STATISTICAL ANALYSIS PLAN
Study BCX9930-201

DATE OF PLAN:

Final Version 1.0 24 May 2023

BASED ON:

Protocol Version 5 Date 01 July 2022
eCRF Date 18 January 2023

STUDY DRUG:

BCX9930

PROTOCOL NUMBER:

BCX9930-201

STUDY TITLE:

A PHASE 2, OPEN-LABEL STUDY TO EVALUATE THE LONG-TERM SAFETY OF ORAL BCX9930 IN SUBJECTS WITH PAROXYSMAL NOCTURNAL HEMOGLOBINURIA (PNH)

SPONSOR:

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This study is being conducted in compliance with good clinical practice, including the archiving of essential documents.

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TECHNICAL SUMMARY REPORT (TSR)

Name of Sponsor/Company {Sponsor Name}	**Individual Study Table Referring to Part of the Dossier:** **Volume:**	***(For National Authority Use Only)*:**
Name of Investigational Product: BCX9930	Page:	
Name of Active Ingredient: [redacted]		
Title Of Study: A Phase 2, Open-label Study to Evaluate the Long-Term Safety of Oral BCX9930 in Subjects with Paroxysmal Nocturnal Hemoglobinuria (PNH)		
Study Center(s): Centers that have participated in a previous BCX9930 PNH study		
Co-ordinating Investigator: [redacted]		
Phase of development: 2		

Objectives

Primary Objective:

- To assess long-term safety and tolerability data in eligible subjects with PNH who previously received BCX9930 in a BioCryst-sponsored study and derived benefit from BCX9930 treatment.

Secondary Objectives:

- To assess the continued effectiveness of BCX9930 in treatment of PNH during long-term administration.
- To evaluate patient-reported outcomes (PRO) of long-term BCX9930 treatment
- To collect pharmacokinetic (PK), pharmacodynamic (PD), and complement biomarker data in subjects with PNH for incorporation into meta-study models of population PK and PK/PD.
- To characterize the effects of BCX9930 in subjects with PNH by clinical measurements and PD and complement biomarkers.
- To evaluate biomarkers of complement activation during episodes of breakthrough hemolysis (BTH).

Primary Endpoint:

- Measurement of safety and tolerability by subject incidence of graded treatment-emergent adverse events (TEAEs), laboratory abnormalities, changes to vital signs, electrocardiogram (ECG) results, and physical examination findings.

Secondary Endpoints:

- Clinical PNH symptom assessments including fatigue, dyspnea, chest pain/discomfort, difficulty swallowing (esophageal pain), abdominal pain, headache, erectile dysfunction, hemoglobinuria, jaundice, incidence of BTH, and incidence of thromboembolic events
- Clinical measurements of PNH (lactate dehydrogenase [LDH], hemoglobin, haptoglobin, reticulocytes, transfusion requirements).
- PRO endpoints will include scores from the Quality of Life Questionnaire for Patients with Aplastic Anemia/PNH (QLQ-AA/PNH), Functional Assessment of Chronic Illness Therapy (FACIT) fatigue scale, and Treatment Satisfaction Questionnaire for Medication (TSQM).
- Concentration of BCX9930 in plasma at steady state in subjects with PNH.

Pharmacodynamic (PD) Endpoint:

- PD and complement biomarker measurements will include PNH red blood cell (RBC) and white blood cell (WBC) clone size, plasma Factor Bb levels and alternative complement pathway (AP) activity (as assessed via AP Wieslab).

Exploratory Endpoints:

- [redacted]

Study Design:

This is an open-label phase 2 study designed to evaluate the long-term safety of daily oral treatment with BCX9930 in subjects who have participated in a previous BCX9930 trial for PNH and showed a benefit of treatment as determined by the Investigator. The study allows continued access to BCX9930 for enrolled subjects.

Methodology:

Subjects who meet all of the inclusion and none of the exclusion criteria will be enrolled into the study. Study visits will occur at Screening, Baseline/Day 1, Week 4, then every 4 weeks up to Week 96. Once subjects have reached Week 96, subsequent study visits will occur every 8 weeks up to Week 144. Additional visits will be required in the case of rising serum creatinine.

Subjects will receive up to 144 weeks of daily BCX9930.

