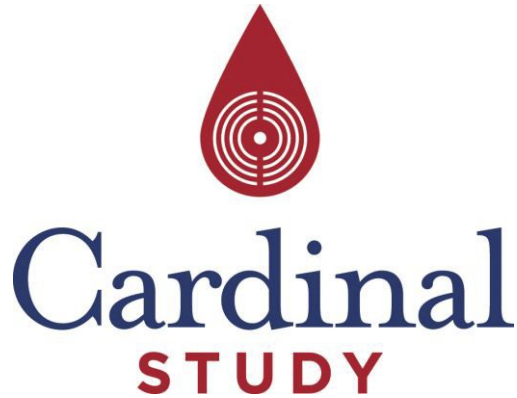

AMENDED CLINICAL TRIAL PROTOCOL 06

BIVV009-03

IND #128,190

EudraCT #2017-003538-10

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 Drug: BIVV009

Bioverativ USA Inc.

[redacted]

This study will be performed in compliance with Good Clinical Practice.

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PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY

Document	Country/Countries impacted by amendment	Date
Amended Clinical Trial Protocol 06	Global	19 December 2019
Clinical Study Protocol Version 5	Global	17 July 2018
Clinical Study Protocol Version 4	Global	29 June 2018
Clinical Study Protocol Version 3.1	Japan	21 March 2018
Clinical Study Protocol Version 3	Global	09 March 2018
Clinical Study Protocol Version 2	Global	22 February 2018
Clinical Study Protocol Version 1.5	Belgium	10 January 2018
Clinical Study Protocol Version 1.4	France	15 December 2017
Clinical Study Protocol Version 1.3	Norway	06 December 2017
Clinical Study Protocol Version 1.2	United Kingdom	29 November 2017
Clinical Study Protocol Version 1.1	Global	09 September 2017
Clinical Study Protocol	Global	24 August 2017

Note: The name and numbering of the protocol is based on a new numbering system followed by the Sponsor.

AMENDED PROTOCOL 06 (19 December 2019)

This amended protocol (06) is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union

OVERALL RATIONALE FOR THE AMENDMENT

The primary reasons for this amendment to Protocol BIVV009-03 (Cardinal) are to extend Part B duration from 1 to 2 years after Last Patient Out from Part A, to provide home infusion facilities to the patients (for US, the Netherlands, Norway, France, Italy, Austria, Germany, and Spain specific amendments), to add new exploratory objective of immunogenicity, to introduce additional time points when samples for ADAs against BIVV009 are collected, to specify that left over PD samples will be used to assess immunogenicity in patients who consented to future use of samples, to introduce additional time points for SLE panel in Part B, and to introduce a correction in Section 10.1 Appendix A.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Title Page	Title was updated to reflect Amended Clinical Trial Protocol 06.	The change was made to reflect the update of the amended clinical trial protocol 06.
Title Page	Protocol Date was changed to reflect 19-Dec-2019.	The change was made to reflect the updated date of approval of the document.
Approval of the Protocol	Protocol Date was changed to reflect 19-Dec-2019.	The change was made to reflect the update of the amended clinical trial protocol 06.
Section 1: Synopsis: Overview of Study Design; Methodology/Study Design; and throughout the document	The Part B open-label extension study will run for 2 years instead of 1 year following last patient out (LPO) under Part A.	The change was made to reflect the extension of Part B duration.
Section 1: Synopsis: Objectives	Secondary Exploratory Objective for Part A was added: To evaluate the immunogenicity of BIVV009.	The change was made to help characterize immunogenicity of BIVV009.
Section 1: Synopsis: Objectives	Exploratory Objectives were added for Part B to describe the safety and patient satisfaction with the convenience of home infusion and to evaluate the immunogenicity of BIVV009.	This change was made to help characterize immunogenicity of BIVV009 and evaluate the safety and patient satisfaction with the convenience of home infusion.
Section 1: Synopsis: Methodology/Study Design:	Collection of ADA samples during the 1st year of treatment in part B, then every 6 months was added for Part B.	This change was made to help characterize immunogenicity of BIVV009.
Section 1: Synopsis: Methodology/Study Design; Duration of Treatment; and Section 4.5 End of Study	The study will be complete 24 months instead of 12 months following LPO for Part A.	The change was made to reflect the extension of Part B duration.
Section 1: Synopsis: Test Product(s), Dose, and Mode of Administration	Text specific to Part B for administration of study drug provided by home infusions was added.	This change was made to evaluate the safety and patient satisfaction with the convenience of home infusion.
Section 1: Synopsis: Efficacy Endpoints and Outcome Measures	Part B Satisfaction with home infusion after first home infusion and after four home infusion will be assessed in patients with home infusion was added.	This change was made to evaluate patient satisfaction with the convenience of home infusion.
Section 1: Synopsis: Safety Outcome Measures	For patients with home infusions, safety assessments include AEs with onset within 24 hours of infusion was added.	This change was made to evaluate the safety of home infusion.
Section 1: Synopsis: Pharmacokinetic Outcome Measures	Collection of PK samples at predose and 1 hour (±15 minutes) postdose was added. Samples will be collected at 3-month intervals during the 1st year of treatment in Part B and then at 6-month intervals for the remainder of the time on study.	This change was made to further define PK sampling schedule.
Section 1: Synopsis: Pharmacodynamic Outcome Measures	Collection of PD samples will be collected at predose and 1 hour (±15 minutes) postdose was added. Samples will be collected at 3-month intervals during the 1st year of treatment in Part B and then at 6-month intervals for the remainder of the time on study.	This change was made to further define PD sampling schedule.

Section # and Name	Description of Change	Brief Rationale
Section 1: Synopsis: Immunogenicity Outcome Measures	This entire section was added to the amended protocol.	This change was made to further define the exploratory objective of immunogenicity.
Section 1: Synopsis: Statistical Methods, and throughout the document	Intent to treat (ITT) has been replaced with Full Analysis Set (FAS)	This change was made to reflect the method used for statistical analysis.
Section 2.2: Background and Study Rationale	Information regarding CAgD was added and that a group of patients at preselected site/countries will be offered the possibility of home infusions during Part B.	This change was made to evaluate the safety and patient satisfaction with the convenience of home infusion.
Section 2.2.4: Potential Risks and Benefits	Home infusion with the study drug will be proposed to a number of patients in countries preselected to participate in home infusion and information about patient qualification was added.	This change was made to evaluate the safety and patient satisfaction with the convenience of home infusion.
Section 3.2: Secondary Objectives (Part A)	Exploratory objective to evaluate the immunogenicity of BIVV009 was added.	This change was made to better characterize the immunogenicity of BIVV009.
Section 3.5: Exploratory Objective (Part B)	This entire section was added.	This change was made to help characterize immunogenicity of BIVV009 and evaluate the safety and patient satisfaction with the convenience of home infusion.
Section 4.1: Study Design Part B	ADA sampling and text specific to Part B for administration of study drug provided by home infusions was added.	This change was made to help characterize immunogenicity of BIVV009 and evaluate the safety and patient satisfaction with the convenience of home infusion.
Section 4.2: Discussion of Study Design	Immunogenicity assessments evaluation, and conditions for ADA testing using available predose PD back-up samples was added.	This change was made to help characterize immunogenicity of BIVV009.
Section 4.3.4: Efficacy Endpoints (Part B)	Part B Satisfaction with home infusion after first home infusion and after fourth home infusion will be assessed in patients with home infusion was added.	This change was made to evaluate satisfaction with the convenience of home infusion.
Section 4.3.5: Safety Endpoints	For patients with home infusions, safety assessments include AEs with onset within 24 hours of infusion was added.	This change was made to evaluate the safety of home infusion.
Section 4.3.6: Pharmacokinetic Endpoints	PK samples will be collected at predose and 1 hour (±15 minutes) postdose was added. Samples will be collected at 3-month intervals during the 1st year of treatment in Part B and then at 6-month intervals for the remainder of the time on study.	This change was made to further define PK sampling schedule.
Section 4.3.7: Pharmacodynamic Endpoints	PD samples will be collected at predose and 1 hour (±15 minutes) postdose was added. Samples will be collected at 3-month intervals during the 1st year of treatment in Part B and then at 6-month intervals for the remainder of the time on study.	This change was made to further define PD sampling schedule.

Section # and Name	Description of Change	Brief Rationale
Section 4.3.8: Immunogenicity Endpoints	This entire section was added.	This change was made to adhere to sponsor standards.
Section 4.4: Duration of the Study	The planned total study duration per patient is increased to reach approximately 2.5 to 3.5 years. The duration of dosing in Part B will last from 2 to 3 years. Part B will run for 2 years following completion of LPO in Part A.	The change was made to gather more evidence on long-term safety, tolerability and durability of response of BIVV009.
Section 5.2: Exclusion Criteria	Reference to home infusion inclusion and exclusion criteria in Section 10.10 Appendix J was added	This change was made to clarify the specific requirements for home infusion.
Section 5.3: Removal of Patients from Study Participation, and Study Suspension and Stopping Rules	Conditions for which patients undergoing home infusions with study drug will return to bi-weekly dosing, and which they may return to home infusions was added.	This change was made to specify rules for discontinuation and return to the home infusion schedule.
Section 6.1: Schedule of Study Procedures, Table 3 Study Schedule of Events	SLE panel testing, and ADAs against BIVV009 was added for Part B Extension Phase. Immunization review/vaccination is to be assessed during entire study. Footnote “l” was edited to include information for qualifying patients at participating site to have study drug dosed at home. Footnote “c” was edited to include information for second sample collection criteria. Footnotes were edited in this section and footnotes “r”, “s”, “t”, and “u” were added to this table.	This change was made to reflect changes introduced with the amendment in the schedule of study procedure.
Section 6.1.1.1: Screening Assessments (initiating at Day -42)	Revaccination with booster doses should be given according to regional guidelines for patients with persistent complement deficiency and in accordance with respective labels.	This change was made to provide clarity to vaccination against encapsulated bacterial pathogens.
Section 6.1.3: Weeks 1-25	ADA: In patients who consented to the use of their blood samples for future research, PD back-up samples collected at the following time points Day 7, 35, 77, 133 and 175, may be used to assay ADA was added.	This change was made to help characterize immunogenicity of BIVV009.
Section 6.1.4: End-of-Treatment Visit in Part A (Week 26)	ADA: In patients who consented to the use of their blood samples for future research, PD back-up samples collected at this visit, may be used to assay ADA.	This change was made to help characterize immunogenicity of BIVV009.
Section 6.1.5.1: Procedures to be Performed Every 2 Weeks	It was specified that the hematology panel and clinical chemistry panel to be performed until week 79.	This change was made to reflect the study assessments frequency in the 2nd year of Part B.
Section 6.1.5.2: Procedure to be Performed Every 4 Weeks	Hematology panel (beginning at Week 79) and Clinical chemistry panel (beginning at Week 79) were added.	This change was made to reflect the study assessments frequency in the 2nd year of Part B.
Section 6.1.5.3: Procedures to be Performed Every 3 Months	Information for SLE panel, and ADA sampling collection was added.	This change was made to reflect changes to Part B introduced with the amendment in the corresponding Study Procedures sub-section.

Section # and Name	Description of Change	Brief Rationale
Section 6.1.6: Infusion of the study drug at patient's home	This entire section was added and section on early termination/end of study/safety follow-up was renumbered as 6.1.7.	This change was made to evaluate the safety and patient satisfaction with the convenience of home infusion.
Section 6.2.1: Drug Supplies and Accountability	Reference to the addition of home infusion inclusion in the preparation and accountability procedures for the investigational product were made.	This change was made to reflect the option of home infusion within the framework of preparation and accountability procedures for the investigational product.
Section 6.2.4: Dose Preparation and Administration	Information for home administration of study drug, slowing or stopping due to AE in the case of home infusion, and monitoring of home infusion was added.	This change was made to describe safety procedures associated with home infusion.
Section 6.5.2: Analytical Methodology (PD)	ADA parameter was added to this section.	This change was made to reflect changes with regards to ADA introduced with the amendment.
Section 6.6: Safety Procedure	ADAs against BIVV009 was added.	This change was made to reflect changes with regards to ADA introduced with the amendment.
Section 7.7: Immunogenicity	This entire section was added and subsequent sections were renumbered.	This change was made to help characterize immunogenicity of BIVV009.
Section 10: Supporting Documentation and Operational Considerations	Appendices were included under section 10 and renamed accordingly throughout the document.	This change was made to comply with Sanofi standards.
Section 10.1: Appendix A Clinical Laboratory Evaluations	"Iron" was removed from the clinical chemistry panel	This change was made to provide clarification of clinical laboratory evaluations.
Section 10.10: Appendix J Country Specific Requirement - Home Infusions with BIVV009	This entire section was added.	This change was made to evaluate the safety and patient satisfaction with the convenience of home infusion.
Section 10.11: Appendix K Home Infusion Patient Satisfaction Survey	This entire section was added.	This change was made to evaluate patient satisfaction with the convenience of home infusion.
Section 10.12: Appendix L Protocol Amendment History	This entire section was added to comply.	This change was made to comply with Sanofi standards.

In addition, other minor editorial changes (eg, grammatical, stylistic, and minor typographical error corrections) were implemented throughout the protocol.

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LIST OF TABLES

LIST OF APPENDICES

LIST OF ABBREVIATIONS

ADA	antidrug antibody
ADL	activities of daily living
AE	adverse event
AMR	antibody-mediated rejection
AUC	area under the concentration-time curve
BLA	Biologics License Application
BP	bullous pemphigoid
CAgD	cold agglutinin disease
CFR	Code of Federal Regulations
CI	confidence interval
CIC	circulating immune complex
C_{max}	maximum observed concentration
CP	complement classical pathway
CRO	Clinical Research Organization
CTCAE	common terminology criteria for adverse events
DAT	direct antiglobulin test
DNA	deoxyribonucleic acid
dsDNA	double-stranded DNA
EC	Ethics Committee
ECG	electrocardiogram
eCRF	electronic Case Report Form
EDC	electronic data capture
EOS	end of study
EOT	end of treatment
EQ-5D-5L	five level EuroQol - five dimensions questionnaire
ET	early termination
FACIT	functional assessment of chronic illness therapy
FAX	facsimile
FDA	Food and Drug Administration
FIH	first in human
GCP	Good Clinical Practice
Hgb	hemoglobin
HIV	human immunodeficiency virus
IB	investigator's brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IM	intramuscularly
IRB	Institutional Review Board
ITT	intent-to-treat
IUD	intrauterine device
IV	intravenous
LDH	lactate dehydrogenase
LPO	last patient out
MAA	Market Authorization Application

mAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
NCI	National Cancer Institute
NHP	non-human primate
NHV	normal healthy volunteer
NOAEL	no observed adverse effect level
PD	pharmacodynamic(s)
PGIC	patient's global impression of change
PGIS	patient's global impression of [fatigue] severity
PI	principal investigator
PK	pharmacokinetic(s)
PP	per-protocol
QOL	quality of life
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SF-12	12-Item Short Form Survey
SLE	systemic lupus erythematosus
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
USA	United States of America
WAIHA	warm autoimmune hemolytic anemia

1 SYNOPSIS

TITLE OF STUDY:	Cardinal Study: A Phase 3, pivotal, open-label, multicenter study to assess the efficacy and safety of BIVV009 in patients with primary cold agglutinin disease who have a recent history of blood transfusion
OVERVIEW OF STUDY DESIGN:	This is an open-label, single-arm, multicenter study in patients with primary cold agglutinin disease (CAgD) who have a recent history of blood transfusion. Eligible patients will receive study drug and undergo safety and efficacy assessments for 6 months (26 weeks) during Part A. Following completion of the initial 6-month treatment period, patients will roll into the long-term safety and durability of response extension phase (Part B) where they will continue to receive study drug. For the purpose of marketing authorization applications, an interim analysis of safety and efficacy data will be performed after all patients have completed the initial 6-month treatment period (Part A). The Part B open-label extension study will run for 2 years following last patient out (LPO) under Part A.
OBJECTIVES:	**Part A** Primary objective: • The primary objective of Part A is to determine whether BIVV009 administration results in a ≥2 g/dL increase in hemoglobin (Hgb) levels or increases Hgb to ≥12 g/dL and obviates the need for blood transfusion during treatment in patients with primary CAgD who have a recent history of transfusion Secondary objectives: Efficacy: • To assess the effect of BIVV009 on clinical events and laboratory parameters related to hemolysis and anemia in patients with primary CAgD • To assess the effect of BIVV009 on quality of life (QOL) in patients with primary CAgD Safety: • To evaluate the overall safety and tolerability of BIVV009 in patients with primary CAgD Exploratory: • To assess the effect of BIVV009 on specific complications of CAgD (acrocyanosis, Raynaud's syndrome, hemoglobinuria, and thromboembolism) • To evaluate the effect of BIVV009 on certain disease-related biomarkers in patients with primary CAgD • To evaluate the pharmacokinetics of BIVV009 • To evaluate the immunogenicity of BIVV009 **Part B** Primary objective: • The primary objective of Part B is to evaluate the long-term safety and tolerability of BIVV009 in patients with primary CAgD. Secondary objective: The secondary objective of Part B is to investigate the durability of response during long-term treatment with BIVV009 in patients with primary CAgD. Exploratory objective: • To describe the safety and patient satisfaction with the convenience of home infusions with BIVV009 in a subset of patients for the US, the Netherlands, Norway, France, Italy, Austria, Germany, and Spain specific amendments • To evaluate the immunogenicity of BIVV009

METHODOLOGY/STUDY DESIGN:

This open-label, single-arm study is designed to evaluate the efficacy, safety, and tolerability of BIVV009 in patients with the complement-mediated disorder primary CAgD who have a recent history of transfusion.

During the 6-week Screening/Observation Period, prospective patients will have a detailed medical history documented (including transfusion history of ≥6 months), physical evaluations for screening, and blood samples collected for characterization of CAgD biomarkers, including Hgb levels on 3 occasions approximately every 2 weeks.

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

Part A

The study will enroll approximately 20 primary CAgD patients who have a recent history of transfusion, defined as at least 1 transfusion during the last 6 months prior to enrollment. Eligible patients will receive an intravenous (IV) infusion of BIVV009 over approximately 60 minutes on Day 0, Day 7, and every 14 days thereafter through Week 25 (ie, Days 21, 35, 49, 63, 77, 91, 105, 119, 133, 147, 161, and 175). Patients who miss a dose (ie, outside the dosing window or >17 days since last dose) should return to the site for an unscheduled visit 1 week prior to the next scheduled dose in order to receive an additional loading dose. Patients will have an End-of-Treatment (EOT) visit in Part A on Day 182 (Week 26).

Patients who meet the transfusion criteria in Table 1 during the 6-month treatment period will receive a transfusion. Patients who receive a transfusion during Part A will not be withdrawn from the study and will be eligible to participate in Part B.

Table 1: Transfusion criteria

A patient will receive a transfusion during Part A or Part B if his or her Hgb level meets either of the following criteria: • Hgb is <9 g/dL and the patient is symptomatic, *or* • Hgb is <7 g/dL and the patient is asymptomatic

A responder analysis will be conducted following completion of the EOT visit at Week 26. The responder definition is provided in Table 2.

Table 2: Responder definition

A patient will be 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 CAgD beyond what is permitted per protocol. Additionally, the patient's Hgb level must meet either of the following criteria: • Hgb level is ≥12 g/dL at treatment assessment endpoint (defined as mean value from Weeks 23, 25, and 26), *or* • Hgb increased ≥2 g/dL from baseline (defined as the last Hgb value before administration of the first dose of study drug) at treatment assessment endpoint Note: Any patient withdrawing from the study after Week 5 and prior to the Week 23 visit will be considered a non-responder.

A list of excluded concomitant medications, as well as allowed concomitant medications with restrictions, is provided in the protocol. Beyond the permitted concomitant medications, study drug, and transfusions, patients may receive no other therapies for the treatment of CAgD while enrolled in this study; patients requiring other treatment for their CAgD in Part A will be withdrawn from the study and counted as non-responders. These patients will not be eligible to participate in Part B.

