NCT03347396

STATISTICAL ANALYSIS PLAN

PART A

Product Studied: BIVV009

Protocol Number(s): 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

Date of Protocol: 17 July 2018 (Version 5)

Date of Statistical Analysis Plan: 25 April 2019

Approved By:

[redacted]

Date

[redacted]

Date

[redacted]

Date

[redacted]

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LIST OF ABBREVIATIONS

AE	adverse event
ADL	activities to daily living
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANA	antinuclear antibodies
AST	aspartate aminotransferase
AUC	area under the curve
BLA	Biologics License Applications
BUN	blood urea nitrogen
CAD	cold agglutinin disease
CI	confidence interval
CIC	circulating immune complexes
C_{max}	maximum concentration
CTCAE	Common Toxicity Criteria for Adverse Events
DBL	database lock
ECG	electrocardiogram
eCRF	electronic Case Report Form
EOT	end of treatment
EQ-5D-5L	EuroQol – five dimensions questionnaire
ET	early termination
FACIT	functional assessment of chronic illness therapy
FAS	full analysis set
GGT	gamma-glutamyl transferase
Hgb	hemoglobin
ICH	International Conference of Harmonisation
ITT	intent-to-treat
IV	intravenous
LDH	lactate dehydrogenase
LLN	lower limit of normal
LPO	last patient out
MAA	Marketing Authorization Application
MAR	missing at random
MCMC	Markov chain Monte-Carlo
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Model for Repeated Measures
MNAR	Missing Not At Random
NCMV	Neighboring-Case Missing Value
PD	pharmacodynamics
PGIC	Patient's Global Impression of Change
PGIS	Patient's Global Impression of Severity
PK	pharmacokinetics
PP	per-protocol
PRO	patient-reported outcome
QOL	quality of life
RBC	red blood cell count

SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SF-12	12-Item Short Form Survey
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic-pyruvate transaminase
SLE	systemic lupus erythematosus
SOC	system organ class
TEAE	treatment-emergent adverse event
TLF	tables, figures, and listings
TOEPH	heterogeneous Toeplitz
ULN	upper limit of normal
WBC	white blood cell count

1. INTRODUCTION

This is an open-label, single-arm, multicenter study in patients with primary cold agglutinin disease (CAD) who have hemoglobin (Hgb) level ≤ 10 g/dL and 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 phase (Part B) where they will continue to receive study drug.

This statistical analysis plan contains information pertaining definitions of analysis sets and derived variables, and statistical methods for the analysis of efficacy, safety, pharmacokinetics (PK), and pharmacodynamics (PD) for Part A of the referenced study.

2. DESCRIPTION OF OBJECTIVES AND ENDPOINTS

2.1. Study Objectives

2.1.1. Primary Objective

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

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

2.1.2. Secondary Objectives

The secondary objectives in Part A are

- To assess the effect of BIVV009 on clinical events and laboratory parameters related to hemolysis and anemia in patients with primary CAD
- To assess the effect of BIVV009 on quality of life (QOL) in patients with primary CAD
- To evaluate the overall safety and tolerability of BIVV009 in patients with primary CAD

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

2.2. Study Endpoints

2.2.1. Primary Endpoint

The primary efficacy endpoint is the responder rate defined as follows (Table 2 of protocol):

A patient will be considered a responder if he or she did not receive a blood transfusion from Week 5 through Week 26 (end of treatment [EOT]) and did not receive treatment for CAD 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

2.2.2. Secondary Efficacy Endpoints

The secondary endpoints are as follows:

- Mean change from baseline in bilirubin (excluding patients with Gilbert's Syndrome) at the treatment assessment endpoint (mean of values at Weeks 23, 25, and 26)
- Mean change from baseline in QOL, as assessed by the change in Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue scale scores at the treatment assessment endpoint
- Mean change from baseline in lactate dehydrogenase (LDH) at the treatment assessment endpoint
- Number of transfusions and number of units after the first 5 weeks of study drug administration
- Mean change from baseline in Hgb at the treatment assessment endpoint

2.2.3. Exploratory 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 patient's perception of changes in CAD 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

2.2.4. Safety Endpoints

- Incidence of treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs)
- Change from baseline in clinical laboratory evaluations
- Change from baseline in systemic lupus erythematosus (SLE) panel
- Change from baseline in vital signs
- Change from baseline in electrocardiogram (ECG) data
- Physical examination findings
- Serum disease-related biomarkers
- Incidence of hemolytic breakthrough (rapid fall in Hgb $\geq$ 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 $\geq$ Grade 3 severity (i.e., requiring intravenous [IV] antibiotics)
- Incidence of thromboembolic events

2.2.5. Pharmacokinetic Endpoints

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

2.2.6. Pharmacodynamic Endpoints

- PD Primary Outcome Measure: Wieslab-CP
- Exploratory Complement System Measures: CH_{50}, Total C4, C1q, C1s

3. STUDY DESIGN

3.1. Overall Study Design and Plan

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 CAD, who have Hgb level ≤ 10 g/dL and 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.

The study will enroll 20 primary CAD patients who have a recent history of transfusion, defined as at least 1 transfusion during the last 6 months prior to enrollment. Additionally, patients who withdraw from study early (prior to Week 5) may be replaced.

3.1.1. Study Sample

Subject inclusion and exclusion criteria can be found in Sections 5.1 and 5.2 of the protocol.

3.1.2. Treatment

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 (i.e., Days 21, 35, 49, 63, 77, 91, 105, 119, 133, 147, 161, and 175). 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. Patients who miss a dose (i.e., 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 EOT visit on Day 182 (Week 26).

During the 6-month treatment period, patients will receive a transfusion 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.

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 approximately one year following last patient out (LPO) under Part A.

3.2. Statistical Hypothesis

The study is designed to test the hypothesis whether patients treated with BIVV009 will achieve a response rate greater than 30%. Statistical hypothesis is written as

H_0: response rate ≤ 30%

H_1: response rate > 30%,

where the response rate is the proportion of patients in the intent-to-treat (ITT) population who meet the response criteria defined in Table 2 of the protocol.

Based on discussions with key opinion leaders and experienced clinicians, a response rate of less than 30% is not considered clinically relevant. It is expected that few patients with transfusion dependent primary CAD would meet the responder definition for the primary endpoint without treatment intervention, and as such a null hypothesis of ≤ 30% responder rate for this patient population is reasonable.

3.3. Sample Size Justification

Approximately 20 patients with primary CAD 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% confidence interval (CI) will be at least 30%.

3.4. Randomization and Blinding

This is an open-label study with no blinding or randomization. Despite the nature of the open-label study, the aggregated summary of efficacy endpoints described below will be not be shared with the Sponsor study team until the execution of Part A analysis.

3.5. Interim Analysis

For the purposes of regulatory submission, an interim analysis of safety and efficacy data (Part A analysis) will be performed for Part A after all patients have completed Part A and the data are cleaned. Parts A and B will have separate database locks to enable submission of the BLA/MAA following completion of Part A. Additional analyses of Part B data will be defined in a separate Part B SAP.

Since Part A analysis constitutes the primary analysis of the study hypothesis, no Type I error adjustment is necessary.

4. ANALYSIS POPULATIONS

The following analysis populations are defined for Part A of the study. For the remainder of the SAP, the term "subjects" will be used to refer to patients in the study to keep consistent with the term used within table, figure, and listing (TFL) displays.

4.1. Full Analysis Set (FAS)

The ITT population consists of all subjects who received at least 1 dose (including partial dose) of study drug. All subjects in the ITT population will be included in the Full Analysis Set. Analyses of efficacy will be performed on the FAS. For analysis, FAS and the ITT population are considered exchangeable in the SAP, but the term FAS will be used in subsequent sections of the SAP and TFLs.

4.2. Per-protocol Set

The per-protocol (PP) population is defined as a subset of FAS who do not have any important protocol deviations impacting their efficacy assessments (defined in Section 6.3). Selected efficacy endpoints will be analyzed for the PP Population.

4.3. Safety Analysis Set

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

4.4. PK Analysis Set

Subjects who received at least 1 dose of study drug and have evaluable PK concentrations will be included in PK analysis set.

4.5. PD Analysis Set

All subjects 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.

4.6. Definitions of Subgroups

The following subgroups will be considered for the selected analyses:

- Age (< 65, ≥ 65)
- Gender (Female, Male)
- Baseline weight (< 75 kg, ≥ 75 kg)
- Number of transfusions within 12 months prior to study entry (≤ 2, > 2 -4, > 4)
- Baseline Hgb level (< 8.5 g/dL, ≥ 8.5 g/dL)

- Previous rituximab therapy and/or cytotoxic therapy (Yes, No)

In case of very few subjects (e.g., < 5) in a category, the cutoff value may be changed to suit the distribution of these factors.

5. DEFINITIONS AND DATA HANDLING

Statistical analysis will be performed by Bioverativ, using SAS® version 9.3 or higher and, where appropriate, additional validated software. This SAP is based on protocol Version 5, dated 17 July 2018.

5.1. General Principles

Safety, efficacy, and PK/PD data will be summarized using standard summary statistics for continuous, categorical, and event time data. Data will be summarized for the populations defined. All statistical hypothesis testing will be performed at the 2-sided, 5% significance level, unless otherwise specified. All p-values will be presented to 3 decimal places; p-values less than 0.001 will be presented as "< 0.001", and p-values greater than 0.999 will be presented as "> 0.999". All baseline, efficacy, and safety data, including derived variables at all visits, will be listed.

5.1.1. Definitions

Study Day

Study Day is defined as days relative to the date of first dose of BIVV009, Day 0. In other words, Study Day 1 is Day 0 as defined in the protocol. The start/stop day of events will be calculated as (date of event – date of Study Day 1 + 1) if the date of event is on or after the first dose date, or (date of event – date of Study Day 1) if the date of event is before the first dose date.

Incomplete dates will be imputed for the calculation of study days, unless specified otherwise:

- If missing day only, the start date will be imputed as the first day of the month, while the end date will be imputed as the last day of the month;
- If missing day and month, the start date will be imputed as the first day of the year, while the end date will be imputed as the last day of the year;

Baseline

Baseline measures are defined as the last value prior to the administration of the study drug. If a transfusion occurs during the screening period, the baseline measure must be at least 7 days after the transfusion.

Part A Study Treatment Period

The Part A study treatment period starts at the date of first study drug administration and ends at the date of Week 26 visit if the subject completes Part A study treatment, or at the date of Early Termination (ET)/Safety Follow-up Visit if the subject discontinues the study treatment prior to Week 25.

Visit Windows

Analysis by study visit will utilize the data recorded on the corresponding nominal visit from electronic Case Report Forms (eCRFs). In case of missing data/assessments for a visit, data from an unscheduled visit, or EOT/ET/Safety Follow-up Visit will be used, if the Study Day of such a visit fits in the analytic window defined in Table 1. If multiple values are identified within the analytic window, the one closest to the target study day will be used.

Table 1: Analytic Visit Windows

Visit	Target Study Day	Analytic Visit Window (Study Day)
Baseline (Day 0)	1	≤ 1
Week 1 (Day 7)	8	2 – 15
Week 3 (Day 21)	22	16 – 29
Week 5 (Day 35)	36	30 – 43
Week 7 (Day 49)	50	44 – 57
Week 9 (Day 63)	64	58 – 71
Week 11 (Day 77)	78	72 – 85
Week 13 (Day 91)	92	86 – 99
Week 15 (Day 105)	106	100 – 113
Week 17 (Day 119)	120	114 – 127
Week 19 (Day 133)	134	128 – 141
Week 21 (Day 147)	148	142 – 155
Week 23 (Day 161)	162	156 – 169
Week 25 (Day 175)	176	170 – 179
Week 26 (Day 182; EOT Visit in Part A)	183	180 – 189

Treatment Assessment Timepoint

The value of an assessment (e.g., Hgb) at the treatment assessment timepoint is defined as the average of the values from Week 23, 25, and 26 visits. In the case of any missing value at any of these visits, it will be calculated as the average of the available values, unless no value is available from all three visits.

Solicited Symptomatic Anemia

The severity of CAD symptomatic anemia is defined in Table 2. The severity grading for symptomatic anemia was adopted based on Common Toxicity Criteria for Adverse Events (CTCAE) grades and is collected in eCRFs at every visit.

Table 2: Severity Grade for Symptomatic Anemia Related CAD

CAD Symptomatic Anemia Term	Grade 1	Grade 2	Grade 3	Grade 4
Fatigue	Fatigue relieved by rest	Fatigue not relieved by rest; limiting instrumental ADL	Fatigue not relieved by rest, limiting self-care ADL	Not defined
Weakness	Uneasiness or lack of well being	Uneasiness or lack of wellbeing; limiting instrumental ADL	Not defined	Not defined
Shortness of Breath	Shortness of breath with moderate exertion	Shortness of breath with minimal exertion; limiting instrumental ADL	Shortness of breath at rest; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated
Palpitations, fast heart beat	Mild symptoms; intervention not indicated	Intervention indicated	Not defined	Not defined
Lightheadedness	Not defined	Present (e.g., near fainting)	Not defined	Not defined
Chest Pain	Mild pain	Moderate pain; limiting instrumental ADL	Pain at rest; limiting self-care ADL	Not defined

ADL = activities of daily living

Thromboembolic Events

The thromboembolic events prior to study entry are recorded as medical history in the eCRFs, while thromboembolic events on study are captured as adverse events. Both medical history and adverse events will be coded according to Medical Dictionary for Regulatory Activities (MedDRA) v20.1 or higher.

In general, thromboembolic events may include but are not limited to:

- Any venous events
    - Portal vein obstruction
    - Deep vein thrombosis
    - Pulmonary embolism
    - Mesenteric (abdominal) venous thrombosis

- Any cerebral events
    - Cerebral infarction, occlusion, and stenosis of cerebral and precerebral arteries
    - Vascular syndromes of brain in cerebrovascular diseases, transient cerebral ischemic attacks, and related syndromes
- Any arterial events
    - Myocardial infarction
    - Mesenteric arterial thrombosis
    - Other arterial embolism and thrombosis

Medical review of medical history and AEs will ascertain thromboembolic events for analysis.

Normalization of Bilirubin

The normalization of bilirubin is defined as total bilirubin ≤ upper limit of normal (ULN) (specified by the central lab).

Normalization of LDH

The normalization of LDH is defined as LDH value ≤ ULN (specified by the central lab).

Normalization of Haptoglobin

The normalization of haptoglobin is defined as haptoglobin above the level of detection.

Hemolytic Breakthrough

Hemolytic breakthrough at any visit is defined as

- A decrease of 2 g/dL or more in Hgb from the last scheduled visit, and
- One of the followings:
    - An increase in LDH from the last scheduled visit,
    - An increase in bilirubin from the last scheduled visit, or
    - A decrease in haptoglobin from the last scheduled visit.

