STATISTICAL ANALYSIS PLAN

STUDY BCX9930-203

DATE OF PLAN:

Final Version 1.0: 04 October 2023

BASED ON:

Protocol Version (Date): Version 4.0: 01 August 2022

STUDY DRUG:

BCX9930

PROTOCOL NUMBER:

BCX9930-203

STUDY TITLE:

A Randomized, Double-Blind, Multicenter, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy, Safety, and Tolerability of Oral BCX9930 Monotherapy for the Treatment of Paroxysmal Nocturnal Hemoglobinuria

SPONSOR:

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This study is being conducted in compliance with Good Clinical Practice, including the archiving of essential documents.

TECHNICAL SUMMARY REPORT (TSR)

Name of Sponsor/Company **BioCryst Pharmaceuticals, Inc.**	**Individual Study Table Referring to Part of the Dossier:** **Volume:**	***(For National Authority Use Only)*:**
Name of Finished Product: BCX9930	Page:	
Name of Active Ingredient: [redacted]		
Title of Study: A Randomized, Double-Blind, Multicenter, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy, Safety, and Tolerability of Oral BCX9930 Monotherapy for the Treatment of Paroxysmal Nocturnal Hemoglobinuria (BioCryst Protocol BCX9930-203)		
Investigators: Study Centers: This study will be conducted at study centers in multiple countries/regions		
Studied period (years): Approximately 2 years (approximately 12-month enrollment period plus approximately 1 month of screening and 1 year of treatment)	**Phase of development:** Phase 2	

Introduction

BioCryst stopped development of BCX9930 in December of 2022 based on changes in the competitive environment. This statistical analysis plan contains a detailed description of the statistical methods to support the abbreviated clinical study report (aCSR) for this study.

Primary Objective:

- To determine the efficacy of oral BCX9930 monotherapy administered for 12 weeks, as compared to placebo, in subjects with paroxysmal nocturnal hemoglobinuria (PNH)

Secondary Objectives:

- To evaluate the safety and tolerability of BCX9930 monotherapy administered for 12 weeks, as compared to placebo, in subjects with PNH

- To characterize the effects of BCX9930 monotherapy administered for 12 weeks, as compared to placebo, using clinical and laboratory measurements, including complement and thrombosis biomarkers, and PNH clone size, in subjects with PNH

- To evaluate the effects of BCX9930 monotherapy administered for 12 weeks, as compared to placebo, on the Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue scale and other patient-reported outcomes (PROs) in subjects with PNH
- To characterize BCX9930 plasma concentrations and pharmacokinetic (PK) parameters in subjects with PNH

For this study, unless indicated otherwise, all endpoints will be assessed at or to Week 12.

Primary Endpoint

- Change from baseline (CFB) in hemoglobin (Hb) [at Week 12]

Key Secondary Endpoints

- Proportion of subjects who are transfusion-free [from Week 4 to Week 12]
- Number of units of packed red blood cells (pRBCs) transfused [from Week 4 to Week 12]
- Percent CFB in lactate dehydrogenase (LDH) [at Week 12]
- CFB in FACIT-Fatigue scale score [at Week 12]

Other Secondary Endpoints:

- Percent reduction in the rate of pRBC and whole blood units transfused [from Week 4 to Week 12 vs. prestudy transfusion rate (12 month prestudy transfusion rate)]
- Proportion of subjects with Hb ≥ 12 g/dL [at Week 12]
- Hb stabilization, defined as avoidance of a > 2 g/dL decrease in the absence of transfusion [from Week 4 to Week 12]
- CFB in total PNH RBC clone size [at Week 12]
- CFB in ratio of total PNH RBC clone size to PNH WBC clone size (i.e., percent PNH RBCs / percent PNH WBCs) [at Week 12]
- CFB in absolute reticulocyte count (ARC) [at Week 12]
- Proportion of subjects with ARC in the normal range [at Week 12]
- CFB in haptoglobin [at Week 12]
- Proportion of subjects with haptoglobin ≥ lower limit of normal reference range (LLN) [at Week 12]
- CFB in total bilirubin [at Week 12]
- CFB in aspartate aminotransferase (AST) [at Week 12]

Safety Endpoints

- Number and proportion of subjects with a treatment-emergent adverse event (TEAE)
- Number and proportion of subjects who discontinue treatment due to a TEAE
- Number and proportion of subjects who experience a treatment-emergent serious adverse event (TESAE)

- Number and proportion of subjects who experience a Grade 3 or Grade 4 TEAE assessed using the United States National Cancer Institute Common Terminology Criteria for Adverse Event (CTCAE) grading scale
- Number and proportion of subjects who experience a treatment-emergent CTCAE Grade 3 or Grade 4 laboratory abnormality

PK and Pharmacodynamic (PD) Endpoints

- PK data will be used to estimate PK parameters using appropriate PK analyses based on the sampling collection approaches
- PD data will be used to estimate PD parameters

Study Design:

This is a randomized, placebo-controlled, double-blind, multicenter, parallel-group, 2-part study in subjects with PNH who are not currently receiving treatment with complement inhibitor therapy. Parts 1 and 2 will be conducted in the same subjects. Subjects will be randomized to receive BCX9930 monotherapy or to placebo under double-blind conditions for the 12-week Part 1 randomized treatment period. All subjects in Part 2 will receive BCX9930. Subjects who are randomized to BCX9930 monotherapy in Part 1 will continue to receive BCX9930 in Part 2. Subjects who are randomized to placebo in Part 1 will discontinue that therapy at the Week 12 visit and receive BCX9930 in Part 2.

Methodology:

Part 1: Eligible subjects will be randomized in a 2:1 ratio to receive BCX9930 monotherapy at a dose of 500 mg twice-daily (BID) or matched placebo under double-blind conditions. Randomization will be stratified based on whether a pRBC transfusion was received within the 6 months prior to baseline (yes vs. no). Subjects will return to the clinic for scheduled study visits at Weeks 1, 2, 4, 8, and 12.

During the blinded treatment phase of the study, any subject who experiences a qualifying event reflecting a significant worsening of their PNH may be allowed to switch to open-label BCX9930.

Data collected through Week 12 will constitute the primary data set for the study.

Part 2: Subjects randomized to placebo during Part 1 will discontinue placebo at the Week 12 visit and be switched to open-label BCX9930 in Part 2, so that all subjects receive BCX9930 monotherapy in Part 2. All subjects will return to the clinic at Weeks 13, 14, and 16, and then every 4 weeks thereafter through Week 52. Data collected through Week 52 will be used to assess the long-term safety of BCX9930.

After completion of Part 2, all subjects continuing to derive clinical benefit will be allowed to continue treatment with BCX9930 through enrollment in the separate BCX9930-201 rollover study, where available. Subjects who do not continue BCX9930 therapy after Week 52, or who are prematurely discontinued from BCX9930 treatment prior to Week 52, will be monitored for potential hemolysis and may be required to return to the clinic for an additional visit(s) to assess for acute symptomatic hemolysis, if and when symptoms occur. Subsequently, they will return

to the clinic approximately 3 weeks after the date of last dose of BCX9930 for end of study assessments.

An independent BCX9930 program-wide data monitoring committee (DMC) will provide oversight of the ongoing exposure of subjects to BCX9930.

Number of Subjects (planned):

Approximately 57 subjects with PNH who are not currently receiving treatment with a complement inhibitor.

Diagnosis and Main Criteria for Inclusion:

Subjects must meet all of the following inclusion criteria, as applicable, to be eligible for participation in this study:

1. Male or female, aged ≥ 18 years old.
2. Body weight ≥ 40 kg.
3. Documented diagnosis of PNH confirmed by flow cytometry with a PNH granulocyte or monocyte clone size of ≥ 10% during screening.
4. Treated with a stable regimen of eculizumab for ≥ 3 months prior to the screening visit or ravulizumab for ≥ 6 months prior to the screening visit.
5. Recorded the following results during screening:
   a. Hb of ≤ 105 g/L (≤ 10.5 g/dL).
   b. ARC of ≥ 100×10^9 cells/L (≥ 100,000 cells/μL; ≥ 100 G/L).
   c. Absolute neutrophil count of ≥ 0.75×10^9 cells/L (≥ 750 cells/μL; ≥ 0.75 × G/L).
   d. Platelet count of ≥ 30×10^9/L (≥ 30,000/μL; ≥ 30 G/L).
   e. Adequate iron reserve based on ferritin ≥ LLN or total iron binding capacity ≤ upper limit of the normal reference range (ULN).
   f. Estimated glomerular filtration rate of ≥ 60 mL/min/1.73 m^2 using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (Levey and Stevens 2010) and no evidence of clinically relevant abnormal renal function unrelated to underlying PNH disease.
6. Contraception requirements:

   Female participants must meet at least one of the following requirements:

   a. Be a woman of nonchildbearing potential.
   b. Be a woman of childbearing potential who agrees to use a highly effective contraceptive method throughout the study and for a duration of 30 days after the last dose of study drug.
   c. Alternatively, true abstinence is acceptable for women of childbearing potential when it is in line with the subject's preferred and usual lifestyle.

