals, though a slightly higher number of patients experienced anaemia in the 35 - <45-week interval. The majority of the events of anaemia were reported to be due to underlying cold agglutinin disease. The frequency of patients with at least 1 TEAE within the SOC of infections and infestation was generally similar across all time intervals. There were no serious TEAEs of hypersensitivity reaction or anaphylaxis or a TESAE suggestive of a potential hypersensitivity reaction.

Treatment-emergent adverse events of hypersensitivity and anaphylaxis

Allergic-type hypersensitivity reactions are a well-recognized risk of monoclonal antibody therapies. Sutimlimab dose times were recorded for each day dosing, however, the specific time of TEAE onset was not recorded for every TEAE. Therefore, the precise temporal relationship between dose administration and TEAE onset could not be determined in all cases. Treatment-emergent AEs with onset time within 24 hours of infusion were flagged.

Overall, 27 CAD patients experienced a total of 31 TEAEs identified as events that may be suggestive of potential hypersensitivity reaction. Of the 31 TEAEs, 17 events were assessed as related to sutimlimab by the Investigator. Ten of the patients experienced TEAEs within 24 hours of infusion. One of the hypersensitivity reactions led to sutimlimab discontinuation (infusion related reaction). Overall, there were no serious TEAEs of hypersensitivity reaction or anaphylaxis or a TESAE suggestive of a potential hypersensitivity reaction reported in either treatment group.

In NHVs, two patients experienced TEAEs that were nonserious where one was deemed possibly related to sutimlimab. No TEAEs suggestive of a serious hypersensitivity reaction or anaphylaxis were reported among the NHVs who were exposed to sutimlimab.

In other CMD patients, nonserious TEAEs suggestive of potential hypersensitivity reactions associated with sutimlimab administration were reported but no serious hypersensitivity reactions or anaphylactic reactions were identified.

Treatment-emergent infections

The risks associated with long-term pharmacological inhibition of the proximal portion of the classical complement system are presently unknown. Subjects with inherited deficiencies of classical complement pathway components have an increased risk of infections with a variety of encapsulated bacterial organisms. Two marketed terminal complement pathway inhibitors, eculizumab and ravulizumab-cwvz, are labelled with a warning for an increased risk of meningococcal infections, which is thought to be due to C5 inhibition preventing the formation of the membrane attack complex which is essential to host defence against this encapsulated bacterium.

CAD patients

Treatment-emergent AEs of infections were defined as all TEAEs listed within the SOC of infections and infestations. Of the 66 patients in the CAD Safety Analysis Set, 49 (74.2%) experienced at least 1 TEAE of infection.

Treatment-emergent AEs of infection reported by >2 of the 66 patients included:

- nasopharyngitis (13 [19.7%] patients)
- upper respiratory tract infection (10 [15.2%] patients)
- Urinary tract infection (8 [10.6%] patients)
- Cystitis, gastroenteritis, rhinitis (7 [10.6%] patients)
- Escherichia urinary tract infection (4 [6.1%] patients)
- Oral herpes, respiratory tract infection, tooth infection, urinary tract infection bacterial (3 [4.5%] patients)

Diverticulitis, eye infection, Herpes zoster, influenza, otitis externa, pneumonia, sinusitis, skin candida, viral infection (2 [3.0%] patients) Treatment-emergent AEs of infection ≥Grade 3 were reported for 13 of the 66 (19.7%) patients including:

- Urinary tract infection (4 [6.1%] patients)
- Appendicitis, asymptomatic COVID-19, COVID-19 pneumonia, erysipelas, Escherichia sepsis, febrile infection, Herpes zoster, pneumococcal sepsis, Klebsiella pneumonia, respiratory tract infection, Staphylococcal skin infection, Streptococcal sepsis, urinary tract infection bacterial, urosepsis, and viral infection (1 [1.5%] patients each)

Treatment-emergent SAEs of infections were reported for 10 of the 66 (15.2%) patients including:

Appendicitis, asymptomatic COVID-19, COVID-19 pneumonia, erysipelas, Escherichia sepsis, febrile infection, Herpes zoster, pneumococcal sepsis, Klebsiella pneumonia, respiratory tract infection, Streptococcal sepsis, urinary tract infection, urinary tract infection bacterial, urosepsis, viral infection, Staphylococcal wound infection (1 [1.5%] patients each)

No reports of meningococcal infection, meningitis, or infections were identified from the medical review of the AE listings and available information from the global safety database. The majority of patients with serious infections had underlying risk factors for infection.

One patient died due to an event of pneumonia caused by Klebsiella pneumoniae. The patient was hospitalized with worsening general condition and acrocyanosis and Klebsiella pneumonia. Fourteen days after the last dose of sutimlimab, the patient died due to Klebsiella pneumonia.

The applicant has provided literature indicating that the risk of meningococcal infection with a selective C1s inhibitor such as sutimlimab is expected to be lower compared to terminal inhibitors (mainly C5b-C8 components). Nevertheless, a causal link between the serious infections recorded in the present studies and sutimlimab cannot be excluded. Consequently, the Applicant has agreed to include `serious infections ´ as an important identified risk which is endorsed.

Other CMD patients

Treatment-emergent AEs of infections were defined as all TEAEs listed within the SOC of infections and infestations. No patients with WAIHA experienced a TEAE of infection. Four of the 10 (40.0%) patients with BP experienced at least 1 TEAE of infection including nasopharyngitis (3 [30.0%] patients), and rhinitis and urinary tract infection (1 [10.0%] patient each). One of the 10 (10.0%) patient with AMR experienced a TEAE of infection (rhinitis).

- Seven of the 12 (58.3%) patients with ITP experienced at least 1 TEAE of infection including viral upper respiratory tract infection (3 [25.0%] patients), viral gastroenteritis and sinusitis (2 [16.7%] patients each), and bacterial bronchitis, diverticulitis, Herpes simplex, infected dermal cyst, nasopharyngitis, suspected Covid-19, tooth infection, and upper respiratory tract infection (1 [8.3%] patient each).

In NHVs, the type and frequency of infections were consistent with that seen in a healthy study population.

In the context of serious infections possible co-treatment with other substances weakening the immune system must be considered. In both BIVV009-03 and BIVV009-04, specific therapies to reduce antibody production, such as rituximab and rituximab combination therapies, were prohibited but such treatment could else be considered for these patients. The applicant has sufficiently clarified the information regarding the patients that received prohibited medications during the studies and the SmPC currently includes a statement in 5.1 that rituximab alone or in combination with cytotoxic agents and this is deemed appropriate.

Serious adverse event/deaths/other significant events

CAD patients

Overall, 25 of 66 (37.9%) patients experienced a total of 68 TESAEs. The SOCs with TESAEs included:

infections and infestations (10 of 66 [15.2%] patients)

vascular disorders (5 of 66 [7.6%] patients each)

Blood and lymphatic system disorders; hepatobiliary disorders; and neoplasms benign, malignant and unspecified (including cysts and polyps) (4 of 66 [6.1%] patients each)

Cardiac disorders; gastrointestinal disorders; injury, poisoning and procedural complications; musculoskeletal and connective tissue disorders; and nervous system disorders (3 of 66 [4.5%] patients each)

General disorders and administration site conditions (2 of 66 [3.0%] patients)

Congenital, familial and genetic disorders; eye disorders; investigations; renal and urinary

disorders (1 of 66 [1.5%] patients each)

All TESAEs by PT were reported for 1 of 66 (1.5%) patients except for urosepsis which was reported by 2 of 66 (3.0%) patients.

Thirty-one of the 66 CAD patients experienced at least 1 TEAE ≥Grade 3 in severity and 13 experienced at least 1 TEAE of infection ≥Grade 3 in severity. Of the 66 patients, 25 experienced a total of 68 TESAEs, 4 patients experienced at least 1 TESAE assessed by the investigator as related to sutimlimab, and 10 patients experienced at least 1 TESAE of infection.