Protocol Prohibited CAD Medications

The following concomitant medications are prohibited during the study treatment period in Part A:

- Rituximab alone or as part of combination therapy
- Cytotoxic drugs (such as fludarabine, bendamustine, ibrutinib, cyclophosphamide)
- Other investigational drug

The efficacy endpoint (estimand) accounting for protocol prohibited CAD medication use will be based on the eCRF questionnaire "Did the subject receive any prohibited medications since the last visit?" at post-baseline visits. The medical review for the list of prohibited medications will be reconciled with the eCRF questionnaire.

5.1.2. Pooling Sites for Analysis

Data from all investigational sites will be pooled for the analysis, unless specified otherwise.

5.1.3. Estimands

Following International Conference on Harmonisation (2014) and National Research Council (2010), the following estimands are considered for efficacy endpoints to provide clarity of what to be estimated and its connection to the trial objectives. Akacha, et. al. (2017) proposed a framework for defining an estimand using three attributes:

- The population of interest;
- The variable to be used for the clinical question, which consists of measurements at a specific timepoint. It could be a composite endpoint that incorporates post-randomization events.
- The measure of intervention effect, which accounts for potential effects of post-randomization events.

A composite estimand will be used for the primary endpoint and a hypothetical estimand will be used for lab parameter defined secondary endpoints. Alternative estimands are also proposed to either assist the interpretation of primary estimand or used for exploratory endpoints.

Composite Estimand

- Population: FAS
- Variable: A composite endpoint: endpoint response criteria, and remain in the study through at least Week 23 visit (i.e., patients who discontinued the study participation prior to Week 23, including those who discontinued prior to Week 5, are considered non-responder)
- Measure of Intervention Effect: Proportion of subjects who respond according to the variable definition

Hypothetical Estimand

- Population: FAS

- Variable: Change from baseline at treatment assessment timepoint (Weeks 23, 25, and 26), where any post-baseline value after transfusion and prohibited medication (from Week 5 to Week 26) is considered missing

- Measure of Intervention Effect: Mean change from baseline, had transfusion and prohibited medications not been available

De-Facto Estimand

- Population: FAS

- Variable: Change from baseline at treatment assessment timepoint (Weeks 23, 25, and 26)

- Measure of Intervention Effect: Mean change from baseline, irrespective of transfusion or prohibited medications

Observed Estimand

- Population: a subset of FAS, subjects who remain in the study through at least the visit of interest (e.g., Week 23) and have at least 1 evaluable parameter or score at target visits.

- Variable: Change from baseline at the visit of interest, or response at the visit of interest

- Measure of Intervention Effect: Mean change from baseline or proportion of subjects who respond, irrespective of transfusion or prohibited medications

5.1.4. Handling of Missing Data

Best efforts will be utilized to minimize missing values. If a subject discontinues study treatment early, the subject will be asked to complete study assessments at EOT/safety follow up visit.

For the primary endpoint, which is a composite endpoint of avoidance of transfusion and improvement of Hgb at the treatment assessment timepoint (i.e., Weeks 23, 25, and 26), missing either component results in a missing value for the endpoint. The improvement of Hgb at the treatment assessment timepoint is missing only if no Hgb value is available for all 3 visits (Weeks 23, 25, and 26). Since pre-treatment Hgb is a key requirement to enroll in the study, it is reasonable to assume that all enrolled subjects have at least 1 Hgb prior to the study treatment, which constitutes the baseline Hgb value (see Section 5.1.1).

For the primary analysis of the primary endpoint, the composite estimand is utilized. Hence, a missing value will be considered a non-response. Other sensitivity analyses specified in Section 7.2.2 will be performed to evaluate the impact of missing values, when appropriate. However, other responder-type endpoints will be analyzed using observed data only.

For the analysis of continuous variables (e.g., secondary endpoints), summary statistics will be computed based on observed data. To analyze lab parameter (e.g., Hgb, bilirubin, LDH) changes attributable to the study treatment (hypothetical estimand), values post any transfusion (after Week 5) or protocol prohibited CAD treatment (defined in Section 5.1.1, after Week 5) will be

censored. The mean change from baseline will be estimated using Mixed Model for Repeated Measures (MMRM) along with its 95% CIs. Multiple Imputation will also be used to estimate the mean change from baseline at treatment assessment timepoint and its associated 95% CI. All these analyses assume missing at random (MAR).

Although the assumption of MAR cannot be verified, the mechanism of missing data due to transfusion or prohibited medication use described below supports such an assumption.

- The protocol (Table 1) specifies the transfusion criteria, which is comprised of the Hgb level.
- Despite the use of prohibited medications not being allowed by the protocol, the potential need for the use of rituximab and/or combination therapy would be mostly due to the lack of response or hematologic breakthrough, which is specified in the protocol by changes in the level of Hgb and other hemolytic markers.

Therefore, the missing data due to the occurrence of transfusion and prohibited medication use is expected to be triggered by low levels of Hgb and other hemolytic markers, which are observable. Because of this mechanism, it is reasonable to assume that the probability of missing data due to transfusion or prohibited medication use is a function of the observed Hgb or other hemolytic marker levels; hence, supports the assumption for MAR.

Additional sensitivity analyses, specified in the particular endpoints, may be carried out to examine the validity of the assumption of MAR. Multiple imputation based on models compatible with Missing Not At Random (MNAR) missing mechanism may be used, where missing values at treatment assessment visit will be imputed by using Neighboring-Case Missing Value (NCMV) restriction. Certain adjustment may be needed for NCMV approach due to the small sample size, where there may be lack of neighboring cases.

Supportive analysis based on de-facto estimand will also be performed using MMRM to estimate the mean change from baseline along with its 95% CIs.

For a QOL endpoint, in the event of missing data, the total score will be estimated according to the provision for missing domains in the calculation algorithm of the score. For example, if a subject has missing data in questionnaires at a visit, the prorated FACIT-F score will be calculated, if more than 50% of items (a minimum of 7 out of 13 items) are available. Otherwise, the score is missing.

For exploratory endpoints, observed estimands will be used unless specified otherwise.

5.1.4.1. Mixed-effect Model for Repeated Measures

For normally distributed continuous efficacy endpoints (e.g., lab parameters), a MMRM will be used for the analysis of such endpoints at study visits (including the treatment assessment time points). The MMRM model will include the baseline value of the endpoint and visit. A heterogeneous Toeplitz (TOEPH) covariance matrix within a subject will be used. For the endpoint at the treatment assessment time points (average of Weeks 23, 25, and 26), the estimate will be calculated as the mean of MMRM estimates at Week 23, 25, and 26 visits.

Normality assumptions will be checked using graphical methods. In the event of non-normality, alternative methods will be proposed as an addendum to the SAP prior to the Part A DBL.

The pseudo SAS code for MMRM is as follows:

```
Proc mixed data=(ADaM dataset) method=reml;
   class usubjid visit;
   model chg = base visit / ddfm = kenwardroger solution;
   repeat visit / type=TOEPH subject=usubjid;
   estimate 'treatment assessment timepoint' visit 0 0 0 0 0 0 0
0 0 0 0 0 0.333 0.333 0.333/cl;
run;
```

5.1.4.2. Multiple Imputation

The following multiple imputation procedure will be used for continuous endpoints. The regression method with monotone missing patterns will be used for the imputation step (implemented by SAS PROC MI, according to Rubin 1987, pp. 166–167). The pseudo SAS code is provided to substantiate the details of the statistical approach. It does not represent runnable SAS codes for the execution of the analysis, as adjustment to the code is necessary to accommodate the data structure, variable names, and test runs.

1. For endpoints with non-monotone missing data patterns, a Markov chain Monte-Carlo (MCMC) method will first be used to fill in the intermittent missing values.

   The pseudo SAS code is as follows, when the input dataset is structured such that variables chg1 - chg11 represent change from baseline at visit Week 1 (Day 7), Week 3, Week 5, Week 7, Week 9, Week 11, Week 13, Week 15, Week 17, Week 19, Week 21, and variable chg_ta represents change from baseline at treatment assessment timepoint:

   ```
   PROC MI data=dat_in seed=1234 SIMPLE NIMPUTE=1 ROUND=1
   OUT=dat_mon;
      MCMC IMPUTE=monotone;
      VAR chg1 - chg11 chg_ta;
   RUN;
   ```

2. Missing values will be imputed as the predicted value from a regression model including explanatory variables of the number of transfusions within 6 months prior to study entry (*ntrans*), the value of the same endpoint at baseline (*base*), and change from baseline at all of the previous scheduled visits. The imputation process may be repeated sequentially starting from the earliest visit with missing value (e.g., Day 7) through the treatment assessment timepoint. The forgoing process will be repeated multiple times (i.e., B=100) to generate B imputed datasets.

   The pseudo SAS code is as follows:

   ```
   PROC MI DATA = dat_mon SEED=4321 NIMPUTE=100 out=mi_mvn SIMPLE;
      VAR base ntrans chg1 - chg11 chg_ta;
      MONOTONE METHOD=REG;
   ```

```
RUN;
```

3. The endpoint of interest (e.g., change from baseline at treatment assessment time points) will be estimated for all B complete datasets.

   The pseudo SAS code as follows:

```
PROC MEANS DATA = mi_mvn out=mi_mvn;
   VAR chg_ta;
   By _IMPUTATION_;
ods output statistics=mi_ests;
RUN;
```

4. The method of Rubin 1987 will be used to combine B estimates for the overall estimate and its 95% CI.

   The pseudo SAS code is as follows:

```
PROC MIANALYZE DATA = mi_ests;
  MODELEFFECTS mean;
  STDERR;
  ods output ParameterEstimates=est;
run;
```

5.2. Data Summaries

5.2.1. Continuous Variables

Continuous variables will be summarized using descriptive statistics including the number of non-missing values (n), mean, standard deviation (SD), median, minimum, and maximum. Where specified in the table shells, the 25th and 75th percentiles will also be provided. Means, medians, and the 25th and 75th percentiles will be presented to one decimal place beyond that with which the data were captured. SDs will be presented to two decimal places beyond that with which the data were captured. Minimum and maximum will be displayed to the same number of decimal places as that with which the data were captured.

Unless impractical within a given table, statistics will be aligned by the decimal place (or assumed decimal place) in the summary tables.

5.2.2. Categorical Variables

Categorical variables will be summarized by counts and percentages. All percentages will be rounded to one decimal place. The percentage will be suppressed when the count is zero. Unless specified otherwise, the denominator for all percentages will be the number of subjects with non-missing data for a given summarization. This number (n) will be included with categorical summaries unless the same variable is also being summarized with descriptive statistics, in which case 'n' will already be provided.

5.2.3. Event Time Variables

Time-to-event variables will be summarized using Kaplan-Meier estimate over time, along with median time to event and probability of an event at specific time points. Partial dates will not be imputed, hence considered unknown. In general, for subjects who do not experience the event, the time-to-event will be censored at the study day of last assessment within a study period (Part A or Part B).

6. STUDY SUBJECTS

6.1. Disposition of Subjects

Subject disposition will be summarized including the number of subjects in the Safety Analysis Set, FAS, PP Set, PK Analysis Set, and PD Analysis Set. The number of subjects with the status of completed, and discontinued study treatment early, including the primary reason for those who discontinued, will be tabulated for Part A. Subject disposition, including the date of the last visit and the reason for early termination for subjects who did not complete the study treatment, will be provided in a data listing.

The number and percentage of subjects attending each visit will be summarized by planned visits for the FAS.

6.2. Demography and Baseline Disease Characteristics

Demographics and baseline disease characteristics will be summarized for FAS.

6.2.1. Demography

Demographic characteristics including age (years), age category (<65, >=65), gender, race, ethnicity, country, geographic location, height (cm), weight (kg), weight category (<75 kg, >=75kg) and body mass index (kg/m^2) will be summarized. Geographic locations are defined as Europe, North America, Asia/Japan and other.

6.2.2. General Medical History

A summary of the medical history by system organ class (SOC) and preferred term for FAS will be presented. A subject will be counted only once if they reported one or more occurrences in the SOC and preferred term.

A summary of prior hematological malignancy within the last 5 years and prior thromboembolic history within the last 1 year will be presented.

6.2.3. Baseline Disease Characteristics

Screening and baseline lab parameters, including hematology (such as Hgb, bilirubin, LDH), Gilbert's Syndrome testing, bone marrow biopsy results, and DAT panel, will be summarized based on the FAS. Prior transfusion history (e.g., number of transfusions within 6 months and 12 months of study entry) will also be summarized.

Summaries of prior CAD therapies within the last 5 years, severity of anemia symptoms, and other CAD related diseases characteristics (e.g., presence of acrocyanosis, Raynaud’s syndrome, hemoglobinuria, disabling circulatory symptoms, and major adverse vascular events) within 3 months of screening will be presented.

Proportion of subjects who had documented vaccines within 5 years and who have received vaccination during the study will be summarized. The vaccines include meningococcal vaccine, S. pneumoniae vaccine, and H. influenza vaccine.

6.3. Protocol Deviations

All protocol deviations will be recorded throughout the study. Major and minor protocol deviations/violations are to be pre-specified prior to database lock. All major protocol deviations will be summarized for the FAS. All deviations, both major and minor, will be provided in a data listing.

Important protocol deviations (within Part A study treatment period) impacting efficacy assessment are defined as any of the following:

- Not meeting eligibility inclusion criteria #3,
- Missing at least 2 consecutive doses or 3 intermittent doses,
- Received protocol prohibited CAD treatment (Section 5.1.1),
- Free of transfusion after Week 5 but missing study assessments at all three visits of Weeks 23, 25, and 26.

Important protocol deviations will be summarized. Subjects who have had any of the important protocol deviations will be excluded from the PP population.

6.4. Non-study Drug Medications

6.4.1. Concomitant Medications

Prior medications are those taken before the first dose of study drug. Concomitant medications are those administered on or after the first dose of study drug, or those administered before the first dose that are ongoing when study treatment begins. Prior and concomitant medications will be coded using World Health Organization drug enhanced dictionary (March 2017 version or higher) and summarized using the FAS.

Separate tables will be generated to summarize prior CAD medical treatment, concomitant CAD medical treatment, and protocol prohibited CAD treatment.

6.4.2. Other Therapies and Procedures

All other therapies received during the study (whether for CAD or other condition) will be summarized for the FAS and listed.

6.5. Study Drug

Study drug exposure and compliance will be summarized using the Safety Analysis Set. Subject-level information on dosing with study drug will also be provided in a data listing.

6.5.1. Exposure

Study drug exposure, measured by the duration of study treatment, number of administrations, and total actual BIVV009 dose, will be summarized for the Safety Analysis Set.

The duration of the study treatment (in weeks) in Part A is defined as:

- (date of Week 26 visit – date of first dose + 1)/7, if a subject enrolls into Part B;
- (date of last dose – date of first dose + 15)/7, if a subject discontinues study treatment early in Part A or does not enroll into Part B.