	Part B Following completion of dosing in the 6-month treatment period, patients will continue to receive BIVV009 dosing during Part B, the long-term safety and durability of response extension phase. Part B will run for 2 years following LPO under Part A. Patients requiring treatment with permitted concomitant medications and/or transfusions will not be discontinued from the study. Patients in Part B will be transfused per the Transfusion Criteria in Table 1. Patients who receive a transfusion during Part B will not be withdrawn from the study. Patients will be dosed with BIVV009 every 2 weeks, as in Part A. Should patients deviate from their scheduled dosing a repeat loading dose may be required. On-site visits will be completed ~ every 3 months (at a minimum) for collection of pharmacodynamic (PD) and pharmacokinetic (PK) samples, ADA samples during the 1st year of treatment in Part B, then every 6 months and for additional safety and efficacy measures. PK, PD and antidrug antibodies (ADA) samples will be collected 9 weeks after administration of the last dose of study drug in patients who discontinue early, as well as in patients who experience a hematological breakthrough event. The study will be complete 24 months following LPO for Part A at which time all patients receiving on-going treatment will proceed to an End-of-Study (EOS) visit.
NUMBER OF PATIENTS:	Approximately 20 male and/or female patients ≥18 years of age with a confirmed diagnosis of primary CAgD who have a recent history of blood transfusion will be enrolled.
NUMBER OF STUDY SITES:	Approximately 55 sites worldwide will be targeted for participation to identify approximately 20 eligible CAgD patients.
MAIN CRITERIA FOR INCLUSION:	All patients must meet all the following inclusion criteria to be enrolled: 1. Adult males and females ≥18 years of age at Screening. 2. Body weight of ≥39 kg at Screening. 3. Confirmed diagnosis of primary CAgD based on the following criteria: a) Chronic hemolysis 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 4. History of at least one documented blood transfusion within 6 months of enrollment. 5. Hemoglobin level ≤10.0 g/dL. 6. Bilirubin level above the normal reference range, including patients with Gilbert's Syndrome. 7. Ferritin levels above the lower limit of normal. Concurrent treatment with iron supplementation is permitted if the patient has been on a stable dose during the previous 4 weeks. 8. Presence of one or more of the following CAgD-related signs or symptoms within 3 months of Screening: a) Symptomatic anemia defined as: i. Fatigue ii. Weakness iii. Shortness of breath iv. Palpitations, fast heart beat v. Light headedness and/or vi. Chest pain

	b) Acrocyanosis c) Raynaud's syndrome d) Hemoglobinuria e) Disabling circulatory symptoms, and/or f) Major adverse vascular event (including thrombosis). 9. Bone marrow biopsy within 6 months of Screening with no overt evidence of lymphoproliferative disease or other hematological malignancy. An additional bone marrow biopsy will be required if the prior bone marrow is deemed unsuitable for analysis by the Sponsor. 10. Documented vaccinations against encapsulated bacterial pathogens (*Neisseria meningitis*, including serogroup B *meningococcus* where available, *Haemophilus influenzae*, and *Streptococcus pneumoniae*) within 5 years of enrollment or as specified in Section 6.1.1.1. 11. Adequate IV access. 12. 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 child-bearing potential will agree to use highly effective contraception from Day 0 until 9 weeks following administration of the last dose of study drug. 14. Able to comprehend and give informed consent. 15. Able to comply with the requirements of the study and to complete the full sequence of protocol-related procedures.
EXCLUSION CRITERIA:	Patients who meet any of the following criteria will be excluded from the study: 1. Cold agglutinin syndrome secondary to infection, rheumatologic disease, or active hematologic malignancy. 2. Clinically relevant infection of any kind within the month preceding enrollment (eg, active hepatitis C, pneumonia). 3. Clinical diagnosis of systemic lupus erythematosus (SLE) or other autoimmune disorders with anti-nuclear antibodies at Screening. Anti-nuclear antibodies of long-standing duration without associated clinical symptoms will be adjudicated on a case-by-case basis during the Confirmatory Review of Patient Eligibility (Section 6.1.1.3). 4. Positive hepatitis panel (including hepatitis B surface antigen and/or hepatitis C virus antibody) prior to or at Screening. 5. Positive human immunodeficiency virus (HIV) antibody at Screening. 6. Treatment with rituximab monotherapy within 3 months or rituximab combination therapies (eg, with bendamustine, fludarabine, ibrutinib, or cytotoxic drugs) within 6 months prior to enrollment. 7. Concurrent treatment with corticosteroids other than a stable daily dose equivalent to ≤10 mg/day prednisone for previous 3 months. 8. Erythropoietin deficiency. Concurrent treatment with erythropoietin is permitted if the patient has been on a stable dose for the previous 3 months. 9. Concurrent usage of iron supplementation unless the patient has been on a stable dose for at least 4 weeks. 10. Clinically significant medical history or ongoing chronic illness that would jeopardize the safety of the patient or compromise the quality of the data derived from his/her participation in this study (as determined by the Investigator [or designee]) at Screening.

<table>
<tr><td></td><td>11. Concurrent treatment with other experimental drugs or participation in another clinical trial with any investigational drug within 30 days or 5 half-lives, whichever is greater, prior to treatment start.
12. Females who are pregnant, lactating, or, if having reproductive potential, are considered potentially unreliable with respect to contraceptive practice.
13. History of hypersensitivity to BIVV009 or any of its components.</td></tr>
<tr><td>TEST PRODUCT(S), DOSE, AND MODE OF ADMINISTRATION:</td><td>Study drug will be administered over approximately 60 minutes by IV infusion in accordance with the Pharmacy Manual. Patients with underlying cardiopulmonary disease may receive a 2-hour infusion with Sponsor approval. At pre-selected countries/sites during Part B administration of the study drug may be provided in the form of home infusions (Section 10.10, Appendix J).
Patients who weigh less than 75 kg will receive fixed doses of 6.5 g of BIVV009.
Patients who weigh 75 kg or more will receive fixed doses of 7.5 g of BIVV009.</td></tr>
<tr><td>DURATION OF TREATMENT:</td><td><table>
<tr><td>Part A</td><td>Screening/observation period:</td><td>6 weeks (Days -42 through Day -1)</td></tr>
<tr><td></td><td>Treatment period:</td><td>25 weeks (Day 0 through Day 175)</td></tr>
<tr><td></td><td>End-of-treatment (EOT) visit:</td><td>Week 26: 1 week after administration of the last dose of study drug in Part A (Day 182)</td></tr>
<tr><td>Part B</td><td>Safety and durability of response extension phase:</td><td>Bi-weekly dosing starting at Week 27 and continuing for 2 years after LPO in Part A</td></tr>
<tr><td>Part A/B</td><td>Early termination (et) visit/safety follow-up visit/EOS visit:</td><td>9 weeks after last dose of study drug administration</td></tr>
</table>Patients who complete Part A per protocol through the EOT visit will participate in Part B, the long-term safety and durability of response extension phase of the study.</td></tr>
<tr><td>EFFICACY ENDPOINTS AND OUTCOME MEASURES</td><td><u>Part A</u>
Primary efficacy endpoint:
The primary efficacy endpoint is the responder rate as defined in Table 2.
Secondary efficacy endpoints:
• Mean change from baseline in bilirubin (excluding patients with Gilbert’s Syndrome) at the treatment assessment endpoint (mean of values at Week 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 Hgb at the treatment assessment endpoint
Exploratory efficacy endpoints:
• Time to first transfusion after the first 5 weeks of study drug administration
• Mean change from baseline in QOL, as assessed by the change in the five level EuroQol - five dimensions questionnaire (EQ-5D-5L) scores at the treatment assessment endpoint
• Mean change from baseline in QOL, as assessed by the change in the 12-Item Short Form Survey (SF-12®) at the end of treatment assessment endpoint
• Incidence of solicited symptomatic anemia at EOT</td></tr>
</table>

	• Proportion of patients with Hgb level of ≥12 g/dL at the treatment assessment endpoint • Incidence of thromboembolic events after the first 5 weeks of study drug administration • Median time to normalization of bilirubin • Median time to normalization of LDH • Median time to normalization of haptoglobin • Median time to obtain Hgb level of ≥12 g/dL • Proportion of patients normalizing haptoglobin at the treatment assessment endpoint • Proportion of patients normalizing bilirubin at the treatment assessment endpoint • Proportion of patients normalizing LDH at the treatment assessment endpoint • Patient's Global Impression of Change (PGIC) to assess patient's perception of changes in CAgD disease burden at EOT • Patient's Global Impression of [Fatigue] Severity (PGIS) to assess patient's perception of changes in fatigue at EOT • Incidence of disabling circulatory symptoms at EOT • Total healthcare resource utilization at EOT <u>Part B</u> The following parameters of disease activity will be assessed: • Hemoglobin • Bilirubin (total) • QOL assessments (FACIT-Fatigue, EQ-5D-5L, SF-12**,** PGIC, and PGIS) • LDH • Transfusion requirements • Haptoglobin • Total healthcare resource utilization at EOT • Satisfaction with home infusion
SAFETY OUTCOME MEASURES	Safety assessments for this study include adverse events (AEs), serious AEs, clinical laboratory evaluations, SLE panel, vital sign measurements, electrocardiograms (ECGs), physical examination findings, and serum disease-related biomarkers. In addition, the following will be assessed for safety evaluation: • Hemolytic breakthrough (rapid fall in Hgb ≥2 g/dL associated with an increase in LDH/bilirubin and/or decrease in haptoglobin since the last scheduled visit) through the EOT at Week 26 • Infections of ≥ Grade 3 severity (ie, requiring IV antibiotics) • Thromboembolic events • For patients with home infusions, safety assessments will additionally include AEs with onset within 24 hours of the infusion
PHARMACOKINETIC OUTCOME MEASURES	Pharmacokinetic endpoints will include: • Plasma concentrations of BIVV009 • PK parameters. Appropriate exposure parameters (C_{max}, AUC) will be derived using a population approach. PK blood samples will be collected at predose and 1 hour postdose (ie, 1 hour after completion of study drug infusion) from all patients on Days 0, 7, 21, 35, 49, 63, 77, 91, 105, 119, 133, 147, 161, and 175. An additional blood sample for PK analysis will be collected during the EOT visit on Day 182 or at ET if patient withdraws early.

	PK samples will be routinely collected at predose and 1 hour (±15 minutes) postdose. Samples will be collected at 3-month intervals during the 1st year of treatment in Part B and then at 6-month intervals for the remainder of the time on study. Samples will also be collected if a patient experiences a hematologic breakthrough event, or a patient withdraws from study.
PHARMACODYNAMIC OUTCOME MEASURES	PD Primary Outcome Measure: • Wieslab-CP Exploratory Complement System Measures: • CH50 • Total C4 • C1q • C1s PD blood samples will be collected at predose and 1 hour postdose (ie, 1 hour after completion of study drug infusion) from all patients on Days 0, 7, 21, 35, 49, 63, 77, 91, 105, 119, 133, 147, 161, and 175. An additional blood sample for PD analysis will be collected during the EOT visit on Day 182 or at ET if patient withdraws early. PD samples will be routinely collected at predose and 1 hour (±15 minutes) postdose. Samples will be collected at 3-month intervals during the 1st year of treatment in Part B and then at 6-month intervals for the remainder of the time on study. Samples will also be collected if a patient experiences a hematologic breakthrough event, or a patient withdraws from study.
IMMUNOGENICITY OUTCOME MEASURES:	Immunogenicity Outcome Measures will include pre-existing ADA and treatment-emergent ADA. During Part A, samples were collected at predose on Day 0 and at ET if a patient withdraws early or if patient experienced a hematological breakthrough event. For immunogenicity assessment in Part A, left over PD samples may be used in patients who consented to future use of samples. During the 1st year of treatment in Part B, ADA samples will be collected at predose at 3-month intervals, and then at 6-month interval and at Safety Follow up visit 9 weeks after last dose. Samples will also be collected if a patient experiences a hematologic breakthrough or withdraws from the study.
SAMPLE SIZE:	If the true responder rate is estimated to be 66% and a minimum of 30% is required for success, then with 20 patients there is 90% probability that the lower limit of the 95% confidence interval (CI) will be at least 30%. The minimal observed rate for a successful efficacy claim is 11/20 = 55%.
STATISTICAL METHODS:	Interim analysis: For the purpose of regulatory submission, an interim analysis of safety and efficacy data will be performed after all patients have completed Part A. Analyses: For Part A, the analysis of the primary endpoint, the proportion of responders will be calculated together with a 95% exact Clopper-Pearson CI. The main analysis will be conducted on the Full Analysis Set (FAS): FAS population, consisting of all patients who received at least one dose of study drug. Under the assumption that a response rate of less than or equal to 30% is not clinically relevant, the success criteria for the primary endpoint will be that the 95% lower bound CI for response rate excludes 30% using the exact Clopper-Pearson method. That is, this criterion is equivalent to demonstrating at the 2-sided 0.05 level of significance that the true response rate is >30%. All secondary endpoints will be analyzed using descriptive statistics, frequency, percentage, and CIs as appropriate. Change from baseline for continuous parameters will be analyzed using a one-sample t-test.

	For Part B, the analyses will be performed for all patients who received at least 1 dose of study drug during the extension period. All efficacy and safety endpoints will be summarized by descriptive statistics. Further details regarding other endpoints and proposed analyses will be described in full in the Statistical Analysis Plans for Part A and Part B.

2 INTRODUCTION[1]

2.1 PHARMACOLOGY OF BIVV009

BIVV009 is a humanized monoclonal antibody (mAb) directed against human complement factor C1s, which along with C1r and C1q is a part of the C1 complex that sits at the apex of the complement classical pathway (CP). By binding C1s, BIVV009 prevents the enzymatic action of the C1 complex on its substrates, complement factors C4 and C2, and thereby blocks formation of the C3 convertase. Note that this site of action of BIVV009 lies above the level of C3, which is the junction of all three pathways of complement activation. This is important to the specificity of the mechanism of action of BIVV009 because it means that the two other complement pathways, the alternative pathway and the lectin pathway, remain functionally intact for the purpose of host defense in the presence of BIVV009. Note, too, that the non-enzymatic role of C1q is left intact by BIVV009; this may be particularly relevant because of the importance of the pro-phagocytic "housekeeping" functions of the complement system including removal of apoptotic cells.

BIVV009 binds with high affinity and specificity to C1s of humans and non-human primates (NHPs). It has no affinity for the related proteases of the lectin pathway, MASP-1, and MASP-2. As discussed above, BIVV009 has disease-relevant inhibitory activity against CP in a variety of human in vitro models of human disease (including cold agglutinin disease [CAgD], bullous pemphigoid [BP], and warm autoimmune hemolytic anemia [WAIHA]). BIVV009 exerts its effect on the CP in a characteristic two-state behavior: complete inhibition at concentrations ≥20 μg/mL, and no inhibition at concentrations <20 μg/mL, with an abrupt transition between the two. This behavior means that graded degrees of inhibition are not readily measurable and that increasing BIVV009 concentration to ≥20 μg /mL results not in greater degrees of inhibition, but only in longer duration of inhibition (ie, longer dwell time in the "off" state of the CP). In turn, this means that the dose-effect relationship is demonstrated in the duration of action, such that higher doses lead to longer possible inter-dose intervals while maintaining full pathway inhibition.

2.2 BACKGROUND AND STUDY RATIONALE

The CP has been implicated in many diseases that are driven by the presence of a pathogenic antibody; CAgD is one such example. Complement inhibition has proven to be a safe and effective treatment for another form of hemolytic anemia, paroxysmal nocturnal hemoglobinuria. Currently, there are approved complement inhibitors being used therapeutically for various indications, including Soliris® (eculizumab), a mAb targeting C5; Berinert® and Cinryze®, both C1 esterase inhibitors purified from human plasma; and Ruconest®, a recombinant form of human C1 esterase inhibitor. Unlike Soliris and the C1 esterase inhibitors, by specifically targeting C1s, BIVV009 inhibits only the CP, leaving the alternative complement pathway and the lectin complement pathway available for immune surveillance. Furthermore, by blocking at the level of the C1 complex, BIVV009 is expected to prevent generation of all anaphylatoxins and opsonins (eg, C3 fragments) that produce pathologic lesions in CP-mediated disorders.

[1] Information supplied by the Sponsor.

CAgD is an autoimmune hemolytic anemia caused by IgM-induced CP activation, which is typically triggered by exposure to cold environmental temperatures or viral infections (Berentsen, Beiske et al. 2007, Petz 2008, Berentsen 2011, Swiecicki, Hegerova et al. 2013, Arthold, Skrabs et al. 2014, Berentsen 2014). CAgD is typically not responsive to treatment with steroids or splenectomy and can only be managed by supportive measures (avoidance of cold, blood transfusions as needed), and/or immunosuppressive, cytotoxic therapies (eg, rituximab with or without fludarabine or bendamustine). A Phase 1b clinical trial of BIVV009 in patients with CAgD showed that it can rapidly induce complete remission of anemia (Jäger, Gilbert et al. 2016).

Patients with CAgD are often elderly and/or have numerous co-morbidities affecting their mobility. Moreover, clinical centers specialized in the management of CAgD are infrequent and may be located far from patients' home. Consequently, some patients may find the option of home infusions with drug against CAgD beneficial. To this end a group of patients at preselected sites/countries will be offered the possibility of home infusions during Part B, assisted by trained health care professional. For the US, the Netherlands, Norway, France, Italy, Austria, Germany, and Spain specific amendments (Section 10.10 Appendix J).

2.2.1 Non-clinical experience

The non-clinical safety foundation for this study includes a completed 6-month toxicology study in which NHPs were treated with weekly doses of BIVV009 as high as 180 mg/kg for 26 weeks. Non-clinical safety studies of BIVV009 have demonstrated no toxicologically adverse findings related to BIVV009 in cynomolgus monkey studies of up to 6-months treatment duration; furthermore, no adverse effects from exaggerated pharmacology (ie, autoimmune diseases, bacterial infections) were observed in those studies. As a result, the no observed adverse effect (dose) level (NOAEL) established for BIVV009 is 180 mg/kg by weekly intravenous (IV) administration for 26 weeks; this translates to a safety margin that more than adequately covers the BIVV009 dose regimen for use in Study BIVV009-03. Hence the NOAEL in cynomolgus monkeys is more than twice the intended fixed doses of 6.5 grams or 7.5 grams, based on an adult weighing ~75 kg.

2.2.2 Clinical experience

The clinical safety foundation for this study includes an ongoing prospective, double-blind, randomized, placebo-controlled, First In Human (FIH) Phase 1a/1b study (BIVV009-01). Phase 1a included Part A, a single-ascending dose study in normal healthy volunteers (NHV), and Part B, a multiple-ascending dose study in NHVs. Phase 1b included Part C, a multi-dose study in patients with complement-mediated disorders including CAgD, WAIHA, BP, and antibody-mediated rejection (AMR) in kidney transplant recipients, and Part E, which was added to both allow continued access to study drug in a subset of study patients with CAgD, and to further characterize the safety and efficacy to BIVV009. Part D was not implemented.

Part A was conducted according to an ascending dose cohort paradigm in which a unique cohort of NHVs was treated at each single dose level. There were 7 cohorts of NHVs. The first 2 cohorts consisted of 4 healthy volunteers each, 3 given BIVV009 (0.3 or 1 mg/kg) by IV infusion, and 1 given placebo. The remaining 5 cohorts consisted of 8 healthy volunteers each, 6 given BIVV009 by IV infusion (3, 10, 30, 60, or 100 mg/kg) and 2 given placebo.

Part B was conducted according to an ascending dose cohort paradigm in which a unique cohort of NHVs was treated at each dose level. There were 2 cohorts of NHVs, each consisting of 8 healthy volunteers, in this part of the study. These cohorts were given 4 weekly IV doses of BIVV009 or placebo (6:2 for active: placebo) at a dose level previously administered to NHVs in Part A of the study (30 or 60 mg/kg).

Part C was conducted in a single cohort of patients enrolled in 4 strata, representing 4 complement-mediated disorders (CAgD, WAIHA, BP, and AMR). Patients in Part C received a single IV test dose of 10 mg/kg followed by 4 weekly doses of 60 mg/kg.

Clinical proof of concept for BIVV009 was achieved in Phase 1b based upon the demonstration of immediate cessation of hemolysis and rapid correction of anemia during short-term treatment of patients with CAgD. These results confirm that continuous C1s inhibition is sufficient to observe a treatment effect, while the observation of relapse of hemolytic anemia upon washout of BIVV009 and restoration of C1s activity confirms that continuous C1s inhibition is necessary for treatment of CAgD.

The clinical safety profile of single- or multiple-dose administration of BIVV009 to healthy volunteers was similar to placebo with respect to type, frequency, or severity of adverse events (AEs) and there have been no clinically meaningful AEs seen in healthy volunteers exposed to BIVV009 at doses up to 60 mg/kg weekly for 4 doses. The clinical safety profile of multiple-dose administration of BIVV009 to patients with a variety of complement-mediated disorders has not revealed any new safety concerns in this older-aged, medically complex population. With respect to the hypothetical, mechanism-related risks from C1s inhibition (ie, autoimmune diseases, bacterial infections), prophylactic vaccination against encapsulated bacterial pathogens per regional guidelines and routine surveillance with systemic lupus erythematosus (SLE) serologic testing are available to mitigate these risks.

A second prospective, double-blind, randomized, placebo-controlled study of multi-dose BIVV009 in healthy volunteers was recently completed under Protocol TNT009-02. A single cohort of 24 NHVs was randomized to BIVV009 (75 mg/kg) or placebo at a ratio of 3:1. Volunteers were dosed on Days 1, 8, 22, and 36. Intensive pharmacokinetic (PK)/pharmacodynamic (PD)/exploratory complement sampling was performed during the study. This study added an additional dose level, which was combined with data from the BIVV009-01 study to augment PK modeling and simulations. The results of this study, in conjunction with existing PK data, was used to propose dose regimens for the current protocol.

2.2.3 Pharmacokinetic experience and dose justification

The PK/PD profile of BIVV009 in healthy volunteers and in patients has been established based on the data collected from the first-in-human clinical trial. A human PK model was constructed from the complete and final Phase 1a data. This model was then augmented with the available PK data emerging from the Phase 1b component of this trial, and the combined model was used to simulate a variety of possible dose regimens for use in patients. The dose regimen proposed for use in current and future clinical trials with BIVV009, including Study BIVV009-03, differs from that used in the Phase 1a and 1b program because weekly IV administration was deemed to be logistically challenging for patients when the period of treatment is increased from weeks to

months. A regimen based upon a single priming dose on Day 0, followed by bi-weekly dosing on Days 7, 21, 35, 49, etc. can provide continuous, complete C1s inhibition while better accommodating to the needs of patients. Human PK modeling suggests that a dose level of 6.5 grams or 7.5 grams (based on body weight of <75 kg or ≥75 kg, respectively) is necessary to protect patients better from potential restoration of CP activity at the end of the inter-dose interval. The weight cut-off of 75 kg was chosen based on the expected weight distribution in CAgD patients with a median weight of 74.8 kg.

The in vitro and in vivo pharmacologic profile of BIVV009 has two especially important features that help to define the optimal dose regimen for clinical use. First, BIVV009 has very high affinity and selectivity for C1s, with negligible off-target activity. Second, it is a potent CP inhibitor with such a steep concentration-effect relationship that it behaves as a switch-like inhibitor of C1s: at concentrations of BIVV009 ≥20 µg/mL, CP activity is virtually undetectable; at BIVV009 concentrations below this threshold the CP is fully active. This property results in the requirement to maintain a blood concentration of BIVV009 that is always at least ≥20 µg/mL, even at trough, lest CP activity be fully restored.