BIVV009-03

Fifteen of the 24 (62.5%) patients experienced at least 1 TESAE for a total of 53 TESAEs. The SOCs with the most TESAEs were infection and infestations (8 of 24 [33.3%] patients); blood and lymphatic system disorders; cardiac disorders; gastrointestinal disorders; hepatobiliary disorders; vascular disorders; and neoplasms benign, malignant and unspecified (including cysts and polyps) (3 of 24 [12.5%] patients each); general disorders and administration site conditions and nervous system disorders (2 of 24 [8.3%] patients each). All TESAEs were reported for 1 of 24 (4.2%) patients each except for cyanosis (acrocyanosis) which was reported by 2 of 24 (8.3%) patients. One of the TESAEs (an event of viral infection) were assessed by the investigator as related to sutimlimab treatment (in Part B).

BIVV009-04 Parts A and B

Four of the 22 (18.2%) patients in the sutimlimab group experienced at least 1 TESAE for a total of 5 TESAEs. One elderly patient in the sutimlimab group had a TESAE of Grade 3 PT cerebral venous thrombosis on Day 86. Study drug was temporarily interrupted due to the event. The event resolved on Day 88 after treatment with antithrombotic agents and sutimlimab was resumed on Day 99. This TESAE was assessed by the Investigator as related to sutimlimab. Additionally, a patient experienced a TESAE of Raynaud's phenomenon associated with extremity necrosis that required amputation of all digits on both hands and bilateral below knee amputation. The TESAE was assessed by the Investigator as not related to the study treatment. Six of the 20 (5.4%) patients in the placebo group reported a total of 10 TESAEs. Two patients had received placebo during Part A of the study. One patient experienced a TESAE of hip fracture as a consequence of accidental fall and a TESAE of hypertension. The event of hypertension was assessed as related to the sutimlimab by the Investigator.

NHV

No NHVs experienced a TESAE.

Other CMD patients

No patient with WAIHA or AMR exposed to sutimlimab experienced a TESAE.

Of the 12 patients with ITP exposed to sutimlimab, 4 (33.3%) experienced 5 TESAEs including events of thrombocytopenia, diverticulitis, migraine, dural arteriovenous fistula, petechiae.

Deaths

Three fatal events were observed in study BIVV009-03 and one fatal event in study BIVV009-04. In BIVV009-03 Part A, a patient experienced a gastrointestinal haemorrhage and was later diagnosed with hepatic cancer and withdrawn from the study and later died. This event was deemed not related to sutimlimab. In BIVV009-03 Part B, one patient had a TESAE of Klebsiella pneumonia on day 949 and died on day 960. Further, one patient in BIVV009-03 Part B with a complex medical history experienced a TESAE reported as "terminal aggravation of cold type haemolytic anaemia" and the patient later died. Neither of the fatal events in Part B were deemed as related to sutimlimab.

In addition, another fatal event was observed in a BP patient that died due to cardiac failure and was deemed unlikely related to sutimlimab.

Malignancy

A single case of malignancy, deemed not related to treatment, was observed (see death above). Nevertheless, on request, the applicant has provided evidence indicating limited clinical and pre-clinical data to support a causal relationship between sutimlimab and malignancy

Laboratory findings

Clinical chemistry

CAD patients

PCSA chemistry laboratory values reported for ≥20% of patients included blood urea nitrogen ≥10.7 mmol/L (16of 66 [24.2%] patients), direct bilirubin >1.5 x ULN (30 of 66 [45.5%] patients), and total bilirubin >1.5 x ULN (34 of 76 [44.7%] patients). High PCSA direct bilirubin values were either transient, isolated, or occurred in study participants with other high direct bilirubin values prior to study drug administration. Abnormalities in total bilirubin are nevertheless not unanticipated as a result of the extravascular and sometimes intravascular haemolytic process seen with CAD and the patients needed to have total bilirubin > ULN at screening in order to qualify for the study.

In BIVV009-03, two patients with high blood urea nitrogen (BUN) and creatinine values during screening had persistent high PCSA BUN and creatinine values postbaseline which were intermittently above the highest screening value of unclear aetiology. One patient had a nonserious Grade 2 TEAE of chronic kidney disease (reported as chronic renal insufficiency - creatinine increased) that was assessed by the Investigator as not related to sutimlimab. Otherwise, the majority of high PCSA BUN values were transient and isolated or intermittent with interval improvements.

NHV

There were no apparent clinically relevant trends in clinical chemistry parameters in the clinical studies in NHVs. Sporadic out-of-range parameters were observed in individual patients at isolated timepoints. The majority of PCSA chemistry values were isolated findings. One NHV had high total bilirubin values of unknown aetiology during screening, baseline, and every postbaseline assessment that increased on Days 1, 8, and 15.

One patient in the TNT009-02 study exposed to sutimlimab 75 mg/kg experienced a nonserious Grade 1 TEAE of increased alanine aminotransferase that was assessed as possibly related to study treatment. This patient's abnormal ALT values did not meet the PCSA criteria for ALT.

Other CMD patients

Overall, the PCSA chemistry values in patients with other CMDs were isolated or transient or consistent with the underlying disease indication (i.e., elevated bilirubin in patients with WAIHA with haemolysis or elevated creatinine in patients with renal allografts).

Haematology

CAD patients

Overall, potentially clinically significant abnormalities (PCSA) haematology laboratory values reported for ≥20% of patients included haematocrit ≤30% (52 of 73 [71.2%] patients), haemoglobin ≤10 g/dL (52 of 76 [68.4%] patients]), and lymphocytes <0.8 x 10^9/L (35 of 75 [46.7%] patients) and neutrophils <1.5 ×10^9/L (16 of 75 [21.3%] patients). Patients needed to have haemoglobin ≤10 g/dL at screening to qualify for the study and it is anticipated that the level would vary with disease fluctuations and although there was an increase in haemoglobin in most patients as a treatment effect there was variability in response and certain non-responders recorded (see efficacy part).

Low values for leukocytes counts were observed in BIVV009-03 (6/24 [25.0%]) and BIVV009-04 in the sutimlimab group (3/22 [113.6%]) with 2/20 [10.0%] observed case in the placebo group (1/20). For neutrophil counts, low values were observed in BIVV009-03 (7/24 [25.0%]) and BIVV009-04 (43/22 [29.2%]), compared to in the placebo-group (5/19 [26.3%]). Notably the decreases appeared transient as they were observed in the first part of the study only.

Other CMD patients and NHV

In NHVs, there were no clinically relevant trends observed. In patients with WAIHA, BP, and AMR there were no clinically meaningful patterns or trends observed in mean haematology laboratory values, change from baseline and shifts as discussed in the BIVV009-01 Part C CSR. Of note, there was a minor increase in the peripheral eosinophil count noted in patients with BP, though the difference was not clinically significant.

Systemic Lupus Erythematosus

Due to the mechanism of action of sutimlimab and the increased incidence of SLE in patients with congenital deficiencies of components of the classical complement pathway, standard clinical biomarkers related to SLE (e.g., double-stranded DNA) and other autoimmune disorders were incorporated into the study design of all studies in the sutimlimab clinical development program. The clinical biomarkers used for SLE, while also including some related to other autoimmune disorders, are broadly referenced as "SLE panel" parameters. Individual studies assessed different SLE panel parameters based on the parameters included in the given study central or local laboratory SLE panel test. The clinical utility and predictive value of positive SLE panel autoantibodies in the absence of clinical signs and symptoms of autoimmune disease is unknown as the positive predictive value may vary in different populations and by laboratory parameter.

In CAD patients, 27 of 76 had all negative results or had all missing results prior to sutimlimab exposure and 49 of 76 had at least 1 positive SLE panel parameter result prior to sutimlimab exposure. Eight out of 76 patients were positive for any post-baseline assessment of SLE parameter and seven were positive for at least 1 SLE panel parameter at the last postbaseline evaluation.

In BIV009-04 Part A, prior to receiving the study drug, 13 patients in the sutimlimab group and 16 patients in the placebo group had ≥1 positive value for an SLE parameter and 9 patients in sutimlimab group and 4 patients in placebo group were negative or had missing values for all SLE panel parameters. In the patients who were negative or had all missing SLE panel assessments prior to receiving study drug, 3 of 9 (33.3%) patients in the sutimlimab group and 1 of 4 (25.0%) patients in

the placebo group switched from negative or missing at baseline to positive for ≥1 SLE parameter at any post baseline assessment. Furthermore, two of the 4 patients exposed to placebo in Part A and then sutimlimab in Part B were negative in all SLE panel parameters prior to exposure had at least 1 positive SLE panel parameter result at any time postbaseline and 1 was positive at the last postbaseline evaluation.