   Male participants must meet at least one of the following requirements:

a. Males with a female partner of childbearing potential must use condoms throughout the study and for a duration of 90 days after the last dose of study drug unless their partner is using a highly effective contraceptive method independent of the study.

b. Alternatively, true abstinence is acceptable when it is in line with the subject's preferred and usual lifestyle.

Additional details are provided in Protocol Section 11.2.1.

7. Documentation of current vaccinations against *Neisseria meningitidis* types A, C, W, and Y, and *Streptococcus pneumoniae*, or willingness to start vaccination series at least 14 days prior to Day 1.
(Note: Vaccination for *N. meningitidis* type B and for *Haemophilus influenzae* type B [Hib] is strongly encouraged where authorized and available.)
8. In the opinion of the investigator, the subject is expected to adequately comply with all required study procedures and restrictions for the study, including compliance with the twice daily (BID) dosing schedule for BCX9930.
9. Willing and able to provide written informed consent.

Subjects must not meet any of the following exclusion criteria to be eligible for participation in the study:

10. Known history of or existing diagnosis of hereditary complement deficiency.
11. History of hematopoietic cell transplant or solid organ transplant or anticipated candidate for transplantation during the study.
12. Myocardial infarction or cerebrovascular accident within 30 days prior to screening, or current and uncontrolled clinically significant cardiovascular or cerebrovascular condition, including unstable angina, severe congestive heart failure, unexplained syncope, arrhythmia, and critical aortic stenosis.
13. History of malignancy within 5 years prior to the screening visit, with exception of adequately treated non-melanoma skin or superficial bladder cancer, curatively treated carcinoma in situ of the cervix, or other curatively treated solid tumor deemed by the investigator and medical monitor to be at low risk for recurrence.
14. Active bacterial, viral, or fungal infection or any other serious infection within 14 days prior to screening.
(Note: Suspected or confirmed coronavirus disease [COVID-19]; persistent or recurrent positive test(s) for severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2] nucleic acids or antigens; and worsening of dyspnea not due to PNH, vasculitic rash, and persistent fever or other symptoms consistent with multisystem inflammatory syndrome in adults [MIS-A] are exclusionary.)
15. Current participation in any other investigational drug study or participation in an investigational drug study within 30 days prior to the screening visit, or 5.5 half-lives of the investigational drug, whichever is longer.
16. Treatment with anti-thymocyte globulin within 180 days prior to the screening visit.

17. Initiation of treatment with an erythropoiesis-stimulating agent (eg, erythropoietin), a thrombopoietin receptor agonist (eg, eltrombopag), or danazol within 28 days prior to the screening visit.
    (Note: Treatment with these medications initiated > 28 days prior to the screening visit is not exclusionary, if the dose is stable and there is a reasonable expectation that treatment will be continued.)
18. Receiving iron supplementation with an unstable dose in the 28 days prior to the screening visit.
19. Clinically significant abnormal electrocardiogram (ECG) at the screening visit.
    (Note: This includes, but is not limited to, a QT interval corrected using Fridericia's method [QTcF] of > 450 msec in males or > 470 msec in females, or ventricular and/or atrial premature contractions that are more frequent than occasional, and/or as couplets or higher in grouping.)
20. Subjects with any of the following results at the screening visit:
    a. Alanine aminotransferase (ALT; also serum glutamic-pyruvic transaminase [SGPT]) > 3 × ULN.
    b. Aspartate aminotransferase (AST; also serum glutamic-oxaloacetic transaminase [SGOT]) > 3 × ULN.
       (Note: Subjects may be enrolled with AST > 3 × ULN if explained by hemolysis.)
    c. Total serum bilirubin > 2 × ULN.
       (Note: Subjects may be enrolled with total serum bilirubin > 2 × ULN if explained by hemolysis or Gilbert's syndrome. In the case of hemolysis, total serum bilirubin must be < 5 × ULN and in the case of Gilbert's syndrome, total serum bilirubin must be < 11 × ULN.)
21. Current use of a prohibited concomitant medication within 7 days prior to Day 1 as detailed in Protocol Section 9.8.1.
22. Positive serology for human immunodeficiency virus, or active infection with hepatitis B virus or hepatitis C virus, unless receiving antiviral therapy and viral load is undetectable.
23. Positive drugs of abuse screen, unless by prescription.
24. Pregnant, planning to become pregnant, or breastfeeding.
25. Known hypersensitivity to BCX9930 or any of its formulation excipients.
26. History of severe hypersensitivity to any medicinal product, which was associated with swelling, severe rash requiring treatment/hospitalization, or anaphylaxis.

Any other clinically significant medical or psychiatric condition that, in the opinion of the investigator or sponsor, would interfere with the subject's ability to participate in the study or increase the risk of participation for that subject.

Investigational Product, Dosage and Mode of Administration:

For subjects randomized to BCX9930 monotherapy in Part 1, and all subjects in Part 2, BCX9930 will be administered orally at a dose of 500 mg BID, approximately 12 hours apart, using tablets. BCX9930 may be administered with or without food.

Per Protocol Amendment 4.0, subjects who previously received 500 mg BID and remain on study treatment will be dose adjusted to 400 mg BID. For all newly enrolled subjects, at the initiation of BCX9930 dosing, subjects will take a dose of 200 mg BID for the first 14 days of treatment before increasing the dose to 400 mg BID. The appropriate quantity of BCX9930 tablets will be taken orally, twice a day, approximately 12 hours apart, without regard to food. Adequate hydration should be maintained to prevent the formation of highly concentrated urine.

Duration of Treatment:

In Part 1, either BCX9930 monotherapy or placebo for 12 weeks. In Part 2, all subjects will receive BCX9930 for 40 weeks.

Reference Therapy, Dosage and Mode of Administration:

For subjects randomized to placebo in Part 1, matched placebo tablets will be administered orally BID, approximately 12 hours apart, without regard to food.

Statistical Methods:

Continuous data will be summarized using the number of subjects with available data, mean, SD, median, minimum, and maximum. Categorical data will be summarized using counts and percentages. For specified PK parameters, the geometric n, geometric mean and associated 95% confidence interval (CI), and the geometric between-subject coefficient of variation (CV%) will be presented in addition to the other descriptive statistics. There will be no formal hypothesis testing.

The necessary results for the aCSR will be summarized in tables and figures. There will be no formal hypothesis testing.

All relevant study data for the aCSR will be listed.

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LIST OF TABLES

1. LIST OF ABBREVIATIONS

Table 1: List of Abbreviations and Definitions of Terms

Abbreviation	Term
aCSR	abbreviated clinical study report
ADaM	analysis data model
AE	adverse event
AKI	acute kidney injury
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ARC	absolute reticulocyte count
AST	aspartate aminotransferase
BID	twice daily
BMI	body mass index
BLQ	below the limit of quantification
BTH	breakthrough hemolysis
COVID-19	coronavirus disease 2019
CTCAE	Common Terminology Criteria for Adverse Event
eCRF	electronic case report form
FACIT	Functional Assessment of Chronic Illness Therapy
FDA	Food and Drug Administration
ICH	International Council for Harmonisation
LLN	lower limit of normal
MAVE	major adverse vascular event
MedDRA	Medical Dictionary for Regulatory Activities
N	total sample size
PNH	paroxysmal nocturnal hemoglobinuria
pRBC	packed red blood cells
PRO	patient-reported outcome
PT	preferred term
RBC	red blood cell
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SE	standard error

SOC	system organ class
TDD	total daily dose
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
ULN	upper limit of normal
WBC	white blood cell
WHO	World Health Organization

2. INTRODUCTION

BioCryst stopped development of BCX9930 in December of 2022 based on changes in the competitive environment.. The purpose of this statistical analysis plan (SAP) is to describe the planned analyses and data displays to be included in the abbreviated clinical study report (aCSR) for Study BCX9930-203 (Study 203).

Protocol Revision Chronology:		
Protocol v1.0	18 March 2021	Original
Protocol v2.0	27 May 2021	Amendment 1
Protocol v3.0	29 June 2022	Amendment 2
Protocol v4.0	01 August 2022	Amendment 3

This SAP was developed in accordance with the International Council for Harmonisation (ICH) E9 guideline. The purpose of this document is to provide details on the statistical methodology used to meet the objectives for Study 203. Study population definitions, derivations of variables, handling of missing data, and other information necessary for analysis of study data are provided. Planned tables, figures, and listings are specified.