The actual dose administered at each visit is calculated as:

(Total volume administered / Total volume prepared) * assigned dose.

The total BIVV009 dose is the summation of all actual dose administered in Part A.

6.5.2. Compliance

Study drug compliance for a subject is measured by the percent of number of doses received out of the number of protocol specified doses. For example, for a subject who completes Part A treatment, the number of protocol specified doses is 14. The compliance of the subject will be the number of doses received divided by 14 expressed in percentage. For a subject who discontinues early in Part A, the number of protocol specified doses is the number of scheduled doses prior to the date of discontinuation. The proportion of subjects whose compliance is less than 80%, 80% – < 100%, and ≥ 100% will also be summarized. In addition, the number of subjects and number of doses administered out of study windows and number of partial infusion doses will also be summarized.

7. EFFICACY ANALYSIS

7.1. General Efficacy Principles

Unless specified otherwise, all analyses described will be performed for Part A.

7.1.1. Multiplicity

The study hypothesis described in Section 3.2 will be tested at a 1-sided significance level of 0.025. No other formal hypothesis will be tested, as secondary endpoints will be estimated along with associated 95% CIs.

7.2. Primary Endpoint

The primary endpoint, defined in Section 2.2.1, is a composite endpoint of the following components:

1. Free of post-baseline transfusion within the range of Week 5 and Week 26 visit dates;
2. Hgb at treatment assessment timepoint >= 12 g/dL, or the change from baseline at treatment assessment >= 2 g/dL,
3. Receive no protocol prohibited medications defined in Section 5.1.1.

Components 1 and 3 will be determined by the corresponding questions in eCRF at all visits (from Week 5 through Week 26) in Part A.

To be evaluable for each of the components, a subject must be observed through at least Week 23 visit. Discontinuation of study treatment prior to Week 23 visit will result in an unknown status for Components 1 and 3. Missing Hgb value at all visits of Week 23, 25, and 26 will result in an unknown status for Component 2.

In the event of unknown status in any of the components, a subject may be a responder, non-responder, or missing for the response status. A subject is considered responder, if the subject meets all of the three components; a subject is considered a non-responder, if the subject is known to not meet any of the three components; otherwise, a subject is considered missing in response status.

7.2.1. Primary Analysis

The primary analysis of the primary endpoint involves the composite estimand (Section 5.1.3), for which **any missing response (above) will be considered a non-responder**. The proportion of subjects who respond according to the estimand (Table 3) will be estimated along with a 95% exact Clopper-Pearson CI.

To reject the null hypothesis of the response rate <= 30%, the lower bound of the 95% CI must be greater than 30%.

In addition, the proportion of subjects who meet each of the response criteria will be summarized.

7.2.2. Sensitivity Analyses

Sensitivity analyses will be carried out based on the completer estimand and the per-protocol estimand (defined in Table 3). The proportion of subjects with treatment response will be summarized along with the 95% exact Clopper-Pearson CI.

Table 3: Estimands for Primary Endpoint

	Composite Estimand	Completer Estimand	Per-protocol Estimand
Population	FAS	A subset of FAS with those who complete treatment at least through Week 23 and have at least 1 evaluable Hgb from Week 23, 25, and 26	A subset of FAS with those who are free of important protocol deviations defined in Section 6.3
Response Variable	Responder if • Free of post-baseline transfusion within the range of Week 5 and Week 26 visit dates, and • Hgb at treatment assessment timepoint >= 12 g/dL, or the change from baseline at treatment assessment >= 2 g/dL, and • Receive no protocol prohibited medications defined in Section 5.1.1 within the range of Week 5 and Week 26 visit dates, and • Remain in study through at least Week 23, and • At least 1 evaluable Hgb from Weeks 23, 25, and 26	Responder if • Free of post-baseline transfusion within the range of Week 5 and Week 26 visit dates, and • Hgb at treatment assessment timepoint >= 12 g/dL, or the change from baseline at treatment assessment >= 2 g/dL, and • Receive no protocol prohibited medications defined in Section 5.1.1 within the range of Week 5 and Week 26 visit dates	Responder if • Free of post-baseline transfusion within the range of Week 5 and Week 26 visit dates, and • Hgb at treatment assessment timepoint >= 12 g/dL, or the change from baseline at treatment assessment >= 2 g/dL
Treatment effect	Proportion of subjects who achieve the composite response variable (defined above)	Proportion of subjects who achieve the treatment response	Proportion of subjects who achieve the treatment response

In the case when there are at least 2 subjects who discontinue study participation prior to Week 5, a supportive analysis, similar to the primary analysis, will be performed by excluding those subjects who discontinue prior to Week 5.

In the case of normal ranges (LLN) varying across local labs, a sensitivity analysis will be performed for the primary endpoint by qualifying normalization of Hgb using >= LLN, instead of >= 12 g/dL.

7.2.3. Subgroup Analyses

The proportion of subjects with response according to the composite estimand will be summarized for subgroups defined in Section 4.6 along with its 95% exact CI. The consistency of the response rates among these sub-populations will be examined by forest plots.

7.3. Secondary Endpoints

7.3.1. Mean Change from Baseline in Bilirubin at the Treatment Assessment Timepoint

The change from baseline in bilirubin at the treatment assessment timepoint will be analyzed for FAS excluding subjects with Gilbert's syndrome. Gilbert's syndrome status is determined by the result of the genetic test at screening. If the result of Gilbert's syndrome test is not available for a patient, the patient will be excluded from the analysis. The primary analysis will be performed according to Hypothetical Estimand (defined in Section 5.1.3), while a sensitivity analysis will be done via De-facto Estimand (Section 5.1.3). Additional details are found in Table 4.

Table 4: Estimands for Change from Baseline in Bilirubin

	Hypothetical Estimand	De-facto Estimand
Population	FAS excluding subjects with Gilbert's syndrome	FAS excluding subjects with Gilbert's syndrome
Variable	Change from baseline at treatment assessment time point, where any value after transfusion and prohibited medication is considered missing	Change from baseline at treatment assessment time point
Treatment effect	Mean change from baseline, if transfusion or prohibited medications had not been available	Mean change from baseline, irrespective of transfusion or prohibited medication use

For either estimand, the mean change from baseline in bilirubin at treatment assessment timepoint, along with its 95% CI, will be estimated by the MMRM model (Section 5.1.4.1).

If the number of subjects with unknown Gilbert's syndrome status is greater than 2, additional sensitivity analysis will be performed to include such subjects (unknown Gilbert's syndrome), whose baseline total bilirubin level is low to be considered less indicative of Gilbert's syndrome.

Additional sensitivity analysis based on multiple imputation (Section 5.1.4.2) will be carried out for the Hypothetical Estimand, utilizing the regression method with monotone missing patterns. Specifically, the following 4 imputation models will be considered:

- Change from baseline in bilirubin at treatment assessment timepoint is modeled as a function of baseline bilirubin value, weight stratum (< 75 kg, >= 75 kg), and bilirubin values from Day 7 through visits Week 21, visits prior to first transfusion, or visits prior to first prohibited medication use, whichever occurs first;

- Change from baseline in bilirubin at treatment assessment timepoint is modeled as a function of baseline bilirubin value, weight stratum (< 75 kg, >= 75 kg), and bilirubin values from Day 7 through visits Week 21, 2nd last visit prior to first transfusion, or visits prior to first prohibited medication use, whichever occurs first;

- Change from baseline in bilirubin at treatment assessment timepoint is modeled as a function of baseline bilirubin value, weight stratum (< 75 kg, >= 75 kg), and bilirubin values from Week 5 through visits Week 21 (observed value through visits prior to first transfusion, or visits prior to first prohibited medication use, whichever occurs first).

- Change from baseline in bilirubin at treatment assessment timepoint is modeled as a function of baseline bilirubin value, weight stratum (< 75 kg, >= 75 kg), and bilirubin values from Day 7 through visits Week 21 (observed value through visits prior to first transfusion, or visits prior to first prohibited medication use, whichever occurs first); but with NCMV restrictions.

7.3.2. Mean Change from Baseline in FACIT-F Score at Treatment Assessment Timepoint

The change from baseline in FACIT-F score at the treatment assessment timepoint will be analyzed for the FAS. The derivation of FACIT-F score is detailed in Section 7.5. The primary analysis will be performed according to Hypothetical Estimand (defined in Section 5.1.3), while a sensitivity analysis will be done via De-facto Estimand (Section 5.1.3). Additional details are found in Table 5.

Table 5: Estimands for Change from Baseline in FACIT-F Score

	Hypothetical Estimand	De-facto Estimand
Population	FAS	FAS
Variable	Change from baseline at treatment assessment time point, where any value after transfusion and prohibited medication is considered missing	Change from baseline at treatment assessment time point
Treatment effect	Mean change from baseline, if transfusion or prohibited medications had not been available	Mean change from baseline, irrespective of transfusion or prohibited medication use

For either estimand, the mean change from baseline in FACIT-F score at treatment assessment timepoint, along with its 95% CI, will be estimated by the MMRM model (Section 5.1.4.1).

Additional sensitivity analyses for hypothetical estimand, similar to those specified for bilirubin, will be performed for the change from baseline in FACIT-F score at treatment assessment timepoint.

7.3.3. Mean Change from Baseline in Lactate Dehydrogenase (LDH) at the Treatment Assessment Timepoint

The change from baseline in LDH at the treatment assessment timepoint will be analyzed for the FAS. The primary analysis will be performed according to Hypothetical Estimand (defined in Section 5.1.3), while a sensitivity analysis will be done via De-facto Estimand (Section 5.1.3). Additional details are found in Table 6.

Table 6: Estimands for Change from Baseline in LDH

	Hypothetical Estimand	De-facto Estimand
Population	FAS	FAS
Variable	Change from baseline at treatment assessment time point, where any value after transfusion and prohibited medication is considered missing	Change from baseline at treatment assessment time point
Treatment effect	Mean change from baseline, if transfusion or prohibited medications had not been available	Mean change from baseline, irrespective of transfusion or prohibited medication use

For either estimand, the mean change from baseline in LDH at treatment assessment timepoint, along with its 95% CI, will be estimated by the MMRM model (Section 5.1.4.1).

Additional sensitivity analyses for hypothetical estimand, similar to those specified for bilirubin, will be performed for the change from baseline in LDH at treatment assessment timepoint.

Additional descriptive analyses will be performed for LDH isoforms.

7.3.4. Number of Transfusions and Number of Units after the First 5 Weeks of Study Drug Administration

The number of transfusions after Week 5 through Week 26 visits will be summarized for the FAS, where the observed data will be used for subjects who discontinue study treatment early in Part A. The number of units transfused during the same period of time will be summarized for subjects who receive at least 1 transfusion.

The transfusions occurring during the first 5 weeks will be listed.

7.3.5. Mean Change from Baseline in Hgb at the Treatment Assessment Timepoint

The change from baseline in Hgb at the treatment assessment timepoint will be analyzed for the FAS. The primary analysis will be performed according to Hypothetical Estimand (defined in

Section 5.1.3), while a sensitivity analysis will be done via De-facto Estimand (Section 5.1.3). Additional details are found in Table 7.

Table 7: Estimands for Change from Baseline in Hgb

	Hypothetical Estimand	De-facto Estimand
Population	FAS	FAS
Variable	Change from baseline at treatment assessment time point, where any value after transfusion and prohibited medication is considered missing	Change from baseline at treatment assessment time point
Treatment effect	Mean change from baseline, if transfusion or prohibited medications had not been available	Mean change from baseline, irrespective of transfusion or prohibited medication use

For either estimand, the mean change from baseline in Hgb at treatment assessment timepoint, along with its 95% CI, will be estimated by the MMRM model (Section 5.1.4.1).

Additional sensitivity analyses for hypothetical estimand, similar to those specified for bilirubin, will be performed for the change from baseline in Hgb at treatment assessment timepoint.

7.4. Exploratory Endpoints

7.4.1. Part A Exploratory Endpoints

The analysis of exploratory endpoints (listed in Section 2.2.3) will be based on Observed Estimand (Section 5.1.3). Additionally, summary of hemolytic parameters (Hgb, bilirubin, LDH, haptoglobin, and reticulocyte) over visit is added to the SAP to examine the time trend of the improvement. Unless specified below, the endpoints will be summarized by visit for continuous and categorical variables, and for time to event variables (e.g., time to obtain Hgb level of ≥ 12 g/dL) for the entire Part A.

7.4.1.1. Continuous Endpoints

The continuous endpoints include:

- Mean change from baseline in QOL, as assessed by the change in the five level EQ-5D-5L scores at the treatment assessment endpoint and by visit
- 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 and by visit
- Mean change from baseline in hemolytic parameters (Hgb, total bilirubin, LDH, haptoglobin, and absolute reticulocyte) by visit
- Mean change from baseline in FACIT-F by visit (see Section 7.5.1)

The endpoints by visit will be summarized for FAS according to Section 5.2.1.

7.4.1.2. Response Endpoints

The response endpoints include:

- Incidence of solicited symptomatic anemia at EOT
- Incidence of thromboembolic events after the first 5 weeks of study drug administration
- Proportion of subjects with Hgb level of ≥ 12 g/dL at the treatment assessment endpoint
- Proportion of subjects normalizing haptoglobin at the treatment assessment endpoint
- Proportion of subjects normalizing bilirubin at the treatment assessment endpoint
- Proportion of subjects normalizing LDH at the treatment assessment endpoint
- PGIC and change from baseline in PGIS to assess subject's perception of changes in CAD disease burden at last scheduled visit of Part A
- Incidence of disabling circulatory symptoms at last scheduled visit of Part A
- Proportion of subjects normalizing Hgb (>= 12 g/dL) by visit
- Proportion of subjects achieving 2 g/dL increase in Hgb by visit
- Proportion of subjects normalizing bilirubin by visit
- Proportion of subjects normalizing LDH by visit
- Proportion of subjects normalizing haptoglobin by visit

The endpoints will be summarized for FAS according to Section 5.2.2.

7.4.1.2.1. Incidence of Solicited Symptomatic Anemia

Incidence of solicited symptomatic anemia will be summarized by visit descriptively using the FAS. The summaries will be based on observed data only. Proportion of subjects with improvement in anemia symptoms will be summarized by visit. The improvement is defined as at least 1 grade reduction in at least 1 symptom, and no worsening in other remaining symptoms. In addition, proportion of subjects with at least 1 grade decrease will be summarized for each anemia symptom by visit.

7.4.1.2.2. Incidence of Thromboembolic Events after the First 5 Weeks of Study Drug Administration

The adverse event data will be reviewed by internal medical staff to identify all thromboembolic events reported. The detailed listing for all events will be provided including date (study day) of onset, verbatim terms of the event, and the flag whether the event occur after first 5 weeks of study drug administration.