In other CMD patients, overall, there were some intermittent changes from negative to positive or from positive to negative in patients with other CMDs exposed to sutimlimab without any clinical correlate.

Although there were some observed positive SLE panel parameters, the values seem to be variable over time and without any obvious pattern. In addition, none of the patients who shifted from being negative at baseline to being positive post baseline for the SLE parameter panel, developed SLE.

Immunogenicity

CAD patients

One patient with primary CAD had an ADA positive test result after sutimlimab dosing at the end-of-treatment assessment. This patient had multiple nonserious TEAEs reported which were assessed by the Investigator as unlikely related to study drug and resolved prior to the ADA positive test result. The patient received a total of 5 doses of sutimlimab and completed the study. The TEAEs in this patient were not suggestive of hypersensitivity reactions.

Two patients enrolled in the BIVV009-03 and 6 patients enrolled in the BIVV009-04 developed treatment-emergent ADAs. The potential presence of treatment-emergent ADAs does not appear to have an impact on the total exposure or PD response of sutimlimab.

NHV

Antidrug antibody data are available in the CSRs for the studies conducted in NHVs. Overall, although several NHVs had a positive ADA test result after exposure to sutimlimab, sutimlimab exposure did not appear to have a clinical impact on the safety profile of sutimlimab administration in NHVs.

Other CMD patients

Three patients with AMR had an ADA positive test result after sutimlimab dosing at the end of treatment assessment. One of these patients also had a positive ADA test at baseline but the titer increased at the end of treatment assessment. Overall, the presence of a positive ADA test did not appear to impact the safety profile of sutimlimab administration in WAIHA, BP, or AMR patients.

Overall, in CAD patients, from the clinical safety summary, the applicant stated that one patient with primary CAD in BIVV009-01 had an ADA positive result. This patient had multiple nonserious TEAEs reported which were assessed by the Investigator as unlikely related to study drug and resolved prior to the ADA positive test result. One patient in BIVV009-03 and three patients in BIVV009-04 developed treatment-emergent ADAs.

In other CMD patients, three patients with AMR had ADA positive test results.

Vital signs

CAD patients

The majority of PCSA vital sign values were consistent with other pre-treatment assessments or underlying medical history (ie, history of hypertension or hypotension).

- Among the 76 patients with CAD, PCSA high/increased or low/decreased systolic blood pressure changes were reported for 22 of 76 (28.9%) and 25 of 76 (32.9%) patients, respectively.
- Potentially clinically significant high/increased or low/decreased diastolic blood pressure changes were reported for 12 of 76 (15.8%) and 28 of 76 (36.8%) patients, respectively.
- Potentially clinically significant high/increased heart rates were reported for 22 of 76 (28.9%) patients and PCSA low/decreased heart rates were reported for 28 of 76 (36.8%) patients.

Two patients with CAD without a history of hypertension (1 in BIVV009-03 and 1 in BIVV009-04 Part A) experienced a TEAE of increased blood pressure. The increased blood pressure was assessed by the Investigator as related to the study drug in 1 of the 2 patients.

A total of 16 of 76 (21%) patients with CAD reported TEAEs of hypertension:

- 1 (1.3%) patient reported a TEAE of essential hypertension:
- 5 patients had pre-existing medical history of hypertension
- 6 patients experienced at least 1 TEAE of hypertension that was assessed by the Investigator as related to sutimlimab
- 6 had reported at least 1 PCSA values for high blood pressure (either systolic or diastolic).

As of the data cut-off date, no apparent trend was observed in temperature, heart rate, or respiratory rate over the duration of treatment.

NHVs

There were no apparent clinically meaningful pattern or trend in vital signs observed.

Other CMD patients

The majority of PCSA vital sign findings in patients with other CMDs were transient and consistent with other predosing values or consistent with underlying medical history. Overall, there were no clinically relevant trends observed in vital sign data.

In CAD patients, potentially clinically significant increased blood pressure changes were reported in 10 subjects and decreased in 22 patients. Potentially clinically significant high/increased heart rates were reported for 17/71 patients and PCSA low/decreased heart rates were reported for 27/71 patients. Two patients without previous history of hypertension experienced TEAE of increased blood pressure and one case was deemed related to study drug. A total of 13/76 patients reported TEAE of hypertension.

Safety in special populations

Age

Overall, 51 of 76 (67.1%) patients were ≥65 years of age and 25 of 76 (32.9%) were <65 years of age. Overall, among the CAD Safety Analysis Set, the mean age at baseline was 68.4 (Range: 46 – 88) years, with the majority (51 of 76 [67.1%]) patients ≥65 years old. A total of 22 of 23 (95.7%) patients <65 years old experienced at least 1 TEAE for a total of 370 TEAEs. A total of 42 of 43 (97.7%) patients ≥65 years old experienced at least 1 TEAE for a total of 702 TEAEs.

Gender

Overall, 18 of 66 (27.3%) patients were male and 48 of 66 (72.7%) patients were female. Each of the 18 male patients experienced at least 1 TEAE for a total of 313 TEAEs. A total of 46 of 48 (95.8%)

female patients experienced at least 1 TEAE for a total of 759 TEAEs. Male patients had a higher frequency of TEAEs than female patients within e.g., the SOC of of blood and lymphatic system disorders (61.1% versus 43.8%), cardiac disorders (27.8% versus 16.7%), gastrointestinal disorders (83.3% versus 62.5%).,. Overall, although there were some differences in the distribution of TEAEs by gender, many of these differences were consistent with patterns that might be attributed to the patient's gender (ie, increased risk of urinary tract infections in female patients or cardiac disease in male patients).

Race

Due to varying global regulations, race information was not collected for 49 of the 66patients in the CAD Analysis Set. Of 17 patients with race information collected, 7 were white and 10 were Asian. Six (85.7%) white patients experienced at least 1 TEAE for a total of 92 TEAEs. All Asian patients experienced at least 1 TEAE for a total of 141 TEAEs.

Overall, it is difficult to draw a firm conclusion due to small numbers of patients in each age/gender/race group. On the other hand, no alarming safety related findings were found in either of these subgroups.

Use in pregnancy and lactation

There is limited data available for the safety of sutimlimab in pregnant and/or lactating women.

Immunological events

Please see above.

Safety related to drug-drug interactions and other interactions

For biologic therapies, drug-drug interaction studies are usually not applicable based on mechanisms of degradation and elimination and hence were not conducted by the applicant.

Discontinuation due to adverse events

CAD patients

One of the 24 (4.2%) patients in BIVV009-03 Part A was withdrawn from the study due to a pre-treatment SAE with onset during the screening period on Day -8 prior to the first dose of study drug. This patient also developed TESAE of arthralgia, which was assessed by the Investigator as unrelated to sutimlimab. This event did not result in discontinuation of study treatment.

Another patient in BIVV009-03 Part B was withdrawn from the study due to TESAEs of cyanosis (acrocyanosis) and Klebsiella pneumonia on day 949. The patient received the last dose of study drug on day 946. Patient died from Klebsiella pneumonia on day 960. Both events were assessed as not related to sutimlimab by the Investigator.

Overall, 9 of the 66 (13.6%) patients in the CAD Safety Analysis Set discontinued treatment with sutimlimab or withdrew from the study due to at least 1 TEAE/TESAE.

NHV

Overall, 1 of the 96 (1.0%) NHVs discontinued treatment and was discontinued from the study due to a TEAE. The patient discontinued from the study due to a vasovagal response prior to planned study treatment administration.

Other CMD patients

No patients with AMR or ITP exposed to sutimlimab discontinued treatment due to a TEAE. One patient with WAIHA permanently discontinued study treatment due to a Grade 2 nonserious TEAE of haemolysis with an onset on Day 9.

Overall, the pattern of AEs leading to discontinuations is not unexpected.

Post marketing experience

This product has not yet been marketed in the European Union or in any other countries.