The document may evolve over time, for example, to reflect the requirements of protocol amendments or regulatory requests. However, the final SAP must be finalized, approved by the sponsor, and placed on file before database is locked. Deviations from the final approved plan will be noted in the CSR.

3. STUDY OBJECTIVES AND ENDPOINTS

This study is comprised of 2 parts in subjects with PNH. Parts 1 and 2 will be conducted in the same subjects.

3.1. Objectives

3.1.1. Part 1 Objective

Part 1 of the study will characterize the effects, safety, and tolerability of treatment with oral BCX9930 monotherapy for 12 weeks versus placebo under double-blind conditions.

To characterize BCX9930 plasma concentrations and pharmacokinetic (PK) parameters in subjects with PNH.

3.1.2. Part 2 Objective

Part 2 of the study will evaluate the long-term safety and tolerability of open-label BCX9930 monotherapy when administered through Week 52. All subjects in Part 2 will receive BCX9930.

To characterize BCX9930 plasma concentrations and pharmacokinetic (PK) parameters in subjects with PNH.

3.2. Endpoints

For this study, unless indicated otherwise, endpoints will be assessed at Week 12.

Primary Endpoint

- Change from baseline (CFB) in hemoglobin (Hb) [at Week 12]

Key Secondary Endpoints

- Proportion of subjects who are transfusion-free [from Week 4 to Week 12]
- Number of units of packed red blood cells (pRBCs) transfused [from Week 4 to Week 12]
- Percent CFB in lactate dehydrogenase (LDH) [at Week 12]
- CFB in FACIT-Fatigue scale score [at Week 12]

Other Secondary Endpoints:

- Percent reduction in the rate of pRBC and whole blood units transfused [from Week 4 to Week 12 vs. prestudy transfusion rate (12 month prestudy transfusion rate)]
- Proportion of subjects with Hb ≥ 12 g/dL [at Week 12]
- Hb stabilization, defined as avoidance of a > 2 g/dL decrease in the absence of transfusion [from Week 4 to Week 12]
- CFB in total PNH RBC clone size [at Week 12]
- CFB in ratio of total PNH RBC clone size to PNH WBC clone size (i.e., percent PNH RBCs / percent PNH WBCs) [at Week 12]
- CFB in absolute reticulocyte count (ARC) [at Week 12]
- Proportion of subjects with ARC in the normal range [at Week 12]
- CFB in haptoglobin [at Week 12]
- Proportion of subjects with haptoglobin ≥ lower limit of normal reference range (LLN) [at Week 12]
- CFB in total bilirubin [at Week 12]
- CFB in aspartate aminotransferase (AST) [at Week 12]

Safety Endpoints

- Number and proportion of subjects with a treatment-emergent adverse event (TEAE)
- Number and proportion of subjects who discontinue treatment due to a TEAE
- Number and proportion of subjects who experience a treatment-emergent serious adverse event (TESAE)
- Number and proportion of subjects who experience a Grade 3 or Grade 4 TEAE assessed using the United States National Cancer Institute Common Terminology Criteria for Adverse Event (CTCAE) grading scale
- Number and proportion of subjects who experience a treatment-emergent CTCAE Grade 3 or Grade 4 laboratory abnormality

PK and Pharmacodynamic (PD) Endpoints

- PK data will be used to estimate PK parameters using appropriate PK analyses based on the sampling collection approaches
- PD data will be used to estimate PD parameters

4. STUDY DESIGN

4.1. Summary of Study Design

This is a randomized, placebo-controlled, double-blind, multicenter, parallel-group, 2-part study conducted in the same subjects.

4.1.1. Part 1 Study Design

Part 1 of the study is designed to evaluate the efficacy, safety, and tolerability of treatment with oral BCX9930 monotherapy for 12 weeks versus placebo in subjects with PNH who are not currently receiving treatment with a complement inhibitor. Eligible subjects will be randomized in a 2:1 ratio to receive either BCX9930 monotherapy or placebo for 12 weeks under double-blind conditions. After completion of all baseline procedures, the first dose of study drug (i.e., BCX9930 or placebo) will be administered on Day 1 under the supervision of clinic staff. Depending on the time of the first dose administration, the second dose of study drug may be taken at home later that day. Subsequent doses of study drug are taken BID, approximately 12 hours apart, through Week 12. Subjects will be required to return to the clinic at Weeks 1, 2, 4, 8, and 12 for study assessments. Additional safety assessments will be performed at Weeks 3, 5, 6, 7, and 10. At the Week 12 visit, the treatment assignment for Part 1 will be unblinded.

During the blinded treatment phase of the study, any subject who experiences a qualifying event reflecting a significant worsening of their PNH may be allowed to switch to open-label BCX9930.

Data collected through Week 12 will constitute the primary data set for the study; hence, the primary database will be locked and analyzed following capture of available data for all subjects through Week 12.

4.1.2. Part 2 Study Design

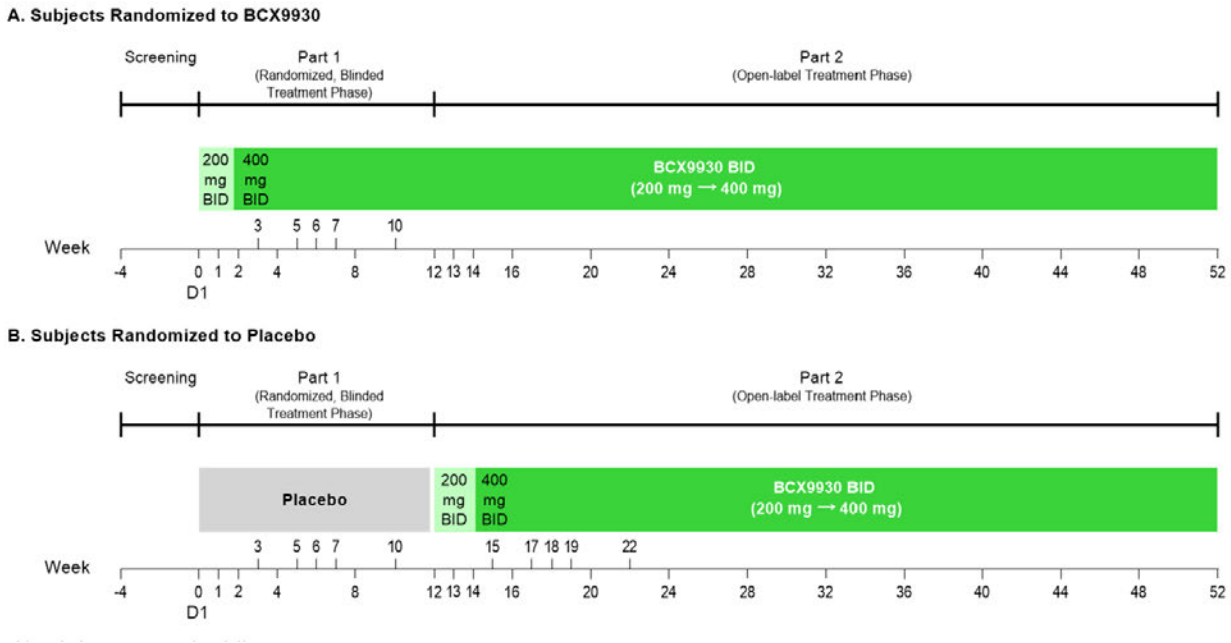
Part 2 of the study is designed to evaluate the long-term safety, tolerability, and effectiveness of BCX9930 monotherapy when administered through Week 52. All subjects will receive BCX9930 in Part 2. Subjects randomized to placebo during Part 1 will discontinue placebo at the Week 12 visit and be switched to open-label BCX9930 monotherapy in Part 2, so that all subjects receive BCX9930 monotherapy in Part 2. All subjects will be required to return to the clinic at Weeks 13, 14, and 16, and then every 4 weeks thereafter through Week 52. Additional safety assessments will be performed at Weeks 15, 17, 18, 19, and 22 for subjects randomized to placebo who are newly switched to BCX9930 for Part 2. Data collected through Week 52 will be used to assess the long-term safety of BCX9930.

After completion of Part 2, all subjects continuing to derive clinical benefit will be allowed to continue treatment with BCX9930 through enrollment in a separate long-term extension study,

or via another access mechanism, where available. Subjects who do not continue BCX9930 therapy after Week 52, or who are prematurely discontinued from BCX9930 treatment prior to Week 52, will be monitored for potential hemolysis and may be required to return to the clinic for an additional visit(s) to assess for acute symptomatic hemolysis, if and when symptoms occur. Subsequently, they will return to the clinic approximately 3 weeks after the date of last dose of BCX9930 for end of study assessments.