Incidence of thromboembolic events will be calculated as the total number of thromboembolic events after the first 5 weeks of study drug administration divided by the total subject-year of time for observation (i.e., time from Week 5 through Week 26 or EOT visit for subjects who discontinue early). All events from Week 5 through Week 26 or EOT visit for subjects who discontinue early will be included. A 95% exact CI will be provided.

Anti-coagulation medication use will be reviewed and identified based on reported concomitant medications, and will be summarized.

7.4.1.3. Time-to-Event Endpoints

Time-to-event endpoints include:

- Time to first transfusion after the first 5 weeks of study drug administration
- Time to first transfusion (including those in the first 5 weeks of study drug administration)
- Time to first normalization of bilirubin
- Time to first normalization of LDH
- Time to first normalization of haptoglobin
- Time to first normalization of Hgb level (≥ 12 g/dL)
- Time to first achieving 2 g/dL increase in Hgb level
- Time to first achieving 2 g/dL increase or normalization of Hgb level (≥ 12 g/dL)

The endpoints will be analyzed for FAS according to Section 5.2.3. For subjects who receive a transfusion after Week 5, the time to normalization of lab parameters above will be censored at the time of transfusion.

7.4.2. Part B Exploratory Endpoints

A separate SAP will be developed for Part B of the study.

7.5. Endpoints Based on Patient-reported Outcomes

The FACIT-Fatigue, the EQ-5D-5L, the SF-12, and the PGIC will be utilized in this study. For continuous variables, the overall score and its change from baseline will be analyzed descriptively for each time point.

When applicable missing items will be handled based on the specific patient-reported outcome (PRO) instrument. Subjects missing baseline evaluations would not be included in the PRO analyses.

7.5.1. Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue Scale

The questionnaires will be analyzed according to the recommendations of the questionnaire authors (see http://www.ser.es/wp-content/uploads/2015/03/FACIT-F_INDICE.pdf). Details of the questionnaire and its algorithm for deriving the score are provided in Appendix A. The questionnaires are considered complete, and the subscale total score can be calculated, if at least 7 of the 13 items were answered by the subject. For each time point, the number and percentage of subjects who complete the questionnaires will be summarized.

The change from baseline in FACIT-F score will be summarized by visit for the FAS.

7.5.2. EQ-5D-5L

The questionnaire will be analyzed according to the recommendations of the authors (see www.euroqol.org). EQ-5D consists of 2 pages – a 5 dimension descriptive system and the EQ visual analogue scale. A copy of the questionnaire is provided in Appendix B.

The descriptive system contains 5 categories: mobility, self-care, usual activities, pain/ discomfort and anxiety/depression. The number and percentage of subjects in each response category were tabulated for the FAS. Percentages are based on the number of subjects for whom an assessment is provided at the respective visit.

The EQ visual analogue scale is a visual scale from 0–100 to record a respondent's overall self-rated health state. The respondent is asked to mark an "X" on the scale then record the corresponding number; 0 refers to the worst possible health state, 100 refers to the best possible health state. This will also be presented alongside the 5 dimension descriptive system scores.

The EQ visual analogue scale will be summarized for the observed response and change from baseline for the FAS.

EQ-5D Index Score

The EQ-5D-5L descriptive system can be converted into a single index value, the EQ-5D index score, by using the "EQ-5D-5L Crosswalk Index Value Calculator" provided by the authors (documents and calculation tools will be downloaded from the EuroQol website). The index scores, derived as country specific, are a major feature of the EQ-5D instrument, facilitating the calculation of quality-adjusted life years (QALYs) that are used to inform economic evaluations of health care interventions.

The derived EQ-5D index scores and change from baseline will be summarized by visit for the FAS.

7.5.3. 12-Item Short Form Survey (SF-12)

The questionnaire will be analyzed according to the recommendations of the authors (see http://campaign.optum.com/optum-outcomes/what-we-do/health-surveys/sf-12v2-health-survey.html). The SF-12 v2 is a 12-item measure, derived from the original 36-item SF-36, which includes eight (8) health domains which are used to generate a physical component score as well as a mental component score. Each score ranges from 0–100 on a normative scale and may be used to derive a health utility index (SF-6D). A copy of the questionnaire is provided in Appendix C.

The derived scores and change from baseline for the 8 health domains, the physical component score, and the mental component score, will be summarized by visit for the FAS.

7.5.4. Patient Global Impression of Change (PGIC)

The questionnaire (listed in Appendix D) will be summarized as an ordinal variable by visit for the FAS.

7.5.5. Patient's Global Impression of [Fatigue] Severity

The change from baseline in questionnaire (listed in Appendix E) will be summarized as an ordinal variable by visit for the FAS.

7.5.6. Healthcare Resource Utilization

The number of healthcare visits by type (office visit, hospital ER visit, hospitalization, and ICU stay) will be collected and presented in a listing.

8. SAFETY ANALYSIS

Safety data will be summarized for subjects in Safety Analysis Set defined in Section 4.3. The summary tables may also be presented by subgroup based on the baseline weight strata (i.e., BIVV009 dose cohorts). However, the limited number of subjects in each dose cohort and non-randomized assignment preclude a direct comparison between the two dose cohorts.

8.1. Adverse Events

AEs will be classified using the MedDRA system organ classes and preferred terms. MedDRA version 20.1 or higher will be used throughout the study.

In general, AEs will be analyzed based on *incidence*, defined as the proportion of subjects who had at least one occurrence of an event out of the number of subjects in the Safety Analysis Set. An adverse event listing will be provided that will include all adverse events reported with the onset and resolution study days relative to Day 0 (Study Day 1).

All summary table analyses will only include treatment-emergent adverse events unless noted otherwise. The algorithm for the determination of treatment emergence when an onset date is partially or completely missing is described below.

- If the onset time of an adverse event (if time is collected) is missing and the date of onset is the date of dosing, the AE is considered to be a TEAE.
- If the onset day of an adverse event is missing and the month and year of the onset of the AE are either the same or later than the month and year of the first treatment, the AE will be considered a TEAE. If the month and year of the onset of the AE precede the month and year of the first treatment, the AE will not be considered a TEAE.
- If the onset month of an adverse event is missing and the year of the onset of the AE is either the same as or later than the year of first treatment, then the AE will be considered a TEAE. If the year of AE onset precedes the year of first treatment, the AE will not be considered a TEAE.
- If the onset day, month, and year of an adverse event are missing, the AE will be considered to be a TEAE.
- If start date is partial but the stop date can be determined to be before the start of the first dose of study drug, then the AE will not be considered a TEAE.

Unless specified otherwise, system organ classes and preferred terms within each SOC will be presented alphabetically. For the purpose of summarization, a subject is counted once in a SOC or preferred term if the subject reported one or more events in that SOC or preferred term. Unless specified otherwise, percentages will be based on the number of subjects in the Safety Analysis Set.

8.1.1. Overall Summary of Adverse Events

An overall summary of TEAEs will be provided which tabulates the number and percentage of subjects who experienced a TEAE, related TEAE, treatment-emergent SAE, treatment-emergent

related SAE, treatment-emergent Grade 3 or higher AE, or TEAE infections of Grade 3 or higher severity; the number and percentage of subjects who had a TEAE within 24 hours of the start of infusion; the number and percentage of subjects who discontinued treatment and/or the study due to an AE; and the number and percentage of subjects who died.

8.1.2. Treatment-emergent Adverse Events

The incidence of TEAEs will be summarized by SOC and preferred term.

8.1.2.1. Adverse Events in Descending Order of Incidence

A table will be provided which displays TEAE preferred terms in descending order of incidence. Only preferred terms will be included in this table (i.e., the display will not include SOCs).

A similar table will be provided for Grade 3 or higher TEAEs. AEs for which the assessment of severity is missing will be included in this table in the TEAE grade 3 or higher category.

8.1.2.2. Severity of Adverse Events

AEs are classified by the Investigator for CTCAE grades v4.03. A summary of TEAEs by system organ class, preferred term, and CTCAE grade will be presented. AEs with a missing severity will be excluded from this table and listed separately to supplement the summary table. A subject will be counted once for each SOC and preferred term based on the greatest severity within that SOC and preferred term, respectively.

8.1.2.3. Relationship of Adverse Events to Study Drug

AEs are classified by the Investigator for relationship to study drug ("Unrelated," "Possible," and "Probable"). For summary tables, an AE with relationship of "Possible" or "Probable" will be considered "Related." A summary of TEAEs by SOC, preferred term, and relationship ("Related" or "Unrelated") will be presented. AEs with a missing relationship will be counted as "Related" in the summary table. A subject will be counted once for each SOC and preferred term based on the highest relationship within that SOC and preferred term, respectively.

8.1.3. Serious Adverse Events

Any AE reported as resulting in death, immediate risk of death (life threatening), inpatient hospitalization or prolongation of existing hospitalization, persistent or significant disability/incapacity, or a congenital/anomaly/birth defect will be classified as an SAE by the Investigator. An SAE may also be any other medically important event that, in the opinion of the Investigator, may jeopardize the subject or may require intervention to prevent one of the other outcomes listed above. In addition, if a subject develops a Grade 3 or higher allergic reaction per Common Terminology Criteria for Adverse Events (CTCAE) grading or an anaphylactic reaction in association with BIVV009 administration, the event should be reported as an SAE per protocol.

All SAEs will be listed; treatment-emergent SAEs and treatment-emergent related SAEs will be summarized by system organ class and preferred term.

8.1.4. Adverse Events Leading to Treatment Discontinuation and/or Study Withdrawal

AEs leading to treatment discontinuation and/or study withdrawal will be listed. All AEs reported on the AE log for the item "Action Taken with Study Drug" with a response of "Study drug permanently discontinued" or for the item "Was the subject terminated from this study due to this AE?" with a response of "Yes" will be included.

8.1.5. Deaths on Study

A listing of deaths occurring on study will be provided.

8.1.6. Adverse Events of Interest

8.1.6.1. AEs Within 24 Hours after the Start of Infusion

All AEs within 24 hours after the start of infusion are captured in the eCRF. Incidence of AEs within 24 hours after the start of infusion will be summarized by SOC and preferred term.

8.1.6.2. Infections and Infections of ≥ Grade 3 Severity

Infections will be captured based on MedDRA SOC of "infections and infestations." Incidence of infections of Grade 3 or higher will be summarized by preferred term. A listing of all infections, infections of Grade 3 or higher and serious infections will be provided.

8.1.6.3. Haemolytic Breakthrough

Proportion of subjects with hemolytic breakthrough (defined in Section 5.1.1) at any visit will be summarized. The date (visit) of onset and hemolytic lab parameters (i.e., Hgb, bilirubin, LDH, and haptoglobin) over time will be listed for subjects with haemolytic breakthrough.

8.2. Clinical Laboratory Evaluations

All laboratory data will be provided in data listings; abnormal values relative to laboratory normal ranges will be identified.

8.2.1. Hematology and Chemistry

All summaries will be structured such that the hematology and chemistry tests are presented in the order shown in the tables below.

Hematology measurements that will be summarized and listed include white blood cell count (WBC), red blood cell count (RBC), differentials (basophils, eosinophils, lymphocytes, monocytes, neutrophils, reticulocytes), hemoglobin, hematocrit, and platelet count.

Chemistry measurements that will be summarized and listed include electrolytes (sodium, potassium, chloride), glucose, total protein, total bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), blood urea nitrogen (BUN), and serum creatinine.

8.2.1.1. Change from Baseline

Hematology and chemistry results at baseline and post baseline visits, along with change from baseline, will be summarized with descriptive statistics for Safety Analysis Set.

8.2.1.2. Shifts

Each subject's laboratory values will be classified according to whether the test result is "low" (below the LLN), "normal" (within the normal range), "high" (above the ULN). Shift tables will be constructed based on both the minimum and maximum post-baseline values for each subject. Data collected from unscheduled visits will be included in the determination of the per subject minimum and maximum values. A separate table will be provided which summarizes the results of the shift tables in which the number and percentage of subjects with a shift to low (from normal, high, or unknown) and the number of subjects with a shift to high (from normal, low, or unknown) will be tabulated; percentages will be based on the number of subjects at risk. The number at risk for a shift to low (high) is the number of subjects whose baseline value was not low (high), including unknown, who had at least one post-baseline value. Only directions of change indicating a clinical concern will be included in this table summarizing the shifts. The direction of concern is provided in Table 8.

Table 8: Direction of Change Indicating Clinical Concern for Laboratory Tests

Laboratory Test	Direction	Laboratory Test	Direction
Chemistry		**Hematology**	
Liver		White blood cells	Low and High
ALT/SGPT	High	Lymphocytes	Low and High
AST/SGOT	High	Neutrophils	Low and High
Total bilirubin	High	Monocytes	Low and High
Indirect bilirubin	High	Eosinophils	Low and High
Renal		Basophils	Low and High
Blood urea nitrogen	High	Red blood cell count	Low and High
Creatinine	High	Hemoglobin	Low and High
Electrolytes		Hematocrit	Low and High
Sodium	Low and High	Platelets	Low and High
Potassium	Low and High		
Chloride	Low and High		
Other			
Glucose	Low and High		
Total protein	Low and High		

8.2.1.3. Potentially Clinically Significant Laboratory Abnormalities

Abnormal laboratory values (excluding Hgb, reticulocytes, haptoglobin, bilirubin, and LDH) will also be evaluated by determining the number and percentage of subjects with at least one potentially clinically significant laboratory abnormality over the course of the study that also represents a worsening from baseline. The potentially clinically significant levels are based on Grade 2 or higher thresholds from the CTCAE v4.03 where possible, or are defined by Sponsor's safety group. Subjects who have a post baseline laboratory value that meets the criteria for being potentially clinically significant but do not have a baseline value will be included in the numerator for determining the percentage of subjects with an abnormality. Data collected from unscheduled visits will be included in this analysis.

8.2.2. SLE Panel and Serum Disease-related Biomarkers

SLE panel (below) and serum disease-related biomarkers (below) at baseline and post baseline visits, along with change from baseline, will be summarized with descriptive statistics for the Safety Analysis Set. Additional exploratory analyses may be performed to examine the relationship between biomarkers and efficacy or safety parameters.

Systemic Lupus Erythematosus Panel

Antinuclear antibody (ANA), multiplex with dsDNA, Anti-La/SSB antibody (SS-B), Anti-riboucleoprotein 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).

Disease-Related Biomarkers

DAT (polyspecific, anti-IgG & anti-C3d), LDH isoforms, cold agglutinin (CAg) titre, IgG subsets (IgA, IgD, IgG, IgM), CAg thermal amplitude. Vaccine titers, if collected, will be presented in a listing only.

8.2.3. Anti-drug Antibody (ADA)

Subjects who discontinue treatment early in Part A will be evaluated for anti-drug antibodies. Subjects with negative and positive anti-drug antibodies will be listed along with the associated titer if available.