Discussion on clinical safety

The safety profile of sutimlimab has been assessed in 6 clinical studies, including four Phase 1 studies and two Phase 3 studies. The studies were conducted to support the indication for the treatment of haemolytic anaemia in adult patients with CAD and all studies are completed. Of note, the Applicant has presented an integrated safety overview with CAD patients only obtained from the BIVV009-03 and BIVV009-04 studies and hence only encompassing 66 patients.

In general, presentation of safety data in the application is considered acceptable. The main limitations relating to the safety data is the small number of patients treated with sutimlimab and only one of the studies conducted in CAD-patients was placebo controlled. However, the difficulty to collect more comprehensive data is acknowledged given the rareness of the disease.

This assessment focuses on the pools for integrated analysis concerning the CAD, NHV (normal healthy volunteers) and other CMD (complement mediated disorders) patients.

Patient exposure

Overall, within the six studies included in the integrated analyses, 208 subjects have participated (76 with CAD, 36 patients with other CMDs, and 96 NHVs). Of the 76 patients with CAD, 20 were exposed to placebo in BIVV009-04 Part A and then sutimlimab in BIVV009-04 Part B. An additional 22 NHVs were exposed to placebo.

The demographic profile of subjects across all 6 clinical trials is generally considered representative for CAD patients, although ethnicity has not been collected; it is however noted that the studies were mostly performed in Europe and North America.

The average age throughout the studies is deemed representative of CAD-patients since a median age of diagnosis late 60s to early 70s is common. It is also noted that a majority of patients were female (74% vs 26%) across all studies and for all patients.

Sutimlimab is intended for long-term treatment of CAD. However, only 43 patients were exposed to sutimlimab over 55 weeks and 18 patients over 145 weeks in the CAD-population. Both the single-armed BIVV009-03 and open-label study part of BIVV009-04 contributes with long-time data (up to 52 weeks). Supportive safety data are available from other phase 1 studies in other CMD patients or in healthy volunteers. Although small and single armed they add to the total safety data base. The applicant has provided the final CSRs for the completed BIVV009-01E (duration of study was 2.5 years), BIVV009-03 Part B (duration of study was 2 years) and BIVV009-04 Part B studies (duration of study was 1 year) along with an RMP update and Cadence registry protocol. The Applicant has also presented an integrated safety analysis with CAD patients obtained from studies BIVV009-03 and BIVV009-04 that includes 66 patients out of the total 76 CAD patients.

Adverse events - total safety population

A majority of CAD patients (64 of 66) experienced at least 1 TEAE for a total of 1072 TEAEs and 36 patients experienced at least 1 TEAE assessed as related to sutimlimab. The most frequently reported TEAEs by SOC were infections and infestations 74%, gastrointestinal disorders 68%, general disorders and administration site conditions 64%, musculoskeletal and connective tissue disorders 53%, vascular disorders 52% and skin and subcutaneous tissue disorders 50%. The most frequently reported TEAEs by PT were anaemia 29%, fatigue 28%, arthralgia 26%, hypertension 24%, diarrhoea 23%, headache 22%, nasopharyngitis and cyanosis 20% and nausea 18%.

Thirty-one of the 66 CAD patients experienced at least 1 TEAE ≥Grade 3 in severity and 13 experienced at least 1 TEAE of infection ≥Grade 3 in severity. Of the 66 patients, 25 experienced a total of 68 TESAEs, 4 patients experienced at least 1 TESAE assessed by the investigator as related to sutimlimab, and 10 patients experienced at least 1 TESAE of infection. In study BIVV009-03 Part A, one patient died from hepatic cancer which was assessed as not related to sutimlimab.

Adverse events - placebo-controlled data

Overall, in BIVV009-04 Part A, there were a greater number of TEAE reported in the sutimlimab group than in the placebo group (146 vs 90 events). The incidence of related TEAEs was higher in the sutimlimab group (n=22) than in the placebo group (n=20) 36% vs 20%, Grade≥3 TEAE 23% vs 15%, TESAEs 14% vs 5% and TEAEs within 24 hours of start of infusion 50% vs 35%.

The most frequently TEAEs reported by SOC compared to placebo were gastrointestinal disorders 50% vs 35%, vascular disorders 41% vs 0%, general disorders and administration site conditions 41% vs 35%, skin and subcutaneous tissue disorders 32% vs 20% and nervous system disorders 32% vs 25%. Of these the imbalance in vascular disorders is the most striking finding with zero cases in the placebo group and almost half of the patients in the test group affected. The events were hypertension, Raynaud's phenomenon and cyanosis. Consequently, hypertension, Raynaud's phenomenon and cyanosis are included in the Section 4.8 of the SmPC.

The most frequent adverse events by PT were headache, hypertension, Raynaud´s phenomenon, Rhinitis and cyanosis and this is also in line with what is presented in the SmPC (in 4.8) and is endorsed.

Serious adverse events and deaths

In the total CAD treated population in BIVV009-03 and BIVV009-04 (n=66), 68 TESAE were reported in 25 subjects. In BIVV009-03, one of the TESAEs (cerebral venous thrombosis) was assessed by the investigator as related to sutimlimab treatment. In BIVV009-04, two events (viral infection and hypertension) were assessed as related to the sutimlimab treatment.

There are small numbers in each group and the TESAEs reported were generally of various nature and individual PTs were often reported in single patients with the exception of infections. Treatment-emergent SAEs of infections were reported for 10 of the 76 (13.2%) patients, 5 of these being sepsis. Infections are expected to occur as a result of inhibition of the complement system.

One fatal event was observed in study BIVV009-03 Part A, where a patient experienced a gastrointestinal haemorrhage and was later diagnosed with hepatic cancer and withdrawn from the study. This event was deemed not related to sutimlimab. Another fatal event was observed in a BP patient that died due to cardiac failure and was deemed unlikely related to sutimlimab. The applicant has provided evidence that indicated that there is limited clinical and pre-clinical data to support a causal relationship between sutimlimab and malignancy and hence it is agreed that malignancy should currently not be added as a safety concern. In BIVV009-03 Part B, two patients died; one patient had a TESAE of Klebsiella pneumonia on day 946 and died on day 960 and another patient in BIVV009-03

Part B with a complex medical history experienced a TESAE reported as "terminal aggravation of cold type haemolytic anaemia". Neither of the fatal events in Part B were deemed as related to sutimlimab.

Clinical chemistry

There were increases in both direct and total bilirubin in BIVV009-03 (42% and 33%) and in both sutimlimab (41% and 50%) and placebo (55% and 15%) groups in BIVV009-04. It is agreed that abnormalities in total bilirubin are anticipated as a result of the extravascular and sometimes intravascular haemolytic process seen with CAD. High PCSA direct bilirubin values were either transient, isolated, or occurred in study participants with other high direct bilirubin values prior to study drug administration. One patient exposed to sutimlimab experienced a nonserious Grade 1 TEAE of increased ALT that was assessed as possibly related to study treatment. The abnormal ALT values did not meet the PCSA criteria for ALT.

Overall, the PCSA chemistry values in patients with other CMDs were isolated or transient or consistent with the underlying disease indication (i.e., elevated bilirubin in patients with warm antibody hemolytic anemia [WAIHA] with haemolysis or elevated creatinine in patients with renal allografts).

Haematology

For some CAD patients, haemoglobin and haematocrit values beyond normal were observed across all studies and in both treatment groups in study BIVV009-04. Patients needed to have haemoglobin ≤10 g/dL at screening to qualify for the study and it is anticipated that the level would vary with disease fluctuations. Although there was an increase in haemoglobin in most patients as a treatment effect there was variability in response and certain non-responders recorded (see efficacy part).

Further, low values for leukocytes were observed in BIVV009-03 (25%) and BIVV009-04 in the sutimlimab group (14%) with no observed cases in the placebo group (10%). For neutrophil counts, low values were observed in BIVV009-03 (29%) and BIVV009-04 (14%), compared to in the placebo-group (26%). In BIVV009-04, the Applicant reports that low neutrophil values were observed from week 1 to 21, after which the values increased to a range similar to the screening values. The applicant has provided clarifications on the fluctuations on laboratory values over time and it is agreed that there was no obvious trend in patients that experienced low leukocyte and/or low neutrophils.