A study schema under Protocol Version 4.0 is shown in Figure 1.

Figure 1: BCX9930-203 Study Schema under Protocol Version 4.0



Abbreviations: BID = twice daily; D1 = Day 1.
Note: Assessments occurring below the x-axis require a visit to the investigational site; assessments shown above the x-axis may be completed at the investigational site, at a laboratory local to the subject, or via a home health service (where permitted and available).

Prior to Version 4.0, subjects randomized to BCX9930 were to receive a dose of 500 mg BID for the entire study. Subjects randomized to placebo were to receive a dose of 500 mg BID in Part 2 of the study.

4.2. Definition of Study Treatments

BCX9930 or matching placebo will be administered orally, approximately 12 hours apart, using tablets. Study drug may be administered with or without food.

Prior to protocol Amendment 4.0 treatment was to be administered orally at a dose of 500 mg BID. Per Protocol Amendment 4.0, subjects who previously received 500 mg BID and remain on study treatment will be dose adjusted to 400 mg BID. For all newly enrolled subjects, at the initiation of BCX9930 dosing, subjects will take a dose of 200 mg BID for the first 14 days of treatment before increasing the dose to 400 mg BID.

4.3. Sample Size Considerations

The sample size calculation assumed a Type 1 error rate of 0.05, a common standard deviation (SD) for Hb of 2.3 g/dL from Lee and colleagues (Lee, Peffault de Latour, et al. 2019), and a randomization ratio of 2:1, a sample size of 57 subjects (38 subjects in the BCX9930 arm, 19 subjects in the control arm) would have 85.3% power to detect a treatment difference of 2.0 g/dL or 90% power to detect a treatment difference of 2.15 g/dL in Hb change from baseline for subjects randomized to BCX9930 compared to placebo, based on Satterthwaite's 2-sample t-test for 2 groups with unequal sample sizes. However, for this aCSR, there will be no formal hypothesis testing.

4.4. Randomization

Subjects will be randomized in a 2:1 fashion to either BCX9930 or placebo for Part 1. Randomization will be stratified based on whether a pRBC transfusion was received within the 6 months prior to baseline (yes vs. no). There will be 2 strata as shown below.

Stratum No.	Stratum Description
1	Received pRBC transfusion within previous 6 months
2	Did not receive pRBC transfusion within previous 6 months

Part 2 will not be randomized. All subjects will receive BCX9930.

4.5. Clinical Assessments

Table 3 in BCX9930-203 Protocol Version 4.0 summarizes the Part 1 Schedule of Study Assessments/Procedures (Screening to Week 12).

Table 4 in BCX9930-203 Protocol Version 4.0 summarizes the Part 2 Schedule of Study Assessments/Procedures (Weeks 13 to Week 52).

4.6. Pharmacokinetic and Pharmacodynamic Blood Sampling

Table 5 in BCX9930-203 Protocol Version 4.0 summarizes the Pharmacokinetic and Pharmacodynamic Blood Sampling.

5. PLANNED ANALYSES

5.1. Interim Analyses

No formal interim analyses are planned. DMC analysis will be conducted on an as-needed basis.

5.2. Final Analyses

Analysis of the data from Parts 1 and 2 will be conducted after all subjects enrolled complete or discontinue the study, the resulting clinical database has been cleaned and quality checked, the analysis populations have been finalized, and the final database lock has occurred.

6. GENERAL CONSIDERATIONS FOR DATA ANALYSES AND HANDLING

This section addresses the definitions, algorithms, imputations, and conventions that will apply to the analysis and handling of the data in general. Rules that are data specific will be addressed in the detailed discussions of individual summary tables.

6.1. General Summary Table and Individual Subject Data Listing Considerations

Version 9.4 or higher of the SAS system will be used to analyze the data and to generate tables, figures, and listings. All SAS programs prepared to analyze the data will be properly annotated to permit uninvolved outside statistical experts to replicate all the analyses specified in this SAP.

A table of contents for the tables, figures and listings can be found in Section 12.1.

6.2. Data Management

The standard operating procedures (SOPs) of PharPoint, the selected data management and statistical and programming vendor for this study, will be used. A data management plan will be developed and approved prior to commencement of data entry. Data will be captured using the Medidata electronic data capture system. Electronic validation steps (edit checks) will be used, and data cleaning will occur in conjunction with each site. Prior to transfer of data provided by vendors (e.g., laboratory data), a data transfer agreement including specifications for the type of file, definitions of variables, and contact information for the sending and receiving parties will be developed and finalized.

Data will be mapped to Study Data Tabulation Model (SDTM)-compliant datasets prior to creation of Analysis Data Model (ADaM)-compliant derived datasets for use in the creation of summary tables.

6.3. Data Presentation Conventions

Summary tables and listings will include “footers” providing:

1. Date and time of output generation.
2. SAS® program name that generates the output.
3. The name(s) and location(s) of any input dataset(s) used in the creation of the output.
4. Any other output-specific details that require elaboration.

Version 9.4 or higher of the SAS system will be used to analyze the data and to generate tables, figures, and listings. All SAS programs prepared to analyze the data will be properly annotated to permit uninvolved outside statistical experts to replicate all the analyses specified in this statistical analysis plan (SAP).

The date of output generation links the output to the locked and archived database to allow replication of the results.

6.4. Analysis Populations

6.4.1. Screen Failures

Subjects who give informed written consent but are not randomized to study treatment and are noted as screen failures in the electronic case report form (eCRF) are considered screen failures. Reasons for screen failure will be summarized using this population.

6.4.2. Randomized Population

The randomized population is defined as all subjects who were randomized regardless of whether treatment was taken or not.

6.4.3. Safety Population

The safety population is defined as all subjects who receive at least 1 dose of study treatment, whether placebo or BCX9930.

6.4.4. All Subjects as Treated

The all subjects as treated population (ASaT) population is defined as all subjects who received at least 1 dose of study drug and had a post baseline laboratory assessment.

6.4.5. Pharmacokinetic/Pharmacodynamic Population

Subjects who have both plasma concentration and PD data for at least one post-dose timepoint will be included in the PK/PD population. Baseline Definition

6.5. Baseline Definition

6.5.1. Study Baseline

For a given subject and assessment the baseline result generally will be the latest non-missing result prior to administration of the first dose of study treatment.

For determination of Hb, ARC, total PNH RBC clone size, the ratio of total PNH RBC clone size to PNH WBC clone size, and haptoglobin, only central lab values that were not impacted by transfusions (collected within 14 days after the subject received a pRBC or whole blood transfusion) will be used. All Hb values that meet these criteria and were collected at any time from the Screening visit up to Day 1 pre-dose will be averaged to determine a baseline value. If no central lab values are available but there are local lab values that were not collected within 14 days after the subject received a pRBC or whole blood transfusion, local lab values that meet the criteria will be used in place of the central lab values.

Note: For South Africa, the local labs are preferred over the central laboratory values. In addition, in the event that other parameters (Hb, ARC, total PNH RBC clone size, the ratio of total PNH RBC clone size to PNH WBC clone size, haptoglobin, and FACIT-Fatigue) that are impacted by pRBC or whole blood transfusion that were not collected outside the transfusion-impacted period, the average of pre-transfusion values from the Screening visit up to Day 1 pre-dose will be used to determine a baseline value, even if these values are themselves impacted by

transfusion. If pre-transfusion values are not available, any value prior to Day 1 pre-dose will be used.

6.6. Derived and Transformed Data

6.6.1. Baseline Age

The subject's baseline age in years will be the age provided in the eCRF as collected at the time of consent.

6.6.2. Study Day

If the date of interest occurs on or after the date of first dose of study treatment, then study day will be calculated as (date of interest – date of first dose) + 1. If the date of interest occurs prior to the date of first dose, then study day will be calculated as (date of interest – date of first dose). There is no study day zero.

6.6.3. Change from Baseline and Percent Change from Baseline

Change from baseline will be calculated as (post-baseline result – baseline result). Percent change from baseline will be calculated as (100 × change from baseline/baseline result). If either the baseline or the post-baseline result is missing, the change from baseline and percent change from baseline will be set to missing as well. If the baseline value is 0, the percent change from baseline cannot be calculated under this definition. In these cases, percent change will remain missing.