- For subjects directly rolling over from another BCX9930 study without treatment interruption, no screening visit is required. The final on-study visit assessments in the prior BCX9930 study will serve as the baseline assessments for this study; however, additional relevant baseline assessments for this study may be performed at the final on-treatment visit for the prior study as needed to satisfy enrollment criteria. Enrollment without treatment interruption into the current study will obviate the requirement for a follow-up visit in the previous BCX9930 study.
- Subjects with an interruption of treatment of 1 to 30 days duration will be required to complete a full baseline visit, but no screening visit.
- Subjects with an interruption of treatment of 31 days or greater will be required to complete a full screening visit and then baseline visit.

Prior to Protocol Version 5, the protocol-specified dosing regimen was 500 mg BCX9930 twice daily (BID). Under Protocol Version 5, subjects will receive 400 mg BCX9930 BID.

Safety and tolerability will be evaluated through assessments of TEAEs, laboratory analyses (clinical chemistry, hematology, coagulation and urinalysis), vital signs, ECGs, and physical examination findings. Safety events of special interest, including infections, will be followed.

Clinical effectiveness will be assessed at each visit, including assessment of PNH-associated clinical symptoms (eg, fatigue, dyspnea, chest pain/discomfort, difficulty swallowing (esophageal pain), abdominal pain, headache, erectile dysfunction, hemoglobinuria, jaundice), LDH, hemoglobin and haptoglobin levels, reticulocyte counts, number of blood transfusions, BTH and thromboembolic events.

PK and PD samples will be collected at each study visit from baseline onwards and at the time of any suspected breakthrough events. PD and complement biomarkers will include PNH RBC and WBC clone size, and plasma Factor Bb and AP activity. [redacted]

Sample Size Justification:

No sample size calculations were conducted for this open-label, long-term safety study. Approximately 200 subjects with PNH may be enrolled in this study to allow continued access to BCX9930 following clinical benefit in a prior BCX9930 trial.

Number of Subjects (planned): Approximately 200 subjects based upon the anticipated clinical programs for BCX9930.

Inclusion Criteria:

1. Able to provide written informed consent
2. Male or non-pregnant, non-lactating female subjects
3. Subjects who have successfully participated in a previous BCX9930 study of PNH and who experienced a clinical benefit, as confirmed by the Investigator. Successful participation is defined as completion of planned duration of dosing with BCX9930 in the prior study, not inclusive of any extension period.
4. Female participants must meet at least 1 of the following contraception requirements:
    a. 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.
    b. Alternatively, true abstinence is acceptable for women of childbearing potential when it is in line with the subject's preferred and usual lifestyle.
    c. Be a woman of nonchildbearing potential.
5. Male participants must meet the following contraception requirements:
    a. Subjects with female partners of childbearing potential must agree to utilize a highly effective contraceptive method.
    b. Alternatively, true abstinence is acceptable when it is in line with the subject's preferred and usual lifestyle.
6. In the opinion of the Investigator, the subject is expected to adequately comply with all required study procedures and restrictions for the duration of the study.

Exclusion Criteria:

1. Any 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 participation would increase the risk for that subject.
2. Any clinically significant history of angina, known coronary artery disease, myocardial infarction, syncope, clinically significant cardiac arrhythmias, left ventricular hypertrophy, cardiomyopathy, aortic stenosis, or any other cardiovascular abnormality.
3. Chronic systemic corticosteroid use. Note: Topical, inhaled, ocular, or nasal sprays containing corticosteroids are allowed.
4. Investigational drug exposure, other than BCX9930, within 30 days of the baseline visit, or 5.5 half-lives of the investigational drug (whichever is longer).
5. For subjects requiring a screening visit:

a. Clinically significant abnormal ECG at the screening visit. This includes, but is not limited to, a QT interval corrected using Fridericia's method (QTcF) > 450 msec in males and > 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.

b. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 3 × upper limit of normal (ULN) (Exception: Subjects may be enrolled with ALT or AST > 3 × ULN if explained by hemolysis. In these cases, ALT and AST must be < 5 × ULN.)

c. Total serum bilirubin > 2 × ULN (Exceptions: Subject may be enrolled with total serum bilirubin > 2 × ULN if the elevated bilirubin is explained by hemolysis or in the case of Gilbert's syndrome. In the case of hemolysis, total serum bilirubin must be < 5 × ULN and in the case of Gilbert's Syndrome, total bilirubin must be < 7 × ULN).