2.2.4 Potential risks and benefits

As previously noted, clinical proof of concept for BIVV009 was achieved in a Phase 1b study, which demonstrated immediate cessation of hemolysis and rapid correction of anemia during short-term treatment of patients with CAgD.

The human safety risk from off-target effects of mAb therapeutics is generally considered to be low, and in this regard BIVV009 is no exception. The human safety risk from short-term inhibition of the complement system also appears to be low, based upon the experience with five approved products in this therapeutic class. Long-term, complement inhibition may increase the risk of infection with encapsulated bacteria, as reflected in the product label for eculizumab (Soliris), an inhibitor of the terminal portion of the complement system. However, to provide optimal protection against infections with encapsulated bacteria, the design of this study includes an appropriate program of prophylactic vaccinations.

The risks associated with long-term inhibition of the proximal portion of the CP are presently unknown. Theoretically, it could increase the risk of SLE or circulating immune complexes (CIC) disease due to the role of the C1 complex in immune complex clearance, as observed in patients with congenital deficiencies of C1 complex components (C1q, C1s, and C1r). However, pharmacologic inhibition of C1s differs from congenital deficiency of the C1 complex because: 1) congenital C1 complex component deficiency are commonly not single gene mutations but typically are associated with second mutations in other immune system genes; 2) pharmacologic inhibition of C1s enzymatic function in the C1 complex leaves intact the non-enzymatic function of C1q, which is important for the opsonization and phagocytic removal of apoptotic cells which protects against autoimmunity; and 3) the phenotype associated with life-long, often total absence of C1 complex structure and function is unlikely to be reproduced by pharmacologic antagonism of C1 enzymatic function in fully developed adults. Nevertheless, standard clinical biomarkers related to SLE (eg, antibodies to double-stranded DNA [dsDNA]) have been incorporated into the study design as safety surveillance measures.

Home infusions with the study drug will be proposed to a number of patients in countries pre-selected to participate in home infusion. Home infusions will be assisted by a trained healthcare professional, and will concern patients who express such wish, after having been qualified by the Investigator and no sooner than after Week 41 (Day 287) and without evidence of intolerance of the study drug as determined by the Investigator. No new risks related to home infusions are anticipated. Like with office visits, medications such as epinephrine and diphenhydramine, and additional emergency equipment will be available in case an allergic reaction or anaphylaxis occurs during home infusion. Professional healthcare caregiver will be qualified to detect and treat allergic reactions and anaphylaxis. The alternating schedule of home infusion visits and office visits every 4 weeks each may be found convenient by patients as less travels to the study site will be necessary

The overall risk/benefit balance for participants in Study BIVV009-03 is favorable based on available data to date.

3 STUDY OBJECTIVES

3.1 PRIMARY OBJECTIVE (PART A)

The primary objective of Part A is to determine whether BIVV009 administration results in a ≥2 g/dL increase in hemoglobin (Hgb) levels or increases Hgb to ≥12 g/dL and obviates the need for blood transfusion during treatment in patients with primary CAgD who have a recent history of blood transfusion.

3.2 SECONDARY OBJECTIVES (PART A)

The efficacy objectives of Part A are:

- To assess the effect of BIVV009 on clinical events and laboratory parameters related to hemolysis and anemia in patients with primary CAgD
- To assess the effect of BIVV009 on quality of life (QOL) in patients with primary CAgD.

The safety objective of Part A is:

- To evaluate the overall safety and tolerability of BIVV009 in patients with primary CAgD

The exploratory objectives of Part A are:

- To assess the effect of BIVV009 on specific complications of CAgD (acrocyanosis, Raynaud's syndrome, hemoglobinuria, and thromboembolism)
- To evaluate the effect of BIVV009 on certain disease-related biomarkers in patients with primary CAgD
- To evaluate the pharmacokinetics of BIVV009
- To evaluate the immunogenicity of BIVV009

3.3 PRIMARY OBJECTIVE (PART B)

The primary objective of Part B is to evaluate the long-term safety and tolerability of BIVV009 in patients with CAgD.

3.4 SECONDARY OBJECTIVE (PART B)

The secondary objective of Part B is to investigate the durability of response during long-term treatment with BIVV009 in patients with CAgD.

3.5 EXPLORATORY OBJECTIVE (PART B)

- To describe the safety and patient satisfaction with the convenience of home infusions with BIVV009 in a subset of patients (for the US, the Netherlands, Norway, France, Italy, Austria, Germany, and Spain specific amendments (Section 10.10 Appendix J).
- To evaluate the immunogenicity of BIVV009.

4 INVESTIGATIONAL PLAN

4.1 STUDY DESIGN

This open-label, single-arm study is designed to evaluate the efficacy, safety, and tolerability of BIVV009 in patients with the complement-mediated disorder, primary CAgD, who have a recent history of blood transfusion.

During the 6-week Screening/Observation Period, prospective patients will have a detailed medical history documented (including transfusion history of ≥6 months), physical evaluations for screening, and blood samples collected on 3 occasions approximately every 2 weeks.

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

Part A

The study will enroll approximately 20 primary CAgD patients who have a recent history of transfusion, defined as at least 1 transfusion during the last 6 months prior to enrollment. Eligible patients will receive an IV infusion of BIVV009 over approximately 60 minutes on Day 0, Day 7, and every 14 days thereafter through Week 25 (ie, Days 21, 35, 49, 63, 77, 91, 105, 119, 133, 147, 161, and 175). Patients who miss a dose (ie, outside the dosing window or >17 days since last dose) should return to the site for an unscheduled visit 1 week prior to the next scheduled dose in order to receive an additional loading dose. Patients will have an End-of-Treatment (EOT) visit on Day 182 (Week 26).

Patients who meet the transfusion criteria in Table 1 during the 6-month treatment period will receive a transfusion. Patients who receive a transfusion during Part A will not be withdrawn from the study and will be eligible to participate in Part B.

Table 1 - Transfusion criteria

A patient will receive a transfusion during Part A or Part B if his or her Hgb level meets either of the following criteria: • Hgb is <9 g/dL and the patient is symptomatic, *or* • Hgb is <7 g/dL and the patient is asymptomatic

A responder analysis will be conducted following completion of the EOT visit at Week 26. The responder definition is provided in Table 2.

Table 2 - Responder definition

A patient will be 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 CAgD beyond what is permitted per protocol. Additionally, the patient's Hgb level must meet either of the following criteria: • Hgb level is ≥12 g/dL at the treatment assessment endpoint (defined as mean value from Weeks 23, 25, and 26), *or* • Hgb increased ≥2 g/dL from baseline (defined as the last Hgb value before administration of the first dose of study drug) at treatment assessment endpoint Note: Any patient withdrawing from the study after Week 5 and prior to the Week 23 visit will be considered a non-responder.

A list of excluded concomitant medications, as well as allowed concomitant medications with restrictions, is provided in Section 6.2.6. Beyond the permitted concomitant medications, study drug, and transfusions, patients may receive no other therapies for the treatment of CAgD while enrolled in this study; patients requiring other treatment for their CAgD in Part A will be withdrawn from the study and counted as non-responders. These patients will not be eligible to participate in Part B.

Part B

Following completion of dosing in the 6-month treatment period, patients will continue to receive BIVV009 dosing during Part B, the long-term safety and durability of response extension phase. Part B will run for 2 years following last patient out (LPO) under Part A. Patients requiring treatment with permitted concomitant medications and/or transfusions will not be discontinued from the study. Patients in Part B will be transfused per the Transfusion Criteria in Table 1. Patients who receive a transfusion during Part B will not be withdrawn from the study.

Patients will be dosed with BIVV009 every 2 weeks, as in Part A. Should patients deviate from their scheduled dosing, a repeat loading dose may be required. On-site visits will be completed ~ every 3 months (at a minimum) for collection of PK, PD and ADA samples during the 1st year of treatment in Part B, then every 6 months and for additional safety and efficacy measures.

A subset of patients from countries pre-selected to participate in home infusion, and who were determined to have tolerated BIVV009 well, will be invited to have infusions with BIVV009 performed at their homes, after having been qualified by the Investigator. Home infusion will be performed by a healthcare professional caregiver contingent upon completion of training delivered by the Investigator or delegated site staff member only in patients willing to be administered study drug in home and who satisfy the criteria mentioned in the Appendix J, Section 10.10. Patients will follow the alternate home infusion scheme, ie, home infusion at the patient's home will be alternating with office visits, so that patients will attend office visit every 4 weeks alternating with home infusions every 4 weeks (±2 days) (Section 10.10 Appendix J).

A safety follow-up visit for collection of AE data, PK, PD, and antidrug antibodies (ADA) samples will be performed 9 weeks after administration of the last dose of study drug in patients who discontinue early. Samples for PK, PD, and ADA will also be collected from patients who experience a hematological breakthrough event. The study will be complete 24 months following LPO for Part A at which time all patients receiving on-going treatment will proceed to an End-of-Study (EOS) visit.

4.2 DISCUSSION OF STUDY DESIGN

The route of administration, dose, and dosing interval for BIVV009 planned for use in this study are based on the initial Phase 1a/1b clinical experience (BIVV009-01) and corresponding non-clinical data for safety, PK, and PD observations. BIVV009 has thus far been administered to healthy human volunteers and patients with complement-mediated disease entities including CAgD, bullous pemphigoid, warm autoimmune hemolytic anemia, and AMR.

Under the current protocol, enrolled patients will receive fixed doses of BIVV009 via IV infusion of either 6.5 grams (if <75 kg) or 7.5 grams (if ≥75 kg), based on their baseline body weight.

The repeated dose regimen is predicted to provide continuous C1s inhibition throughout the dosing interval, with an adequate safety margin based on comparative drug exposures in NHPs (Section 2.2.1) and in healthy volunteers given a single dose of 100 mg/kg in Phase 1a (Section 2.2.2).

Safety, tolerability, PK, and PD and immunogenicity assessments will be evaluated at the time points indicated in the study schedule of events (Table 3). In patients having consented to the use of their blood samples for future research, ADA may be tested using available predose PD back-up samples.

4.3 STUDY ENDPOINTS

4.3.1 Primary endpoint (Part A)

The primary efficacy endpoint is the responder rate as defined in Table 2.

4.3.2 Secondary efficacy endpoints (Part A)

- 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 (Section 10.3, Appendix C) 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 Hgb at the treatment assessment endpoint

4.3.3 Exploratory efficacy endpoints (Part A)

- Time to first transfusion after the first 5 weeks of study drug administration
- Mean change from baseline in QOL, as assessed by the change in the five level EuroQol - five dimensions questionnaire (EQ-5D-5L) scores at the treatment assessment endpoint
- Mean change from baseline in QOL, as assessed by the change in the 12-Item Short Form survey (SF-12®) at the end of treatment assessment endpoint
- Incidence of solicited symptomatic anemia at EOT
- Proportion of patients with Hgb level of ≥12 g/dL at the treatment assessment endpoint
- Incidence of thromboembolic events after the first 5 weeks of study drug administration
- Median time to normalization of bilirubin
- Median time to normalization of LDH
- Median time to normalization of haptoglobin
- Median time to obtain Hgb level of ≥12 g/dL
- Proportion of patients normalizing haptoglobin at the treatment assessment endpoint
- Proportion of patients normalizing bilirubin at the treatment assessment endpoint
- Proportion of patients normalizing LDH at the treatment assessment endpoint
- Patient's Global Impression of Change (PGIC) to assess the patient's perception of changes in CAgD disease burden at EOT
- Patient's Global Impression of [Fatigue] Severity (PGIS) to assess the patient's perception of changes in fatigue at EOT
- Incidence of disabling circulatory symptoms at EOT
- Total healthcare resource utilization at EOT

4.3.4 Efficacy endpoints (Part B)

- Hemoglobin
- 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

4.3.5 Safety endpoints

- Incidence of treatment-emergent AEs (TEAEs) and serious AEs (SAEs)
- Change from baseline in clinical laboratory evaluations
- Change from baseline in SLE panel
- Change from baseline in vital signs
- Change from baseline in electrocardiogram (ECG) data
- Physical examination findings
- Serum disease-related biomarkers
- Incidence of hemolytic breakthrough (rapid fall in Hgb ≥2 g/dL associated with an increase in LDH/bilirubin and/or decrease in haptoglobin since the last scheduled visit) through the EOT at Week 26
- Incidence of infections of ≥ Grade 3 severity (ie, requiring IV antibiotics)
- Incidence of thromboembolic events
- For patients with home infusions, safety assessments will include AEs with onset within 24 hours of the infusion at home

4.3.6 Pharmacokinetic endpoints

- Plasma concentrations of BIVV009
- PK parameters. Appropriate exposure parameters (C_{max}, AUC) will be derived using a population approach

PK blood samples will be collected at predose and 1 hour postdose (ie, 1 hour after completion of study drug infusion) from all patients on Days 0, 7, 21, 35, 49, 63, 77, 91, 105, 119, 133, 147, 161, and 175. An additional blood sample for PK analysis will be collected during the EOT visit on Day 182 or at early termination (ET) if a patient withdraws early.

PK samples will be routinely collected at predose and 1 hour (±15 minutes) postdose. Samples will be collected at 3-month intervals during the 1st year of treatment in Part B and then at 6-month intervals for the remainder of the time on study. Samples will also be collected if a patient experiences a hematologic breakthrough event or a patient withdraws from study.

4.3.7 Pharmacodynamic endpoints

PD Primary Outcome Measure:

- Wieslab-CP

Exploratory Complement System Measures:

- CH50
- Total C4
- C1q
- C1s

PD blood samples will be collected at predose and 1 hour postdose (ie, 1 hour after completion of study drug infusion) from all patients on Days 0, 7, 21, 35, 49, 63, 77, 91, 105, 119, 133, 147, 161, and 175. An additional blood sample for PD analysis will be collected during the EOT visit on Day 182 or at ET if a patient withdraws early.

PD samples will be routinely collected at predose and 1 hour (±15 minutes) postdose. Samples will be collected at 3-month intervals during the 1st year of treatment in Part B and then at 6-month intervals for the remainder of the time on study. Samples will also be collected if a patient experiences a hematologic breakthrough event or a patient withdraws from study.

4.3.8 Immunogenicity endpoints

Immunogenicity endpoints will include the evaluation of pre-existing ADA and treatment-emergent ADA. During Part A, ADA samples were collected at predose on Day 0 and at ET if a patient withdrew early or if a patient experienced a hematological breakthrough event. During Part B, ADA samples will be collected at predose at 3-month intervals during the 1st year of treatment in Part B and then at 6-month intervals and at Safety Follow up visit 9 weeks after last dose. Samples will also be collected if a patient experiences a hematologic breakthrough or withdraws from the study. In patients who consented to the use of their blood samples for future research, ADA may be tested using available predose PD back-up samples collected at the following time-points Day 7, 35, 77, 133, 175 and Day 182 in Part A and then every 3 months in Part B, prior to implementation of protocol version 06.

4.4 DURATION OF THE STUDY

The planned total study duration per patient is approximately 2.5 to 3.5 years:

- Screening/Observation Period: 6 weeks (Day -42 through Day -1)
- Part A treatment period: 25 weeks (Day 0 through Day 175)
- Part A EOT visit: 1 week after administration of the last dose of study drug during Part A (Week 26/Day 182)

Patients who complete study Part A per protocol through the EOT visit will participate in Part B, the long-term safety and durability of response extension phase of the study.

- Part B safety and durability of response extension phase: bi-weekly dosing starting at Week 27 visit. For individual patients, dosing in Part B may last from 2 to 3 years, depending on when the patient enters Part B. Part B will run for 2 years following completion of LPO in Part A.

- Part A/B ET/Safety Follow-up visit: 9 weeks after administration of the last dose of study drug.

4.5 END OF STUDY

The study will be considered complete 24 months following LPO from Part A. When this occurs, all ongoing patients in Part B will return to the clinic for EOS assessments (see Section 6.1.7 and Table 3). The EOS will occur when the last patient has had his or her last visit (Last Patient Last Visit).

5 PATIENT SELECTION

This study will enroll approximately 20 adult patients with primary CAgD who have a recent history of transfusion, defined as at least one transfusion during the last 6 months prior to enrollment. Patients who meet all the inclusion criteria and for whom none of the exclusion criteria apply will be eligible for enrollment.

5.1 INCLUSION CRITERIA

All patients must meet all the following inclusion criteria to be enrolled:

1. Adult males and female patients ≥18 years of age at Screening.
2. Body weight of ≥39 kg at Screening.
3. Confirmed diagnosis of primary CAgD based on the following criteria:
   a) Chronic hemolysis
   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
4. History of at least one documented blood transfusion within 6 months of enrollment.
5. Hemoglobin level ≤10.0 g/dL.
6. Bilirubin level above the normal reference range, including patients with Gilbert's Syndrome
7. Ferritin levels above the lower limit of normal. Concurrent treatment with iron supplementation is permitted if the patient has been on a stable dose during the previous 4 weeks.
8. Presence of one or more of the following CAgD-related signs or symptoms within 3 months of Screening:
   a) Symptomatic anemia defined as:
      i. Fatigue
      ii. Weakness
      iii. Shortness of breath
      iv. Palpitations, fast heart beat
      v. Light headedness, and/or
      vi. Chest pain
   b) Acrocyanosis

c) Raynaud's syndrome

d) Hemoglobinuria

e) Disabling circulatory symptoms, and/or

f) Major adverse vascular event (including thrombosis)

9. Bone marrow biopsy within 6 months of Screening with no overt evidence of lymphoproliferative disease or other hematological malignancy. An additional bone marrow biopsy will be required if the prior bone marrow is deemed unsuitable for analysis by the Sponsor.
10. Documented vaccinations against encapsulated bacterial pathogens (*Neisseria meningitis*, including serogroup B *meningococcus* where available, *Haemophilus influenzae*, and *Streptococcus pneumoniae*) within 5 years of enrollment or as specified in Section 6.1.1.1.
11. Adequate IV access.
12. 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 child-bearing potential will agree to use highly effective contraception from Day 0 until 9 weeks following administration of the last dose of study drug.
14. Able to comprehend and give informed consent.
15. Able to comply with the requirements of the study and to complete the full sequence of protocol-related procedures.

5.2 EXCLUSION CRITERIA

Patients who meet any of the following criteria will be excluded from the study:

1. Cold agglutinin syndrome secondary to infection, rheumatologic disease, or active hematologic malignancy.
2. Clinically relevant infection of any kind within the month preceding enrollment (eg, active hepatitis C, pneumonia).
3. Clinical diagnosis of SLE; or other autoimmune disorders with anti-nuclear antibodies at Screening. Anti-nuclear antibodies of long-standing duration without associated clinical symptoms will be adjudicated on a case-by-case basis during the Confirmatory Review of Patient Eligibility (Section 6.1.1.3).
4. Positive hepatitis panel (including hepatitis B surface antigen and/or hepatitis C virus antibody) prior to or at Screening.
5. Positive human immunodeficiency virus (HIV) antibody at Screening.

6. Treatment with rituximab monotherapy within 3 months or rituximab combination therapies (eg, with bendamustine, fludarabine, ibrutinib, or cytotoxic drugs) within 6 months prior to enrollment.
7. Concurrent treatment with corticosteroids other than a stable daily dose equivalent to ≤10 mg/day prednisone for previous 3 months.
8. Erythropoietin deficiency. Concurrent treatment with erythropoietin is permitted if the patient has been on a stable dose for the previous 3 months.
9. Concurrent usage of iron supplementation unless the patient has been on a stable dose for at least 4 weeks.
10. Clinically significant medical history or ongoing chronic illness that would jeopardize the safety of the patient or compromise the quality of the data derived from his/her participation in this study (as determined by the Investigator [or designee]) at Screening.
11. Concurrent treatment with other experimental drugs or participation in another clinical trial with any investigational drug within 30 days or 5 half-lives, whichever is greater, prior to treatment start.
12. Females who are pregnant, lactating, or, if having reproductive potential, are considered potentially unreliable with respect to contraceptive practice.
13. History of hypersensitivity to BIVV009 or any of its components.

For country specific requirement - home infusion in/exclusion criteria see Section 10.10, Appendix J.

5.3 REMOVAL OF PATIENTS FROM STUDY PARTICIPATION, AND STUDY SUSPENSION AND STOPPING RULES

Patients will be informed that they are free to withdraw from the study at any time and for any reason. Patients should inform the site of withdrawal in writing. The Investigator (or designee) may remove a patient from the study if, in the Investigator's (or designee's) opinion, it is not in the best interest of the patient to continue the study. Patients may be withdrawn due to the following:

- Change in compliance with inclusion/exclusion criteria that is clinically relevant and affects patient safety.
- Occurrence of AEs that, in the opinion of the Investigator, may jeopardize patient safety or data integrity. This includes clinically significant hematologic breakthrough events attributable to the development of ADA and/or the development of positive SLE auto-antibody titers.
- Occurrence of pregnancy in patient while receiving study drug.
- Intake of non-permitted concomitant medication that might affect patient safety or study assessments/objectives.
- Clinical signs of SLE or any other immune complex disease.

The Investigator will immediately notify the Sponsor's Study Monitor of all patients who withdraw from treatment. In case of withdrawal, all ET assessments should be performed as applicable (Section 6.1.4). The date the patient is withdrawn from the study and the reason for withdrawal will be recorded on the patient's electronic Case Report Form (eCRF). All withdrawn patients will be followed until resolution of all their AEs or until the unresolved AEs are judged by the Investigator (or designee) to have stabilized. Patients who withdraw from study early (prior to Week 5) may be replaced at the discretion of the Sponsor. Patients who withdraw from study after Week 5 and prior to Week 23 will not be eligible to participate in Part B.