6.6.4. Treatment-emergent Adverse Events

An AE is considered treatment-emergent if its start date and time is on or after the date and time of first dose of study treatment and will be assigned to the relevant treatment depending on when the TEAE began. If the AE start date is missing and the AE stop date is after the start date of the first dose of study treatment (or the AE is ongoing) then the AE will be considered treatment emergent. If either or both times are missing, then dates alone will be compared. See Section 6.7.3 for incomplete dates or times.

AEs occurring 30 days after the last dose for subjects who discontinue treatment will be considered as TEAEs. All AEs that occurred prior to the initiation of study treatment or those recorded more than 30 days after the last dose of study treatment will be excluded from the tables but will be included in the listings.

6.6.5. Prior and Concomitant Medications

A medication will be classified as prior if it stopped before the first dose of study treatment; that is, its end date and time are on or before the date and time of the first dose of study treatment. Otherwise, the medication will be classified as concomitant; that is, its start date and time are on or after the date and time of the first dose of study treatment, or its end date and time are after the start date and time of the first dose of study treatment, or the medication is flagged as ongoing. If

either or both times are missing, then dates alone will be compared. See Section 6.7.2 for incomplete dates or times.

6.6.6. Visit Windows

For summary purposes in general, records will be assigned to the scheduled visit collected on the eCRF. There will be no time windowing efficacy analyses for this aCSR (i.e., all longitudinal efficacy analysis will be based on the values recorded at the scheduled visits). However, unscheduled visits values will be used for safety analyses of most severe event.

All information collected at an unscheduled visit will be identified as such and presented in the listings.

6.6.7. Multiple Assessments

Where multiple planned scheduled measurements are recorded for a given time point, the mean of the measurements will be calculated and used in any derivation of summary statistics. All available data will be listed.

For baseline Hb calculation when there are multiple assessments between Screening and Day 1, see Section 6.5.1.

All available data will be listed. The endpoint will be listed and summarized.

For subjects with multiple lab values on the same day, special rules will be used to choose values eligible for display on tables and figures. On days with multiple test results from both central labs and local labs, results from the central lab will be used. If central labs are not available, local lab test results will be used. If there are still multiple records on the same date, then the median of available records on that date will be used and the median will be graded for toxicity.

For subjects with multiple lab values during the same nominal visit, special rules will be used to choose values eligible for display on tables. For South African sites: on visits with multiple test results, results from the local lab will be used. For other sites: on visits with multiple test results, results from the central lab will be used. If there are still multiple records on the same visit, then the latest occurring result from the available records on that visit will be used. Results from Unscheduled visits are not included.

6.6.8. Proportion Endpoints

The various endpoints involving proportions are defined below.

- Proportion of subjects who are transfusion-free from Week 4 to Week 12 is defined for each treatment group as the number of subjects who do not receive any transfusions (pRBCs or whole blood) during the period of interest from the start to the end, inclusive, divided by the total number of subjects in that treatment group at the start of the period of interest.
- Note: Subjects who either (1) discontinue treatment prior to Week 12, or (2) have an on-study Hb value ≤ 7 g/dL regardless of symptoms will not be considered transfusion-free.

6.6.9. Number of Units of Packed RBCs Transfused

The number of units of pRBCs will be the total count per subject of units of pRBCs or whole blood that are administered to the subject from Week 4 to Week 12 as recorded in the eCRF. Transfusions of 1 unit of whole blood will count as 1 unit of pRBCs. The period of interest is Week 4 to Week 12 and includes Week 4 to the time of last dose of 9930. For subjects who discontinue treatment, the number of units will be calculated through the date of study treatment discontinuation.

6.7. Handling of Missing Data

Every effort will be made to obtain all data. In cases where this is not possible, various methods for handling the missing data will be employed.

6.7.1. Missing Efficacy Endpoints

For the primary endpoint (change from baseline in hemoglobin at Week 12) as well as key secondary endpoints LDH and FACIT-Fatigue Scale, results will be presented for (1) the subjects with a Week 12 change from baseline and (2) the Week 12 change from baseline using the last observation carried forward.

6.7.2. Missing Start and Stop Dates for Prior and Concomitant Medication

For analysis of medications, a complete date should be established to identify medication as occurring during treatment or not. For the purposes of handling partially reported start and stop dates for medication, the following algorithm will be applied:

- Missing start day, but month and year present:

  If study medication had been taken in the same month and year as the occurrence of the medication, then the start day of the medication will be assigned to the day of first dose of study medication.

  Otherwise, the start day will be set to the first day of the month.

- Missing start day and month, but year present:

  If study medication had been taken in the same year as the occurrence of the medication, then the start date of the medication will be assigned to the date of first application of study medication.

  Otherwise, the start day and month will be set to 01 January.

- Missing end day, but month and year present:

  The day will be set to the last day of the month.

- Missing end day and month, but year present:

  The end day and month will be set to the date of trial termination.

6.7.3. Missing Start Date, Stop Date, Severity, or Relationship for Adverse Events

The same conventions to address incomplete dates for prior and concomitant medications will also be used for AEs. Should an event have a missing severity or relationship, it will be classified as having the highest severity and/or strongest relationship to study treatment.

6.7.4. Missing Time of First Dose

In case of missing time for first dose, it will be assumed that baseline measures that were to be taken prior to first dose according to the protocol were in fact taken prior to dosing.

6.7.5. Transfusion-impacted Period

The 14-day period following a transfusion of pRBCs or whole blood is defined as the transfusion-impacted period (i.e., the interval between the transfusion day and the current study day is ≤ 13 days and includes the day of transfusion). An exception to this rule is that the transfusion-impacted period for haptoglobin is the 3-day period following a transfusion (i.e., the interval between the transfusion day and the current study day is ≤ 2 days and includes the day of transfusion).

The following parameters are impacted by pRBC or whole blood transfusion:

- Hemoglobin
- Reticulocytes
- PNH RBC (Type II and III red blood cells)
- Ratio of PNH RBC to PNH WBC
- FACIT-Fatigue
- Haptoglobin (transfusion-impacted period is limited to 3 days instead of 14)

7. STUDY POPULATION

All study population data to support the aCSR will be presented in data listings.

A CONSORT diagram will be created based on the subject disposition and analysis populations summary tables for the study report.

7.1. Subject Disposition

The subject disposition table for all subjects will summarize the number and percentage of subjects that screen failed, were randomized, received at least one dose of study drug, discontinued treatment, the reasons for discontinuation, and subjects that completed the study. Results will be summarized for the BCX9930 and placebo groups and overall.

The percentages for subjects dosed, discontinued, and completed will be based on the number of subjects randomized. Percentages for discontinuation reason will be based on the number of subjects that discontinued.

7.2. Analysis Populations

The analysis population table for all subjects in the safety population will summarize the number and percentage of subjects in the ASaT and PK/PD substudy populations with percentages based on the number of subjects in the safety population. The results will be presented for the BCX9930 and placebo and overall.

7.3. Demographic and Baseline Characteristics

The subject demographic and baseline characteristics table for the subjects in the safety population will descriptively summarize results for age at consent, race, ethnicity, and sex. Results will be summarized for the BCX9930 and placebo groups and overall.

7.4. PNH History

The PNH history table for the subjects in the safety population will descriptively summarize results for the assessments recorded in the Paroxysmal Nocturnal Hemoglobinuria History CRF page. The results will be presented for the BCX9930 and placebo groups and overall.

7.5. Prior and Concomitant Medications

Medications will be classified as prior or concomitant, coded using the World Health Organization (WHO) drug dictionary version B3 March 2021, and summarized by Anatomical Therapeutic Class (ATC) 4 term, preferred term (PT), and treatment group. Multiple uses of the same medication (by preferred name) will be counted once only per subject per study treatment.

7.5.1. Summary of Concomitant Medications

The concomitant medications table for the subjects in the safety population will summarize the number and percentage of subjects taking concomitant medication(s) by ATC 4 term and PT. The results will be presented for the BCX9930 and placebo groups and overall.

7.5.2. Summary of 12-Month Pre-study Transfusion Details

The 12-month pre-study transfusion detail history table for the subjects in the safety population will descriptively summarize results for the assessments recorded in the Blood Transfusions History CRF page. Results will be summarized for the BCX9930 and placebo groups and overall.

7.6. Exposure to Study Treatment

The exposure to study treatment table for the subjects in the safety population will descriptively summarize for each treatment group the number and percentage of subjects dosed and descriptive statistics (i.e., mean, standard deviation, etc.) for the number of days of exposure.