6. Daily use of medications listed in the currently applicable prohibited medications list.
7. Pregnant, planning to become pregnant, or having been pregnant within 90 days of baseline, or lactating.

Investigational Product, Dosage and Mode of Administration:

BCX9930 tablets for oral administration. Under this amendment, subjects will take 400 mg BCX9930 BID orally. Dosage forms may include 100, 200, and/or 250 mg tablets to allow for dose adjustments if needed for the safety management of the subject. Clinical effectiveness and safety will be monitored.

Duration of Treatment:

Subjects will be eligible to receive study drug (BCX9930) for 144 weeks, or until drug is available by another mechanism (eg, expanded or market access) or until the Sponsor discontinues development of the product for PNH; whichever comes first.

Reference Therapy, Dosage and Mode of Administration:

N/A.

Criteria for Evaluation:

Safety:

Safety will be evaluated by TEAEs, laboratory analyses (clinical chemistry, hematology, coagulation, urinalysis with microscopy), vital signs, electrocardiograms (ECGs), and physical examination findings. An independent data monitoring committee (DMC) will review safety data in accordance with a separate DMC Charter.

Effectiveness:

Clinical measurements of PNH include LDH, hemoglobin and haptoglobin levels, reticulocyte counts, PNH symptoms (eg, fatigue, dyspnea, chest pain/discomfort, difficulty swallowing (esophageal pain), abdominal pain, headache, erectile dysfunction, hemoglobinuria, jaundice), number of blood transfusions, BTH, and thromboembolic events will be used to assess ongoing effectiveness.

Patient Reported Outcomes:

Questionnaires will be used to evaluate quality of life (QLQ-AA/PNH), effectiveness of therapy (FACIT fatigue scale) and treatment satisfaction (TSQM).

Pharmacokinetics:

Plasma samples for determination of BCX9930/metabolite concentrations will be collected at each study visit. Spot urine samples for determination of BCX9930/metabolite concentrations will be collected at each study visit. The resulting PK data will be incorporated into meta-study population PK and PK/PD analyses. Metabolites of BCX9930 will be analyzed as appropriate.

Pharmacodynamics and Complement Biomarkers:

Ex-vivo PD and complement biomarker effects of BCX9930 will be assessed using exploratory assays. Samples collected for PD and complement biomarker analysis may be run in more than one assay to elucidate the PD effects of BCX9930. These include:

• Plasma Factor Bb

• PNH RBC and WBC clone size

• AP activity

The ongoing assessment of the activity of BCX9930 and/or availability of a suitable assay may change the required PD assessments over time. [redacted]

Statistical Methods:

Analysis of Safety

Safety endpoints will be summarized and will include the proportion of subjects: with TEAEs; who discontinue due to a TEAE; who receive a reduced dose due to tolerability issues; who experience a treatment-emergent serious adverse event (SAE); who experience a Grade 3 or 4 TEAE; who experience a treatment-emergent, treatment-related adverse event (AE) consistent with a drug rash (eg, rash, maculo-papular exanthem, papular rash); and who experience Grade 3 or 4 laboratory abnormalities.

AEs will be mapped to a Medical Dictionary for Regulatory Activities (MedDRA) preferred term and system organ classification. The occurrence of TEAEs will be summarized using MedDRA preferred terms, system organ classifications, and severity. In addition to severity, AEs and SAEs will also be summarized based on Investigator assessment of relationship to study drug.

Time to dose reduction, time to discontinuation due to a TEAE, and time to development of drug-related rash will be estimated using the Kaplan-Meier method. For those with a drug-related rash, clinical and laboratory findings will be summarized as will the proportion of subjects who successfully continue therapy following onset of rash.

Descriptive statistics for vital signs, weight, and clinical laboratory results will be presented by study visit. Laboratory abnormalities will be graded according to the Division of Microbiology and Infectious Diseases (DMID) Adult Toxicity Table. The number and percentage of subjects experiencing treatment-emergent graded toxicities will be summarized.

Laboratory toxicity shifts from baseline to the worst post-baseline value as well as the last visit will be summarized. The number and percentage of subjects having elevations in ALT, AST, or bilirubin abnormalities in relation to fold above ULN will be summarized according to the United States Food and Drug Administration's Premarketing Clinical Evaluation on Drug-Induced Liver Injury Guidance for Industry.