The entire study may be discontinued at the discretion of the Sponsor based on the occurrence of the following:

- Adverse events unknown to date or increased frequency and/or severity, and/or duration of known AEs
- Results of the interim analysis (Section 7.9) demonstrating absence of clinically significant increases in Hgb
- Medical or ethical reasons affecting the continued performance of the study
- Difficulties in the recruitment of patients
- Cancellation of or change in drug development program per the discretion of the Sponsor

Patients undergoing home infusions with BIVV009 will return to bi-weekly dosing at the study site if they develop adverse event that in the opinion of the Investigator, may jeopardize patient safety if home infusions are continued. Patients may return to home infusions if the AE, which led to the interruption of home infusions according to the Investigator's judgment is considered to be unrelated to BIVV009 and once resolved or stabilized (Section 10.10, Appendix J).

6 STUDY PROCEDURES

6.1 SCHEDULE OF STUDY PROCEDURES

A schedule of events is presented in Table 3. Laboratory tests, including PD assays, are specified in Section 10.1, Appendix A.

Table 3 - Study schedule of events

Study visit (Week/Day)	Screening/ observation period[a]	Baseline	Part A		Part B Extension phase	ET/EOS/Safety follow-up[b]
			Weeks 1-25	Week 26 (EOT)		
	Days -42, -28 and -14	Day 0	Days 7, 21, 35, 49, 63, 77, 91, 105, 119, 133, 147, 161, 175	Day 182	Every 2 weeks after Week 25	9 weeks after last dose
Visit windows	**±3 days**	**N/A**	**±2 days**	**±2 days**	**±2 days**	**±2 days**
Written informed consent	X					
Demographic & baseline characteristics	X					
Detailed medical history	X					
Inclusion/exclusion criteria	X	X				
Immunization review/vaccination[c]	When applicable, vaccinations should be initiated on Day - 42 or as soon as possible during Screening. The primary vaccine series should be completed during Screening when possible and otherwise prior to Week 5 of Part A. See Section 10.9, Appendix I for the vaccination schedule for Japan. Revaccination with booster doses should be given according to regional guidelines for patients with persistent complement deficiency and in accordance with respective labels.					
Bone marrow biopsy report review[c]	X					
Optional bone marrow testing for MYD88 status for consenting patients	X					
Pregnancy test (if applicable)[e]	X	X	X (Prior to study drug infusion on Days 21, 49, 77, 105, 133, and 161)[e]	X	X[e]	X
Body weight and height[f]	X	X		X	X[l]	X
Physical examination, full	X			X		X
Physical examination, brief		X	X		X[l]	
Vital signs (BP, PR, RR, body temperature)[g]	X	X	X	X	X[l]	X

Study visit (Week/Day)	Screening/ observation period[a]	Baseline	Part A		Part B Extension phase	ET/EOS/Safety follow-up[b]
			Weeks 1-25	Week 26 (EOT)		
	Days -42, -28 and -14	Day 0	Days 7, 21, 35, 49, 63, 77, 91, 105, 119, 133, 147, 161, 175	Day 182	Every 2 weeks after Week 25	9 weeks after last dose
Visit windows	**±3 days**	**N/A**	**±2 days**	**±2 days**	**±2 days**	**±2 days**
12-lead electrocardiogram (predose and 1 hour after infusion on dosing days)	X	X	X (Day 91 only)		X[o]	
Virology/serology panel[h]	X					
Gilbert's Syndrome test (UGT1A1 gene)	X					
SLE panel[h]	X			X	X[s]	X
Iron panel and erythropoietin[h]	X					
Hematology panel[h]	X	X	X	X	X[t]	X
Coagulation panel[h]	X	X		X		X
Clinical chemistry panel[h]	X	X	X	X	X[t]	X
Urinalysis[h]	X	X		X	X[l]	X
FACIT-Fatigue[q]		X	X	X	X[l]	X
PGIS[q]		X	X (Days 35, 77, and 119 only)	X	X[l]	X
PGIC[q]		X	X (Days 35, 77, and 119 only)	X	X[l]	X
SF-12[q]		X	X (Days 35, 77, and 119 only)	X	X[l]	X
EQ-5D-5L[q]		X	X (Days 49, 91, and 133 only)	X	X[l]	X
Solicited symptomatic anemia	X (Day -42 only)	X	X	X	X	X
Study drug administration[i]		X	X		X	

Study visit (Week/Day)	Screening/ observation period[a]	Baseline	Part A		Part B Extension phase	ET/EOS/Safety follow-up[b]
			Weeks 1-25	Week 26 (EOT)		
	Days -42, -28 and -14	Day 0	Days 7, 21, 35, 49, 63, 77, 91, 105, 119, 133, 147, 161, 175	Day 182	Every 2 weeks after Week 25	9 weeks after last dose
Visit windows	**±3 days**	**N/A**	**±2 days**	**±2 days**	**±2 days**	**±2 days**
ADAs against BIVV009		X			X[r]	X
PK samples[j]		X	X	X	X[u]	X
PD samples[h, j]	X[m]	X	X	X	X[u]	X
Disease-related biomarkers[h]	X	X	X[n] (Day 91 only)	X		
Prior & concomitant medications including transfusions	X	X	X	X	X	X
Healthcare resource utilization	X	X	X (Days 21, 49, 77, 105, 133, and 161)	X	X[p]	X
Adverse events[k]	X	X	X	X	X	X

ADA = antidrug antibodies; BP = blood pressure; EOS = End of Study; EOT = End of Treatment; EQ-5D-5L = five level EuroQol five dimensions questionnaire; SF-12 = 12-Item Short Form Survey; ET = Early Termination visit; FACIT-Fatigue = functional assessment of chronic illness therapy - Fatigue; N/A = not applicable; PD = pharmacodynamic; PGIC = Patient's Global Impression of Change; PGIS = Patient's Global Impression of [Fatigue} Severity; PK= pharmacokinetic; PR = pulse rate; QOL = quality of life; RR = respiratory rate; SLE = systemic lupus erythematosus.

a The 6-week Screening/Observation Period may be extended by 1 week for patients requiring a blood transfusion prior to study drug administration.

b Patients should return to the site 9 weeks after last dose for ET procedures, EOS assessment, or Safety Follow-up procedures upon completion of dosing in the study. If patient experiences a hematological breakthrough event, a PK, PD, and ADA sample should be collected at the time of the event.

c Applicable to patients who do not have documented vaccination against encapsulated bacterial pathogens within 5 years of enrollment. Refer to immunization recommendations per Section 6.1.1.1 for patients requiring vaccination. A blood sample for vaccine titers will be collected on Day 0 prior to study drug infusion to be used to determine serum relevant antibody titers should the patient be diagnosed with an infection associated with an encapsulated organism during the course of the study. A second sample will be collected during the study period if a patient presents with symptoms concerning for an infection with Streptococcus pneumonaie, Neisseria meningitidis or Haemophilus influenzae and analyzed if the infection is confirmed with one of the aforementioned organisms.

d Prior bone marrow biopsy report review, prior tissue assessment, or new bone marrow biopsy (as applicable). Sites will submit de-identified biopsy reports to independent central reader for eligibility adjudication. If biopsy is deemed unsuitable or insufficient to determine eligibility, either prior tissue may be submitted for additional hematopathology assessment or a new bone marrow biopsy will be performed during the screening period.

e Females of child-bearing potential only. Serum pregnancy test to be performed at Screening. Serum or urine pregnancy test to be performed on Days 0, 21, 49, 77, 105, 133, and 161, and at Week 26/EOT or at the ET Visit. Repeat serum or urine pregnancy test every 4 weeks (±2 days) during Part B.

f Height measured at Screening only. Body weight measured every 3 months during Part B.

g Vital signs measurements (supine BP, PR, RR, and oral temperature) are to be obtained at Screening and at each subsequent visit, with measurements performed predose and 1 hour (±5 minutes) after completion of administration of each dose of study drug.

h For a complete list of analytes, see protocol (Section 10.1, Appendix A).

i BIVV009 doses of 6.5 grams (if <75 kg) or 7.5 grams (if ≥75 kg) based on patient's baseline body weight will be administered via IV infusion over ~60 ±5 minutes on Days 0, 7, and every 14 days thereafter during Part A, and every 2 weeks starting at Week 27 during Part B. Patients with underlying cardiopulmonary disease may receive a 2-hour infusion with Sponsor approval. If a patient misses a scheduled dose (outside of the 2-day window or >17 days since last dose), they must return to site (unscheduled visit) to receive another loading dose 1 week prior to the next scheduled dose. Qualifying patients at participating sites may have study drug dosed at home during certain visits in Part B, according to the rules specified in Section 10.10 Appendix J (US, the Netherlands, Norway, France, Italy, Austria, Germany, Spain, and specific amendments.

j During Part A, PK and PD samples will be collected at predose and 1 hour (±15 minutes) postdose (ie, 1 hour after completion of study drug infusion) from all patients on Days 0, 7, 21, 35, 49, 63, 77, 91, 105, 119, 133, 147, 161, and 175. An additional blood sample for PK and PD analysis will be collected during the EOT visit on Day 182 or at ET if a patient withdraws early. During Part B, PK and PD samples will be collected routinely at 3-month intervals during the 1st year of treatment in Part B, and then at 6-month intervals. PK and PD samples will also be collected if a patient experiences a hematologic breakthrough event at any point during the study.

k AEs will be recorded from the time the patient signs the informed consent form until 9 weeks after administration of the last dose of study drug.

l To be performed every 3 months.

m Refer to the Laboratory Manual for details of sample collection during Screening.

n Samples will be collected for a subset of the disease-related biomarkers at Day 91 only. Refer to the Laboratory Manual for details.

o During Part B, a 12-lead ECG will be conducting pre- and postdose at 3 months (Day 273).

p During Part B, the healthcare resource utilization data will be recorded every 4 weeks.

q To be performed in the following order: FACIT-Fatigue first, PGIS second, PGIC third, SF-12 fourth, and EQ-5D-5L fifth.

r During Part B, ADA samples will be collected at predose at 3-month intervals during the 1st year of treatment in Part B and then at 6-month intervals and at safety follow up visit 9 weeks after last dose. Samples will also be collected if a patient experiences a hematologic breakthrough event or withdraws from the study early.

s SLE panel will be performed every 6 months in Part-B of the study.

t In Part B, hematology and clinical chemistry panels to be performed every 2 weeks after Week 25 and up to Week 79. For the remainder of Part B after Week 79, hematology and clinical chemistry panels to be performed every 4 weeks.

u To be performed at 3-month intervals during the 1st year of treatment in Part B, and then at 6-month intervals.

6.1.1 Screening/observation period (Day -42 to Day -1)

Patients (or their legally authorized representative) must provide informed consent before any study-specific screening tests are performed. Participating study sites are required to document all screened candidates initially considered for inclusion in the study. Patients will be designated as screened following completion of all screening assessments.

Screen failures are defined as patients who sign the informed consent form (ICF) but are not subsequently dosed with BIVV009. If a patient is considered a screen failure, the reason(s) will be documented on the screening log and in source records.

A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAEs.

6.1.1.1 Screening assessments (initiating at Day -42)

The following assessments and procedures will be initiated following collection of written informed consent at Day -42 and completed during the 6-week Screening/Observation Period:

- Written informed consent
- Demographic data and baseline characteristics including height and body weight
- Detailed medical history
- Immunization review and vaccination, if applicable
- Serum pregnancy test (if applicable)
- Physical examination (full)
- Vital signs
- Virology/serology panel
- Gilbert's Syndrome testing (UGT1A1 gene)
- SLE panel
- Hematology panel
- Coagulation panel
- Clinical chemistry panel
- Urinalysis
- PD samples (refer to Laboratory Manual)
- Iron panel and erythropoietin assays
- Disease-related biomarkers
- 12-lead ECG
- Prior bone marrow biopsy report review, prior tissue assessment, or new bone marrow biopsy (as applicable)

- Optional bone marrow testing for MYD88 status
- Inclusion/exclusion criteria review for determination of eligibility
- Solicited symptomatic anemia assessment
- Record healthcare resource utilization data from previous 6 months
- Record prior and concomitant medications/procedures including transfusions
- Adverse event monitoring

The Screening/Observation Period may be extended by 1 week for patients requiring a blood transfusion during screening to ensure that first study drug administration occurs at least 1 week following the transfusion.

Bone marrow biopsy

A bone marrow biopsy is required to have been performed within 6 months of Screening to rule out overt evidence of lymphoproliferative disease or other hematological malignancy prior to enrollment. Sites will submit de-identified biopsy *reports* to an independent central reader for eligibility adjudication. If biopsy is deemed unsuitable or insufficient to determine eligibility, then either the prior tissue may be submitted for additional hematopathology assessment or a new bone marrow biopsy will be performed during the screening period. Patients will have the option to consent to additional testing of bone marrow for MYD88 status. Further instructions for bone marrow biopsy assessment will be available in the study procedural manual.

Vaccination against encapsulated bacterial pathogens

In the event a patient does not have documented vaccination against encapsulated bacterial pathogens (*Neisseria meningitis*, including serogroup B *meningococcus* where available, *Haemophilus influenzae*, and *Streptococcus pneumoniae*) within 5 years prior to enrollment, vaccination should be initiated during the Screening/Observation Period prior to enrollment (see Table 3). Vaccination series for these pathogens should be completed as per current regional guidelines specified for patients with persistent complement deficiency and in accordance with their respective labels, as applicable. Where no regional guidelines are available for patients with persistent complement deficiency, it is recommended that vaccinations include meningococcal conjugate, meningococcal serogroup B, 13-valent pneumococcal, 23-valent pneumococcal, and *Haemophilus influenza* type b vaccines where commercially available. Revaccination with booster doses should be given according to regional guidelines for patients with persistent complement deficiency and in accordance with respective labels.

Vaccinations should be initiated on Day -42 or as early as possible during the Screening/Observation period. The primary vaccine series should be completed during Screening when possible and otherwise prior to Week 5 of Part A. Patients must be advised that vaccination may not prevent meningococcal infections and that they should immediately report fevers or other symptoms consistent with acute infection to the Investigator.

Patients who develop symptoms consistent with an infection due to the encapsulated bacterial pathogens Streptococcus pneumoniae, Neisseria meningitidis, or Haemophilus influenzae during the study period will have a blood sample collected to test vaccine related titers if the infection is confirmed with one of the aforementioned organisms.

A separate vaccination schedule for Japan is provided in Section 10.9, Appendix I.

Laboratory tests

The first set of laboratory test results collected during the Screening Period will be utilized to assess patient eligibility for the study. Screening assessments may be repeated once at the discretion of the Principal Investigator (PI). Additional repeat screening tests may not be performed without Sponsor (or designee) approval.

6.1.1.2 Interim visits during screening/observation period

During the 6-week Screening/Observation Period, the patient will return to the clinical site approximately every 2 weeks (Day -28 and Day -14) after the initial visit for collection of laboratory samples to assess and characterize their CAgD. During these visits the following assessments and procedures will be performed:

- Vital signs
- Collection of blood samples for assessment of the following indicators of CAgD:
  - Hemoglobin
  - Bilirubin
  - LDH
  - Haptoglobin
  - Reticulocytes
  - CH50
- Record prior and concomitant medications/procedures including transfusions
- Adverse event monitoring

Detailed information on sample collection and a list of analytes to be tested may be found in the Study Schedule of Events (Table 3) in Section 6.1, Section 10.1, Appendix A, and the Laboratory Manual.

6.1.1.3 Confirmatory review of patient eligibility

Upon completion of screening assessments, the site will compile de-identified, key eligibility data for each patient and forward to the Study Medical Monitor for review and confirmation of eligibility prior to study enrollment. Details on the eligibility data review forms and the adjudication process may be found in the study procedural manual.

6.1.2 Day 0 visit (first dose)

On Day 0, patients will undergo the following procedures before administration of the study drug:

- Inclusion/exclusion criteria for confirmation of continued eligibility
- Serum or urine pregnancy test (if applicable)
- Vaccine titers

- Body weight
- Physical examination (brief)
- Vital signs
- 12-lead ECG
- Hematology panel
- Coagulation panel
- Clinical chemistry panel
- Urinalysis
- Solicited symptomatic anemia assessment
- QOL assessments
  - FACIT-Fatigue (see Section 10.3, Appendix C)
  - EQ-5D-5L (see Section 10.4, Appendix D)
  - SF-12 (see Section 10.5, Appendix E)
  - PGIC (see Section 10.6, Appendix F)
  - PGIS (see Section 10.8, Appendix H)
- ADAs against BIVV009
- PK and PD sampling
- Disease related biomarkers
- Record healthcare resource utilization data (see Section 10.7, Appendix G) since previous assessment
- Record prior and concomitant medications/procedures including transfusions
- Adverse event monitoring

At 0 hour, study drug will be infused via an indwelling IV catheter over a period of 60 ±5 minutes. Patients with underlying cardiopulmonary disease may receive a 2-hour infusion with Sponsor approval. Additionally, study drug infusion may be interrupted or slowed in the event of suspicion of an allergic reaction or anaphylaxis.

After completion of the infusion, patients will undergo the following procedures:

- Vital signs at 1 hour (±5 minutes) postdose
- 12-lead ECG at 1 hour (±15 minutes) postdose
- PK and PD sampling at 1 hour (±15 minutes) postdose.

6.1.3 Weeks 1-25

On Days 7, 21, 35, 49, 63, 77, 91, 105, 119, 133, 147, 161, and 175, patients will undergo the following procedures before administration of the study drug:

- Serum or urine pregnancy test, if applicable, on Days 21, 49, 77, 105, 133, and 161

- Physical examination (brief)
- Vital signs
- 12-lead ECG (Day 91 only)
- Hematology panel
- Clinical chemistry panel
- Solicited symptomatic anemia assessment
- QOL assessments
  - FACIT-Fatigue: all scheduled visits
  - PGIS: Days 35, 77, and 119 only
  - PGIC: Days 35, 77, and 119 only
  - SF-12: Days 35, 77, and 119 only
  - EQ-5D-5L: Days 49, 91, and 133 only
- PK and PD sampling
- ADA: In patients who consented to the use of their blood samples for future research, PD back-up samples collected at the following time points Day 7, 35, 77, 133 and 175, may be used to assay ADA.
- Disease-related biomarkers (subset at Day 91 only); refer to Laboratory Manual for details
- Record healthcare resource utilization data since previous assessment on Days 21, 49, 77, 105, 133, and 161
- Record concomitant medications/procedures including transfusions
- Adverse event monitoring

At 0 hour, study drug will be infused via an indwelling IV catheter over a period of 60 ±5 minutes. Patients with underlying cardiopulmonary disease may receive a 2-hour infusion with Sponsor approval. Additionally, study drug infusion may be interrupted or slowed in the event of suspicion of an allergic reaction or anaphylaxis.

After completion of the infusion, patients will undergo the following procedures:

- Vital signs at 1 hour (±5 minutes) postdose
- 12-lead ECG (Day 91 only) at 1 hour (±15 minutes) postdose
- PK and PD sampling at 1 hour (±15 minutes) postdose.

Vaccinations should be administered according to Section 6.1.1.1, if applicable, or Section 10.9, Appendix I for Japan.

Note: Patients who miss a dose (ie, outside the dosing window or >17 days since last dose) should return to the site for an unscheduled visit 1 week prior to the next scheduled dose in order to receive an additional loading dose. The patient should then resume subsequent dosing visits every 14 days after the loading dose.

6.1.4 End-of-treatment visit in Part A (Week 26)

On Day 182, patients will undergo the following procedures:

- Serum or urine pregnancy test (if applicable)
- Body weight
- Physical examination (full)
- Vital signs
- SLE panel
- Hematology panel
- Coagulation panel
- Clinical chemistry panel
- Urinalysis
- Solicited symptomatic anemia assessment
- QOL assessments (FACIT-Fatigue, EQ-5D-5L, SF-12, PGIS, and PGIC)
- PK and PD sampling
- ADA: In patients who consented to the use of their blood samples for future research, PD back-up samples collected at this visit, may be used to assay ADA.
- Disease-related biomarkers
- Record healthcare resource utilization data since previous assessment
- Record concomitant medications/procedures including transfusions
- Adverse event monitoring

6.1.5 Part B extension phase

6.1.5.1 Procedures to be performed every 2 weeks

For patients completing Part A, the following procedures will be performed every 2 weeks (beginning at Week 27) during Part B prior to administration of study drug:

- Hematology panel (until Week 79)
- Clinical chemistry panel (until Week 79)
- Solicited symptomatic anemia assessment
- Record concomitant medications/procedures including transfusions
- Adverse event monitoring

6.1.5.2 Procedure to be performed every 4 weeks

- Women of childbearing potential will undergo serum or urine pregnancy testing every 4 weeks (beginning at Week 27) during Part B prior to administration of study drug
- Hematology panel (beginning at Week 79)
- Clinical chemistry panel (beginning at Week 79)
- Record healthcare resource utilization data since previous assessment

6.1.5.3 Procedures to be performed every 3 months (unless noted otherwise)

In addition, the following procedures will be performed every 3 months beginning after Week 27 (or as otherwise noted) during Part B prior to administration of study drug:

- Body weight
- Physical examination (brief)
- Vital signs
- 12-lead ECG (once at 3 months [Day 273], and at end of treatment visit)
- Urinalysis
- QOL assessments:
  - FACIT-Fatigue
  - EQ-5D-5L
  - SF-12
  - PGIS
  - PGIC
- SLE panel (every 6 months)
- PK, PD and ADA sampling during the 1st year of treatment in Part B then every 6 months

At 0 hour, study drug will be infused via an indwelling IV catheter over a period of 60 ±5 minutes. Patients with underlying cardiopulmonary disease may receive a 2-hour infusion with Sponsor approval. Additionally, study drug infusion may be interrupted or slowed in the event of suspicion of an allergic or anaphylactic reaction.

After completion of the infusion, patients will undergo the following procedures:

- Vital signs at 1 hour (±5 minutes) postdose
- 12-lead ECG (once at 3 months [Day 273]) at 1 hour (±15 minutes) postdose, and at end of treatment visit
- PK and PD sampling (every 3 months during the 1st year of treatment in Part B then every 6 months) at 1 hour (±15 minutes) postdose.