SLE

Due to the mechanism of action of sutimlimab and the increased incidence of SLE in patients with congenital deficiencies of components of the classical complement pathway, standard clinical biomarkers related to SLE (eg, double-stranded DNA) and other autoimmune disorders were incorporated into the study design of all studies in the sutimlimab clinical development program.

In CAD patients, 28 of 76 had all negative results or had all missing results prior to sutimlimab exposure and 48 of 76 had at least 1 positive SLE panel parameter result prior to sutimlimab exposure. Eight out of 76 patients were positive for any post-baseline assessment of SLE parameter and seven were positive for at least 1 SLE panel parameter at the last postbaseline evaluation.

In BIV009-04 Part A, prior to receiving the study drug, 13 patients in the sutimlimab group and 16 patients in the placebo group had ≥1 positive value for an SLE parameter and 9 patients in sutimlimab group and 4 patients in placebo group were negative or had missing values for all SLE panel parameters. In the patients who were negative or had all missing SLE panel assessments prior to receiving study drug, 3 of 9 (33%) patients in the sutimlimab group and 1 of 4 (25%) patients in the placebo group switched from negative or missing at baseline to positive for ≥1 SLE parameter at any post baseline assessment. Furthermore, two of the 4 patients exposed to placebo in Part A and then

sutimlimab in Part B were negative in all SLE panel parameters prior to exposure had at least 1 positive SLE panel parameter result at any time postbaseline and 1 was positive at the last postbaseline evaluation.

Although there were some observed positive SLE panel parameter, the values seem to be variable over time and without any obvious pattern. In addition, none of the patients that shifted from negative at baseline to positive post baseline for the SLE parameter panel, developed SLE.

Development of SLE is concluded as an `important potential risk´ in the RMP by the applicant, which is endorsed. A warning is also included in section 4.8 of the SmPC.

Immunogenicity

In CAD patients, from the clinical safety summary, the Applicant stated that one patient with primary CAD in BIVV009-01 had an ADA positive result. This patient had multiple nonserious TEAEs reported which were assessed by the Investigator as unlikely related to study drug and resolved prior to the ADA positive test result. Two patients in BIVV009-03 and 6 patients in BIVV009-04 developed treatment-emergent ADAs.

In other CMD patients, three patients with AMR had ADA positive test results. It is unclear if the cases were related to study drug or not. Overall, it appears that the presence of positive ADA tests did not affect the safety profile of sutimlimab, however the conclusions to be drawn are substantially limited by the low number of exposed subjects. The applicant has clarified and updated on the number of subjects that developed treatment emergent ADAs accordingly.

Vital signs

In CAD patients, potentially clinically significant increased blood pressure changes were reported in 12 subjects and blood pressure decreased in 25 patients. Potentially clinically significant high/increased heart rates were reported for 22/76 patients and PCSA low/decreased heart rates were reported for 28/76 patients. Two patients without previous history of hypertension experienced TEAE of increased blood pressure and one case was deemed related to study drug. A total of 16/76 patients reported TEAE of hypertension.

Overall, it is agreed that there were no clinically significant trends in ECG finds in CAD patients, NHV nor other CMD patients exposed to sutimlimab. Any potential abnormality found during the physical examination was reported as an AE and hence the physical examination data were not formally analysed.

Safety in special populations

Age

In CAD patients, a total of 22 of 23 (95.7%) patients <65 years old experienced at least 1 TEAE for a total of 370TEAEs. A total of 42 of 43 (92.2%) patients ≥65 years old experienced at least 1 TEAE for a total of 702 TEAE. Data are almost exclusively derived from elderly patients.

Gender

In CAD patients, 18 of 66 (27.3%) patients were male and 48 of 66 (72.7%) patients were female. Literature suggests a slightly higher prevalence of CAD in females. No clinically meaningful differences in the type of AEs were observed between gender subgroups for the integrated dataset of patients with CAD.

Use in pregnancy and lactation

It is agreed that there is limited data available for the safety of sutimlimab in pregnant and/or lactating women. Human IgG antibodies are known to cross the placental barrier and to pass into human milk, however, there is no available data evidence in the literature suggesting that C1s inhibitors would have a potential of adversely impacting fertility and ability to get pregnant. The applicant has stated that onset of disease is normally after menopause in women (after the age of 55). As a precautionary measure, it is preferable to avoid the use of sutimlimab during pregnancy. Sutimlimab should be given during pregnancy only if clearly indicated (SmPC section 4.6)

Discontinuation due to adverse events

In CAD patients, 6 of 76 patients discontinued treatment due to at least 1 TEAE/TESAE. The TEAEs for two patients regarding dysphagia/cyanosis and the infusion-related reaction were deemed as related to sutimlimab. These TEAEs are already listed as adverse reactions in the SmPC section 4.8 and this is considered sufficient.

Another patient in BIVV009-03 Part B was withdrawn from the study due to TESAEs of cyanosis (acrocyanosis) and Klebsiella pneumonia on day 949. The patient received the last dose of study drug on day 946. Patient died from Klebsiella pneumonia on day 960. Both events were assessed as not related to sutimlimab by the Investigator. Overall, the pattern of AEs leading to discontinuations is not unexpected.

Overall, it is difficult to draw a firm conclusion due to small numbers of patients in each age/gender/race group. On the other hand, no alarming safety related findings were found in either of these subgroups.

<u>Adverse events of special interest</u>

Thromboembolic events

In CAD patients, thromboembolic events, 5 (7.6%) patients experienced a total of 5 TEAEs of a thromboembolic event which included cerebral venous sinus thrombosis (n=1), device-related thrombosis (n=1), peripheral artery thrombosis (n=1), transient ischemic attack (n=1), and deep vein thrombosis (n=1). In BIVV009-03 Part B, one patient had reported a serious thromboembolic event of peripheral artery thrombosis and one patient had a nonserious thromboembolic event of device-related thrombosis. Both events were assessed by the Investigator as unrelated to sutimlimab. In BIVV009-04, three patients experienced treatment-emergent thromboembolic events (cerebral venous thrombosis, deep vein thrombosis and transient ischemic attack). The event of cerebral venous thrombosis was assessed as related to treatment.

In general, CAD patients experience an increased risk of thromboembolic events. Due to low numbers in the available dataset, it is difficult to draw any conclusion on the thromboembolic events observed. However, one of the patients in BIVV009-04 experienced a serious thromboembolic event of cerebral venous thrombosis that was deemed related to sutimlimab.

In BIVV009-04 there were 4 cases of thromboembolic events reported in sutimlimab group and none in the placebo group.

In BIVV009-03, 1 patient experienced 1 thromboembolic event in part B. No patients experienced a treatment-emergent thromboembolic event during Part A. The applicant has sufficiently described the patients suffering from thromboembolic events and routine pharmacovigilance activities are deemed sufficient including findings in studies and hence, these events should be presented in PSURs.

In other CMD patients, no thromboembolic events were observed. Despite the fact that patients with ITP have an increased risk of these events. However, the conclusions that can be drawn are limited by the low number of subjects with other CMD exposed to sutimlimab.

The Applicant has agreed to follow thromboembolic events in routine pharmacovigilance activities including findings in studies and presented in PSURs and this is deemed acceptable.

TEAEs with onset within 24 hours of infusion

In CAD patients, 35 of 66 (53.0%) patients with CAD experienced a total of 61 TEAEs within 24 hours of infusion. The most frequently reported TEAEs that occurred within 24 hours of the start of infusion of sutimlimab by PT were infusion-related reaction 6%, and hypertension and nausea 3%.

The most common TEAEs by SOC that occurred within 24 hours were general disorders and administration site conditions, gastrointestinal disorders injury, poisoning and procedural complications, vascular disorders, skin and subcutaneous tissue disorders, and nervous system disorders, musculoskeletal and connective tissue disorders, and infections and infestations.

A total of 23 patients with CAD were exposed to at least 1 undiluted infusion of sutimlimab in study BIVV009-04 Part B and 43.5 % experienced at least 1 TEAE for a total of 24 TEAEs within 24 hours of infusion. None of these patients discontinued from the study. The applicant has satisfactorily clarified what undiluted infusions means (i.e., the drug was not diluted in saline, resulting in a reduced volume of infusion solution).