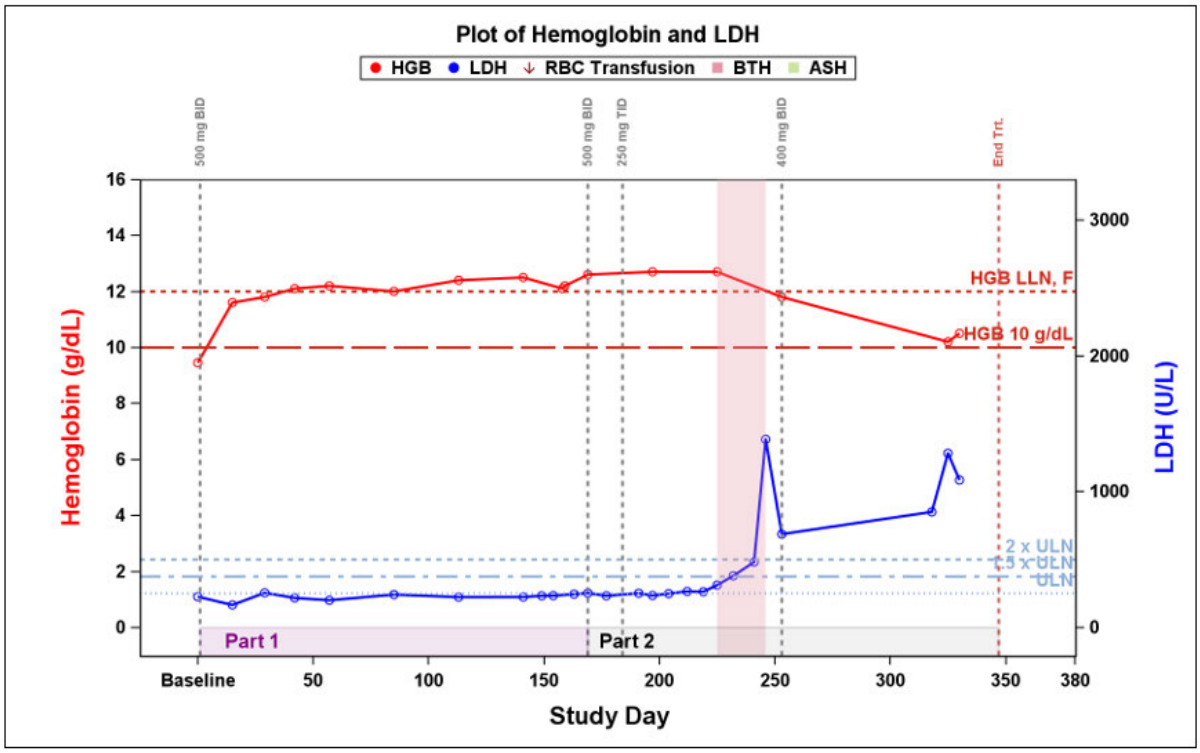
The compliance data as reported on the eCRF will be listed.

8. EFFICACY

All study efficacy data to support the aCSR will be presented in data listings.

Summary figures to support efficacy for the aCSR will include:

- Plot of Hemoglobin, LDH, hemolysis events and transfusion events (see example below)



Hypothesis testing will not be conducted due to sponsor discontinuation of the study. No subgroup analyses are planned.

8.1. Primary Efficacy Analysis of Hemoglobin

Descriptive statistics for the observed values and changes from baseline in hemoglobin in the ASaT population will be presented for all scheduled visits during the 12-week double-blind treatment period. A last observation carried forward summary, based on scheduled visits only, will also be provided. Results will be presented for the BCX9930 and placebo groups. Values recorded within 14 days after the subject received a pRBC or whole blood transfusion will be excluded from the summary statistics. Unscheduled visits will be presented in the data listings but not summarized in the table.

In addition, hemoglobin changes from baseline at the Week 12 scheduled time point will be summarized for the following dose groups: BCX9930 200 mg BID, BCX9930 750 mg TDD, BCX9930 400 mg BID, BCX9930 500 mg BID, All BCX9930 Subjects, placebo as well as the total across all groups.

8.2. Key Secondary Efficacy Endpoints

8.2.1. Proportion of Subjects Who Are Transfusion-Free from Week 4 to Week 12

The number and percentage of subjects who are transfusion-free in the ASaT population from Week 4 to Week 12 will be summarized. Results will be presented for the BCX9930 and C5-INH groups. Subjects who either (1) discontinue treatment prior to Week 24, or (2) a Hb value ≤ 7 g/dL regardless of symptoms will not be considered transfusion-free.

8.2.2. Number of Packed Red Blood Cells (pRBCs) Transfused from Week 4 to Week 12

Descriptive statistics for the number of units of pRBCs transfused from Week 4 to Week 12 in the ASaT population will be summarized. Results will be presented for the BCX9930 and placebo groups.

8.2.3. Percent CFB in Lactate Dehydrogenase (LDH)

Descriptive statistics for the observed values, changes from baseline, and percent changes from baseline in LDH in the ASaT population will be presented for all scheduled visits during the 12-week double-blind treatment period. A last observation carried forward to Week 12 summary, based on scheduled visits only, will also be provided. Results will be presented for the BCX9930 and placebo groups. Unscheduled visits will be presented in the data listings but not summarized in the table.

8.2.4. CFB in FACIT-Fatigue scale

Questions and scoring for the FACIT-Fatigue scale can be found in Section 12.3.

Descriptive statistics for the observed values and changes from baseline in the FACIT-Fatigue scale in the ASaT population will be presented for all scheduled visits during the 12-week double-blind treatment period. A last observation carried forward to Week 12 summary, based on scheduled visits only, will also be provided. Results will be presented for the BCX9930 and placebo groups. Values recorded within the Transfusion-Impacted period will be excluded from the summary statistics. Unscheduled visits will be presented in the data listings but not summarized in the table.

9. SAFETY AND TOLERABILITY

All study safety data to support the aCSR will be presented in data listings.

Summary figures to support safety for the aCSR will include individual subject profiles of ALT, ALP, AST, Hemoglobin, and Total Bilirubin.

AEs will be assessed and recorded from the time of signing of the informed consent through the appropriate follow-up period. AEs will be mapped to MedDRA version 24 preferred term (PT) and system organ class (SOC). Relationship to study treatment will be assessed as not related, unlikely related, possibly related, probably related, or definitely related. AEs will be graded according to the CTCAE scales (Version 5.0, 27 November 2017). AEs not covered by CTCAE criteria will be assessed for severity as mild, moderate, severe, or life-threatening, corresponding to toxicity Grades 1 through 4.

9.1. Overall Summary of Treatment-emergent Adverse Events

The overall summary of TEAEs table for all subjects in the safety population will summarize the number and percentage of subjects that report at least 1 TEAE, have a treatment-related TEAE, have a TEAE leading to treatment withdrawal, have a serious TEAE requiring concomitant medication, have a severe (Grade 3) or life-threatening (Grade 4) TEAE, have a serious TEAE, have a TEAE leading to study discontinuation, and have a TEAE leading to death. In addition to summarizing the number and percentage of subjects that have at least 1 of these events, the table will also summarize the total number and percentage for each of these events. Results will be summarized for the BCX9930 and placebo groups and overall. The percentages for number of subjects will use the safety population sample size as the denominator; the percentages for the number of events will use the total number of TEAEs as the denominator.

In addition, the overall summary of TEAEs results will also be summarized for the following dose groups: BCX9930 200 mg BID, BCX9930 750 mg TDD, BCX9930 400 mg BID, BCX9930 500 mg BID, All BCX9930 Subjects, placebo as well as the total across all groups.

Note: For BCX9930, a subject could appear in more than one dose column.

9.2. Adverse Event Preferred Term and Body/Organ System Summary Tables

9.2.1. Treatment-emergent Adverse Events by System Organ Class and Preferred Term

A summary of the number and percentage of subjects with treatment-emergent adverse events by system organ class and preferred term will be presented along with the number of events for all subjects in the safety population. Results will be summarized for the BCX9930 and placebo groups and overall. The percentages for number of subjects will use the safety population sample size as the denominator.

In addition, the same summary will be presented by: BCX9930 200 mg BID, BCX9930 750 mg TDD, BCX9930 400 mg BID, BCX9930 500 mg BID, All BCX9930 Subjects, placebo as well as overall.

Note: For BCX9930, a subject could appear in more than one dose column.

9.2.2. Other Adverse Event Summary Tables

9.2.2.1. Treatment-emergent Adverse Events by Preferred Term and Treatment Regimen and Dose Group

A summary of the number and percentage of subjects with treatment-emergent adverse events by preferred term will be presented along with the number of events for all subjects in the safety population. Results will be summarized for the BCX9930 and C5-INH groups and overall. The percentages for number of subjects will use the safety population sample size as the denominator. In addition, the same summary will be presented by: BCX9930 200 mg BID, BCX9930 750 mg TDD, BCX9930 400 mg BID, BCX9930 500 mg BID, All BCX9930 Subjects, placebo as well as overall.