Clinically significant abnormal ECG findings will be summarized by study visit. Changes from baseline in ECG parameters will also be summarized by study visit. The number and proportion of subjects with clinically important absolute and change-from-baseline thresholds in QTcF will be summarized.

Analysis of Clinical Measurements of PNH

Clinical measurements of PNH (eg, LDH, hemoglobin, absolute reticulocyte count, haptoglobin levels, number of blood transfusions, incidence of BTH, incidence of thromboses and major thromboses, AST, total bilirubin, and direct bilirubin) will be summarized by summary statistics, including change from baseline, by treatment group and study visit. Categorical measurements will be summarized with frequencies and percentages by treatment group and study visit.

Analysis of Effectiveness and Patient Reported Outcomes

Effectiveness and PROs will be monitored with disease-specific clinical assessments,

laboratory assessments, and questionnaires. Responses for subjects with PNH will be categorized using published draft criteria (Risitano, Marotta, et al. 2019) into complete response, major response, good response, partial response, minor response, and no response, modified for study duration and visit schedule.

PROs will include FACIT fatigue scale, TSQM, and QLQ-AA/PNH questionnaires.

Analysis of Pharmacokinetic Data

Plasma and urine concentrations of BCX9930 and metabolites (as applicable) will be summarized by dose regimen and study visit. The resulting PK data will be pooled in a meta-analysis of population PK.

Analysis of Pharmacodynamic Data

Descriptive statistics, including change from baseline, will be provided by study visit and dose regimen. The resulting PD data will be explored using model-based techniques pooled in meta-analyses of PK/PD, as applicable.

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1. LIST OF ABBREVIATIONS

Table 1: List of Abbreviations

Abbreviation	Term
ADaM	Analysis Data Model
AE	adverse event
AKI	acute kidney injury
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AP	alternative complement pathway
ARC	absolute reticulocyte count
AST	aspartate aminotransferase
BID	twice daily
BMI	body mass index
BTH	breakthrough hemolysis
C3	complement 3
C5-INH	C5 inhibitor
CI	confidence interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
COVID-19	coronavirus disease 2019
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
DHHS	Department of Health and Human Services
DMC	Data Monitoring Committee
DMID	Division of Microbiology and Infectious Diseases
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
EOSI	events of special interest
EOSM	events of special monitoring
EVH	extravascular hemolysis
FACIT	Functional Assessment of Chronic Illness Therapy
FDA	United States Food and Drug Administration
FSH	follicle-stimulating hormone
HR	heart rate
IB	investigator's brochure
ICH	International Council on Harmonisation
IMP	investigational medicinal product
INR	international normalized ratio
IV	intravenous
KIM-1	kidney injury molecule 1
LDH	lactate dehydrogenase
L-FABP	liver-type fatty acid-binding protein
MAVE	major adverse vascular event
MedDRA	Medical Dictionary for Regulatory Activities
NCI	National Cancer Institute
PD	pharmacodynamic(s)

pDILI	potential drug induced liver injury
PK	pharmacokinetic(s)
PNH	paroxysmal nocturnal hemoglobinuria
PT	preferred term
pRBC	packed red blood cell(s)
PRO	patient reported outcome
QLQ-AA/PNH	Quality of Life Questionnaire for patients with Aplastic Anemia / Paroxysmal Nocturnal Hemoglobinuria
QTcF	QT interval corrected for heart rate using Fridericia's formula
RBC	red blood cell
SAE	serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SBP	systolic blood pressure
sCr	serum creatinine
SD	standard deviation
SDTM	Study Data Tabulation Model
SE	standard error of the mean
SOC	system organ class
SOP	standard operating procedure
TEAE	treatment-emergent adverse event
TSQM	Treatment Satisfaction Questionnaire for Medication
uACR	urine albumin to creatinine ratio
ULN	upper limit of (the) normal (range)
uNGAL	urine neutrophil gelatinase-associated lipocalin
WBC	white blood cell
WHO	World Health Organization

2. INTRODUCTION

Paroxysmal nocturnal hemoglobinuria (PNH) is a chronic, non-malignant disorder of the hematopoietic stem cells associated with significant morbidity and mortality. Disease control with complement C5 inhibitors such as eculizumab and ravulizumab is incomplete, with persistent transfusion dependence in approximately 50% of patients, development of extravascular hemolysis because of uncontrolled opsonization of erythrocytes, and concomitant bone marrow dysfunction. The currently approved treatments are administered by repeated intravenous infusions. See the Protocol for references and further details.