TEAEs of hypersensitivity and anaphylaxis

Allergic-type hypersensitivity reactions are a well-recognised risk of monoclonal antibody therapies. In CAD patients, TEAEs that were suggestive of potential hypersensitivity reactions associated with sutimlimab included infusion-related reactions (5%) and pruritus and flushing (1%). One event suggestive of serious hypersensitivity reactions or anaphylaxis associated with sutimlimab was identified in the small available dataset. A warning regarding hypersensitivity has been added by the applicant in section 4.4 in the SmPC and is deemed appropriate. Hypersensitivity is also listed as an 'important potential risk' in the safety specification of the RMP which is endorsed.

Treatment emergent infections

Based on the functions of the classical complement pathway and evidence from subjects with congenital classical complement deficiencies, or treated with complement inhibitors, potential risks with sutimlimab administration include the development of infections, including those with encapsulated bacteria.

In CAD patients, 74% experienced at least one TEAE of infections across all studies. TEAEs reported by more than 2 patients included: nasopharyngitis 20%, upper respiratory tract infection 15%, urinary tract infection 11%, cystitis, gastroenteritis, rhinitis (11%), Escherichia urinary tract infection 6%, oral herpes, respiratory tract infection, tooth infection, urinary tract infection bacterial 5%, diverticulitis, eye infection, Herpes zoster, influenza, otitis externa, pneumonia, sinusitis, skin candida, viral infection 3%. Treatment-emergent SAEs of infections were reported for 13 of the 66 (19.7%) patients. Serious infections with encapsulated bacteria were reported, including 1 TESAE of pneumococcal sepsis caused by an encapsulated protocol-defined vaccine-targeted organism.

The applicant has provided literature evidence that the risk of meningococcal infection with a selective C1s inhibitor such as sutimlimab is expected to be lower compared to terminal inhibitors (mainly C5b-C8 components). A causal link between the serious infections recorded in the present studies and sutimlimab cannot be excluded. The Applicant has agreed to include serious infections as an 'important identified risk' which is endorsed.

It is noted that 5 of the 10 TEASAE observed regarding infections were sepsis (Escherichia Sepsis, Pneumococcal Sepsis, Pulmonary Sepsis, Streptococcal Sepsis and Urosepsis). The Applicant has

amended section 4.4 of the SmPC which now includes a statement regarding sepsis. Meningococcal infections is listed as `important potential risk´ which is endorsed.

In both BIVV009-03 and BIVV009-04, specific therapies to reduce antibody production, such as rituximab and rituximab combination therapies, were prohibited. Thus, there is no safety data available to support such treatment concomitantly with sutimlimab and potentially treated individuals will be at risk for a weakened defence against infections. The Applicant has sufficiently clarified the information regarding the patients that received prohibited medications during the studies and the SmPC currently includes a statement in 5.1 referring to rituximab alone or in combination with cytotoxic agents; this is currently deemed appropriate.

From the safety database all the adverse reactions reported in clinical trials <and post-marketing> have been included in the Summary of Product Characteristics.

Conclusions on clinical safety

The safety profile of sutimlimab in the target indication is considered acceptably characterised by the submitted safety data from the 6 studies, in particularly by the data from studies BIVV009-03 and BIVV009-04. However, some concerns need to be followed post-marketing such as serious infections, SLE and infections. In conclusion, overall, the safety profile of sutimlimab appears similar in the different sub-populations CAD, NHV and other CMD patients.

4. Risk management plan

Safety Concerns

Summary of safety concerns

Summary of the safety concerns

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

Pharmacovigilance plan

Table 26. Ongoing and planned additional pharmacovigilance activities

Study Status	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
N/A				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				

N/A				
Category 3 - Required additional pharmacovigilance activities				
Cold Agglutinin Disease Real World Evidence Registry (Cadence) Planned	The safety objective of the post-approval safety and effectiveness drug cohort study is to: • describe the long-term safety of sutimlimab in the treatment of patients with CAD in a real-world setting including CAS patients with off-label use or sutimlimab).	• Serious infections • Meningococcal infections • Development of SLE • Serious hypersensitivity reactions and/or anaphylaxis	• Synopsis submission (along with the initial RMP) • Protocol submission • Start of data collection • End of data collection • Interim reports • Final report of study results	Oct-2021 Apr-2022 Q2 2022 Q3 2028 Annually throughout the cohort study Q4 2031
A Survey of Physicians in Europe to Evaluate the Effectiveness of the ENJAYMO Physician's Guide Planned	• Describe physicians' reported levels of receipt and reading of the Physician's Guide. • Assess physicians' knowledge levels of key information included in the sutimlimab Physician's Guide. • Assess impact of the Physician's Guide on clinical action.	• Serious infections • Meningococcal infections	• Synopsis submission (along with the RMP) • Protocol submission • Start of data collection • End of data collection • Final study report	Oct-2021 Apr-2022 Q2 2023/Q2 2024 Q2 2025/Q2 2026 Q4 2026

Risk minimisation measures

Table 27. Description of risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities	Additional risk minimisation measures
Meningococcal infections	**Routine risk communication:** SmPC section 4.2 and 4.4 PL section 2 and 4 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** SmPC section 4.2: Patients should be vaccinated according to the most current local recommendations for patients with persistent complement deficiencies. SmPC section 4.4: Patients should be monitored for early signs and symptoms of infections and evaluated immediately if infection is suspected. **Other Routine risk minimisation measures beyond the Product Information:** Legal status: medicinal product subject to medical prescription	**Physician's Guide** Educate physicians that patients should be vaccinated (according to most current local vaccination guidelines for vaccine use in patients with persistent complement deficiencies) prior to initiating sutimlimab. Recommend on-treatment monitoring for early signs and symptoms of infection. Recommend individualized patient counselling. **Patient's Guide** Enhance awareness of increased risk of infection and the need for vaccination. Enhance awareness of early signs and symptoms of infections and the need to seek immediate medical attention should they occur.

Serious infections	**Routine risk communication:** SmPC section 4.2, 4.4 and 4.8 PL section 2 and 4 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** SmPC section 4.2: Patients should be vaccinated according to the most current local recommendations for patients with persistent complement deficiencies. SmPC section 4.4: Patients should be monitored for early signs and symptoms of infections and evaluated immediately if infection is suspected. **Other routine risk minimisation measures beyond the Product Information:** Legal status: medicinal product subject to medical prescription	**Physician's Guide** Educate physicians that patients should be vaccinated (according to most current local vaccination guidelines for vaccine use in patients with persistent complement deficiencies) prior to initiating sutimlimab. Recommend on-treatment monitoring for early signs and symptoms of infection. Recommend individualized patient counselling. **Patient's Guide** Enhance awareness of increased risk of infection and the need for vaccination. Enhance awareness of early signs and symptoms of infections and the need to seek immediate medical attention should they occur.
Development of Systemic Lupus Erythematosus	**Routine risk communication:** SmPC section 4.4 PL sections 2 and 4 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** SmPC section 4.4: Patients being treated with sutimlimab should be monitored for signs and symptoms of SLE and evaluated appropriately. **Other routine risk minimisation measures beyond the Product Information:** Legal status: Medicinal product subject to medical prescription	

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

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

Conclusion on the RMP

The CHMP considers that the risk management plan version 1.2 is acceptable.

5. Pharmacovigilance

Pharmacovigilance system

It is considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 04 February 2022. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

6. Product information

User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on*

the readability of the label and package leaflet of medicinal products for human use.

Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Enjaymo (sutimlimab) is included in the additional monitoring list as it is a biological product that is not covered by the previous category and authorised after 1 January 2011.

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

4. Benefit risk assessment

1. Therapeutic Context

Disease or condition

Enjaymo (sutimlimab) is proposed for treatment of haemolytic anaemia in adult patients with cold agglutinin disease (CAD).

Primary CAD is a rare disease caused by autoantibodies ("cold agglutinins") that bind to RBCs at temperatures below normal core body temperature, leading to agglutination of the RBCs causing cold-related symptoms of ischaemia and/or complement activation through the classical pathway (CP) with subsequent haemolysis. Chronic extravascular haemolysis is the hallmark of CAD and could be associated with symptoms of anaemia such as fatigue, weakness, dizziness, chest pain, as well as thromboembolic events.