Note: For BCX9930, a subject could appear in more than one dose column.

9.2.2.2. Serious Treatment-emergent Adverse Events by MedDRA System Organ Class and Preferred Term

A summary of the number and percentage of subjects with serious treatment-emergent adverse events by SOC and PT term will be presented along with the number of events for all subjects in the safety population. Results will be summarized for the BCX9930 and placebo groups and overall. The percentages for number of subjects will use the safety population sample size as the denominator.

9.2.2.3. Renal Treatment-emergent Adverse Events by System Organ Class and Preferred Term

A summary of the number and percentage of subjects with renal treatment-emergent adverse events by system organ class and preferred term will be presented along with the number of events for all subjects in the safety population. The table will include events in the Acute Renal Failure SMQ, Chronic Kidney Disease SMQ, and Tubulointerstitial Diseases. The percentages for number of subjects will use the safety population sample size as the denominator.

9.2.2.4. Hepatic Treatment-emergent Adverse Events by System Organ Class and Preferred Term

A summary of the number and percentage of subjects with hepatic treatment-emergent adverse events by system organ class and preferred term will be presented along with the number of events for all subjects in the safety population. The table will include events in the drug related hepatic disorders (comprehensive search SMQ). The percentages for number of subjects will use the safety population sample size as the denominator.

9.2.2.5. Treatment-emergent Grade 3 and 4 Laboratory Parameters by Visit and Overall

A summary of treatment-emergent Grade 3 and 4 laboratory parameters will be summarized by visit and overall. For each visit the number of subjects meeting the criteria and the total number of subjects in the relevant treatment group with observations at the specified visit will be presented as well as the resulting percentage.

10. PHARMACOKINETICS AND PHARMACODYNAMICS

Plasma and urine samples for analysis of BCX9930 concentration will be collected according to the schedules presented in Protocol Table 4 to Table 6. Plasma PK sampling will include both sparse (all subjects) and serial (subjects participating in the PK/PD substudy only) collection. Urine sampling will include spot collections only.

10.1.1. Blood Sample Collection

At study centers with appropriate facilities for the collection and processing of serial plasma samples, an optional PK/PD substudy will be performed to characterize the single-dose and steady-state PK parameters of BCX9930 in this patient population.

At these centers, subjects consenting to participate in the optional PK/PD substudy will be asked to complete up to two serial PK sample collections. The first sample collection will assess the single-dose PK of BCX9930, with samples collected on Day 1 for subjects randomized to BCX9930 or during the Week 12 visit for subjects randomized to placebo. The second sample collection will assess the PK of BCX9930 at steady state, with samples collected during the Week 2 or any later visit for subjects randomized to BCX9930 or after at least 2 weeks on BXC9930 for subjects randomized to placebo.

Serial PK For subjects randomized to BCX9930:

- On Day 1, 4 PK blood samples will be collected at 0.5 (± 0.25), 1.5 (± 0.5), 3.5 (± 0.5), and 6 (± 1) hours after administration of the first dose of BCX9930.
- At the Week 2 or later visit, 5 PK blood samples will be collected; the first sample will be collected prior to BCX9930 dosing (≤ 15 minutes), with subsequent samples collected at 0.5 (± 0.25), 1.5 (± 0.5), 3.5 (± 0.5), and 6 (± 1) hours post-dose.

Serial PK For subjects randomized to placebo:

- At the Week 12 visit (or first visit after switching to BCX9930), 4 PK blood samples will be collected at 0.5 (± 0.25), 1.5 (± 0.5), 3.5 (± 0.5), and 6 (± 1) hours after administration of the first dose of BCX9930.
- After at least 2 weeks on BCX9930, 5 PK blood samples will be collected; the first sample will be collected prior to BCX9930 dosing (≤ 15 minutes), with subsequent samples collected at 0.5 (± 0.25), 1.5 (± 0.5), 3.5 (± 0.5), and 6 (± 1) hours post-dose.

Sparse PK For All Subjects:

- Single venous blood samples for analysis of plasma BCX9930 concentration will be collected from all subjects randomized to BCX9930 at each scheduled study visit, beginning Week 1, and at any unscheduled visits.

10.1.2. Urine Sample Collection

Spot urine samples will be collected for analysis of the concentration of BCX9930 and metabolites during Part 1 for subjects randomized to BCX9930 and from all subjects in Part 2.

Urine samples for determination of BCX9930 will be analyzed using validated liquid chromatography-mass spectrometry assays. The concentration of BCX9930 metabolites may also be analyzed using these samples.

For each sample collected, the actual date and time of sample collection, the actual date and time of the last two BCX9930 doses taken prior to the urine collection (where applicable), and whether those doses were taken with or without food will be recorded in the eCRF.

10.2. Pharmacodynamics

10.2.1. Blood Sample Collection

Subjects will have 5 PD samples collected at each substudy visit.

For subjects randomized to BCX9930:

- On Day 1, the first sample will be collected prior to BCX9930 dosing (≤ 2 hours), with subsequent samples collected at 0.5 (± 0.25), 1.5 (± 0.5), 3.5 (± 0.5), and 6 (± 1) hours post-dose.
- At the Week 2 or later visit, the first sample will be collected prior to BCX9930 dosing (≤ 15 minutes), with subsequent samples collected at 0.5 (± 0.25), 1.5 (± 0.5), 3.5 (± 0.5), and 6 (± 1) hours post-dose.

For subjects randomized to placebo:

- At the Week 12 visit, the first sample will be collected prior to BCX9930 dosing (≤ 2 hours), with subsequent samples collected at 0.5 (± 0.25), 1.5 (± 0.5), 3.5 (± 0.5), and 6 (± 1) hours post-dose.
- At the Week 12 or later visit, the first sample will be collected prior to BCX9930 dosing (≤ 15 minutes), with subsequent samples collected at 0.5 (± 0.25), 1.5 (± 0.5), 3.5 (± 0.5), and 6 (± 1) hours post-dose.

As applicable, PD blood samples will be collected at the same time as the corresponding PK blood sample (ie, excluding the pre-dose sample on Day 1 or Week 12).

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10.3. DATA CONVENTIONS

10.3.1. Handling of Data Below the Limit of Quantification

10.3.1.1. Pharmacokinetic Data Below the Limit of Quantification

Concentrations that are BLQ will be presented as “BLQ” in listings. Any table or listing that contains concentration data will include the lower limit of quantification (LLOQ) for the applicable assay(s) as a footnote.

For calculation of summary statistics for plasma and urine concentration data, concentrations that are below the limit of quantification (BLQ) will be treated as zero. Individual BLQ concentrations may alternatively be set to missing if deemed appropriate by the clinical pharmacologist (e.g., BLQ result is implausible based on the totality of available data). If any values are set to missing for concentration analyses, this will be described in the CSR along with the rationale for doing so. These values will be reported as "BLQ" in individual-subject summaries (including listings) with a flag to denote the rationale for excluding in calculation of summary statistics.

If ≥ 33% of the available concentration values at a given timepoint (or interval) are BLQ or missing, only the number of samples, minimum, and maximum will be included in the summary tables. All other descriptive statistics parameters will be reported as "NC" (not calculable).

For estimation of plasma PK parameters, all BLQ concentrations that occur prior to the first quantifiable concentration will be set to 0. All BLQ concentrations that occur after the first quantifiable concentration will be treated as missing. Quantifiable concentrations occurring after 2 consecutive BLQ concentrations and occurring during the terminal elimination phase (as assessed by the clinical pharmacologist) will be treated as missing.

10.3.1.2. Pharmacodynamic Data Below the Limit of Quantification

For calculation of summary statistics for PD measures, values that are BLQ will be treated as zero.

For the calculation of change from baseline and percent change from baseline and PD parameters, values that are BLQ will be handled the same as for summary statistics (i.e., set to zero).

PD values that are BLQ will be presented as reported by the laboratory (e.g., "<LLOQ") in the listings. Any table or listing that contains PD data should have the LLOQ for the applicable assay(s) as a footnote (unless the LLOQ is defined within the body of the listing).

Alternative approaches to handling BLQ PD data may be considered if scientifically justified, and, if used, will be described in the CSR and will also be noted in the statistical outputs, as appropriate.

Note: Some PD assays refer to a "limit of detection" rather than a "limit of quantification". If applicable, BLQ and LLOQ may be updated to BLD (below the limit of detection) and LLOD (lower limit of detection), respectively.

10.3.1.3. Rounding

For reporting, PK and PD data should be rounded to decimal places (DP) or significant figures (SF), depending on the variable. SF refers to the number of nonleading zero digits to report, always counting from the left.