PK, PD, and ADA samples will be collected if a patient experiences a hematologic breakthrough event (rapid fall in Hgb ≥2 g/dL associated with an increase in LDH/bilirubin and/or decrease in haptoglobin since the last scheduled visit).

6.1.6 Infusion of the study drug at patient's home

Home infusions will be performed at pre-selected countries/sites by a healthcare professional caregiver contingent upon completion of training delivered by the Investigator or delegated site staff member only in patients willing to be administered study drug at home, and in whom previous on-site infusions were uncomplicated (for the US, the Netherlands, Norway, France, Italy, Austria, Germany, and Spain, specific amendments) (see Section 10.10, Appendix J).

6.1.7 Early termination/end of study/safety follow-up visit

Upon completion of dosing in the study, or if a patient terminates the study early, the following assessments should be completed 9 weeks after administration of the last dose of study drug:

- Serum or urine pregnancy test (if applicable)
- Body weight
- Physical examination (full)
- Vital signs
- SLE panel
- Hematology panel
- Coagulation panel
- Clinical chemistry panel
- Urinalysis
- Solicited symptomatic anemia assessment
- QOL assessments (FACIT-Fatigue, EQ-5D-5L, SF-12, PGIS, and PGIC)
- ADAs against BIVV009
- PK and PD sampling
- Record healthcare resource utilization data since previous assessment
- Record concomitant medications/procedures including transfusions
- Adverse event monitoring

If a patient experiences a hematological breakthrough event during the safety follow-up period, a PK, PD, and ADA sample should be collected at the time of the event.

6.2 STUDY TREATMENT

6.2.1 Drug supplies and accountability

Patients will receive doses of either 6.5 grams or 7.5 grams of BIVV009, depending on their body weight. BIVV009 is supplied to the pharmacy for preparation for infusion in either 10 mL vials (18 mg/mL) or 25 mL vials (50 mg/mL). The Sponsor (or designee) will provide the Investigators (or designees) with adequate quantities of the study drug.

BIVV009 drug product will be provided as a sterile, nonpyrogenic, isotonic aqueous solution containing 18 mg/mL or 50 mg/mL BIVV009 with 10 mM sodium phosphate buffer, 140 mM NaCl, 0.02% polysorbate 80 (Tween-80), and water for injection; the pH is 6.1. Each Type 1 glass vial, which has a bromobutyl rubber stopper and an aluminum seal, contains sufficient overfill to account for vial, needle, and syringe loss. Drug product can be used for IV administration only.

BIVV009 should be stored at 2°C to 8°C, protected from light, and kept under secure conditions until immediately before use. It is to be administered via IV infusion according to the instructions given in the Pharmacy Manual for this study. Preparation and accountability procedures for the investigational product including those associated with home infusions (for the US, the Netherlands, Norway, France, Italy, Austria, Germany, and Spain specific amendments) (Section 10.10, Appendix J), whenever applicable, are described in further detail in the Pharmacy Manual.

6.2.2 Patient number and identification

Patients will be assigned unique study numbers that will be used on all study documentation during the course of the trial. For patients who are withdrawn by an Investigator (or designee) or who voluntarily withdraw prematurely from the study, replacement patients will be enrolled only if deemed necessary by the Sponsor. Numbers will not be reused. Details on patient number assignments will be available in the study procedural manual.

6.2.3 Randomization

Not applicable.

6.2.4 Dose preparation and administration

Qualified pharmacy or clinical staff will prepare each unit dose of study drug for IV infusion. Dose preparation shall proceed as detailed in the Pharmacy Manual for this study. Briefly, an appropriate number of 10 mL drug product vials (each containing 180 mg of BIVV009) or 25 mL drug product vials (each containing 1.1 grams of BIVV009) will be pooled and diluted with saline solution to a total volume of 500 mL to administer either a 6.5 gram dose (for patients <75 kg) or a 7.5 gram dose (for patients ≥75 kg), depending on the patient's baseline (Day 0) body weight. Details are provided in the Pharmacy Manual.

BIVV009 will be infused IV by a suitable infusion pump over a period of approximately 60 minutes. (Patients with underlying cardiopulmonary disease may receive a 2-hour infusion with Sponsor approval.) The infusion catheter and tubing will be flushed both immediately before and immediately following completion of the infusion with a sufficient quantity of sterile saline for injection. For each dose, the patient's actual dose and time of dosing and if the administration is being performed at the patient's home (Section 10.10, Appendix J) will be recorded in the source documents and transcribed onto the eCRFs. The administration location, rate, start time, stop time, any infusion interruptions, and total volume of investigational product actually administered will be recorded in the eCRFs. If an AE occurs during the administration of study drug, the infusion may be slowed or stopped at the discretion of the Investigator or the professional healthcare caregiver in case of home infusions (see Section 10.10, Appendix J).

Patients must be monitored for acute allergic reactions during infusion and for at least 2 hours after the completion of the first administration of study drug or 1 hour after the completion of each administration of study drug thereafter. Additionally, patients undergoing home infusions will be monitored by the professional healthcare caregiver for 2 hours after the completion of the first home infusion or 1 hour after the completion of each subsequent home infusion (see Section 10.10, Appendix J). Like with office visits, medications such as epinephrine and diphenhydramine, and additional emergency equipment will be available in

case an allergic reaction or anaphylaxis occurs during home infusion. Site personnel, or professional healthcare caregiver in case of home infusions (see Section 10.10, Appendix J), must be qualified to detect and treat allergic reactions and anaphylaxis. See Section 6.3.8 for further details regarding additional testing.

Patients should be instructed to report the development of rash, hives, pruritus, flushing, urticaria, etc, that may represent an allergic reaction to study drug. If any signs or symptoms of an allergic or anaphylactic reaction are observed during the infusion, administration of study drug must be immediately discontinued, and the patient treated as appropriate, and in case of home infusion, the investigator should be notified immediately (see Section 10.10, Appendix J).

6.2.5 Blinding

Not applicable; this is an open-label study.

6.2.6 Concomitant medications

Patients will refrain from participation in any other investigational study drug trial in which receipt of any investigational drug occurred within 5 half-lives or 30 days, whichever is longer, prior to Day 0 and during the entire study.

Treatment with rituximab monotherapy or rituximab combination therapies (eg, with bendamustine, fludarabine, ibrutinib, or cytotoxic drugs) is prohibited.

During Part A, patients will not 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.

As noted in Section 5.2, concurrent administration of erythropoietin and/or a daily dose of corticosteroids (equivalent to ≤10 mg/day of prednisone) is acceptable provided the patient has been on a stable dose during the previous 3 months; concurrent use of vitamin B12, folate and iron supplementation is acceptable provided the patient has been on a stable dose during the previous 4 weeks.

Topical therapies without risk of systemic absorption may be allowed, and non-prescription medications for treatment of minor intercurrent illnesses (headache, viral upper respiratory tract infections, etc.) are permitted at the discretion of the PI. Hormonal contraception in female patients is allowed provided patients are receiving stable treatment ≥3 months prior to Screening. Any medication taken by the patient during the study, along with its strength, frequency of dosing, and reason for its use, will be documented in the patient's source data and the eCRF.

6.2.7 Contraception

Women of non-childbearing potential are defined as permanently sterile (ie, due to hysterectomy, bilateral salpingectomy, bilateral oophorectomy) or postmenopausal (defined as at least 12 months post-cessation of menses without an alternative medical cause). Women who are of non-childbearing potential will not be required to use contraception.

Female patients of childbearing potential must be established on (≥3 months prior to Screening) and agree to continue to use the same highly effective methods of birth control (ie, contraceptive measure with a failure rate of <1% per year) in conjunction with male barrier contraception (ie, male condom with spermicide) throughout the study and for 9 weeks after the administration of the last dose of study drug. Highly effective methods of contraception include:

- Intrauterine device (IUD; Mirena®)
- Established use of oral, implanted, transdermal, or hormonal method of contraception associated with inhibition of ovulation
- Bilateral tubal ligation
- Permanent birth control via the Essure procedure

Male patients will be surgically sterile for at least 90 days or when sexually active with female partners of childbearing potential will be required to use a male condom with spermicide (if locally approved for use) throughout the study and for 9 weeks after the last dose of study drug.

Patients who practice true abstinence because of the patient's lifestyle choice (ie, the patient should not become abstinent just for the purpose of study participation) are exempt from contraceptive requirements. Periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not acceptable methods of contraception. If a patient who is abstinent at the time of signing the ICF becomes sexually active, they must agree to use contraception as described above.

For male patients, sexual intercourse with female partners who are pregnant or breastfeeding should be avoided unless condoms are used from the time of administration of the first dose until 9 weeks after administration of the last dose of study drug. Male patients are required to refrain from donation of sperm from Day 0 until 9 weeks after administration of the last dose of study drug.

6.3 STUDY ASSESSMENTS

Please refer to Table 3 in Section 6.1 for an overview of the study procedures and schedule of events. Data will be collected via an eCRF for each enrolled patient. All patients will provide written informed consent before any study-specific assessment is performed. A study-specific assessment is defined as a procedure that is not part of the routine assessments performed for diagnostic purposes or standard care. Screening assessments should occur within 6 weeks prior to administration of the study treatment (ie, on Days -42 to -1). The immunization status should be confirmed at least 14 days prior to the planned administration of study drug (ie, on or before Day -14).

6.3.1 Demographic data

The date of birth, sex, race, and ethnicity will be documented, as permitted by local regulations.

6.3.2 Medical history

A detailed general medical history of clinically significant diseases and surgeries will be collected during screening. Additionally, a detailed medical history of the patient's primary CAgD as well as history of all blood transfusions will be reviewed and recorded.

6.3.3 Height, body weight, and vital signs

Height, body weight, and vital signs will be documented. Vital sign measurements (including oral temperature, respiratory rate, supine blood pressure, and pulse rate) will be obtained at the time points specified in Table 3. Vital signs will be measured after the patient has been supine for at least 5 minutes.

6.3.4 Electrocardiograms

A 12-lead ECG will be obtained at the time points specified in Table 3. Patients will be supine for at least 5 minutes prior to obtaining an ECG measurement. The ECG should be performed before any other procedures that may affect heart rate (eg, blood draws).

The Investigator's overall interpretation of the ECG will be recorded and any abnormalities reported.

6.3.5 Physical examinations

Full and brief physical examinations will be performed at the time points specified in Table 3. The time and date of the physical examinations will be recorded in the source document and eCRF, and any clinically significant changes from baseline will be recorded as AEs.

Full physical examinations will consist of the following: general appearance, head and neck, eyes and ears, nose and throat, chest, lungs, heart, abdomen, extremities and joints, lymph nodes, skin, and neurology.

Brief physical examinations will consist of the following: general appearance, chest, lungs, heart, abdomen, and skin.

6.3.6 Immunization review

The patient's medical and vaccination history will be reviewed to ensure that each patient is up-to-date with all required immunizations; if not already vaccinated against *Neisseria* meningitidis, including serogroup B *meningococcus* where available, *Haemophilus influenzae*, and/or *Streptococcus pneumoniae* within 5 years of enrollment, these will be administered following informed consent, as applicable, per Table 3 and Section 6.1.1.1 (screening procedures) or Section 10.9, Appendix I for Japan.

6.3.7 Clinical laboratory evaluations

Clinical laboratory evaluations (including hematology panel, clinical chemistry panel, iron panel, erythropoietin, coagulation safety panel, SLE panel, virology/serology panel, disease related biomarkers and urinalysis) as outlined in Section 10.1, Appendix A will be performed at the time points specified in Table 3. Clinical laboratory results will be reviewed by the Investigator and results outside of the reference ranges will be documented and clinical significance noted.

Local laboratory values may be utilized for eligibility evaluation and medical management of the patient, including assessing the Hgb criteria necessitating blood transfusions. For efficacy evaluations, results from the central laboratory (when collected and available) will be recorded in the eCRF and utilized for analyses. Detailed information on the allocation of samples for central or local laboratory processing will be available in the Laboratory Manual.

6.3.8 Additional testing in case of hypersensitivity/allergic reaction

If a patient exhibits signs of a hypersensitivity/allergic reaction during study drug administration, the study drug infusion should be stopped immediately, and medical treatment provided, as appropriate.

If a suspected anaphylactic reaction occurs (Simons 2010), the following labs may be obtained per the discretion of the Investigator, after discussion with the Sponsor Medical Monitor:

- Approximately 30 to 120 minutes after the start of symptoms: blood draw for ADAs (including isotyping), tryptase, IL-6, IL-33, plasma histamine, CICs, and complement levels (CH50). A follow-up tryptase level should be obtained 8 days following the reaction.
- 24-hour urine collection for methylhistamine analysis (ideally collection should be started within 6 hours of onset of symptoms and collected even if the patient is sent to the emergency room; patient can be provided with a container for the collection.

6.4 PHARMACOKINETIC PROCEDURES

6.4.1 Pharmacokinetic and ADA blood sample collection and processing

Blood samples for PK analysis of BIVV009 levels and ADAs against BIVV009 will be collected via an indwelling catheter and/or via direct venipuncture from the arm opposite from the site of infusion. Blood samples will be collected at the time points specified in Table 3. If an indwelling catheter is used, saline flushes will be used.

6.4.2 Analytical methodology (PK and ADA)

Plasma concentrations of BIVV009 and ADA titer will be determined using a validated analytical procedure. Specifics of the analytical methods will be provided in a separate document.

6.5 PHARMACODYNAMIC PROCEDURES

6.5.1 Pharmacodynamic blood sample collection and processing

Blood samples for PD analysis of the Complement System Classical Pathway levels (Wieslab assay) will be obtained via an indwelling catheter and/or via direct venipuncture. Blood samples for analysis will be collected at the time points specified in Table 3. Complement assays will also be performed on samples, including:

- Total complement (CH50)

- Total C4
- C1q
- C1s

If an indwelling catheter is used, saline flushes will be used.

6.5.2 Analytical methodology (PD)

PD parameters will be determined using a validated analytical procedure. Specifics of the analytical methods and appropriate matrices for the different parameters will be provided in a separate document.

6.6 SAFETY PROCEDURES

Safety evaluations as needed for medical management of the patient may be repeated at the Investigator's (or designee's) discretion.

Every effort will be made to schedule and perform the procedures in accordance with the nominal time, giving considerations to appropriate posture conditions, practical restrictions, and the other procedures to be performed at the same time point.

The order of priority for scheduling procedures around a time point is (in descending order of priority):

- PK and PD blood sampling
- ADAs against BIVV009
- Vital sign measurements
- ECGs
- Blood and urine samples for clinical laboratory testing
- Physical examinations

6.7 ADVERSE EVENTS AND LABORATORY ABNORMALITIES

It is the responsibility of the Investigator to report all AEs in the eCRF. The AE and SAE reporting period will begin from the time the patient signs the ICF and continue through 9 weeks after administration of the last dose of study drug. Any SAE must be reported within 24 hours of the knowledge of the occurrence to the Study Medical Monitor and the designated Clinical Research Organization's (CRO) Clinical Safety Group. Refer Section 6.7.4 for further details regarding SAE reporting procedures.

For urgent medical issues in which the study's Medical Director should be contacted, please refer to the study reference manual's Official Study Contact List for complete contact information.

6.7.1 Definition of adverse events

An AE is defined in the International Council for Harmonisation (ICH) Guideline for Good Clinical Practice (GCP) as "any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment" (ICH E6: Section 1.2). An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product.

6.7.1.1 Definition of adverse drug reactions

Adverse drug reactions are defined as all noxious and unintended responses to a medicinal product related to any dose administered. The phrase "responses to a medicinal product" means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility (ie, the relationship cannot be ruled out).

The following categories for determining the causal relationship to the investigational medicinal product are to be used:

Probable (must have first three):

- It follows a reasonable temporal sequence from administration of study drug.
- It cannot be reasonably explained by the known characteristics of the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient.
- It disappears or decreases on cessation or reduction in dose.
- It follows a known pattern of response to the suspected drug.
- It reappears upon re-challenge.

Possible (must have first two):

- It does not follow a reasonable temporal sequence from administration of the drug.
- It may readily have been produced by the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient.
- It does not reappear or worsen when the drug is re-administered.

Unrelated:

An AE will be considered "Unrelated" to the use of the investigational drug if there is not a reasonable possibility that the event has been caused by the product under investigation and does not meet the criteria for drug relationship listed under possible or probable. Factors pointing toward this assessment include, but are not limited to, the lack of reasonable temporal relationship between administration of the drug and the event, the presence of a biologically implausible relationship between the product and the AE (eg, the event occurred before administration of drug), or the presence of a more likely alternative explanation for the AE.

In case of missing causality assessment in the eCRF or SAE reporting form, the event will be regarded as possibly related unless further specified. Any SAE recorded as probably or possibly related will be categorized as "related" for regulatory reporting purposes.

A serious drug reaction is an adverse drug reaction that meets the definition of a serious event (provided below).

6.7.1.2 Definition of serious adverse events

An SAE is defined as any untoward medical occurrence (AE) that at any dose:

- Results in death
- Is life-threatening (patient was at immediate risk of death at the time of the event)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Any other significant medical condition

A hospitalization meeting the regulatory definition for "serious" is any inpatient hospital admission. Any AE that does not meet one of the definitions of serious (ie, important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require interventions to prevent one of the other outcomes listed above [eg, emergency room visit, outpatient surgery, or requires urgent investigation]) may be considered by the Investigator to meet the "other significant medical condition" criterion for classification as an SAE. Examples include allergic bronchospasm, convulsions, and blood dyscrasias.

If a subject develops a Grade 3 or higher allergic reaction per Common Terminology Criteria for Adverse Events (CTCAE) grading or an anaphylactic reaction (see Section 6.3.8) in association with BIVV009 administration, the event should be reported as an SAE.

Exceptions from SAE reporting:

Hospitalization for performing protocol-required procedures or administration of study treatment is not classified as an SAE.

6.7.1.3 Definition of unexpected adverse event/SUSAR

An unexpected AE is any adverse drug event, the specificity or severity of which is not consistent with the current Investigator's Brochure (IB) of BIVV009. Also, reports that add significant information on specificity or severity of a known, already documented AE constitute unexpected AEs. An event more specific or more severe than described in the IB would be considered "unexpected."

A suspected unexpected serious adverse reaction (SUSAR) is a serious adverse reaction, the nature or severity of which is not consistent with the IB. All suspected adverse reactions related to BIVV009 that occur in the concerned clinical trial and that are both unexpected and serious (SUSARs) are subject to expedited reporting as per national regulatory requirements in participating countries.

6.7.2 Clinical adverse events

The Investigator is responsible for ensuring that all AEs observed by the Investigator or reported by the patient are properly captured in the patient's medical records.

The following AE attributes must be assigned by the Investigator:

- Adverse event term
- Dates of onset and resolution
- Seriousness (yes/no)/seriousness criterion
- Severity
- Assessment of relatedness to study drug
- Outcome
  - Recovered/resolved
  - Recovered/resolved with sequelae
  - Not recovered/not resolved
  - Fatal
  - Unknown (only applicable if patient is lost to follow-up)
- Action taken:
  - None
  - Study drug temporarily interrupted
  - Study drug permanently discontinued

During the study, serious and non-serious AEs will be followed until resolved or clinically stable. At the end of the study, all ongoing SAEs will be followed until resolved, stabilized, or returned to baseline.

It will be left to the Investigator's clinical judgment to determine whether an AE is related and of sufficient severity to require the patient's removal from treatment or from the study. A patient may also voluntarily withdraw from treatment due to what he or she perceives as an intolerable AE. If either of these situations arises, the patient should be strongly encouraged to undergo an ET visit assessment and be under medical supervision until symptoms cease or the condition becomes stable.

All clinical AEs encountered during the clinical study will be reported on the AE page of the eCRF, regardless of causality. Severity of AEs will be graded using the CTCAE, version 4.03 (see Section 10.2, Appendix B).

If an AE occurs that is not contained in the CTCAE version 4.03, the five-point scale below will be used.

Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated

Grade 2: Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)

Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limited self-care ADL

Grade 4: Life-threatening consequences; urgent intervention indicated

Grade 5: Death related to AE

6.7.3 Laboratory test abnormalities

Laboratory test value abnormalities that have worsened from baseline should not be reported on the AE page of the eCRF as AEs unless they satisfy one or more of the following conditions for clinical significance:

- Accompanied by clinical symptoms
- Leading to a change in study medication (eg, dose modification, interruption, or permanent discontinuation)
- Requiring a change in concomitant therapy (eg, addition of, interruption of, discontinuation of, or any other change in a concomitant medication, therapy, or treatment)

Any laboratory result abnormality fulfilling the criteria for an SAE should be reported as such, in addition to being recorded as an AE in the eCRF.

6.7.4 Serious adverse event reporting - procedures for Investigators

All SAEs occurring from the time of informed consent through the final study visit, or 9 weeks after administration of the last dose of study drug whichever occurs later, must be reported to the Sponsor's designated CRO's Clinical Safety Group within 24 hours of the knowledge of the occurrence. All SAEs that the Investigator considers related to study drug occurring after the follow-up period must be reported directly to the Sponsor.

To report the SAE, the SAE form for the study should be completed and submitted within 24 hours of the site becoming aware of the event to the designated CRO's Clinical Safety Group via email or facsimile (FAX) per the instructions provided on the SAE report form.

The Sponsor (or designee) will report SUSARs to the appropriate regulatory authorities and Investigators according to local regulatory requirements and procedures.

6.7.5 Follow-up of adverse events

All serious and non-serious AEs, regardless of whether or not they are assessed as related to study drug, should be followed up during the study until they have resolved, returned to baseline status, or stabilized. If a clear explanation is established, it should be recorded on the eCRF. If there is a unifying diagnosis, the diagnosis should be reported rather than a collection of signs and symptoms.