BCX9930 is a small molecule inhibitor of human factor D that is being developed as an oral treatment of PNH and other complement-mediated diseases. As subjects with PNH successfully complete a BCX9930 study and show clinical benefit, they will be offered the opportunity to continue treatment with BCX9930 by participation in this long term open-label study where all subjects will be provided treatment with open-label BCX9930 for up to 144 weeks.

Because PNH is a severely debilitating, life threatening disorder with limited treatment options, it is considered reasonable to offer continued dosing with BCX9930 to subjects who demonstrate a clinical benefit from treatment as assessed by the site investigator during a prior BCX9930 trial, consistent with International Council for Harmonisation (ICH) M3 and the FDA guidance on severely debilitating or life-threatening hematologic disorders (FDA 2019).

This open-label safety study is designed to assess the long-term safety and effectiveness of BCX9930 in subjects who participated in a previous study of BCX9930. BCX9930-201 offers subjects who participated in a BCX9930 study additional or continued access to BCX9930 treatment for 144 weeks or until the Sponsor discontinues development of the product, whichever comes first.

Eligible subjects may enroll in the current study if the investigator assesses that they may benefit from continued daily administration of BCX9930. The development of BCX9930 may be of benefit to patients with PNH and other complement mediated diseases that are serious, associated with chronic morbidity, and are potentially life-threatening. In Study 101, administration of BCX9930 at doses of 400 mg or 500 mg twice daily (BID), both in subjects who are naïve to C5 inhibitors and in those who are receiving C5 inhibitors and had an inadequate response, resulted in sustained clinical responses, as measured by improvement in Hb levels, and decreases in lactate dehydrogenase (LDH) and C3 opsonization of red blood cells (RBC). Subjects participating in this study may similarly derive a benefit with BCX9930 in controlling the symptoms and/or improving laboratory parameters related to PNH disease. Thorough monitoring and assessment of adverse events (AEs) will be performed for subjects enrolled in this study, and protocol-mandated safety assessments include vital sign measurements, physical examination, electrocardiograms (ECGs), and clinical laboratory testing. Potential risks associated with complement inhibitors for the treatment of PNH, as well as potential risks associated with BCX9930 based on nonclinical and clinical data to date are described in the investigator's brochure (IB) for BCX9930 and summarized below.

- As BCX9930 blocks the alternative complement pathway (AP) of complement, subjects may have increased susceptibility to bacterial infections; subjects receiving BCX9930 will be monitored closely for signs and symptoms of infection; infection risk will be mitigated by requiring subjects to have up to date vaccinations against appropriate bacterial strains, and if required on an individual basis, prophylactic antibiotic administration will be allowed.

- BCX9930 is not expected to increase the risk of contracting coronavirus disease 2019 (COVID-19) following infection with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) or to increase the risk of severe illness with COVID-19; Vaccination against SARS-CoV-2, the causal agent for COVID-19 infection, is allowed, if authorized and available in country or area, and based on investigator's judgment.
- In Phase 3 studies of adult patients with PNH who received eculizumab or ravulizumab, headache considered related to ravulizumab and eculizumab commonly occurred early after the initiation of treatment; in Study BCX9930-101, early onset headache was the most common treatment-emergent adverse event (TEAE) in subjects with PNH treated with BCX9930; therefore subjects will be monitored closely for signs and symptoms of headache.
- A benign maculopapular rash with consistent onset and clinical course has been observed with multiple-day dosing of BCX9930 in both healthy subjects and subjects with PNH; resolving with no intervention while continuing dosing of BCX9930; although there is no evidence for any systemic hypersensitivity, any subject with a rash believed to be related to BCX9930 should be evaluated as deemed medically appropriate.
- Discontinuation of treatment may result in increased risk of hemolysis of PNH RBCs; accordingly, subjects who discontinue or interrupt BCX9930 for any reason will be closely monitored to detect serious hemolysis.