Individual-subject plasma and urine concentration data will rounded to 3 significant figures.

For summary statistics, the following conventions will be applied:

- Number of subjects/samples (n) will be reported as a whole number.
- Minimum and maximum values will be reported to the same number of DP or SF as the individual-subject data.
- All other summary statistics will be reported to 3 SF.

10.4. Pharmacokinetic Analyses

Plasma PK parameters for each subject will be estimated over the sampling interval by non-compartmental analysis (NCA) using Phoenix® WinNonlin® (Certara, New Jersey, USA) version 8.3 or higher.

The following plasma PK parameters will be calculated on days in which serial PK was collected, see Section 10.1.1:

Pharmacokinetic Parameter	Units	Definition	Phoenix WinNonlin Parameter Output
N	N/A	Number of samples	N_Samples
$AUC_{0\text{-last}}$	ng·h/mL	AUC from time zero to the last measurable concentration	AUClast
C_{last}	ng/mL	Last measurable concentration	Clast
C_{max}	ng/mL	Maximum observed concentration	Cmax
T_{max}	h	Time of C_{max}	Tmax
T_{last}	h	Time of C_{last}	Tlast

PK parameters will not be calculated for urine.

10.5. Reporting of Pharmacokinetic Concentration Data and Pharmacokinetic Parameters

Plasma concentrations, urine concentrations, and plasma PK parameters will be listed.

10.6. Pharmacodynamic Analyses

Observed and change from baseline in blood samples for PD and complement biomarkers will be listed.

11. CHANGES FROM PROTOCOL-SPECIFIED ANALYSES

Due to the discontinuation of the BCX9930 drug development by the sponsor, only variables relevant to the aCSR will be summarized and listed. Many of the summaries that were planned for the full CSR are excluded from the aCSR and this SAP. All hypothesis testing including any sensitivity analysis was removed from the SAP.

12. REFERENCES

12.1. Table of Contents for Data Display Specifications

This table of contents provides the expected titles and numbers of the tables, listings, and figures of the final report. Changes to titles or numbering in the final report, additional data listings supporting the tables, or displays being split into multiple smaller displays for clarity will not necessitate a revision to the SAP, nor will they be considered a deviation from planned analyses.

12.1.1. Tables and Figures

Title		Population
Study Population Section		
Figures		
14.1.1	CONSORT Diagram	All Subjects
Tables		
14.1.1	Subject Disposition	All Subjects
14.1.2	Analysis Populations	Safety Population
14.1.3	Demographic and Baseline Characteristics	Safety Population
14.1.4	PNH History	Safety Population
14.1.5.1	Concomitant Medications	Safety Population
14.1.5.2	12-Month Pre-study Transfusion Details	Safety Population
14.1.6.1	Exposure to Study Treatment by Treatment Group	Safety Population
14.1.6.2	Exposure to BCX9930 by Dose	Safety Population
Efficacy Section		
Figures		
14.2.1	Subject Profiles of Hemoglobin, LDH, Hemolysis Events and Transfusion Events	ASaT
14.2.2	Subject Profiles of Creatinine, Hemoglobin, and LDH	ASaT
Tables		

Title		Population
14.2.1.1	Observed and Change from Baseline Hemoglobin (g/dL) by Treatment Group and Visit	ASaT
14.2.1.2	Change from Baseline in Hemoglobin (g/dL) at Week 12 by BCX9930 Dose	ASaT Population
14.2.2.1	Proportion of Subjects Who Were Transfusion-free from Week 4 to Week 12 (Subjects Warranting but Not Receiving Transfusion Were Not Considered Transfusion-free)	ASaT Population
14.2.2.2	Units of pRBCs Transfused from Week 4 to Week 12	ASaT Population
14.2.2.3	Observed, Change from Baseline, and Percent Change from Baseline LDH by Visit	ASaT Population
14.2.2.4	Observed and Change from Baseline FACIT-Fatigue Scale by Visit	ASaT Population
Safety Section		
Figures		
14.3.1	Subject Profiles of ALT, ALP, AST, Total Bilirubin, and Hemoglobin	Safety Population
Tables		
14.3.1.1	Overall Summary of Treatment-emergent Adverse Events by Treatment Group	Safety Population
14.3.1.2	Overall Summary of Treatment-emergent Adverse Events by BCX9930 Dose	Safety Population
14.3.2.1	Treatment-emergent Adverse Events by MedDRA System Organ Class and Preferred Term	Safety Population
14.3.2.2.1	Treatment-emergent Adverse Events by Treatment Group and Preferred Term	Safety Population
14.3.2.2.2	Treatment-emergent Adverse Events by Treatment Group and Preferred Term and BCX9930 Dose Group	Safety Population
14.3.2.3	Serious Treatment-emergent Adverse Events by MedDRA System Organ Class and Preferred Term	Safety Population
14.3.2.4	Renal Treatment-emergent Adverse Events by System Organ Class and Preferred Term: Events in the Acute Renal Failure SMQ, Chronic Kidney Disease SMQ, and Tubulointerstitial Diseases SMQ	Safety Population

Title		Population
14.3.2.5	Hepatic Treatment-emergent Adverse Events by System Organ Class and Preferred Term: Events in the Drug related hepatic disorders - comprehensive search SMQ	Safety Population

12.1.2. Data Listings

Listing 16.2.1	Listing of Subject Disposition	All Subjects
Listing 16.2.2	Listing of Protocol Deviations	All Subjects
Listing 16.2.4.1	Listing of Demographics and Baseline Characteristics	Safety Population
Listing 16.2.4.2	Listing of PNH History	Safety Population
Listing 16.2.4.3	Listing of Concomitant Medications	Safety Population
Listing 16.2.4.4	Listing of 12-month Pre-study Transfusion Details	Safety Population
Listing 16.2.4.5	Listing of Transfusion Details	ASaT Population
Listing 16.2.4.6	Listing of Medical History	Safety Population
Listing 16.2.5.1	Listing of Exposure to Study Treatment by Treatment Group and Dose Level	Safety Population
Listing 16.2.5.2	Listing of Study Drug Compliance	Safety Population
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Listing 16.2.7.2	Listing of Serious Adverse Events	Safety Population
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Listing 16.2.7.4	Listing of Hepatic Treatment-emergent Adverse Events	Safety Population
Listing 16.2.8	Listing of Grade 3 or Grade 4 Laboratory Abnormalities by CTCAE Scale	Safety Population
Listing 16.4.1	Listing of Serial Plasma BCX9930 Pharmacokinetic Concentrations	Safety Population
Listing 16.4.2	Listing of Serial Plasma BCX9930 Pharmacokinetic Parameters	PK/PD Sub-study Population
Listing 16.4.3	Listing of Observed and Change from Baseline in Blood Samples of PD and Complement Biomarkers	PK/PD Sub-study Population
Listing 16.4.4	Listing of Sparse Plasma BCX9930 Concentration	Safety Population
Listing 16.4.5	Listing of Spot Urine BCX9930 Concentration	Safety Population

12.2. Data Display Specifications

Specifications for data displays will be provided in a separate document.

12.3. FACIT-Fatigue Scale

The FACIT-Fatigue scale is portrayed in Table 3 below.

Table 2: FACIT-Fatigue Scale

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.**

		Not at all	A little bit	Some-what	Quite a bit	Very much
HI7	I feel fatigued	0	1	2	3	4
HI12	I feel weak all over	0	1	2	3	4
An1	I feel listless ("washed out")	0	1	2	3	4
An2	I feel tired	0	1	2	3	4
An3	I have trouble <u>starting</u> things because I am tired	0	1	2	3	4
An4	I have trouble <u>finishing</u> things because I am tired	0	1	2	3	4
An5	I have energy	0	1	2	3	4
An7	I am able to do my usual activities	0	1	2	3	4
An8	I need to sleep during the day	0	1	2	3	4

An12	I am too tired to eat	0	1	2	3	4
An14	I need help doing my usual activities	0	1	2	3	4
An15	I am frustrated by being too tired to do the things I want to do	0	1	2	3	4
An16	I have to limit my social activity because I am tired	0	1	2	3	4

The scoring algorithm for the FACIT-Fatigue scale is as follows:

1. Reverse scores from all items except for items An5 and An7 (i.e. calculate 4 – item score to reverse).
2. If at least 7 of the 13 items are answered, sum the individual items to obtain a score. Missing results or results of "Not Done" or "Subject missed question" will be considered unanswered.
3. Multiply the sum of the item scores by the number of items in the subscale (13), then divide by the number of items answered.

This produces a score on a scale from 0 to 52, with higher scores indicating better quality of life.