8.3. ECG and Vital Signs

8.3.1. Electrocardiograms (ECG)

The proportion of subjects with clinically significant change from baseline in ECG findings will be summarized by visit.

8.3.2. Vital Signs

Vital signs (systolic and diastolic blood pressure, pulse, respiratory rate, and temperature) will be summarized for the observed values and change from baseline using descriptive statistics for the Safety Analysis Set.

The number and percentage of subjects with potentially clinically relevant post-baseline abnormalities will be presented. The criteria for potentially clinically relevant post-baseline abnormalities are shown below in Table 9.

Table 9: Criteria to Determine Potentially Clinically Relevant Abnormalities in Vital Signs

Vital Sign	Criteria for Abnormalities
Temperature	> 38ºC and an increase from pre-dosing of at least 1ºC
Pulse	> 120 beats per minute post-baseline or an increase from pre-dosing of more than 20 beats per minute; < 50 beats per minute post-baseline or a decrease from pre-dosing of more than 20 beats per minute
Systolic Blood Pressure	> 180 mmHg post-baseline or an increase from pre-dosing of more than 40 mmHg; < 90 mmHg post-baseline or a decrease from pre-dosing of more than 30 mmHg
Diastolic Blood Pressure	> 105 mmHg post-baseline or an increase from pre-dosing of more than 30 mmHg; < 50 mmHg post-baseline, or a decrease from pre-dosing of more than 20 mmHg
Respiratory Rate	> 35 breaths per minute post-baseline; < 10 breaths per minute post-baseline

9. PHARMACOKINETIC AND PHARMACODYNAMIC ANALYSIS

9.1. Pharmacokinetic Analysis

Plasma BIVV009 concentrations will be listed by subject, nominal visit, date and time of collection and study day. Summary statistics of plasma BIVV009 concentrations will be presented by nominal visit and study day including n, mean, standard deviation, coefficient of variation, geometric mean, median and range. Individual and mean plasma BIVV009 concentration-versus-time profiles will be plotted.

9.2. Pharmacodynamic Analysis

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 subject listings will be presented for all PD parameters by time point and study day.

10. CHANGES FROM PREVIOUS VERSION

The following changes have been made to Version 1.0 of the SAP:

- Calculation of exposure have been clarified.
- Components for the primary endpoint (receiving transfusion and prohibited medication from Week 5 to Week 26) have been clarified.
- Analysis of rate of change in hemoglobin has been removed.
- Summaries and analyses of solicited symptomatic anemia have been clarified.
- Summaries of FACIT-Fatigue individual item responses have been removed as they will be provided in a separate FACIT-Fatigue analysis plan.
- Summaries of SF-12 have been clarified.

11. REFERENCES

International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (2014), "Final Concept Paper: E9(R1): Addendum to Statistical Principles for Clinical Trials on Choosing Appropriate Estimands and Defining Sensitivity Analyses in Clinical Trials,"

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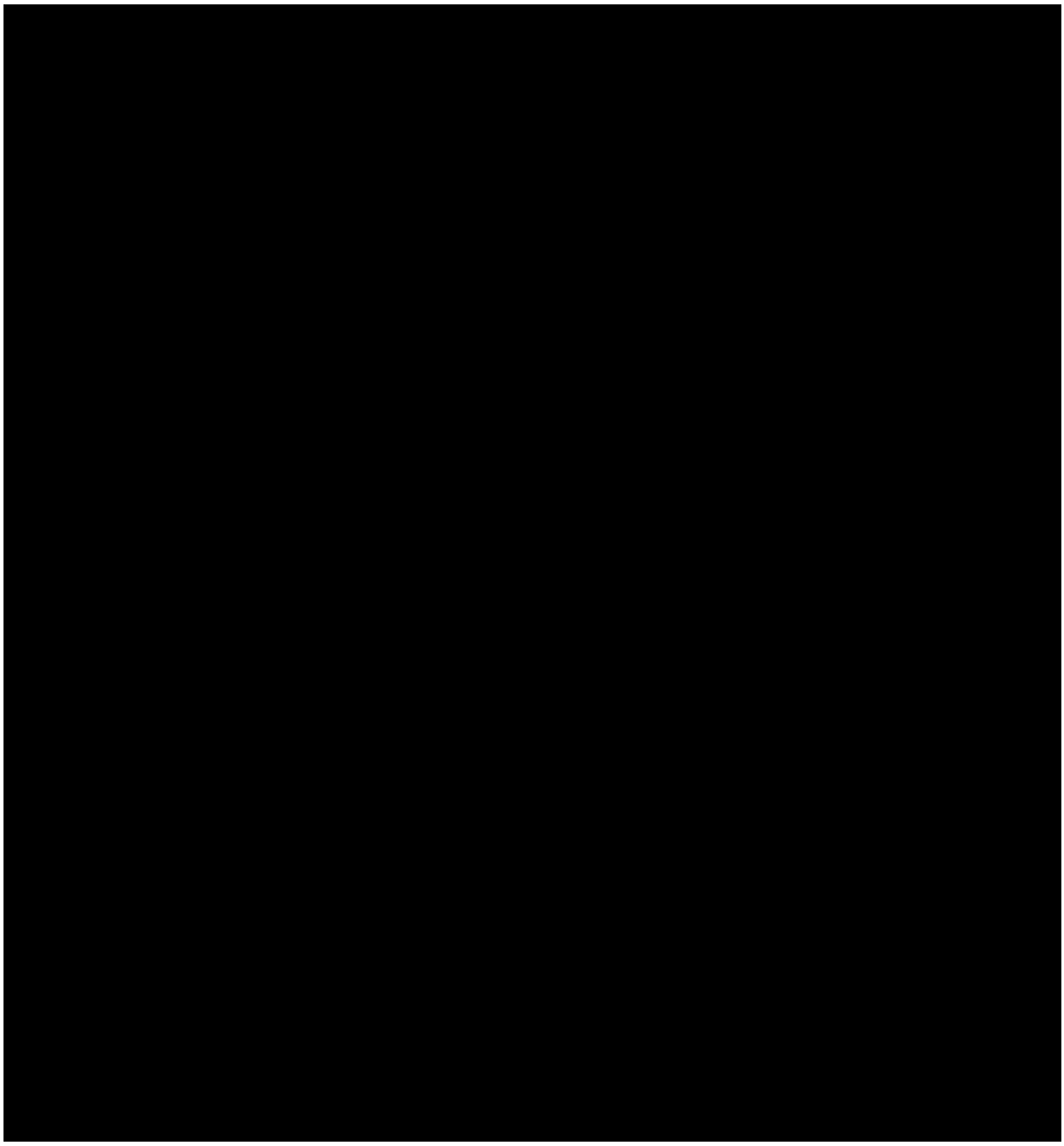
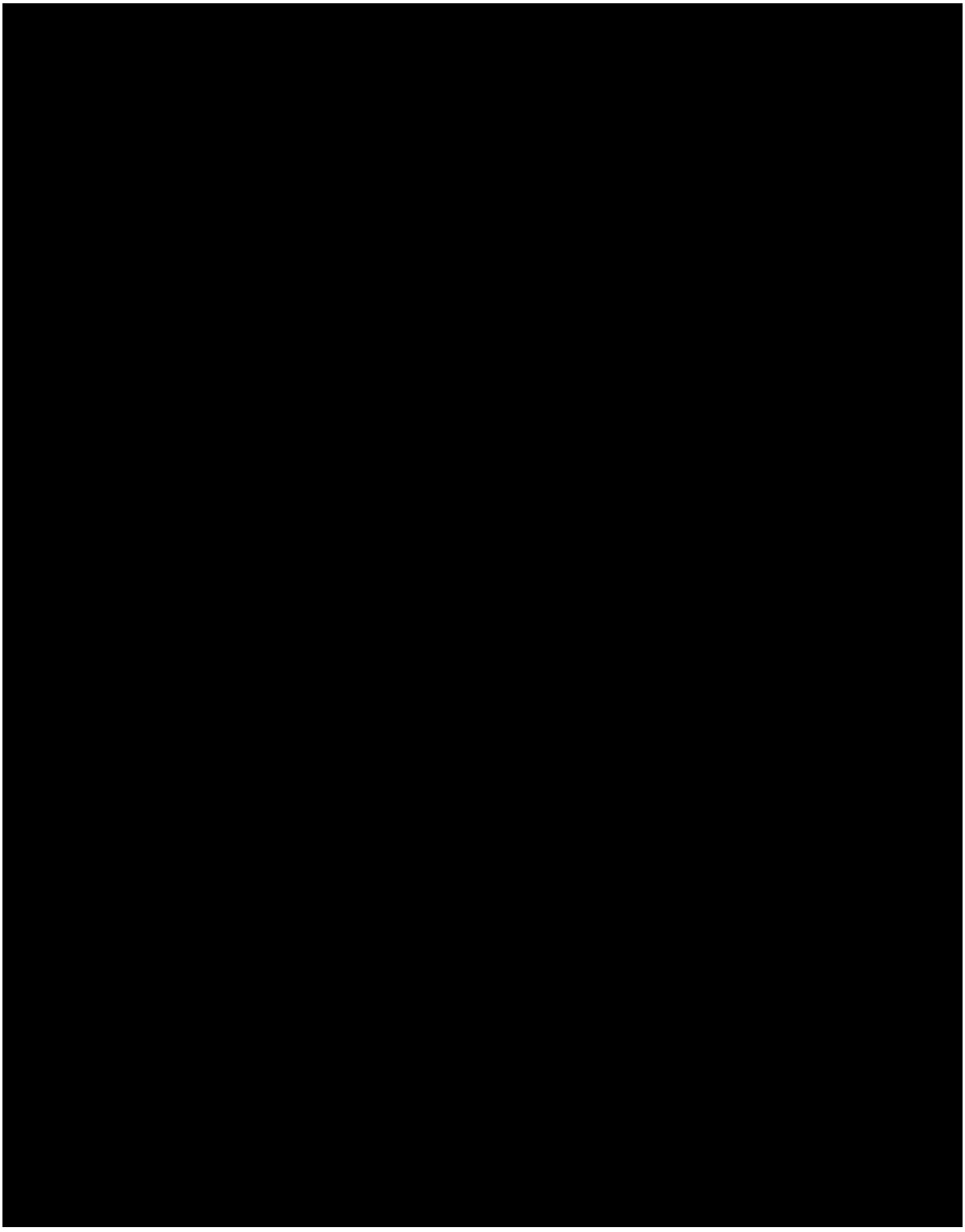
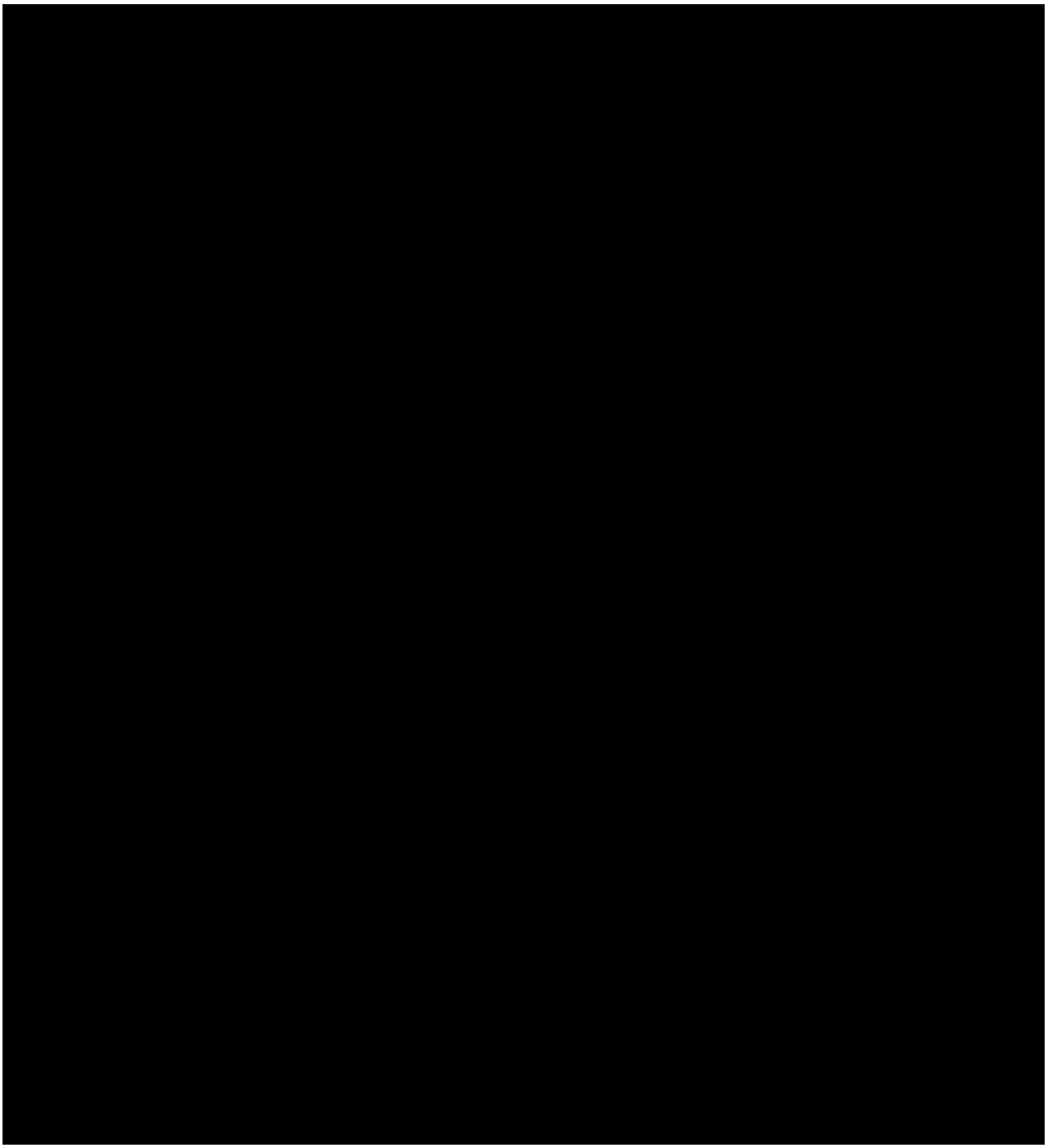
13. APPENDICES