The aim of sutimlimab is to inhibit the CP activation through inhibition of C1s and thereby avoid haemolysis and subsequent anaemia. As opposed to secondary cold agglutinin syndrome (CAS), primary CAD is not related to underlying malignancy or infectious disease although an indolent lymphoproliferative disorder could be found. The mean age at presentation is mid to late 60s.

The recommended dosage is 6,500 mg for patients weighing 39-<75 kg and 7,500 mg for patients weighing ≥75 kg, intravenously (IV) weekly for the first two weeks, with administration every two weeks thereafter.

Available therapies and unmet medical need

Current standard of care in primary CAD includes supportive measures such as RBC transfusions and avoidance of cold exposure. In patients with more severe disease, antibody-reducing therapy is often recommended; however, no such therapy is currently approved for primary CAD.

Approximately 90% of patients have anaemia with median Hb at 9.5 g/dL, a similar proportion have elevated markers of haemolysis and approximately 50% of patients have cold-induced symptoms such as acrocyanosis. Less than 50% warrant transfusion. Thus, some patients are asymptomatic and some experience symptoms only in relation to e.g., cold exposure or in relation to infectious disease, surgery or trauma. Nevertheless, a large proportion of patients have chronic or frequent episodes of considerable haemolytic anaemia for which there is currently no approved treatment.

Main clinical studies

The main evidence of efficacy and safety in the intended target population relies on two phase III studies. Study BIVV009-04 is a randomized, double-blind, placebo-controlled, phase 3 study with a duration of 26 weeks to evaluate the efficacy and safety of sutimlimab in 42 patients (n=22 on sutimlimab and n=20 on placebo) with primary CAD without a recent history of blood transfusion (within 6 months). Key eligibility criteria were a baseline Hb ≤10 g/dL, active haemolysis with a bilirubin level above the normal reference range, presence of at least one CAD-related sign or symptom, exclusion of patients with a history of blood transfusion within 6 months of screening, or history of more than one blood transfusion within 12 months of screening. Secondary Cold agglutinin Syndrome (CAS) was excluded. The primary efficacy endpoint was a composite endpoint, defined as the responder rate, where patients meeting all 3 of the following criteria: 1) Hb level increased ≥1.5 g/dL from baseline at treatment assessment endpoint AND 2) The patient did not receive a blood transfusion from Week 5 through Week 26, AND 3) The patient did not receive treatment for CAD beyond what was permitted per protocol from Week 5 through Week 26. Important secondary endpoints included change of Hb levels, haemolysis markers (total bilirubin, lactate dehydrogenase (LDH)) and quality of life (QoL) evaluations.

By design, this study is considered to provide the more robust data.

Study BIVV009-03 is a phase 3, open-label, uncontrolled, multicentre study with a duration of 26 weeks to assess the efficacy and safety of sutimlimab in 24 patients with primary CAD who had a recent history of blood transfusion. The inclusion and exclusion criteria are generally in line with those of the CADENZA trial, though with the exception that patients with a transfusion history of ≥1 blood transfusions within 6 months of enrolment were included. The primary composite endpoint and the secondary endpoints were also generally similar to those selected in BIVV009-04, but the primary composite endpoint needed a higher increase in Hb (i.e. ≥12 g/dL at TAT or an increase of >2 g/dL from baseline to end of treatment) as compared to the increase of Hb (>1.5 g/dL) in BIVV009-04.

For both study BIVV009-04 and BIVV009-03, extension parts interim and final results have been provided.

2. Favourable effects

BIVV009-04 (CADENZA)

The primary endpoint was the rate of responders defined as patients who had a ≥1.5 g/dL increase in Hgb levels at the treatment assessment endpoint (TAT; defined as the mean value of Weeks 23, 25, and 26), did not receive a blood transfusion from Week 5 through Week 26 and did not receive treatment for CAD beyond what is permitted per protocol. There were 16/22 or 72.7% (95% CI 49.8-89.3) and 3/20 or 15% (95% CI 3.2-37.9) responders in the sutimlimab and placebo group, respectively.

The difference was statistically significant (odds ratio of 15.94 (95% CI: 2.88 to 88.04; p<0.001)).

The outcome of the sensitivity analyses was consistent with the primary efficacy endpoint. Sutimlimab treatment effects were similar across the investigated small subgroups of age, gender, baseline Hb and previous use of rituximab.

Key secondary endpoints were:

- LS mean change from baseline in Hb at the TAT, which was 2.66 g/dL (95% CI: 2.09 to 3.22) and 0.09 g/dL (95% CI: -0.50 to 0.68) for sutimlimab and placebo, respectively with an LS mean difference of 2.56 g/dL (p<0.001; 95% CI: 1.75 to 3.38).

- LS mean change from baseline in QoL, as assessed by the change in FACIT-Fatigue scale scores at the TAT, with an increase of 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 a statistically significant LS mean difference of +8.93 points (p<0.001; 95% CI: 4.0 to 13.9).

Additional secondary endpoints of importance include change in markers of haemolysis at the TAT. For bilirubin, there was a mean decrease of 22.129 (SD 10.468) µmol/L in the sutimlimab group and 1.829 (SD 13.894) µmol/L in the placebo group. For LDH, there was a mean decrease of 150.833 U/L (SD 160.824) in the sutimlimab group and a mean increase of 7.600 U/L (SD 212.690) in the placebo group.

BIVV009-03 (CARDINAL)

The primary endpoint was the proportion of responders defined as patients who did not receive a blood transfusion from Week 5 through Week 26, did not receive treatment for CAD beyond what is permitted per protocol and had a ≥2 g/dL increase from baseline in Hb levels or increases Hb to ≥12 g/dL at the treatment assessment endpoint (TAT; defined as the mean value of Weeks 23, 25, and 26). These criteria were fulfilled in 13/24 (54%) of subjects.

Secondary endpoints were:

- Change from baseline in bilirubin at the TAT, which in mean decreased by 38 µmol/L.
- Change from baseline in QoL, assessed by change in FACIT-Fatigue scale scores at the TAT, which in mean increased by 10.85
- Change from baseline in lactate dehydrogenase (LDH) at the TAT, which in mean decreased by 126.95 U/L.
- Number of transfusions after the first 5 weeks of study drug administration, which were in mean 0.9.
- Change from baseline in Hb at the TAT, which was 2.6 g/dL.

Effects of sutimlimab treatment on the secondary endpoints in study BIVV009-03 were generally similar to those observed in study BIVV009-04.

Sustainability of efficacy

At the end of the extension periods, the patients, who switched in study BIVV009-04 from placebo in Part A to open-label sutimlimab in Part B, showed the same response on Hb, bilirubin and FACIT-Fatigue score as seen in the sutimlimab-treated patients upon initiation of Part A. The effect on Hb, haemolytic parameters and FACIT-Fatigue score appear mostly retained. The long-term data in BIVV009-03 demonstrated generally similar data as observed in the long-term BIVV009-04 trial.

3. Uncertainties and limitations about favourable effects

Due to the rareness of the condition the number of subjects included in clinical trials is limited but more than 90 % of subjects remained in the studies for more than 52 weeks. The effect diminished shortly following treatment discontinuation making episodic treatment less appropriate.

The use of CAD specific treatment such as antibody-reducing therapy, is unclear for both phase 3 studies and there is thus no data available supporting concomitant treatment.

4. Unfavourable effects

A majority of CAD patients (64 of 66) experienced at least one adverse event among which at least 36 had TEAEs deemed related to sutimlimab. The most frequently reported TEAEs by SOC were infections and infestations 74%, gastrointestinal disorders 68%, general disorders and administration site conditions 64%, musculoskeletal and connective tissue disorders 53%, vascular disorders 52% and skin, subcutaneous tissue disorders 50%, blood and lymphatic system disorders 49% and nervous system disorders 47%. Placebo controlled data (study BIVV009-04) showed an imbalance for certain SOCs with more adverse events recorded for gastrointestinal disorders (50 vs 35 %), vascular disorders (41 vs 0%), subcutaneous tissue disorders (32 vs 20%) and nervous system disorders (32 vs 25%). Most cases of vascular disorders were hypertension, Raynaud's phenomenon and cyanosis. Of the serious events most cases represented single events, but treatment-emergent serious infections were reported for 10 of the 76 (13.2%) patients, 5 or these being cases of sepsis. In this context it should be mentioned that certain patients experienced low values for leukocytes in the studies. Five patients experienced thromboembolic events of which one was deemed related to treatment. Of the four fatal cases none was deemed related to treatment.