Ongoing SAEs at the end of study should continue to be followed until the event has resolved, returned to baseline status, the condition becomes chronic in nature, stabilizes (in the case of persistent impairment), or the patient dies. Within 24 hours of receipt of any

follow-up information, the Investigator must update the eCRF, complete and submit an SAE follow-up form along with any supporting documentation (eg, patient discharge summary or autopsy reports) to the designated CRO's Clinical Safety Group via email or FAX per the instructions provided on the SAE report form.

6.7.6 Follow-up of abnormal laboratory results

In the event of unexplained abnormal laboratory test values, the tests should be repeated immediately and follow-up until they have returned to the normal range and/or an adequate explanation of the abnormality is found. If a clear explanation is established, it should be recorded on the eCRF. Regarding the documentation of abnormal laboratory tests, please refer to Section 6.7.3.

6.7.7 Pregnancy

If a patient becomes pregnant during the study or within 9 weeks of receiving study drug, or if the partner of a patient participating in the study conceives after the patient has received the first dose of study drug and up to 9 weeks after receiving the last dose of study drug, the Investigator should report the pregnancy to the designated CRO's Clinical Safety Group by completing and forwarding a Pregnancy Report Form within 24 hours of being notified.

A patient becoming pregnant while on study drug will immediately be withdrawn from the study, study treatment will be stopped, and early study termination procedures will be performed.

The patient or patient's partner should be followed by the Investigator until the end of the pregnancy. If the pregnancy ends for any reason before the anticipated date, the Investigator should notify the designated CRO's Clinical Safety Group by completing and forwarding an updated Pregnancy Report Form. At the end of the pregnancy, the Investigator should document the outcome of the pregnancy and provide a final update via an updated Pregnancy Report Form. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (ie, postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly), the Investigator should follow the procedures for reporting an SAE.

6.7.8 Overdose

An overdose is any dose of study treatment administered to a subject or taken by a subject that exceeds the dose assigned to the subject according to the protocol. Overdoses are not considered AEs and should not be recorded as an AE on the CRF; however, all overdoses must be recorded on an Overdose form and faxed or emailed to the designated CRO's Clinical Safety Group within 24 hours of the site becoming aware of the overdose. An overdose must be reported to the designated CRO's Clinical Safety Group even if the overdose does not result in an AE. If an overdose results in an AE, the AE must be recorded. If an overdose results in an SAE, both the SAE and Overdose forms must be completed and faxed or emailed to the designated CRO's Clinical Safety Group. All study treatment-related dosing information must be recorded on the dosing CRF.

7 DATA ANALYSES AND SAMPLE SIZE

Data from Part A and Part B of this study will be analyzed and reported separately. A separate Statistical Analysis Plan (SAP) for each part of the study will be produced providing full details of all analyses to be performed for Part A and Part B. Should there be any differences between the analyses plan and methodology described within the SAP versus the clinical protocol, the SAP will take precedence.

For the purposes of regulatory submission, an interim analysis of the Part A data will be performed after all patients have completed Part A.

7.1 DESCRIPTION OF OBJECTIVES AND ENDPOINTS

The objectives of the study and the endpoints to be analyzed are described in Section 4.3. In general, continuous variables will be summarized by descriptive statistics, including: number, mean, median, standard deviation (SD), minimum, and maximum. Categorical variables and response variables will be presented with the number and percentage in each category. Any hypothesis tests will be performed at a two-sided 0.05 significance level. Unless otherwise specified, all data will be presented in patient data listings.

For analyses purposes in Part A baseline is defined as the last value obtained during Screening immediately prior to administration of the first dose of study drug.

For endpoints involving laboratory parameters, results from the central laboratory will be used. Local laboratory values will be utilized for medical management of the patient, including assessing the Hgb criteria necessitating blood transfusions.

7.2 DEMOGRAPHICS AND BASELINE DISEASE CHARACTERISTICS

Demographic and other baseline disease characteristics will be summarized using descriptive statistics for the overall population. Data to be tabulated will include, but not be limited to, age, race, medical history, and other disease-specific measures.

7.3 EFFICACY - PART A

7.3.1 Analysis populations

Full Analysis Set (FAS): The FAS Population is defined as all patients who received at least 1 dose of study drug.

Per-Protocol (PP) Population: The PP Population is defined as a subset of FAS Population who do not have any important protocol deviations impacting their efficacy assessments.

The FAS analyses will be the primary analyses and the PP analyses will be considered as supportive.

The patients in the FAS population that are excluded from the PP Population will be listed, together with the reason for exclusion from the PP Population.

7.3.2 Methods of analysis

Each patient in the FAS Population will be classified as a responder or non-responder per the response criteria, and the proportion of responders will be calculated together with a 95% exact Clopper-Pearson confidence interval (CI). To assess the hematology component of response, the mean of the non-missing Hgb assessments at the Week 23, Week 25, and Week 26 analysis visits (treatment assessment endpoint) will be used. Visit windows will be used to assign analysis visits, as detailed in the SAP. Patients missing all three analysis visits will be counted as non-responders.

Under the assumption that a response rate of less than or equal to 30% is not clinically relevant, the success criteria for the primary endpoint will be that the 95% lower bound CI for response rate excludes 30% using the exact Clopper-Pearson method. That is, this criterion is equivalent to demonstrating at the 2-sided 0.05 level of significance that the true response rate is >30%.

The hypotheses to be tested are:

H_0: response rate $\leq$30%

H_a: response rate >30%

Because this is a one-sided test, the level of statistical significance (Type I error) will be controlled at the one-sided 0.025 level, which is equivalent to a two-sided 0.05 level test and corresponds to a two-sided 95% CI. Sensitivity analyses will be carried out to evaluate the impact by the missing data, if appropriate. Details will be specified in SAP.

All secondary endpoints will be analyzed using descriptive statistics, frequency, percentage, and 95% CIs as appropriate. Change from baseline for continuous parameters will be analyzed using a one-sample t-test. All hypothesis tests will be performed at a two-sided 0.05 significance level.

As a secondary sensitivity analysis, the efficacy analysis will be repeated with patients stratified by previous rituximab therapy and/or cytotoxic therapy versus patients who are naïve to rituximab therapy and/or cytotoxic therapy using the FAS populations.

Other efficacy assessments will be summarized by overall population using descriptive statistics, proportions, and graphically where applicable.

7.4 EFFICACY - PART B

7.4.1 Analysis populations

Full Analysis Set (FAS): FAS is defined as all patients who received at least 1 dose of study drug in Part B.

Per-Protocol Population: The PP Population is defined as a subset of FAS Population who do not have any important protocol deviations impacting their efficacy assessments.

7.4.2 Methods of analysis

All endpoints will be analyzed using descriptive statistics, frequency, percentage, 95% CIs, and graphically, as appropriate.

7.5 PHARMACOKINETICS

7.5.1 Analysis population

Part A - all patients who receive at least 1 dose of study drug and have at least 1 evaluable PK sample will be included in the PK analysis population.

Part B - all patients who receive at least 1 dose of study drug and have at least 1 evaluable PK sample during the extension phase will be included in the PK analysis population.

For the purposes of PK parameter analysis, an evaluable patient is defined as a patient who has received at least 1 dose of BIVV009 and has completed the relevant blood sample collections enabling acceptable determination of PK parameters.

7.5.2 Methods of analysis

In general, descriptive statistics including number of observations, mean, SD, median, minimum, and maximum will be presented for continuous parameters. Summary descriptive statistics and individual patient listings will be presented for all PK parameters by time point and study day.

BIVV009 concentrations and individual PK parameter estimates will be listed for each patient and summarized descriptively by time point and study day. Summary descriptive statistics will include the number of observations, arithmetic and geometric means, and their associated CIs, SD, coefficient of variation, median, minimum, and maximum. Mean BIVV009 concentration-versus-time profiles will be plotted.

PK parameters will be log-transformed for these analyses and estimated means, mean differences, and CIs on the log scale will be exponentiated to obtain estimates for geometric means, geometric mean ratios, and CIs, respectively, on the original scale. In addition, untransformed PK parameters will be used to calculate arithmetic means and arithmetic mean ratios.

7.6 PHARMACODYNAMICS

7.6.1 Analysis population

Part A - all patients who receive at least 1 dose of study drug and have at least 1 evaluable PD sample during Part A will be included in the PD analysis population.

Part B - all patients who receive at least 1 dose of study drug and have at least 1 evaluable PD sample during the extension period will be included in the PD analysis population.

7.6.2 Methods of analysis

In general, descriptive statistics including number of observations, mean, SD, median, minimum, and maximum will be presented for continuous parameters. Categorical variables will be presented with the number and percentage in each category. Summary descriptive statistics (absolute values and changes from baseline) and individual patient listings will be presented for all PD parameters by time point and study day.

7.7 IMMUNOGENICITY

7.7.1 Analysis population

Part A - All patients who receive at least 1 dose of study drug and have at least 1 evaluable ADA sample during Part A will be included in the ADA analysis population.

Part B - All patients who receive at least 1 dose of study drug and have at least 1 evaluable ADA sample during the extension period will be included in the ADA analysis population.

7.7.2 Methods of analysis

Methods of analysis will be described in the statistical analysis plan (SAP).

7.8 SAFETY

7.8.1 Analysis population

Part A - all patients who receive at least 1 dose of study drug will be evaluable for the analysis of safety.

Part B - all patients who received at least 1 dose of study drug during the extension period will be evaluable for the analysis of safety.

7.8.2 Methods of analysis

Adverse events will be classified using the Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class and Preferred Term. Tabulations of TEAEs and serious TEAEs by frequency, relatedness, and severity will be presented. Patient listings will be provided for SAEs, AEs resulting in discontinuation of the study or study treatment, and all deaths. In addition, specific summary tables will be presented for hemolytic breakthrough, infections (Grade 3 or above), and thrombolytic events.

Changes from baseline in clinical laboratory parameters (except those considered efficacy and PD endpoints), vital signs, and ECG parameters will be summarized over time using descriptive statistics. The number and percentage of patients who have positive ADAs will be presented.

Concomitant medications and physical exam data will be displayed in listings only.

7.9 INTERIM ANALYSES

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. Additional interim analyses of Part B data may be performed at the Sponsor's discretion for purposes of regulatory filings, publications, or future planning.

7.10 SAMPLE SIZE CONSIDERATIONS

Approximately 20 patients with primary CAgD who have a recent history of transfusion will be enrolled.

If the true responder rate is estimated to be 66% and a minimum of 30% is required for success, then with 20 patients, there is 90% probability that the lower limit of the 95% CI will be at least 30%. The minimal observed rate for a successful efficacy claim is 11/20 = 55%.

7.11 DATA HANDLING AND RECORD KEEPING

Any changes to information in the study progress notes and other source documents will be initialed and dated on the day the change is made by a clinical site staff member authorized to make the change. Changes will be made by striking a single line through erroneous data and clearly entering the correct data (eg, ~~wrong data~~ right data). If the reason for the change is not apparent, a brief explanation for the change will be written adjacent to the change by the clinician.

Patient information will be captured and managed by study sites on eCRFs by a web-based electronic data capture (EDC) tool developed and supported by CRO and approved by the Sponsor. Data should be entered into the EDC system in a timely manner as outlined within the CRF Completion Guidelines.

Data management will be performed by CRO according to their Standard Operating Procedures (SOPs). The Data Management Plan will be approved by the Sponsor.

7.12 QUALITY CONTROL AND QUALITY ASSURANCE

Quality control procedures will be implemented at each stage of data handling to ensure that all data are reliable and have been processed correctly. Data anomalies will be communicated to the sites for clarification and resolution, as appropriate.

During and/or after completion of the study, quality assurance officers assigned by the Sponsor or the regulatory authorities may wish to perform onsite audits or inspections. The Investigator will be expected to cooperate with any audit or inspection and to provide assistance and documentation (including source data) as requested.

8 ADMINISTRATIVE ASPECTS

8.1 CHANGE IN PROTOCOL

There will be no alterations in the protocol without agreement between the Sponsor and the Investigator.

There will be no alterations in the protocol affecting patient safety without the express written approval of the Sponsor, Investigator, and the Institutional Review Boards/Ethics Committee (IRBs/ECs) (see form FDA 1572).

All protocol amendments must be submitted to the IRBs/ECs and regulatory authorities if required by local law. Protocol modifications that affect patient safety, the investigational scope, or the scientific quality of the study must be approved by the IRB/EC before implementation of such modifications to the conduct of the study. If required by local law, such modifications must also be approved by the appropriate regulatory agency before implementation. However, the Sponsor may, at any time, amend this protocol to eliminate an apparent immediate hazard to a patient. In this case, the appropriate regulatory authorities will be notified subsequent to the modification.

8.2 SITE INITIATION VISIT/INVESTIGATOR MEETING

Prior to the start of the clinical study, the representative(s) of the Sponsor will meet with the Investigator and appropriate clinical staff to familiarize the Investigator and clinical staff with the clinical protocol and the materials necessary for conducting the clinical study.

8.3 DISCLOSURE

All information provided regarding the study, as well as all information collected/documented during the study, will be regarded as confidential. The Investigator (or designee) agrees not to disclose such information in any way without prior written permission from the Sponsor.

Any publication of the results, either in part or in total (eg, articles in journals or newspapers, oral presentations, abstracts) by the Investigator or their representative(s), shall require prior notification and review, within a reasonable time frame, by the Sponsor, and cannot be made in violation of the Sponsor's confidentiality restrictions or to the detriment of the Sponsor's intellectual property rights.

Sponsor will register the study and post study results regardless of outcome on a publicly accessible website in accordance with the applicable laws and regulations.

8.4 MONITORING

The Monitor has the responsibility to familiarize the Investigator(s) and the entire center staff involved in the study with all study procedures including the administration of study drug. The Monitor will monitor the study conduct, proper eCRF and source documentation completion and retention, and accurate study drug accountability. To this end, the Monitor

will visit the clinical site at suitable intervals and be in frequent contact through verbal and written communication. It is essential that the Study Monitor has access to all documents (related to the study and the individual participants) at any time these are requested. In turn, the Monitor will adhere to all requirements for patient confidentiality as outlined in the ICF. The Investigator and Investigator's staff will be expected to cooperate with the Study Monitor, to be available during a portion of the monitoring visit to answer questions, and to provide any missing information.

8.5 ETHICAL ASPECTS

The Sponsor, CRO, and the Investigator must comply with all instructions, regulations, and agreements in this protocol and applicable ICH and GCP guidelines and conduct the study according to local regulations. The Investigator may delegate responsibilities for study-related tasks where appropriate to individuals sufficiently qualified by education, training, and experience, in accordance with applicable ICH and GCP guidelines. The Investigator should maintain a list of the appropriately qualified persons to whom significant study-related duties have been delegated. The Investigator is responsible for supervising those individuals and for implementing procedures to ensure the integrity of the tasks performed and any data generated.

8.5.1 Declaration of Helsinki/Good Clinical Practice

The Declaration of Helsinki is the accepted basis for clinical study ethics and must be fully followed and respected by all engaged in research on human beings. Any exceptions must be justified and stated in the protocol. The latest version of the Declaration of Helsinki is available under www.wma.net/en/30publications/10policies/b3/index.html.pdf. Additionally, it is the responsibility of all engaged in research on human beings to ensure that the study is performed in accordance with the international GCP standards and according to all local laws and regulations concerning clinical studies.

8.5.2 Patient information and informed consent

It is the responsibility of the Investigator to obtain written informed consent from each patient participating in this study, after adequate explanation of aim, importance, anticipated benefits, and potential hazards and consequences of the study according to applicable local laws. Written informed consent must be obtained before any study-specific procedures are performed. It must be also explained to the patient that he/she is completely free to refuse to enter the study or to withdraw from it at any time for any reason without incurring any penalty or withholding of treatment on the part of the Investigator.

With the declaration of consent the patient agrees that data on his/her medical history are recorded within the framework of the clinical study and that they are transferred to the Sponsor in a pseudo-anonymized manner. Patients will be informed that their race and ethnicity will be collected and will be used during analysis of study results.

The patient also agrees to allow the monitor/auditor/health authorities to verify the collected patient data against the patient's original medical records for the purpose of source data verification.

The ICF - personally signed and dated by the patient and the Investigator - must be kept on file by the Investigator(s) and documented in the eCRF and the patient's medical records. The Investigator confirms to the Sponsor to obtain the written informed consent from any patient before participating in the study.

If new safety information results in significant changes in the risk/benefit assessment, the consent form should be reviewed and updated if necessary. All patients (including those already being treated) should be informed of the new information and must give their written informed consent to continue in the study.

If the family doctors are informed of their patients' participation in the clinical study, this should be mentioned in the consent form.

8.6 INDEPENDENT ETHICS COMMITTEE/INSTITUTIONAL REVIEW BOARD AND REGULATORY AUTHORITIES

It is the responsibility of the Sponsor to obtain and maintain independent approval from the applicable Regulatory Authorities to conduct the study in accordance with applicable regulatory requirements. It is the responsibility of the Sponsor to ensure that a positive opinion from the EC/IRBs to conduct the study in accordance with applicable regulatory requirements is in place.

8.7 RECORDS

Data collected at Screening and during the study will be recorded in the patient's source documents and retained at the study site for all patients who sign informed consent. Patients who are enrolled in the study will have their data retained in the source documents at the site and also have their data entered into the eCRF. To maintain confidentiality, patients will be identified only by screening and patient numbers.

The completed eCRFs will be transferred to the Sponsor (or designee). Copies of each source document will be retained by the Investigator (or designee). A compact disk containing the site eCRF data will be provided to the site at the completion of the study. All source documents, records, and reports will be retained by the clinical site in accordance with 21 CFR 312.62(c). The minimum retention time for study records will meet the strictest standard applicable to that site, as dictated by any institutional requirements or local, national, or regional laws or regulations. Prior to proceeding with destruction of records, the Investigator must notify the Sponsor in writing and receive written authorization from the Sponsor to destroy study records.

In addition, the Investigator must notify the Sponsor of any changes in the archival arrangements including but not limited to archival at an offsite facility or transfer of ownership if the Investigator leaves the site.

All primary data, or copies thereof (eg, laboratory records, eCRFs, data sheets, correspondence, photographs, and computer records), which are a result of the original observations and activities of the study and are necessary for the reconstruction and evaluation of any study report, will be retained in the clinical site archives.

9 REFERENCES

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Berentsen, S., K. Beiske and G. E. Tjonnfjord (2007). "Primary chronic cold agglutinin disease: an update on pathogenesis, clinical features and therapy." Hematology **12**(5): 361-370.

Jäger, U., J. C. Gilbert, S. Panicker, G. C. Parry, M. Fillitz, T. Schenk, C. Sillaber, J. Bartko and B. Jilma (2016). "The anti C1s complement antibody TNT009 induces rapid complete remissions of anaemia in patients with primary cold agglutinin disease." 21st European Haematology Association (EHA) Conference, Abstract LB2237, 341.

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Swiecicki, P. L., L. T. Hegerova and M. A. Gertz (2013). "Cold agglutinin disease." Blood **122**(7): 1114-1121.

INVESTIGATOR AGREEMENT

Study Drug: BIVV009

Protocol: BIVV009-03

A PHASE 3, PIVOTAL, OPEN-LABEL, MULTICENTER STUDY TO ASSESS THE EFFICACY AND SAFETY OF BIVV009 IN PATIENTS WITH PRIMARY COLD AGGLUTININ DISEASE WHO HAVE A RECENT HISTORY OF BLOOD TRANSFUSION

Version 06

19 December 2019

I have read the foregoing protocol and agree to conduct the study as described herein.

Principal Investigator (signature)	Date
Principal Investigator (print)	

SPONSOR AGREEMENT

Study Drug: BIVV009

Protocol: BIVV009-03

A PHASE 3, PIVOTAL, OPEN-LABEL, MULTICENTER STUDY TO ASSESS THE EFFICACY AND SAFETY OF BIVV009 IN PATIENTS WITH PRIMARY COLD AGGLUTININ DISEASE WHO HAVE A RECENT HISTORY OF BLOOD TRANSFUSION

Version 06

19 December 2019

I have read the foregoing protocol and agree to conduct the study as described herein.