Appendix A: Scoring Algorithm for FACIT-F

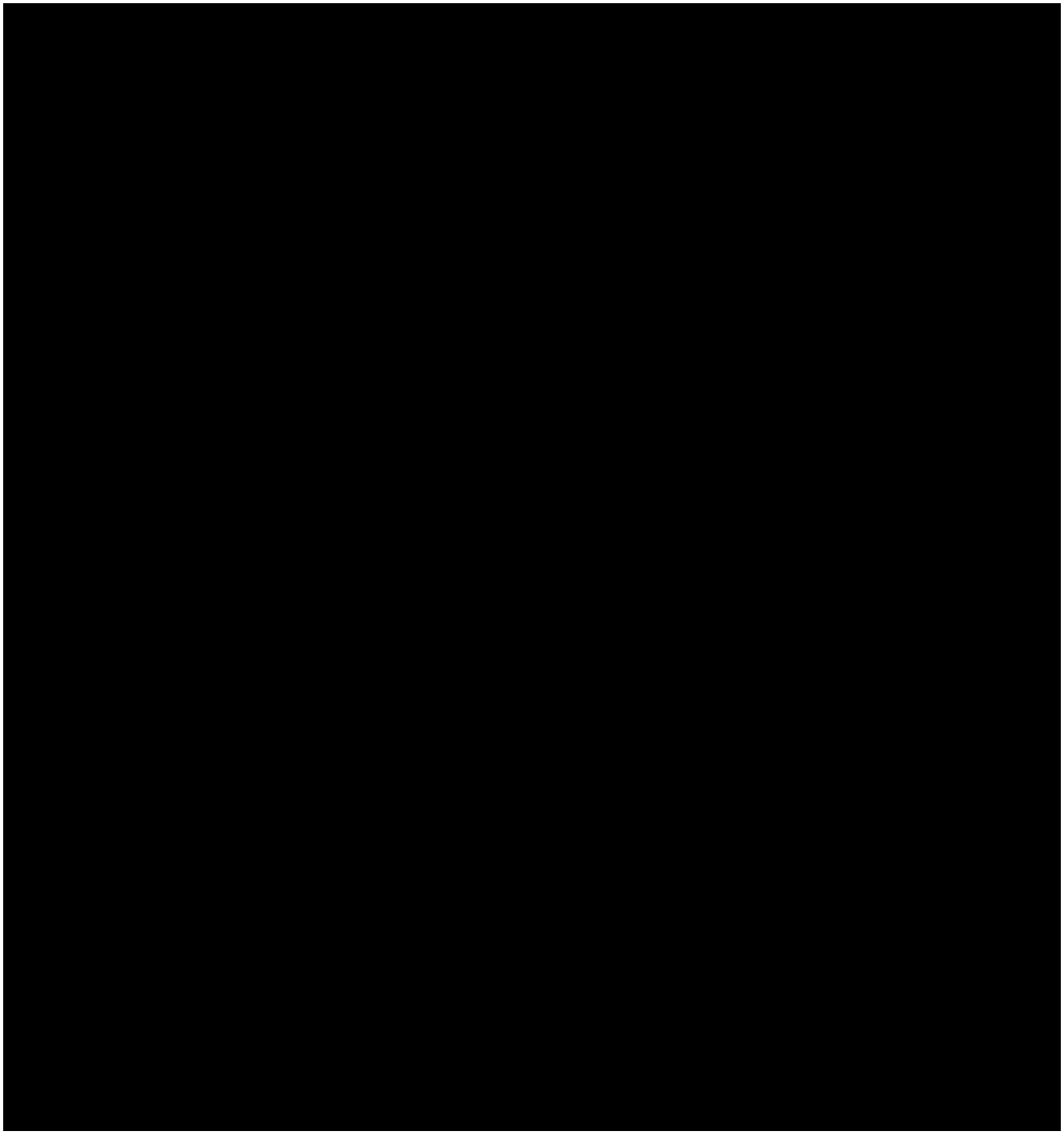


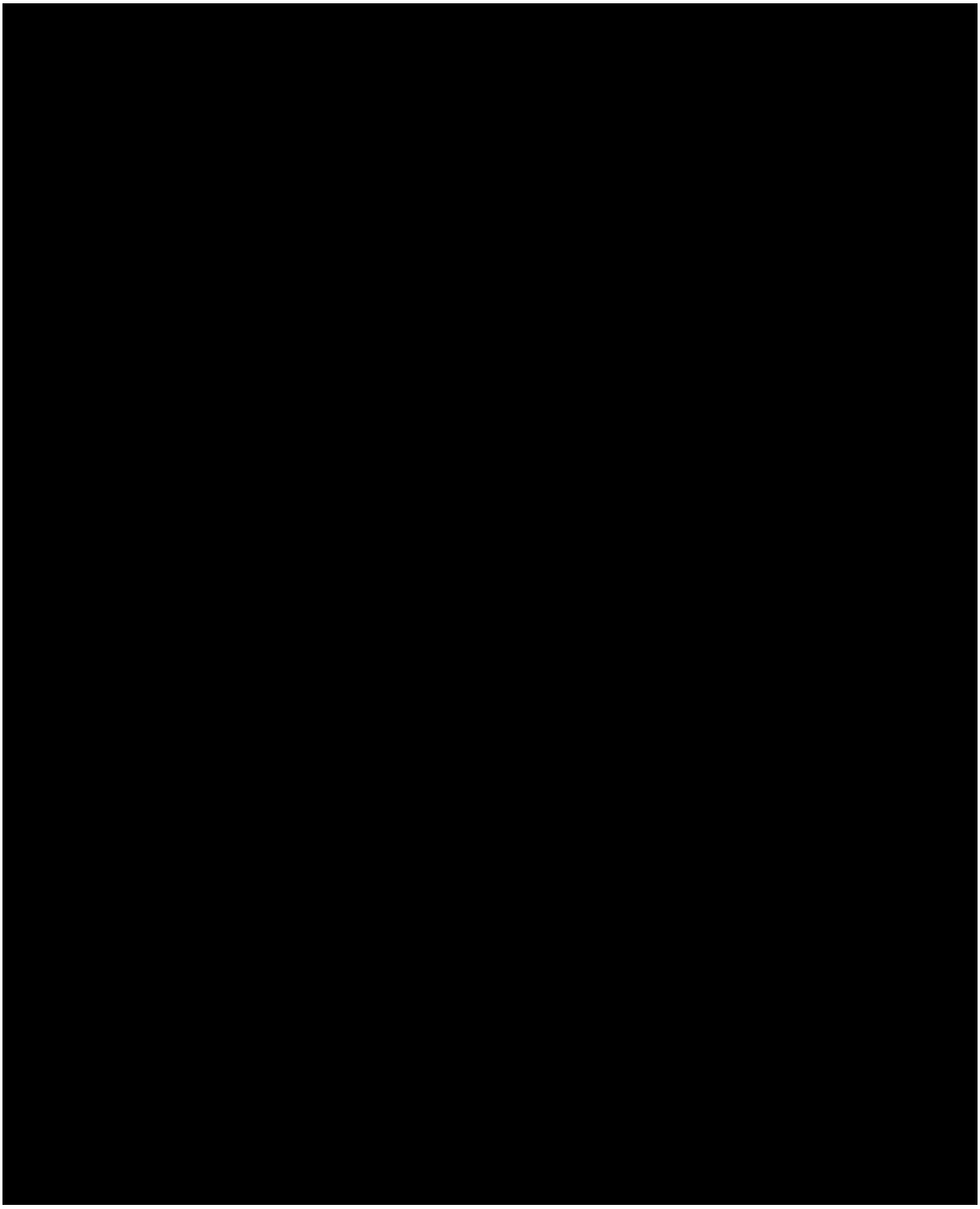
Appendix B: EQ-5D-5L Questionnaire Score Definitions

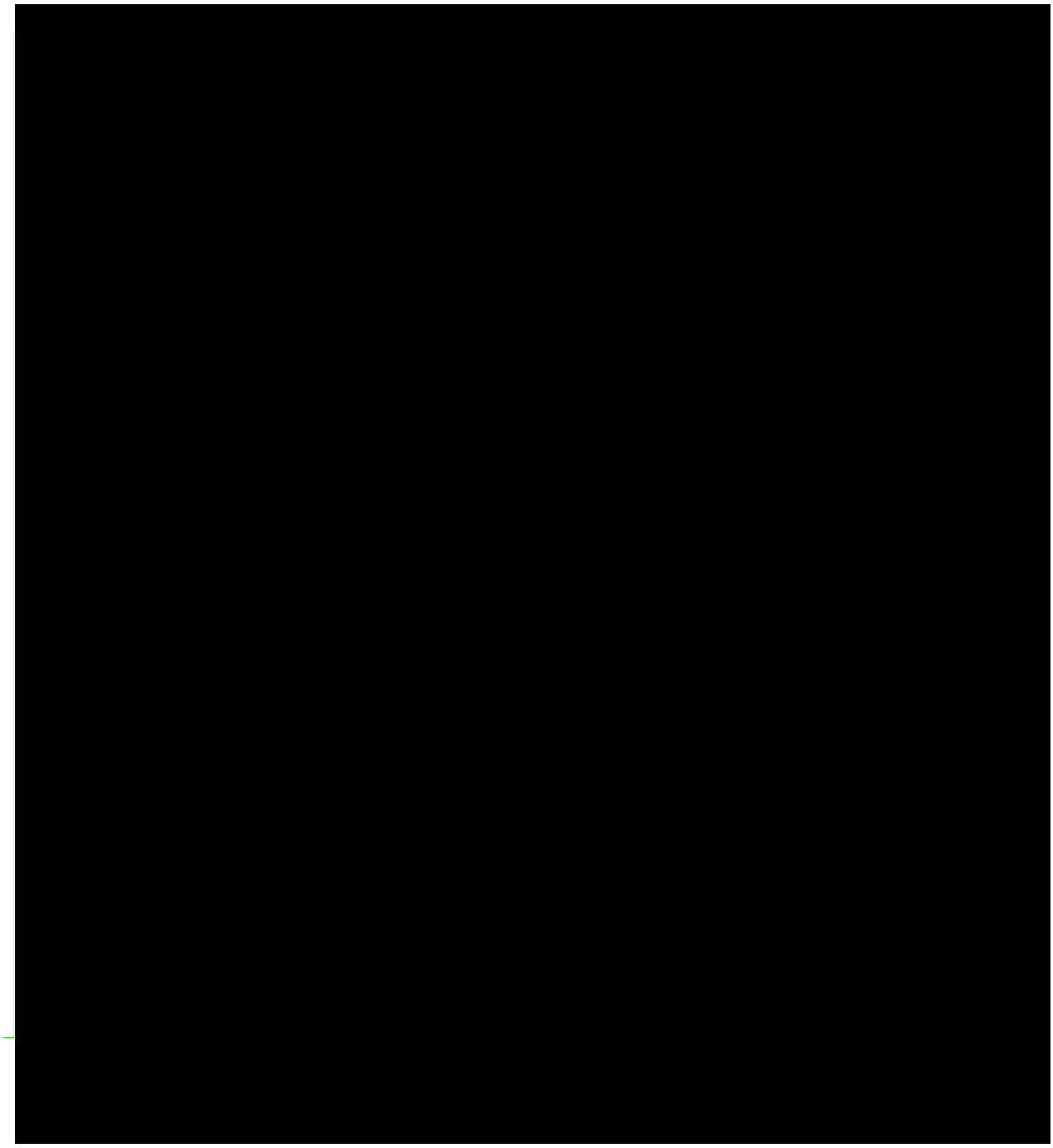




Appendix C: 12-item Short Form Survey (SF-12)







Appendix D: Patient's Global Impression of Change (PGIC)

Appendix E: Patient's Global Impression of [Fatigue] Severity

NCT03347396

STATISTICAL ANALYSIS PLAN

PART B

Product Studied: BIVV009

Protocol Number(s): 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

Date of Protocol: 17 July 2018 (Version 5)

Date of Statistical Analysis Plan: 29 May 2019

Approved By:

[redacted]

[redacted]

Date

[redacted]

Date

[redacted]

[redacted]

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AE	adverse event
ADL	activities to daily living
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANA	antinuclear antibodies
AST	aspartate aminotransferase
AUC	area under the curve
BLA	Biologics License Applications
BUN	blood urea nitrogen
CAD	cold agglutinin disease
CI	confidence interval
CIC	circulating immune complexes
C_{max}	maximum concentration
CTCAE	Common Toxicity Criteria for Adverse Events
DBL	database lock
ECG	electrocardiogram
eCRF	electronic Case Report Form
EOT	end of treatment
EQ-5D-5L	EuroQol – five dimensions questionnaire
ET	early termination
FACIT	functional assessment of chronic illness therapy
FAS	full analysis set
GGT	gamma-glutamyl transferase
Hgb	hemoglobin
HUI	health utility index
ICH	International Conference of Harmonisation
ITT	intent-to-treat
IV	intravenous
LDH	lactate dehydrogenase
LLN	lower limit of normal
LPO	last patient out
MAA	Marketing Authorization Application
MAR	missing at random
MCMC	Markov chain Monte-Carlo
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Model for Repeated Measures
MNAR	Missing Not At Random
NCMV	Neighboring-Case Missing Value
PD	pharmacodynamics
PGIC	Patient's Global Impression of Change
PGIS	Patient's Global Impression of Severity
PK	pharmacokinetics
PP	per-protocol
PRO	patient-reported outcome
QOL	quality of life

RBC	red blood cell count
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SF-12	12-Item Short Form Survey
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic-pyruvate transaminase
SLE	systemic lupus erythematosus
SOC	system organ class
TEAE	treatment-emergent adverse event
TLF	tables, figures, and listings
TOEPH	heterogeneous Toeplitz
ULN	upper limit of normal
WBC	white blood cell count

1. INTRODUCTION

BIVV009-03 is an open-label, single-arm, multicenter study in patients with primary cold agglutinin disease (CAD) who have hemoglobin (Hgb) level ≤ 10 g/dL and a recent history of blood transfusion. Eligible patients received study drug and underwent safety and efficacy assessments for 6 months (26 weeks) in Part A of the study.

Following completion of the initial 6-month treatment period, patients will roll into the long-term safety study (Part B) where they will continue to receive the study drug, BIVV009. Part B will run for 1 year following last patient out (LPO) under Part A. As in Part A, patients will be dosed with BIVV009 every 2 weeks. On-site visits will be completed approximately every 3 months (at a minimum) for collection of pharmacokinetics (PK) and pharmacodynamics (PD) samples and for additional safety and efficacy measures. The study will be complete 12 months following LPO for Part A at which time all patients receiving on-going treatment will proceed to an End-of-Study (EOS) visit 9 weeks after the last administration of study drug.

This statistical analysis plan contains information pertaining to definitions of analysis sets and derived variables, and statistical methods for the analysis of efficacy, safety, PK, and PD for Part B of the referenced study.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Study Objectives

2.1.1. Primary Objective

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

2.1.2. Secondary Objective

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

2.2. Study Endpoints

2.2.1. Safety Endpoints

The following are the safety-related endpoints for Part B:

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

Details of the analysis of safety endpoints are described in Section 8.