5. Uncertainties and limitations about unfavourable effects

The main limitations relating to the safety data is the small number of patients treated with sutimlimab and only one of the studies conducted in CAD-patients was placebo controlled. Only 43 patients were exposed to sutimlimab >55 weeks and 18 patients >145 weeks in the CAD-population. There are some safety concerns regarding serious infections (including sepsis), development of SLE and hypersensitivity reactions for Enjaymo. However, these are all listed in the safety specifications in the RMP and hence are being followed up on. In addition, thromboembolic events will be monitored during routine pharmacovigilance activities including findings in studies and will be presented in PSURs. Furthermore, additional pharmacovigilance activities have been required which include a long-term post-approval safety and effectiveness drug cohort study (CAD real word evidence registry – Cadence) and a survey of healthcare professionals in Europe (see RMP).

6. Effects Table

Table 28. Effects Table for Enjaymo for treatment of haemolysis in adult patients with cold agglutinin disease (CAD)

Effect	Short Description	Unit	Sutimlimab	Placebo	Uncertainties (Unc)/ Strength of evidence (SoE)	References
Favourable Effects						

Effect	Short Description	Unit	Sutimlimab	Placebo	Uncertainties (Unc)/ Strength of evidence (SoE)	References
Haemoglobin (Hb)	Increase in Hb (at least 1.5 g/dL) at TAT without RBC transfusion or other CAD specific therapy	RR	16/22 or 72.7% (95% CI 49.8, 89.3)	3/20 or 15% (95% CI 3.2-37.9)	**Unc:** -Low numbers **SoE:** -Odds ratio of 15.94 (95% CI: 2.88 to 88.04); p<0.001 -Consistent effect in 3 sensitivity analyses. -Similar primary endpoint, but increase in Hb ≥2 g/dL, in study BIVV009-03 was met in 13/24 (54%)	BIVV009-04 Part A CSR BIVV009-03 Part A CSR
	Mean change from baseline at TAT	g/dL (LS mean)	2.66 (95% CI 2.09, 3.22)	0.09 (95% CI -0.50, 0.68)	**Unc:** -Low numbers **SoE:** -LS mean difference of 2.56 g/dL (95% CI: 1.75 to 3.38); p<0.001 -LS mean change in study BIVV009-03 +2.60 g/dL (95% CI: 0.74 to 4.46)	
QoL	Change in FACIT-Fatigue from baseline at TAT	Score (LS mean)	10.83 (95% CI 7.45, 14.22)	1.91 (95% CI -1.65, 5.46)	**Unc**: Low numbers **SoE:** LS mean difference of 8.93 points (95% CI: 4.0 to 13.9); p<0.001 LS mean change in study BIVV009-03 +10.9 points (95% CI: 8.0 to 13.7)	
Haemolysis	Change from baseline in bilirubin	(umol/ L) (mean)	-22.1	-1.8	**Unc:** -Low numbers **SoE:** -LS mean change in study BIVV009-03 -38.2 umol/L (95% CI: -42.5 to -33.8)	
	Change from baseline in LDH	(U/L) (mean)	-150.8	7.6	**Unc:** -Low numbers **SoE:** LS mean change in study BIVV009-03 -127.0 (95% CI: -218.5 to -35.4)	
Unfavourable Effects						
GI-disorders			50 %	35 %		BIVV009-04

Effect	Short Description	Unit	Sutimlimab	Placebo	Uncertainties (Unc)/ Strength of evidence (SoE)	References
Vascular events	Including hypertension, Raynaud's syndrome, cyanosis and thromboembolic events (venous and arterial).		41 %	0 %		BIVV009-04
Serious Infections			13 %		Few serious infections were recorded in the placebo-controlled study	Pooled safety data CAD patients

Abbreviations: CAD = cold agglutinin disease; Hb = haemoglobin; RBC = red blood cell RR = responder rate; TAT = treatment assessment timepoint (mean of values at Week 23, 25 and 26)

7. Benefit-risk assessment and discussion

Importance of favourable and unfavourable effects

Sutimlimab is claimed to be the first-in-class, humanized IgG4 monoclonal antibody that inhibits specifically the classical CP and is expected to result in inhibition of haemolysis in patients with primary CAD, while other complement pathways remained functionally intact. In line with its mechanism of action, the initially proposed indication of sutimlimab is, therefore, the treatment of haemolytic anaemia in adult primary CAD patients.

The current application is mainly based on the results of two phase 3 studies, controlled study BIVV009-04/CADENZA and uncontrolled single-arm study BIVV009-03/CARDINAL in patients with primary CAD. The CAD patients included in both studies had anaemia, haemolysis and one or more CAD-related sign and/or symptom which could be an anaemia-related symptom or another CAD-related symptom. Study BIVV009-04 aimed at a population free from RBC transfusions as opposed to study BIVV009-03; together, they are considered to be representative of a primary CAD population with haemolytic anaemia. The studies were in general well-conducted, and the choice to select placebo as comparator for the controlled study is considered acceptable, as currently no approved treatments for CAD are available.

The primary endpoints in both phase 3 studies are considered to support that sutimlimab provides an increase in Hb of clear clinical relevance in a symptomatic CAD population with moderate to severe anaemia at baseline. These results are supported by the secondary efficacy endpoints from both studies, with an increase in Hb levels, a clear and rapid decrease in markers of haemolysis and an increase in QoL measures. Despite the limited number of study participants, the clinical data are considered comprehensive enough to support that efficacy is considered adequately shown, in the target population i.e., patients with haemolytic anaemia.

The adverse events of concern are infections as serious infections (including exacerbations of infections with incapsulated bacteria is known to be linked to complement system inhibition) and vascular disorders where a clear unbalance was shown in placebo-controlled data. Overall, based on the currently available data, the safety pattern appears acceptable and sutimlimab appears to be generally well tolerated over time in line with the earlier assessed interim data. The proposed target population is broader than the studied populations with respect to severity of haemolysis and in that only symptomatic, primary CAD patients were included. This is acceptable.

Balance of benefits and risks

In terms of benefit, sutimlimab provides a relevant beneficial treatment effect on auto-immune haemolytic anaemia as measured by an increase in Hb level in the absence of blood transfusions or other medicinal treatment, as compared to placebo. This was accompanied by improvement in haemolysis markers and QoL. The use of sutimlimab appeared to be well tolerated with an acceptable safety profile and without major safety signals.

Additional considerations on the benefit-risk balance

The Applicant is applying for a full marketing authorisation. The provided efficacy data (derived from one placebo-controlled study, one single arm trial) is considered as comprehensive. The safety data is considered as rather limited, but acceptable considering the rareness of the disease. A full marketing authorisation is acceptable.

8. Conclusions

The overall benefit/risk balance of Enjaymo is positive, subject to the conditions stated in section 'Recommendations'.

5. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Enjaymo is favourable in the following indication(s):

Enjaymo is indicated for the treatment of haemolytic anaemia in adult patients with cold agglutinin disease (CAD).

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Additional risk minimisation measures

The MAH shall ensure that in each member state where Enjaymo is marketed, all healthcare professionals (HCPs) who are expected to prescribe Enjaymo are provided with the following educational materials:

- Physician's guide
- Patient's guide

These tools will convey key safety messages on the important identified risk of serious infections and important potential risk of meningococcal infections.

For Physician's guide:

- Educate physicians that patients should be vaccinated (according to most current local vaccination guidelines for vaccine use in patients with persistent complement deficiencies) prior to initiating Enjaymo.
- Recommend on-treatment monitoring for early signs and symptoms of infection.
- Recommend individualized patient counselling.

For Patient's guide:

- Enhance awareness of increased risk of infection and the need for vaccination.
- Enhance awareness of early signs and symptoms of infections and the need to seek immediate medical attention should they occur.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that sutimlimab is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union.
Refer to Appendix on new active substance (NAS).

6. Appendix

1. CHMP AR on New Active Substance (NAS) dated 15 September 2022