Date

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 APPENDIX A: CLINICAL LABORATORY EVALUATIONS

Clinical Chemistry Panel:
Alanine aminotransferase
Albumin
Alkaline phosphatase
Aspartate aminotransferase
Blood urea nitrogen
Calcium
Chloride
Creatinine
Glucose
Haptoglobin
Lactate dehydrogenase (LDH)
Potassium
Sodium
Total bilirubin
Direct bilirubin
Indirect bilirubin
Total protein
Uric acid

Hematology Panel:
Hematocrit
Hemoglobin
Mean corpuscular hemoglobin
Mean corpuscular hemoglobin concentration
Mean corpuscular volume
Platelet count
Red blood cell (RBC) count
RBC distribution width
Reticulocyte count
White blood cell (WBC) count
WBC differential (absolute):
- Basophils
- Eosinophils
- Lymphocytes
- Monocytes
- Neutrophils

Urinalysis:
Bilirubin
Color and appearance
Glucose
Ketones
Leukocyte esterase
Nitrite
Occult blood
pH and specific gravity
Protein
Urobilinogen
Microscopic exam including
- bacteria, casts, crystals, epithelial cells, RBCs, and WBCs (if protein, leukocyte esterase, nitrite, or blood is positive)

Pregnancy Test
(for women of childbearing potential): serum test during screening, serum or urine test at all other time points

Hepatic Panel/HIV:
Hepatitis B surface antigen
Hepatitis C virus antibody
Human immunodeficiency virus antibody

Pharmacodynamic (PD) Assays:
Complement System Classical Pathway (Wieslab-CP)
CH50
Total C4
C1q
C1s

Systemic Lupus Erythematosus Panel:
Antinuclear antibodies (ANA) multiplex with double stranded DNA
Anti-La/SSB antibody (SS-B)
Anti-ribonucleoprotein antibody (RNP)
Anti-Smith antibody (Sm)
Anti-Ro/SSA antibody (SS-A)
Anti-scleroderma antibody (Scl-70)
Anti-Chromatin antibody
Anti-Jo-1 antibody
Anti-Centromere B antibody
Circulating immune complexes (CIC)

Coagulation Panel:
Prothrombin time or the international ratio of PT (PT-INR)
Activated partial thromboplastin time (aPTT)
D-dimer
Thrombin-antithrombin assay

Iron Panel and Erythropoietin
Erythropoietin
Serum iron
Total iron binding capacity (TIBC)
Transferrin saturation
Ferritin

Gilbert's Syndrome test
UGT1A1 gene

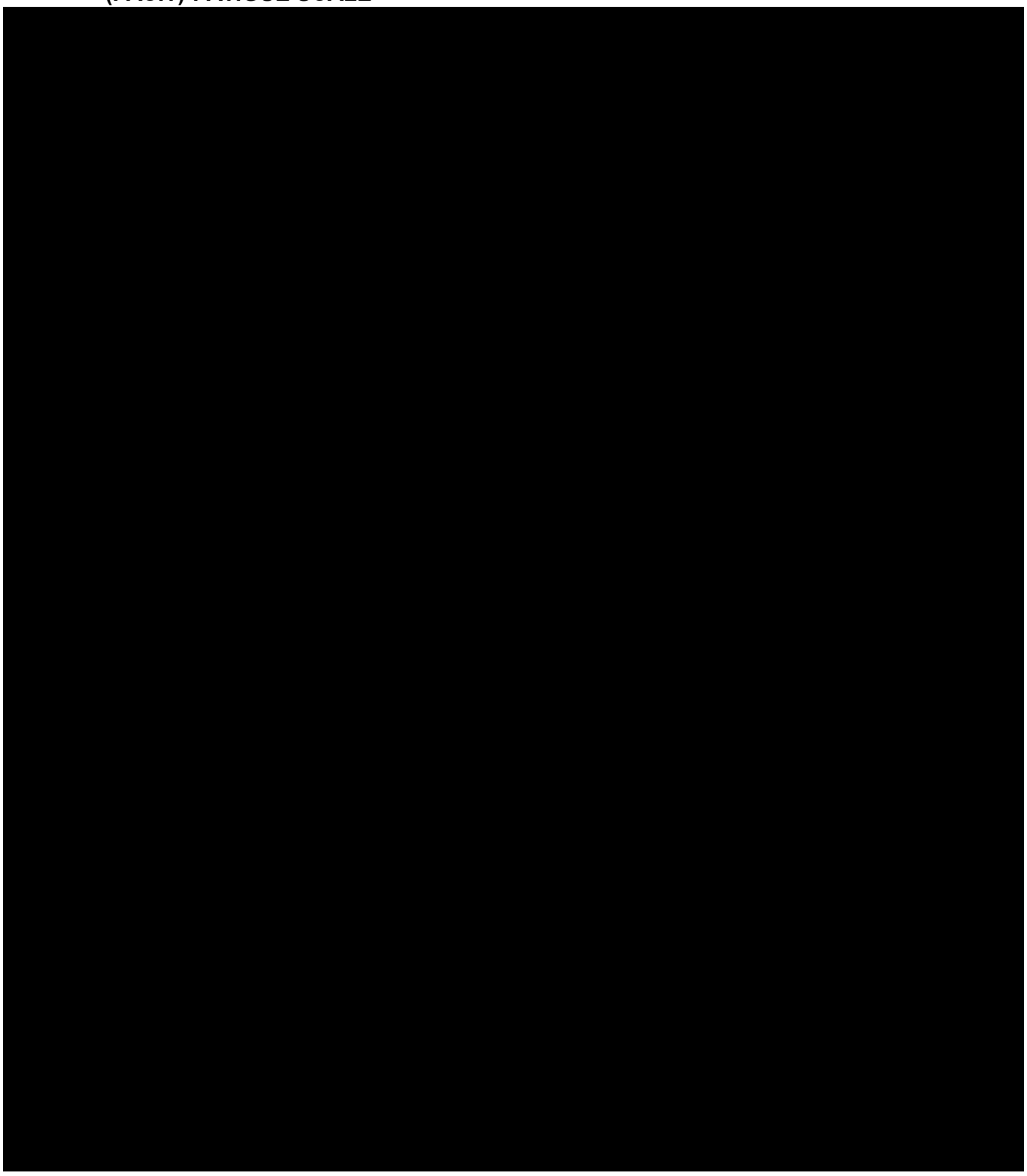
Disease-Related Biomarkers
DAT (polyspecific, anti-IgG & anti-C3d)
LDH isoforms
Cold agglutinin (CAg) titer
IgG subsets (IgA, IgD, IgG, IgM)
Vaccine titers
CAgD Thermal Amplitude

For information on the anti-drug antibody (ADA) and PK evaluations, please refer to the Laboratory Manual.

10.2 APPENDIX B: NCI-CTC VERSION 4.03 (CTCAE V4.03)

https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

10.3 APPENDIX C: FUNCTIONAL ASSESSMENT OF CHRONIC ILLNESS THERAPY (FACIT)-FATIGUE SCALE



10.4 APPENDIX D: EQ-5D-5L

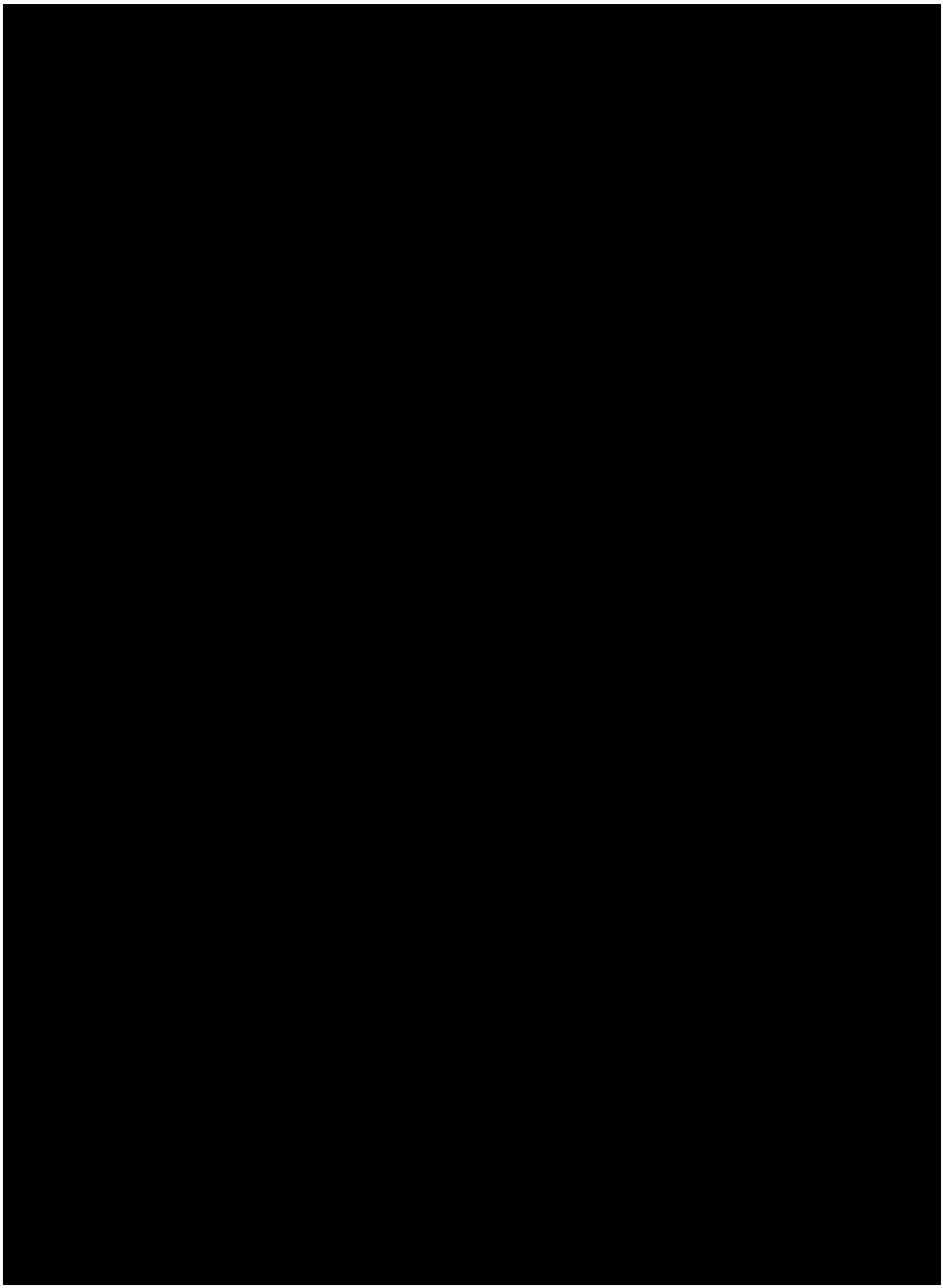
Health Questionnaire

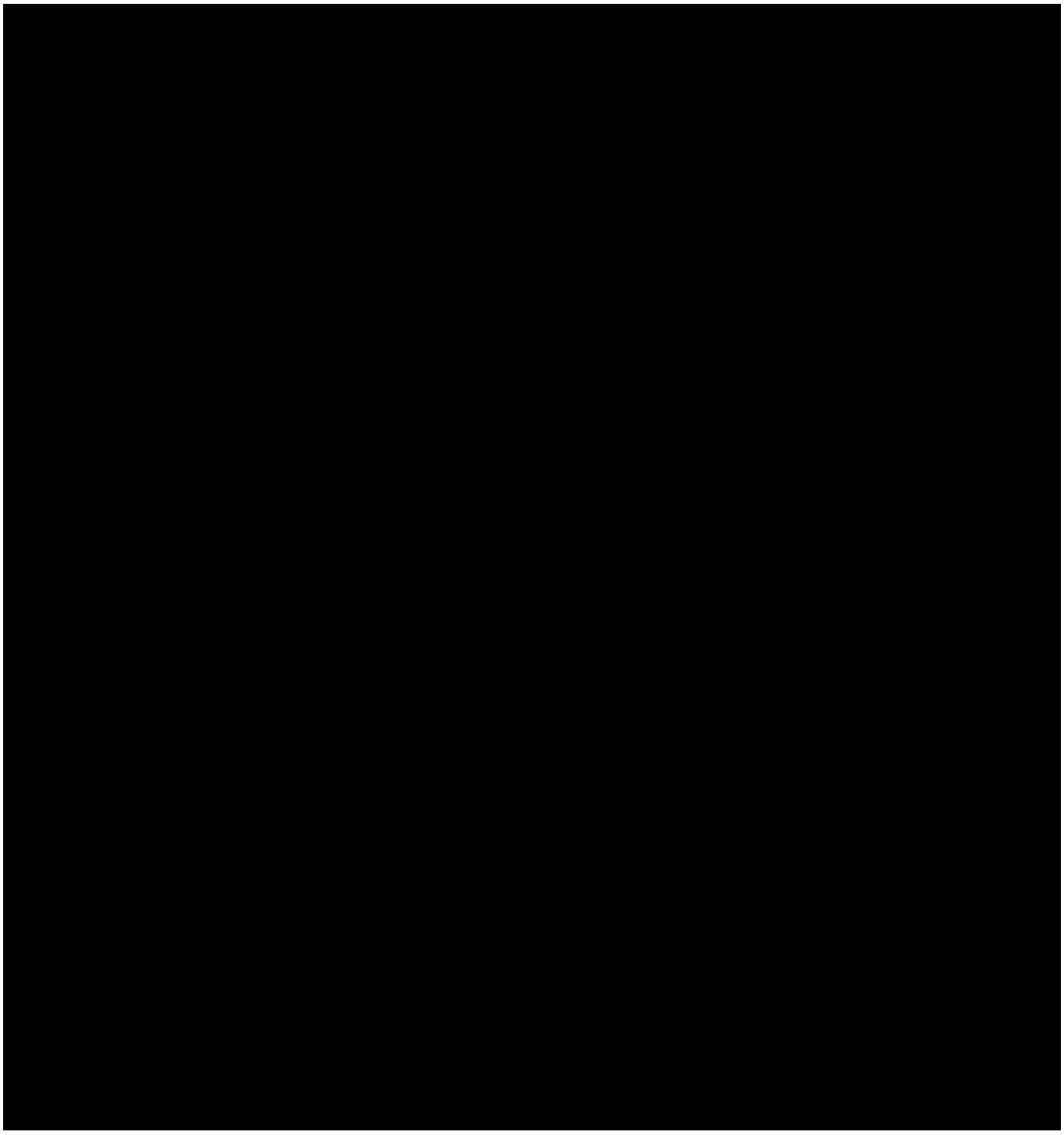
English version for the USA

Sample

USA (English) © 2009 EuroQol Group EQ-5D™ is a trade mark of the EuroQol Group

10.5 APPENDIX E: 12-ITEM SHORT FORM SURVEY (SF-12)





10.6 APPENDIX F: PATIENT'S GLOBAL IMPRESSION OF CHANGE (PGIC)

10.7 APPENDIX G: HEALTHCARE RESOURCE UTILIZATION

Healthcare resource utilization data will be collected during the Screening/Observation Period; on Day 0; on Days 1, 49, 77, 105, 133, and 161; at EOT for Part A; every 4 weeks during Part B; and at the ET/EOS visit.

For screening, please provide the healthcare resource utilization data for the past 6 months prior to the start of the Screening/Observation period.

Has the patient had any additional non-study outpatient visits, emergency room visits, or inpatient hospitalizations related to their cold agglutinin disease during the last 4 weeks?

Yes or No

If yes, please provide the information below including the number of visits.

		Yes/No	How Many
A.	Extra or unscheduled (non-study) visit to the office of the study doctor	_____	_____
B.	Visit to a generalist doctor	_____	_____
C.	Visit to a specialist doctor	_____	_____
D.	Visit to another healthcare professional (eg, nurse, therapist)	_____	_____
E.	Complementary/alternative visit (eg, homeopathic, herbalist)	_____	_____
F.	Visit to an urgent care or walk-in clinic (excluding a hospital emergency room)	_____	_____
G.	Visit to a hospital emergency room Reason(s) for the visit (diagnosis): _____	_____	_____
H.	Use of an ambulance service	_____	_____
I.	Hospitalization		

Date of hospital admission _____ and date of discharge _____

Discharge diagnosis: _____

Was the patient admitted to the intensive care unit (ICU)? Yes or No

If yes, please provide dates or duration in the ICU.

Date of ICU admission: _____and date of ICU discharge: _____

OR

Duration of ICU stay: _____

10.8 APPENDIX H: PATIENT'S GLOBAL IMPRESSION OF [FATIGUE] SEVERITY

Attach when completed. See below for an example.

10.9 APPENDIX I: VACCINE SCHEDULE FOR PATIENTS IN JAPAN ONLY

The vaccine schedule for patients in Japan who do not have documented vaccination in the 5 years prior to enrollment is provided below:

1. Meningococcal conjugate vaccine (MenACWY) (2-dose series 8 weeks apart)
   a) The first dose should be given on Day -42 when possible and no later than Day -28 during the Screening/Observation Period.
   b) The second dose should be given 8 weeks after the first dose, between Day 14 and Day 32 in Part A.
2. Pneumococcal vaccine (PPSV23)
   a) Single dose should be given on Day -42 when possible and no later than Day -28 during the Screening/Observation Period.

Notes: If necessary, vaccinations may be administered at an unscheduled visit per patient and vaccine availability.

For vaccination requirements in countries other than Japan, please vaccinate per local vaccine availability and vaccination guidelines for patients with complement deficiency as discussed in Section 6.1.1.1.

10.10 APPENDIX J: COUNTRY SPECIFIC REQUIREMENT - HOME INFUSIONS WITH BIVV009

Compared to the global protocol, the following country specific changes are applicable to the US, the Netherlands, Norway, France, Italy, Austria, Germany, and Spain:

Synopsis (Objectives)

Part B

Exploratory objective:

- To describe the safety and patient satisfaction with the convenience of home infusions with BIVV009 in a subset of patients.

Synopsis (Test Product(s), Dose, and Mode of Administration)

Home infusion will be performed by a healthcare professional caregiver contingent upon completion of training delivered by the investigator or delegated site staff member only in patients willing to be administered study drug in home, in whom previous on-site infusions were uncomplicated, and who satisfy the following criteria:

1. Able to comprehend and give informed consent for participation in the alternate home infusion scheme and willing to be infused at home for at least 4 doses, alternating with regular office visits.
2. No history of hypersensitivity reaction to BIVV009
3. Considered by the investigator to be a good candidate for home infusions.

Qualifying patients who consent for home infusions will have study drug administered in home every other bi-weekly visit alternating with regular office visit with drug infusion. Qualification for home infusions and informed consent will be collected no later than at office visit two weeks before first planned home infusion.

For subjects receiving drug injections in home as administered by a healthcare professional during the Part B open-label phase, the healthcare professional will collect during home visits specific information (AEs, concomitant medications, solicited anemia assessment as well as, after the 1st and 4th home infusions, Home Infusion Patient Satisfaction Questionnaires (Section 10.11, Appendix K). The data collected on dedicated paper forms will be provided to the Investigator within 24 hours for entry in EDC. The healthcare professional will monitor the subject during infusion lasting 1-hour or, in certain patients 2-hour (eg, patients with underlying cardiopulmonary disease, with sponsor's approval) and for 2 hours after completion of the first home infusion and 1 hour after the completion of each subsequent home infusion. Any adverse events occurring during home visits should be immediately reported by the healthcare professional caregiver to the Investigator.

First office visit 2 weeks after first home infusion will include assessments normally planned to be performed every 3 months. After the 1st and 4th home infusion, the patient will answer (by filling up the form) the Home Infusion Patient Satisfaction which will be applied after the end of study drug administration. Neither blood samples nor urine or serum pregnancy tests will be performed during home infusion visits; blood tests scheduled to be performed at 2, or 4 weeks intervals as well urine or serum pregnancy tests in WOCBP (ie, women of child bearing potential) will be performed during office visits every four weeks while the patient is within the home infusion scheme.

In case a home infusion visit coincides with a visit with assessments scheduled to occur every 3 months, the patient will attend office visit and will have study drug infused at the site; the next home infusion visit will occur 2 weeks after this office visit and the schedule with home infusion visits every other bi-weekly visit alternating with regular office visit with drug infusion will be resumed. Patients who miss a dose (ie, outside the dosing window or >17 days since last dose, regardless if last dose was given at home or at the site) should return to the site for an unscheduled visit to receive another loading dose prior to their next scheduled visit which will also take place at the office. Such patient may return to the schedule of home visits alternating with regular office visits if eligibility criteria for home infusions are still met.

Infusions given in the home setting versus at the investigational site will be captured through the case report form (CRF) for drug administration.

Table 4 - Study schedule of events (Part B) for patients with home infusions

Study visit (Week/Day)	Part B Open-label extension phase	Part B Open-label extension phase[m]	ET/EOS/Safety follow-up[a]
	On site visit	Home visit	9 weeks after last dose on site visit
Visit windows	**±2 days**	**±2 days**	**±2 days**
Pregnancy test (if applicable)[b]	X		X
Body weight	X[h]		X

Study visit (Week/Day)	Part B Open-label extension phase	Part B Open-label extension phase[m]	ET/EOS/Safety follow-up[a]
	On site visit	Home visit	9 weeks after last dose on site visit
Visit windows	**±2 days**	**±2 days**	**±2 days**
Physical examination, full			X
Physical examination, brief	X[h]		
Vital signs (BP, PR, RR, body temperature)[c]	X[h]		X
SLE panel[d, p]	X[d]		X
Hematology panel[d, o]	X		X
Coagulation panel[d]			X
Clinical chemistry panel[d, o]	X		X
Urinalysis[d]	X[h]		X
FACIT-Fatigue[j]	X[h]		X
PGIS[j]	X[h]		X
PGIC[j]	X[h]		X
SF-12[j]	X[h]		X
EQ-5D-5L[j]	X[h]		X
Solicited symptomatic anemia	X	X	X
Study drug administration[e]	X	X	
ADAs against BIVV009 and neutralizing anti bodies	X[k]		X
PK Samples[f]	X		X
PD Samples[f]	X		X
Concomitant medications including transfusions	X	X	X
Healthcare resource utilization	X[i]		X
Adverse events[g]	X	X[n]	X
Home infusion satisfaction survey		X[l]	
ECG			X
Vaccination	Revaccination with booster doses should be given according to regional guidelines for patients with persistent complement deficiency and in accordance with respective labels.		