2.2.2. Efficacy Endpoints

The efficacy endpoints are the following parameters of disease activity:

- Hemoglobin
- Bilirubin (total)
- Lactate dehydrogenase (LDH)
- Haptoglobin
- Reticulocyte Count

- Transfusion requirements
- Incidence of solicited symptomatic anemia
- Incidence of thromboembolic events
- Incidence of hemolytic breakthrough
- Healthcare resource utilization parameters
- QOL assessments (FACIT-Fatigue, EQ-5D-5L, SF-12, PGIS, and PGIC)

Details of the analysis of efficacy endpoints are described in Section 7.

2.2.3. Pharmacokinetic Endpoints

- Plasma concentrations of BIVV009

Details of the analysis of PK endpoints are described in Section 9.1.

2.2.4. Pharmacodynamic Endpoints

- PD Primary Outcome Measures: Wieslab-CP
- Exploratory Complement System Measures: CH_{50}, Total C4, C1q, C1s

Details of the analysis of PD endpoints are described in Section 9.2.

3. STUDY DESIGN

3.1. Overall Study Design and Plan

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 CAD, who have Hgb level ≤ 10 g/dL and a recent history of blood transfusion.

Following completion of dosing in the 6-month treatment period in Part A of the study, 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 1 year following LPO under Part A.

3.1.1. Study Sample

Patients in Part B will be a subset of the patients enrolled in Part A. All patients who complete Part A, including those receiving transfusions, will be eligible for Part B. Patients who withdraw from the study in Part A, including those who received prohibited concomitant medications, will not be eligible to participate in Part B. Subject inclusion and exclusion criteria for Part A can be found in Sections 5.1 and 5.2 of the protocol.

3.1.2. Treatment

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.

Patients requiring treatment with permitted concomitant medications and/or transfusions will not be discontinued from either Part A or Part B of the study. Patients in Part B will be transfused 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 patients is asymptomatic

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 hemolytic breakthrough event.

The study will be complete 12 months following LPO for Part A. At this time, all ongoing patients receiving treatment in Part B will discontinue additional treatment visits and will follow-up with an EOS visit 9 weeks after last dose.

3.1.3. End of Study

The study will be considered complete 12 months following LPO from Part A. When this occurs, all ongoing patients in Part B will discontinue treatment and will return to the clinic for EOS assessments 9 weeks after last dose. End of study will occur when the last patient has had his or her last visit (Last Patient Last Visit).

3.2. Statistical Hypothesis

No formal statistical hypotheses will be tested. Analyses of efficacy endpoints will be primarily descriptive.

3.3. Sample Size Justification

No power and sample size analysis was conducted for Part B. Patients from Part A were enrolled into Part B following Part A EOT. The power and sample size calculation for Part A can be found in the Part A SAP.

3.4. Randomization and Blinding

This is an open-label study with no blinding or randomization.

3.5. Interim Analysis

For the purposes of regulatory submission, an interim analysis of safety and efficacy data will be performed for Part B after all patients have completed Part A, while Part B is still ongoing. Additional interim analyses of Part B data may be performed to obtain interim safety and efficacy results at the Sponsor's discretion for purposes of regulatory filings and requests, publications, or future planning. In general, these analyses will include safety and efficacy endpoints indicated in Section 2.2.1 and Section 2.2.2 through certain cutoff dates.

4. ANALYSIS POPULATIONS

The following analysis populations are defined for Part B of the study. For the remainder of the SAP, the term "subjects" will be used to refer to patients in the study to keep consistent with the term used within table, figure, and listing (TFL) displays.

In order to be consistent with Part B study objectives, the Per-Protocol Population described in the protocol was determined to have little utility and thus was not included in this SAP.

4.1. Full Analysis Set (FAS)

The Full Analysis Set is defined as all subjects who enroll into the Part B study and receive at least 1 dose (including partial dose) of study drug. The Full Analysis Set is synonymous with the Intent-to-Treat Population described in the protocol.

4.2. Safety Analysis Set

Subjects who receive at least 1 dose (including partial dose) of study drug in Part B will be included in the Safety Analysis Set. Note that Safety Analysis Set is the same as the Full Analysis Set in this study.

4.3. PK Analysis Set

Subjects who received at least 1 dose of study drug in Part B and have evaluable PK concentrations will be included in PK analysis set.

4.4. PD Analysis Set

Subjects who received at least 1 dose of study drug in Part B and have at least 1 evaluable PD sample will be included in the PD analysis set.

5. DEFINITIONS AND DATA HANDLING

Statistical analysis will be performed by Bioverativ, using SAS® version 9.4 or higher and, where appropriate, additional validated software.

5.1. General Principles

Safety, efficacy, and PK/PD data will be summarized using standard summary statistics for continuous, categorical, and time-to-event data. Data will be summarized for the populations defined. All efficacy and safety data, including derived variables, will be listed for all visits.

No statistical hypothesis testing is planned.

5.1.1. Definitions

Study Day

Study Day is defined as days relative to the date of first dose of BIVV009 in Part A, Day 0. The start/stop day of events will be calculated as (date of event – date of Day 0 +1).

Incomplete dates will be imputed for the calculation of study days, unless specified otherwise:

- If missing day only, the start date will be imputed as the first day of the month, while the end date will be imputed as the last day of the month;
- If missing day and month, the start date will be imputed as the first day of the year, while the end date will be imputed as the last day of the year;

Baseline

Baseline is defined as the last non-missing value prior to the first administration of study drug in Part A. If a transfusion occurred during the screening period, the baseline measure must be at least 7 days after the transfusion.

Study Treatment Period

For subjects who enroll into Part B, the Part A study treatment period starts at the date of first study drug administration and ends at the date of Week 26 visit. The Part B study treatment period starts following completion of Part A (ie, immediately following Week 26 visit) and ends at the ET/EOS/Safety follow-up visit, which is 9 weeks after each subjects' last dose.

The Combined Study Period includes all visits in Part A and Part B and will be utilized for a subset of analyses in order to support regulatory submissions and/or publications.

Visit Windows

Analysis by study visit will utilize the data recorded on the corresponding nominal visit from electronic Case Report Forms (eCRFs). In case of missing data/assessments for a visit, data from an unscheduled visit, or ET/Safety Follow-up Visit will be used, if the Study Day of such a

visit fits in the analytic window defined below. If multiple values are identified within the analytic window, the one closest to the target study day will be used.

- Starting at Week 27 and every 2 weeks thereafter, analytic visit windows in Part B will be -6 days to +7 days from the Target Study Days of the protocol-defined visits. An example of the first few visits in Part B can be seen in Table 1, below.

Table 1: Analytic Visit Windows

Visit	Target Study Day	Analytic Visit Window (Study Day)
Week 27	189	183-196
Week 29	203	197-210
Week 31	217	211-224
Week 33	231	225-238
Etc.		

Solicited Symptomatic Anemia

Refer to the Part A SAP for definitions regarding the severity of CAD symptomatic anemia.

Thromboembolic Events

Thromboembolic events prior to Part A study entry are recorded as medical history in the eCRFs, while thromboembolic events on Part A and Part B study are captured as adverse events. Both medical history and adverse events will be coded according to Medical Dictionary for Regulatory Activities (MedDRA) v20.1 or higher.

All thromboembolic events reported (as AEs) will be reviewed and determined by internal medical staff via medical adjudication.

Hemolytic Breakthrough

Hemolytic breakthrough at any visit is defined as

- A decrease of 2 g/dL or more in Hgb from the last scheduled visit, and
- One of the followings:
  - An increase of LDH from the last scheduled visit, or
  - An increase of bilirubin from the last scheduled visit, or
  - A decrease in haptoglobin from the last scheduled visit.

Protocol Prohibited CAD Medications

The following concomitant medications are prohibited during the study treatment period:

- Rituximab alone or as part of combination therapy
- Cytotoxic drugs (such as fludarabine, bendamustine, ibrutinib, cyclophosphamide)
- Other investigational drug

The eCRF questionnaire "Did the subject receive any prohibited medications since the last visit?" will be used to account for protocol-prohibited CAD medication use. Medical review for the list of protocol-prohibited CAD medications will be reconciled with the eCRF questionnaire.

5.1.2. Pooling Sites for Analysis

Data from all investigational sites will be pooled for the analysis, unless specified otherwise.

5.1.3. Handling of Missing Data

Best efforts will be utilized to minimize missing values. If a subject discontinues study treatment early, the subject will be asked to complete study assessments at ET/safety follow up visit.

For the analysis of both continuous and categorical data, summary statistics will be computed based on observed data. Since the duration of treatment period varies in Part B, efficacy endpoints by visit will be summarized through 12 months during Part B. Additional summaries beyond 12 months may be computed depending on the enrollment pattern, i.e., the number of subjects attending visits after the Week 77 visit. AE endpoints by visit will be summarized through LPLV in Part B.

For a QOL endpoint, in the event of missing data, the total score will be estimated according to the provision for missing domains in the calculation algorithm of the score. For example, if a subject has missing data in FACIT-F questionnaire at a visit, the prorated FACIT-F score will be calculated if more than 50% of the items (a minimum of 7 out of 13 items) are available. Otherwise, the score is missing.

For the analysis of AEs and concomitant medications/procedures, if the start/stop date of an AE/concomitant medication/procedure is missing or partial, the corresponding study day will be left blank. However, inferences will be made from the partial and missing dates to classify medications as prior and/or concomitant and AEs as treatment emergent or not treatment emergent. These inferences are described in Section 8.1.

5.2. Data Summaries

5.2.1. Continuous Variables

Continuous variables will be summarized using descriptive statistics including the number of non-missing values (n), mean, standard deviation (SD), median, minimum, and maximum.

Where specified in the table shells, the 25th and 75th percentiles will also be provided. Means, medians, and the 25th and 75th percentiles will be presented to one decimal place beyond that with which the data were captured. SDs will be presented to two decimal places beyond that with which the data were captured. Minimum and maximum will be displayed to the same number of decimal places as that with which the data were captured.

Unless impractical within a given table, statistics will be aligned by the decimal place (or assumed decimal place) in the summary tables.

5.2.2. Categorical Variables

Categorical variables will be summarized by counts and percentages. All percentages will be rounded to one decimal place. The percentage will be suppressed when the count is zero. Unless specified otherwise, the denominator for all percentages will be the number of subjects with non-missing data for a given summarization. This number (n) will be included with categorical summaries unless the same variable is also being summarized with descriptive statistics, in which case 'n' will already be provided.

5.2.3. Time-to-Event Variables

Time-to-event variables will be summarized using Kaplan-Meier estimate over time, along with median time to event and probability of an event at specific time points. Additionally, a Kaplan-Meier plot over time will be constructed. Partial dates will not be imputed, hence considered unknown. In general, for subjects who do not experience the event, the time-to-event will be censored at the study day of last assessment within the study period.

6. STUDY SUBJECTS

6.1. Disposition of Subjects

Subject disposition will be summarized including the number of subjects in FAS, Safety Analysis Set, PK Analysis Set, and PD Analysis Set. The number of subjects with the status of completed Part B and discontinued Part B early, including the primary reason for those who discontinued, will be tabulated for all subjects enrolled in Part B.

Subject disposition, including the date of the last visit and the reason for early termination for subjects who did not complete the study treatment, will be provided in a data listing.

6.2. Demography and Baseline Disease Characteristics

Demographics and baseline disease characteristics will be summarized for FAS.

6.2.1. Demography

Demographic characteristics including age (years), age category (<65, ≥65), gender, race, ethnicity, country, geographic location, height (cm), weight (kg), weight category (<75 kg, ≥75 kg), and body mass index (kg/m^2) will be summarized. Geographic locations are defined as follows:

- Europe includes Austria, Germany, Italy, United Kingdom, and Norway.
- North America includes the United States.
- Asia includes Japan.
- Other includes Australia and New Zealand.

6.3. Protocol Deviations

All protocol deviations will be recorded throughout the study. Major and minor protocol deviations/violations are to be pre-specified prior to database lock. All major protocol deviations will be summarized for FAS. All deviations occurring in Part B, both major and minor, will be provided in a data listing.

6.4. Non-study Drug Medications

6.4.1. Concomitant Medications

Concomitant medications within Part B are those administered on or after the Part B start date. Concomitant medications will be coded using World Health Organization drug enhanced dictionary (March 2018 version or higher) and will be summarized using FAS.

Separate tables will be generated to summarize the concomitant CAD medical treatment(s) and protocol prohibited CAD treatment(s) (both determined via medical adjudication).

Additionally, all concomitant medications taken during Part B will be provided in a data listing.

6.4.2. Non-drug treatments and procedures

Non-drug treatments and procedures administered during Part B (whether for CAD or other condition), excluding transfusions, will be summarized for FAS and listed.

6.5. Study Drug

Study drug exposure will be summarized using Safety Analysis Set. Subject-level information on dosing with study drug during Part B will also be provided in a data listing.

6.5.1. Exposure

Study drug exposure, measured by the duration of study treatment, the number of BIVV009 administrations and total actual BIVV009 dose, will be summarized by study period for the Safety Analysis Set.

The duration of the study treatment (in weeks) is calculated as follows:

1. Combined Study Period: (date of last dose – date of first dose in Part A + 15)/7

2. Part B Study Period: (date of last dose – Part B start date + 15)/7

The actual dose administered at each visit is calculated as:

Total volume administered / Total volume prepared * assigned dose.

The total BIVV009 dose will be summarized as follows:

1. Combined Study Period: The summation of all actual doses administered in Parts A and B.

2. Part B Study Period: The summation of all actual doses administered in Part B, alone.

7. EFFICACY ANALYSIS

7.1. General Efficacy Principles

Unless specified otherwise, all analyses described will be performed using FAS and will include summaries (see Section 5.2) and listings only. No formal hypothesis will be tested with regards to efficacy endpoints.

Additionally, all efficacy data will be provided in data listings.

7.2. Analysis of Efficacy Endpoints (Part B Study Period)

All analyses described below will be performed on the Part B Study Period, starting at Week 27.

7.2.1. Continuous Endpoints

The continuous endpoints include:

- LDH
- Haptoglobin
- Reticulocyte count

The above endpoints will be summarized by visit, including change from baseline, starting at Week 27, and will continue through the Week 77 visit. All change from baseline tables will also include a summary of Baseline statistics and individual summary statistics will follow those presented in Section 5.2.1. For patients with more than 12 months of follow-up in Part B, all endpoints at the Week 79 visit and beyond will be provided in a data listing.

7.2.2. Categorical Endpoints

The categorical endpoints include:

- Incidence of solicited symptomatic anemia
- Incidence of other CAD-related symptoms

The above endpoints will be summarized by visit descriptively using the FAS and will be based on the observed data starting at Week 27, continuing through the Week 77 visit. Baseline summaries will be included for comparative purposes. For patients with more than 12 months of follow-up in Part B, observed data at the Week 79 visit and beyond will be provided in the listings.