ADA = anti-drug antibodies; BP = blood pressure; EOS = End of Study; EQ-5D-5L = five level EuroQol five dimensions questionnaire; ET = Early Termination Visit; FACIT-Fatigue = functional assessment of chronic illness therapy - fatigue; N/A = not applicable; PD = pharmacodynamic; PGIC = Patient's Global Impression of Change; PGIS = Patient's Global Impression of [Fatigue] Severity; PK = pharmacokinetic; PR = pulse rate; QOL = quality of life; RR = respiratory rate; SF-12 = 12-Item Short Form Survey;

a Patients should return to site 9 weeks after last dose for ET procedures, EOS assessment, or Safety Follow-up procedures upon completion of dosing in the study. If patient experiences a hematological breakthrough event, a PK, PD, and ADA sample should be collected at the time of the event.

b Females of child-bearing potential only. Serum or urine pregnancy test every 4 weeks (+/- 2 days) during Part B at on-site visit and at ET/EOS safety follow-up visit

c Vital signs measurements (supine BP, PR, RR, and oral temperature) are to be obtained with measurements performed predose and 1 hour (±5 minutes) after completion of administration of each dose of study drug (on site visits only).

d For a complete list of analytes, see protocol Section 10.1, Appendix A.

e Study drug doses of 6.5 grams (if <75 kg) or 7.5 grams (if ≥75 kg) based on patient's baseline body weight will be administered via IV infusion over ~ 60 ±5 minutes, every 2 weeks during Part B. Patients with underlying cardiopulmonary disease may receive a 2-hour infusion with Sponsor approval. If a patient misses a scheduled dose (outside of the 2-day window or >17 days since last dose), they must return to site (unscheduled visit) to receive another loading dose 1 week prior to the next scheduled dose which will also be given at site.

f During Part B, PK and PD samples will continue to be collected routinely at predose and 1 hour (±15 minutes) postdose at 3-month during the 1st year of treatment in Part B and then every 6 months. PK and PD samples will also be collected if a patient experiences a hematologic breakthrough event at any point during the study.

g AEs will be recorded from the time the patient signs the informed consent form until 9 weeks after administration of the last dose of study drug. For patients with home infusions, safety assessments will additionally include AEs with onset within 24 hours of the infusion.

h To be performed every 3 months during the on-site visits.

i During Part B, the healthcare resource utilization data will be recorded every 4 weeks, at on site visit.

j To be performed in the following order: FACIT-Fatigue first, PGIS second, PGIC third, SF-12 fourth, and EQ-5D-5L fifth.

k During Part B, ADA samples will be collected every 3 months predose, during the 1st year of treatment in Part B and then every 6 months and at Safety Follow up visit 9 weeks after last dose. Samples will also be collected if a patient experiences a hematologic breakthrough event or withdraws from the study early.

l After the 1st and 4th home infusions (which will be applied after the end of study drug administration).

m In Part B, home visit is alternating with every 4 weeks with site visit and if needed, a loading dose can be infused at the site visit.

n HCP records and AEs will be collected on paper forms and will be forwarded to PI within 24h; site will be informed of any AEs immediately; All SAE reporting timelines still apply (ie need to be reported to sponsor safety database within 24 hours of awareness by the home infusion healthcare professional).

o In Part B, hematology and clinical chemistry panels to be performed every 2 weeks after Week 25 and up to Week 79 (every 4 weeks in patients within the home infusion scheme). For the remainder of Part B after Week 79, hematology and clinical chemistry panels to be performed every 4 weeks.

p SLE panel testing should occur every 6 months at on site visits in Part B.

Section 2.2 (Background and Study Rationale)

Patients with CAgD are often elderly and/or have numerous co-morbidities affecting their mobility. Moreover, clinical centers specialized in the management of CAgD are infrequent and may be located far from patients' home. Consequently, some patients may find the option of home infusions with drug against CAgD, beneficial. To this end a group of patients at preselected sites/countries will be offered the possibility of home infusions during Part B, assisted by trained health care professional.

Section 2.2.4 (Potential Risks and Benefits)

Home infusions with the study drug will be proposed to a number of patients in countries pre-selected to participate in home infusion. Home infusions will be assisted by a trained healthcare professional, and will concern patients who express such wish, after having been qualified by the Investigator and no sooner than after Week 41 (Day 287) and without evidence of intolerance of the study drug as determined by the Investigator. No new risks related to home infusions are anticipated. Like with office visits, medications such as epinephrine and diphenhydramine, and additional emergency equipment will be available in case an allergic reaction or anaphylaxis occurs during home infusion. Professional healthcare caregiver will be qualified to detect and treat allergic reactions and anaphylaxis. The alternating schedule of home infusion visits and office visits every 4 weeks each may be found convenient by patients as less travels to the study site will be necessary.

Section 3.5 (Exploratory objective [Part B])

- To describe the safety and patient satisfaction with the convenience of home infusions with BIVV009 in a subset of patients in the US, the Netherlands, Norway, France, Italy, Austria, Germany, and Spain.

Section 4.1 (Study Design: Part-B)

A subset of patients from selected sites/countries and who were determined to have tolerated BIVV009 well, will be invited to have infusions with BIVV009 performed at their homes, after having been qualified by the Investigator. Home infusions will be carried out by a trained nurse. Patients will follow the alternate home infusion scheme, ie, home infusion at the patient's home will be alternating with office visits, so that patients will attend office visit every 4 weeks alternating with home infusions every 4 weeks (+/-2 days).

Section 5.3 (Removal of Patients from Study Participation, and Study Suspension and Stopping Rules)

Patients undergoing home infusions with BIVV009 will return to bi-weekly dosing at the study site if they develop any adverse event that in the opinion of the Investigator, may jeopardize patient safety if home infusions are continued. Patients may return to home infusions if the AE, which led to the interruption of home infusions according to the Investigator's judgement, is considered unrelated to BIVV009 and once resolved or stabilized.

Section 6.1, Table -3 (Footnote "i")

Study drug doses of 6.5 grams (if <75 kg) or 7.5 grams (if ≥75 kg) based on patient's baseline body weight will be administered via IV infusion over ~60 ±5 minutes on Days 0, 7, and every 14 days thereafter during Part A and every 2 weeks (+/-2 days) starting at Week 27 during Part B. Patients with underlying cardiopulmonary disease may receive a 2-hour infusion with Sponsor approval. If a patient misses a scheduled dose (outside of the 2-day window or >17 days since last dose), they must return to site (unscheduled visit) to receive another loading dose 1 week prior to the next scheduled dose. Qualifying patients at participating sites may have study drug dosed at home, alternating with study drug dosed during office visits in Part B.

Section 6.1.6 (Infusion of the study drug at patient's home)

Home infusions will be performed at pre-selected countries/sites, during Part B and will be performed by a healthcare professional caregiver contingent upon completion of training delivered by the Investigator or delegated site staff member only in patients willing to be administered study drug at home, and in whom previous on-site infusions were uncomplicated, who satisfy the following criteria:

1. Able to comprehend and give informed consent for participation in the alternate home infusion scheme and willing to be infused at home for at least 4 doses, alternating with regular office visits.
2. No history of hypersensitivity reaction to BIVV009
3. Considered by the investigator to be a good candidate for home infusions.

Qualifying patients who consent for home infusions will have study drug administered in home every other bi-weekly visit alternating with regular office visit with drug infusion. Qualification for home infusions and informed consent will be collected no later than at office visit two weeks before first planned home infusion.

For subjects receiving drug injections in home as administered by a healthcare professional during the Part B open-label phase, the healthcare professional will collect specific information (AEs, concomitant medications, Home Infusion Patient Satisfaction Questionnaires, after the 1st and 4th home infusions, as well as solicited anemia assessment) during home visits which will be applied after the end of study drug administration. The data collected on dedicated paper forms will be provided to the Investigator within 24 hours for entry in EDC. The healthcare professional will monitor the subject during 1-hour or, in certain patients 2-hour infusion (eg, patients with underlying cardiopulmonary disease, with sponsor's approval) and for at least 2 hours after the completion of the first home infusion or 1 hour after the completion of each subsequent home infusion. Any adverse events occurring during home visits will be immediately reported by the healthcare professional caregiver to the Investigator.

In case a home infusion visit coincides with a visit with assessments scheduled to occur every 3 months the patient will attend office visit and will have study drug infused at the site; the next home infusion visit will occur 2 weeks after this office visit and the schedule with home infusion visits every other bi-weekly visit alternating with regular office visit with drug infusion will be resumed. Patients who miss a dose (ie, outside the dosing window or >17 days since last dose, regardless if last dose was given at home or at the site) should return to the site for an unscheduled visit to receive another loading dose prior to their next scheduled visit which will also take place at the office. Such patient may return to the schedule of home visits alternating with regular office visits if eligibility criteria for home infusions are still met.

First office visit 2 weeks after first home infusion will include assessments normally planned to be performed every 3 months. Neither blood samples nor urine pregnancy tests will be collected/performed during home infusion visits; blood tests scheduled to be performed at 2, or 4 weeks intervals as well urine pregnancy tests in WOCBP (ie, women of child bearing potential) will be performed during office visits every four weeks while the patient is within the home infusion scheme.

Infusions given in the home setting versus at the investigational site will be captured through the case report form (CRF) for drug administration.

Section 6.2.1 (Drug Supplies and Accountability)

Preparation and accountability procedures for the investigational product, including those associated with home infusions whenever applicable, are described in further detail in the Pharmacy Manual.

Section 6.2.4 (Dose Preparation and Administration)

Patients must be monitored for acute allergic reactions during infusion and for at least 2 hours after the completion of the first administration of study drug at a home infusion visit or 1 hour after the completion of each administration of study drug thereafter at subsequent home infusion visits. Like with office visits, medications such as epinephrine and

diphenhydramine, and additional emergency equipment will be available in case an allergic reaction or anaphylaxis occurs during home infusion. Site personnel, or professional healthcare caregiver in case of home infusions, must be qualified to detect and treat allergic reactions and anaphylaxis. See Section 6.3.8 for further details regarding additional testing.

Patients should be instructed to report the development of rash, hives, pruritus, flushing, urticaria, etc, that may represent an allergic or hypersensitivity reaction to study drug. If any signs or symptoms of an allergic or anaphylactic reaction are observed during the infusion, administration of study drug must be immediately discontinued and the patient treated as appropriate, and in case of home infusion, the Investigator notified immediately.

10.11 APPENDIX K: HOME INFUSION PATIENT SATISFACTION SURVEY

How satisfied or dissatisfied are you with the overall convenience of being infused at home?

Very satisfied	Satisfied	Dissatisfied	Very dissatisfied
▼	▼	▼	▼
☐ 1	☐ 2	☐ 3	☐ 4

10.12 APPENDIX L: PROTOCOL AMENDMENT HISTORY

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

Clinical Study Protocol 5 (17 July 2018)

This clinical study protocol 5 (amendment 5) is not considered to be substantial based on the criteria set **forth** in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

The following corrections or changes were made to the protocol for clarity, consistency, and accuracy:

- The page headers were updated with Version 5 of the protocol.
- The abbreviation list was updated.
- The tables of contents were updated.
- The Investigator's and Sponsor's agreement pages were updated with Version 5 and the date of approval.
- Minor grammatical and formatting changes were made throughout the protocol.
- Clarification as to how data corrections would be shown
- Changed PK and PD postdose sample collection time from 2 hours to 1 hour postdose

Clinical Study Protocol 4 (29 June 2018)

This clinical study protocol 4 (amendment 4) is not considered to be substantial based on the criteria set forth in Article 10(a) of **Directive** 2001/20/EC of the European Parliament and the Council of the European Union.

The following corrections or **changes** were made to the protocol for clarity, consistency, and accuracy:

- The page headers were updated with Version 4 of the protocol.
- The abbreviation list was updated.
- The tables of contents were updated.
- The Investigator's and Sponsor's agreement pages were updated with Version 4 and the date of approval.
- Minor grammatical and formatting changes were made throughout the protocol.
- Added the PGIS [Fatigue] as a QOL assessment at the request of the US FDA.
- Increased the frequency of sample collection for PK and PD assessments. Specified that PK and PD
    - samples were to be collected predose and 2 hours (±15 minutes) postdose (1 hour after the completion of study drug infusion) from all patients on Days 0, 7, 21, 35, 49, 63, 77, 91, 105, 119, 133, 147, 161, and 175. An additional blood sample for PK and PD analysis was to be collected during the EOT visit on Day 182 or at ET if a patient withdraws early.
- Added that "documentation" of all vaccinations was required in text where it was not previously included
- Added the vaccine schedule for Japan as an appendix.
- Changed the PGIC assessment from every 6 months to every 3 months in Part B to coincide with the timing of PGIS assessments.

Clinical Study Protocol 3.1 (21 March 2018)

This clinical study protocol 3.1 (amendment 3.1) is not considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

The following corrections or changes were made to the protocol for clarity, consistency, and accuracy:

- The page headers were updated with Version 3.1 of the protocol.
- The abbreviation list was updated.
- The tables of contents were updated.
- The Investigator's and Sponsor's agreement pages were updated with Version 3.1 and the date of approval.
- Minor grammatical and formatting changes were made throughout the protocol.

- Removed serogroup B meningococcus from vaccination requirements.
- Specified that vaccinations should be initiated on Day -42 and no later than Day -28.
- Added the vaccine schedule for Japan as an appendix.

Clinical Study Protocol 3 (09 March 2018)

This clinical study protocol 3 (amendment 3) is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

The following corrections or changes were made to the protocol for clarity, consistency, and accuracy:

- The page headers were updated with Version 3 of the protocol.
- The abbreviation list was updated.
- The tables of contents were updated.
- The Investigator's and Sponsor's agreement pages were updated with Version 3 and the date of approval.
- Minor grammatical and formatting changes were made throughout the protocol.
- Excluded from Part B patients who received prohibited medications in Part A.
- Clarified that patients who received a transfusion in Part A would not be withdrawn and would still be eligible to participate in Part B.
- Inclusion criterion 7, "Ferritin levels within the normal reference ranges unless outside normal range and deemed not clinically significant by the Investigator (or designee)," was changed to: "Ferritin above the lower limit of normal. Concurrent treatment with iron supplementation is permitted if the patient has been on a stable dose for the previous 4 weeks."
- Extended the requirement for highly effective contraception from 6 weeks following the last administration of study drug to 9 weeks.
- The exclusion criterion "Clinical diagnosis of systemic lupus erythematosus (SLE) or other autoimmune disorders with antinuclear antibodies at Screening" was modified to add that antinuclear antibodies of long-standing duration without associated clinical symptoms will be adjudicated on a case-by-case basis.
- Specified that vaccinations should be administered in accordance with regional guidelines.
- Extended the follow-up visit for collection of AE data, PK, PD, and ADA samples from 6 weeks to 9 weeks after the last administration of study drug in patients who discontinue early.
- Total healthcare resource utilization was added as an exploratory efficacy endpoint in Part A and as an efficacy endpoint in Part B.
- Safety follow-up visit changed from 6 weeks to 9 weeks after the last dose of study drug.

- Added the occurrence of clinically significant hematologic breakthrough events attributable to the development of ADA and/or the development of positive SLE autoantibody titers as a criterion for the removal of a patient from study participation if, in the opinion of the Investigator, it could jeopardize the safety of the patient.
- Increased the frequency of pregnancy testing (serum or urine).
- Added solicited symptomatic anemia as a study assessment.
- Clarified that patients must be monitored for allergic reactions and anaphylaxis rather than infusion-related reactions.
- Extended the recording period for AEs from 6 to 9 weeks after administration of the last dose of study drug.
- Extended the reported period for SAEs from 6 to 9 weeks after the last dose of study drug or through the final study visit, whichever occurs later.

Clinical Study Protocol 2 (22 February 2018)

This clinical study protocol 2 (amendment 2) is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

The following corrections or changes were made to the protocol for clarity, consistency, and accuracy:

- The page headers were updated with Version 2 of the protocol.
- The abbreviation list was updated.
- The tables of contents were updated.
- The Investigator's and Sponsor's agreement pages were updated with Version 2 and the date of approval.
- Minor grammatical and formatting changes were made throughout the protocol.
- Beginning on Day 0, urine pregnancy testing was changed to serum or urine pregnancy testing.
- Clarified that patients who received a transfusion in Part A would not be withdrawn and would still be eligible to participate in Part B.
- Excluded from Part B patients who received prohibited medications in Part A.
- Changed the collection of PK, PD, and ADA samples from 6 to 9 weeks after the last dose of study drug in patients who discontinue early and those who have a hematologic breakthrough event.
- Inclusion criterion 7, "Ferritin levels within the normal reference ranges unless outside normal range and deemed not clinically significant by the Investigator (or designee)," was changed to: "Ferritin above the lower limit of normal. Concurrent treatment with iron supplementation is permitted if the patient has been on a stable dose for the previous 4 weeks."
- Extended the requirement for highly effective contraception from 6 weeks following the last administration of study drug to 9 weeks.

- The exclusion criterion "Clinical diagnosis of SLE or other autoimmune disorders with antinuclear antibodies at Screening" was modified to add that antinuclear antibodies of long-standing duration without associated clinical symptoms will be adjudicated on a case-by-case basis.
- Total healthcare resource utilization was added as an exploratory efficacy endpoint in Part A and as an efficacy endpoint in Part B.
- Specified that vaccinations should be administered in accordance with regional guidelines.
- Extended the follow-up visit for the collection of AE data, PK, PD, and ADA samples from 6 to 9 weeks after the last administration of study drug in patients who discontinue early.
- Added the occurrence of clinically significant hematologic breakthrough events attributable to the development of ADA and/or the development of positive SLE autoantibody titers as a criterion for the removal of a patient from study participation if, in the opinion of the Investigator, it could jeopardize the safety of the patient.
- Extended the recording period for AEs from 6 to 9 weeks after administration of the last dose of study drug.
- Extended the reporting period for SAEs from 6 to 9 weeks after the last dose of study drug or through the final study visit, whichever occurs later.
- Clarified that patients must be monitored for allergic reactions and anaphylaxis rather than infusion-related reactions.
- Extended the reporting period for pregnancies from 6 to 9 weeks after the last dose of study drug.

Clinical Study Protocol 1.5 (10 January 2018)

This clinical study protocol 1.5 (amendment 1.5) is not considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

The following corrections or changes were made to the protocol for clarity, consistency, and accuracy:

- The page headers were updated with Version 1.5 of the protocol.
- The abbreviation list was updated.
- The tables of contents were updated.
- The Investigator's and Sponsor's agreement pages were updated with Version 1.5 and the date of approval.
- Minor grammatical and formatting changes were made throughout the protocol.
- Increased the frequency of urine pregnancy tests for women of childbearing potential.

Clinical Study Protocol 1.4 (15 December 2017)

This clinical study protocol 1.4 (amendment 1.4) is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

The following corrections or changes were made to the protocol for clarity, consistency, and accuracy:

- The page headers were updated with Version 1.4 of the protocol.
- The abbreviation list was updated.
- The tables of contents were updated.
- The Investigator's and Sponsor's agreement pages were updated with Version 1.4 and the date of approval.
- Minor grammatical and formatting changes were made throughout the protocol.
- Extended the requirement for highly effective contraception from 6 weeks following the last administration of study drug to 9 weeks.
- The exclusion criterion "Clinical diagnosis of SLE or other autoimmune disorders with antinuclear antibodies at Screening" was modified to add that antinuclear antibodies of long-standing duration without associated clinical symptoms will be adjudicated on a case-by-case basis.
- The inclusion criteria "Bilirubin level above the normal reference range" was changed to "Bilirubin level above the normal reference range, including patients with Gilbert's Syndrome".
- Extended the Early Termination visit from 6 to 9 weeks from the last dose of study drug.
- Extended the safety follow-up visit for patients who discontinue early from 6 to 9 weeks after the last dose of study drug.
- Added the occurrence of clinically significant hematologic breakthrough events attributable to the development of ADA and/or the development of positive SLE autoantibody titers as a criterion for the removal of a patient from study participation if, in the opinion of the Investigator, it could jeopardize the safety of the patient.
- Extended the reporting period for AEs from 6 to 9 weeks after the last dose of study drug or through the final study visit, whichever occurs later.
- Extended the reporting period for pregnancies from 6 to 9 weeks after the last dose of study drug.

Clinical Study Protocol 1.3 (06 December 2017)

This clinical study protocol 1.3 (amendment 1.3) is not considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

The following corrections or changes were made to the protocol for clarity, consistency, and accuracy:

- The page headers were updated with Version 1.3 of the protocol.
- The abbreviation list was updated.
- The tables of contents were updated.
- The Investigator's and Sponsor's agreement pages were updated with Version 1.3 and the date of approval.
- Minor grammatical and formatting changes were made throughout the protocol.
- Inclusion criterion 6, "Ferritin levels within the normal reference ranges unless outside normal range and deemed not clinically significant by the Investigator (or designee)," was removed and reframed as an exclusion criterion: "Ferritin below the lower limit of normal. Concurrent treatment with iron supplementation is permitted if the patient has been on a stable dose for the previous 4 weeks."
- Increased the frequency of urine pregnancy tests for women of childbearing potential to monthly.

Clinical Study Protocol 1.2 (29 November 2017)

This clinical study protocol 1.2 (amendment 1.2) is not considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

The following corrections or changes were made to the protocol for clarity, consistency, and accuracy:

- The page headers were updated with Version 1.2 of the protocol.
- The abbreviation list was updated.
- The tables of contents were updated.
- The Investigator's and Sponsor's agreement pages were updated with Version 1.2 and the date of approval.
- Minor grammatical and formatting changes were made throughout the protocol.
- Excluded from Part B patients who withdraw from the study after Week 5 and prior to Week 23 of Part A.
- Excluded from Part B patients who received prohibited medications in Part A
- Specified that patients who receive a transfusion in Part B will not be withdrawn from the study and will not be considered nonresponders.
- Specified that vaccinations should be given in accordance with regional guidelines, where applicable. Where no regional guidelines are available, the vaccinations were to be initiated on Day -42 or as early as possible during the Screening/Observation Period. The primary vaccine series was to be completed during Screening when possible and otherwise prior to Week 5 of Part A.

Clinical Study Protocol 1.1 (09 September 2017)

This clinical study protocol 1.1 (amendment 1.1) is not considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

The following corrections or changes were made to the protocol for clarity, consistency, and accuracy:

- The page headers were updated with Version 1.1 of the protocol.
- The abbreviation list was updated.
- The tables of contents were updated.
- The Investigator's and Sponsor's agreement pages were updated with Version 1.1 and the date of approval.
- Minor grammatical and formatting changes were made throughout the protocol.
- The PGIS assessment was removed.
- The frequency of the ECG assessment was reduced. Specifically, the Day 175 and Day 182 time points were removed. In addition, during Part B, the ECGs were only to be conducted predose and postdose at 3 months (Day 217).
- Quantitative immunoglobulin was removed.

Signature Page for VV-CLIN-0562006 v1.0
bivv009-03-16-1-1-amended-protocol06

Approve & eSign	[redacted]	
Approve & eSign		