Additionally, the following endpoints will be summarized using all data in Part B (including data from the Week 79 visit and beyond):

- Incidence of thromboembolic events

- Incidence of hemolytic breakthrough

7.2.3. Endpoints Based on Patient-reported Outcomes

The patient-reported outcome (PRO) endpoints are as follows:

- Continuous Endpoints
  - FACIT-Fatigue score
  - EQ-5D index score
  - EQ-5D-5L visual analogue scale
  - SF-12 physical component score (PCS) and mental component score (MCS)
  - SF-12 sub-scale scores
- Categorical Endpoints
  - Patient's Global Impression of Change (PGIC)
  - Patient's Global Impression of [Fatigue] Severity (PGIS)
  - EQ-5D-5L Descriptive System

Details of the above PRO instruments and algorithms for deriving the scores can be found in the Part A SAP. For continuous variables, the overall score and its change from baseline will be summarized descriptively for each time point, starting at Week 27 and continuing through the Week 77 visit based on the FAS.

PGIC and PGIS will be summarized as ordinal variables by visit for the FAS, starting at Week 27 and continuing through the Week 77 visit.

When applicable missing items will be handled based on the specific PRO instrument. Subjects missing baseline evaluations would not be included in the PRO analyses. For patients with more than 12 months of follow-up in Part B, observed data at the Week 79 visit and beyond will be provided in the listings.

7.2.4. Healthcare Resource Utilization

The number of healthcare visits by type (office visit, hospital ER visit, hospitalization, and ICU stay) will be collected and presented in a listing.

7.3. Analysis of Efficacy Endpoints (Combined Study Period)

All analyses below will be conducted on the FAS for the Combined Study Period starting at Baseline/Day 0.

7.3.1. Continuous Endpoints

The continuous endpoints include:

- Hemoglobin
- Bilirubin (total)

The above endpoints will be summarized by visit, starting at Baseline/Day 0 and will continue through the Week 77 visit. Summary tables will include change from baseline and individual summary statistics will follow those presented in Section 5.2.1. For patients with more than 12 months of follow-up in Part B, all endpoints at the Week 79 visit and beyond will be provided in a data listing.

Line plots of mean hemoglobin and bilirubin over time, starting at Baseline/Day 0, will be presented. Additionally, a line plot of mean change from baseline in hemoglobin over time, starting at Baseline/Day 0, will be presented.

Additionally, the following continuous endpoints will be summarized by Study Period using FAS as specified in Section 5.2.1:

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

For number of transfusions and total transfusion units, data up to Week 77 will be considered, for both Part B and Combined Study Period summaries. All data after Week 77 will be provided in the listing.

For annualized number of transfusions and annualized transfusion units, all Part B data will be considered. Annualized values will be calculated for each patient using the following formula:

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

7.3.2. Time-to-event Endpoints

The time-to-event endpoints include:

- Time to first transfusion (after the first 5 weeks of study drug administration in Part A)

The above endpoint will be summarized using FAS as specified in Section 5.2.3. All data, including those beyond the Week 77 visit, will be utilized for calculating the above, time-to-event endpoints. However, summary tables and figures will only present data up to and including Day 539 (ie, Study Day 540, target study day for the Week 77 visit). All other data after Study Day 540 will be provided in a listing.

8. SAFETY ANALYSIS

Unless stated otherwise, all safety data will be summarized for subjects in the Safety Analysis Set defined in Section 4.2. The summary tables may also be presented by subgroup based on the BIVV009 dose cohort. However, the limited number of subjects in each dose cohort and non-randomized assignment preclude a direct comparison between the two dose cohorts.

8.1. Adverse Events

AEs will be classified using the MedDRA system organ classes and preferred terms. MedDRA version 20.1 or higher will be used throughout the study. In general, AEs will be analyzed based on *incidence*, defined as the proportion of subjects who had at least one occurrence of an event out of the number of subjects in the Safety Analysis Set.

All summary tables and listings will only include treatment-emergent adverse events in Part B unless noted otherwise. An AE will be regarded as treatment-emergent for Part B if the date of AE onset is on or after the Part B start date. If an AE started in Part A but worsened in Part B, a new record will be created in Part B and be treated as a TEAE in Part B.

Unless specified otherwise, system organ classes and preferred terms within each SOC will be presented alphabetically. For the purpose of summarization, a subject is counted once in a SOC or preferred term if the subject reported one or more events in that SOC or preferred term. Unless specified otherwise, percentages will be based on the number of subjects in the Safety Analysis Set.

8.1.1. Overall Summary of Adverse Events

An overall summary of TEAEs will be provided which tabulates the number and percentage of subjects who experienced a TEAE, related TEAE, treatment-emergent SAE, treatment-emergent related SAE, treatment-emergent Grade 3 or higher AE, treatment-emergent infections of Grade 3 or higher severity, TEAE thromboembolic event, and TEAEs within 24 hours after the start of infusion; the number and percentage of subjects who discontinued treatment and/or the study due to an AE; and the number and percentage of subjects who died. In addition, the number of TEAEs, TESAEs, TEAE thromboembolic events and TEAEs within 24 hours after the start of infusion will be presented.

8.1.2. Treatment-emergent Adverse Events

The incidence of TEAEs will be summarized by SOC and preferred term.

8.1.2.1. Adverse Events in Descending Order of Incidence

Tables will be provided which display TEAE and TESAE preferred terms in descending order of incidence. Only preferred terms will be included in these tables (i.e., the display will not include SOCs).

A similar table will be provided for Grade 3 or higher TEAEs. AEs for which the assessment of severity is missing will be included in this table.

8.1.2.2. Severity of Adverse Events

AEs are classified by the Investigator for CTCAE grades v4.03. A summary of TEAEs by system organ class, preferred term, and CTCAE grade will be presented. AEs with a missing severity will be excluded from this table and listed separately to supplement the summary table. A subject will be counted once for each SOC and preferred term based on the greatest severity within that SOC and preferred term, respectively.

8.1.2.3. Relationship of Adverse Events to Study Drug

AEs are classified by the Investigator for relationship to study drug ("Not related," "Possible," and "Probable"). For summary tables, an AE with relationship of "Possible" or "Probable" will be considered "Related." A summary of TEAEs by SOC, preferred term, and relationship ("Related" or "Not related") will be presented. AEs with a missing relationship will be counted as "Related" in the summary table. A subject will be counted once for each SOC and preferred term based on the highest relationship within that SOC and preferred term, respectively.

8.1.3. Serious Adverse Events

Any AE reported as resulting in death, immediate risk of death (life threatening), inpatient hospitalization or prolongation of existing hospitalization, persistent or significant disability/incapacity, or a congenital/anomaly/birth defect will be classified as an SAE by the Investigator. An SAE may also be any other medically important event that, in the opinion of the Investigator, may jeopardize the subject or may require intervention to prevent one of the other outcomes listed above.

All SAEs will be listed; treatment-emergent SAEs and treatment-emergent related SAEs will be summarized by system organ class and preferred term.

8.1.4. Adverse Events Leading to Treatment Discontinuation and/or Study Withdrawal

AEs leading to treatment discontinuation and/or study withdrawal will be listed. All AEs reported on the AE log for the item "Action Taken with Study Drug" with a response of "Study drug permanently discontinued" or for the item "Was the subject terminated from this study due to this AE?" with a response of "Yes" will be included.

8.1.5. Deaths on Study

A listing of deaths occurring on study will be provided.

8.1.6. Adverse Events of Interest

8.1.6.1. AEs within 24 Hours after the Start of Infusion

All AEs within 24 hours after the start of infusion are captured in the eCRF. Incidence of AEs within 24 hours after the start of infusion will be summarized by SOC and preferred term.

8.1.6.2. Infections and Infections of ≥ Grade 3 Severity

Infections will be captured based on MedDRA SOC of "infections and infestations." Incidence of infections of Grade 3 or higher will be summarized by preferred term. Listings of all infections, infections of Grade 3 or higher and serious infections will be provided.

8.2. Clinical Laboratory Evaluations

Unless specified otherwise, all analyses described below will be performed on the Part B Study Period, starting at Week 27. All laboratory data will be provided in data listings; abnormal values relative to laboratory normal ranges will be identified.

8.2.1. Hematology and Chemistry

All summaries will be structured such that the hematology and chemistry tests are presented in the order shown in the tables below. All hematology and chemistry lab summaries will be analyzed using the Safety Analysis Set.

Hematology measurements that will be collected and listed include white blood cell count (WBC), red blood cell count (RBC), differentials (basophils, eosinophils, lymphocytes, monocytes, neutrophils, reticulocytes), hemoglobin, hematocrit, and platelet count.

Chemistry measurements that will be collected and listed include electrolytes (sodium, potassium, chloride), glucose, total protein, total bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), blood urea nitrogen (BUN), and serum creatinine.

8.2.1.1. Change from Baseline

Hematology and chemistry results at baseline and Part B post-baseline visits, along with change from baseline, will be summarized with descriptive statistics. These by-visit summaries will be presented through the end of Part B.

8.2.1.2. Shifts

Each subject's laboratory values will be classified according to whether the test result is "low" (below the LLN), "normal" (within the normal range), "high" (above the ULN). Shift tables will be constructed based on both the minimum and maximum post-baseline values for each subject. A separate table will be provided which summarizes the results of the shift tables in which the number and percentage of subjects with a shift to low (from normal, high, or unknown) and the number of subjects with a shift to high (from normal, low, or unknown) will be tabulated; percentages will be based on the number of subjects at risk. The number at risk for a shift to low (high) is the number of subjects whose baseline value was not low (high), including unknown, who had at least one post-baseline value. Only directions of change indicating a clinical concern will be included in this table summarizing the shifts. The direction of concern is provided in Table 2.

All data collected during Part B, including data collected from unscheduled visits, will be included in the above-mentioned analyses.

Table 2: Direction of Change Indicating Clinical Concern for Laboratory Tests

Laboratory Test	Direction	Laboratory Test	Direction
Chemistry		**Hematology**	
Liver		White blood cells	Low and High
ALT/SGPT	High	Lymphocytes	Low and High
AST/SGOT	High	Neutrophils	Low and High
Total bilirubin	High	Monocytes	Low and High
GGT	High	Eosinophils	Low and High
Renal		Basophils	Low and High
Blood urea nitrogen	High	Red blood cells	Low and High
Creatinine	High	Hemoglobin	Low and High
Electrolytes		Hematocrit	Low and High
Sodium	Low and High	Platelets	Low and High
Potassium	Low and High		
Chloride	Low and High		
Other			
Glucose	Low and High		
Total protein	Low and High		

8.2.1.3. Potentially Clinically Significant Laboratory Abnormalities

Abnormal laboratory values (excluding LDH, haptoglobin, and reticulocytes) will also be evaluated by determining the number and percentage of subjects with at least one potentially clinically significant laboratory abnormality over the course of Part B of the study that also represents a worsening from baseline. The potentially clinically significant levels are based on Grade 2 or higher thresholds from the CTCAE v 4.03 where possible, or are defined by Bioverativ's safety group. Subjects who have a post baseline laboratory value that meets the criteria for being potentially clinically significant but do not have a baseline value will be included in the numerator for determining the percentage of subjects with an abnormality.

All data collected during Part B, including data collected from unscheduled visits, will be included in this analysis.

8.2.2. Systemic Lupus Erythematosus (SLE) Panel

SLE panel (below) will be summarized with descriptive statistics for the Safety Analysis Set. The number of subjects with all negative results prior to receiving BIVV009, the number of subjects with at least one positive prior to receiving BIVV009, the number of subjects who tested negative at all post-baseline assessments, and the number of subjects who tested positive at any post-baseline assessment will be summarized for the individual SLE parameters as well as the combined (overall) SLE panel results.

Systemic Lupus Erythematosus Panel

Antinuclear antibody (ANA), multiplex with dsDNA, Anti-La/SSB antibody (SS-B), Anti-riboucleoprotein 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).

8.2.3. Anti-drug Antibody (ADA)

Subjects will be evaluated for anti-drug antibodies at Baseline and at the ET/EOS/Safety Follow-up visit in Part B. Subjects with negative or positive anti-drug antibodies at baseline and post baseline, as well as the incidence and prevalence will be summarized for the Combined Study Period. A listing will be provided for subjects with negative or positive anti-drug antibodies along with the associated titer if available. If applicable, TEAEs for those subjects will be included in the same listing.

8.3. ECG and Vital Signs

Unless specified otherwise, all analyses described below will be performed on the Part B Study Period, starting at Week 27, and by-visit summaries will be presented through the end of Part B.

8.3.1. Electrocardiograms (ECG)

The proportion of subjects with specific clinical interpretations (Normal; Abnormal, not an AE; Abnormal, AE) will be summarized by visit, through the end of Part B.

The proportion of subjects with a shift in clinical interpretation from baseline will be summarized. All data collected during Part B, including data collected from unscheduled visits, will be included in this analysis.

8.3.2. Vital signs

Vital signs (systolic and diastolic blood pressure, pulse, respiratory rate, and temperature) will be summarized by visit, through the end of Part B, for the observed values and change from baseline using descriptive statistics for the Safety Analysis Set.

The number and percentage of subjects with potentially clinically relevant post-baseline abnormalities will be presented. All data collected during Part B, including data collected from

unscheduled visits, will be included in this analysis. The criteria for potentially clinically relevant post-baseline abnormalities are shown below in Table 3.

Table 3: Criteria to Determine Clinically Relevant Abnormalities in Vital Signs

Vital Sign	Criteria for Abnormalities
Temperature	> 38°C and an increase from pre-dosing of at least 1°C
Pulse	> 120 beats per minute post-baseline or an increase from pre-dosing of more than 20 beats per minute; < 50 beats per minute post-baseline or a decrease from pre-dosing of more than 20 beats per minute
Systolic Blood Pressure	> 180 mmHg post-baseline or an increase from pre-dosing of more than 40 mmHg; < 90 mmHg post-baseline or a decrease from pre-dosing of more than 30 mmHg
Diastolic Blood Pressure	> 105 mmHg post-baseline or an increase from pre-dosing of more than 30 mmHg; < 50 mmHg post-baseline, or a decrease from pre-dosing of more than 20 mmHg
Respiratory Rate	> 35 breaths per minute post-baseline; < 10 breaths per minute post-baseline

9. PHARMACOKINETIC ANALYSIS

Plasma BIVV009 concentrations will be listed by subject, nominal visit, date and time of collection and study day. Summary statistics of plasma BIVV009 concentrations will be presented by nominal visit and study day including n, mean, standard deviation, coefficient of variation, geometric mean, median and range. Individual and mean plasma BIVV009 concentration-versus-time profiles will be plotted. The above analyses will be conducted using the PK Analysis Set for the Cumulative Study Period.

10. PHARMACODYNAMIC ANALYSIS

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 subject listings will be presented by time point and study day. The above analyses will be conducted using the PD Analysis Set for the Cumulative Study Period.

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