[redacted]

- Blood will be drawn from study subjects for safety, pharmacokinetic (PK), and pharmacodynamic (PD) assessments; to reduce the risk of vasovagal syncope and associated sequelae, venipuncture will be performed with the subject seated or supine; and to limit the risk of anemia, blood volume collected for study-related procedures will be limited to the minimum necessary.
- Subjects will be closely monitored to ensure any local irritation from ECG stickers on chests and limbs does not persist.

Treatment-emergent increases in [redacted] Based on the sponsor's preliminary investigation, reducing the BCX9930 dose to 400 mg BID is anticipated to mitigate the risk of [redacted] to subjects while maintaining the potential for demonstrating clinical benefit in the PNH patient population.

BCX9930 is expected to provide greater efficacy than the currently available C5 inhibitors by not only preventing intravascular hemolysis, but also by preventing C3 mediated extravascular hemolysis (EVH), thereby reducing symptom burden, reducing hemolysis, including EVH and breakthrough hemolysis (BTH), improving patient function, changing the administration route from intravenous (IV) to oral, and improving health-related quality of life. Study subject selection criteria, dose selection, and study monitoring assessments have been included to optimize benefit and to minimize the risk of toxicities to study participants. Regular monitoring of safety parameters, including AEs, clinical laboratory abnormalities, vital signs measurements, ECGs, and physical examination findings, will ensure that the

benefit-risk profile supports continued dosing. In addition, an independent, program-wide data monitoring committee (DMC) will continue to provide oversight of the ongoing exposure of subjects to BCX9930 in this and other clinical studies. The overall benefit-risk balance is therefore considered to be acceptable.

3. STUDY OBJECTIVE(S) AND ENDPOINT(S)

3.1. Study Objective(s)

3.1.1. Primary Objective

- To collect long-term safety and tolerability data in eligible subjects with PNH who previously received BCX9930 in a BioCryst-sponsored study and derived benefit from BCX9930 treatment.

3.1.2. Secondary Objectives

- To assess the continued effectiveness of BCX9930 in treatment of PNH during long-term administration.
- To evaluate patient reported outcomes (PROs) of long-term BCX9930 treatment.
- To collect PK, PD, and complement biomarker data in subjects with PNH for incorporation into meta-study models of population PK and PK/PD.
- To characterize the effects of BCX9930 in subjects with PNH by clinical measurements and PD and complement biomarkers.
- To evaluate biomarkers of complement activation during episodes of BTH.

3.2. Study Endpoint(s)

3.2.1. Primary Endpoints

- Measurement of safety and tolerability by subject incidence of graded TEAEs, laboratory abnormalities, changes to vital signs, ECG results, and physical examination findings.

3.2.2. Secondary Endpoints

- Clinical PNH symptom assessments including fatigue, dyspnea, chest pain/discomfort, difficulty swallowing (esophageal pain), abdominal pain, headache, erectile dysfunction, hemoglobinuria, jaundice, incidence of BTH, and incidence of thromboembolic events.
- Clinical measurements of PNH (LDH, hemoglobin, haptoglobin, reticulocytes, transfusion requirements).
- PRO endpoints will include scores from the Quality of Life Questionnaire for patients with Aplastic Anemia / Paroxysmal Nocturnal Hemoglobinuria (QLQ-AA/PNH), Functional Assessment of Chronic Illness Therapy (FACIT) fatigue scale, and Treatment Satisfaction Questionnaire for Medication (TSQM).
- Concentration of BCX9930 in plasma at steady state in subjects with PNH.

3.2.3. Pharmacodynamic (PD) Endpoint

- PD and complement biomarker measurements will include PNH RBC and white blood cell (WBC) clone size, plasma Factor Bb and AP activity (as assessed via AP Hemolysis and AP Wieslab).

[redacted]

3.3. Statistical Hypotheses

This is an open-label Phase 2 study without a control group; therefore, estimation is emphasized above hypothesis testing.

3.4. Study Design

This is an open-label phase 2 study designed to evaluate the long-term safety of daily oral treatment with BCX9930 in subjects who have participated in a previous BCX9930 trial. The study will also evaluate the long-term effectiveness and impact on quality of life or general well-being of BCX9930 treatment, and the subject's satisfaction with the medication.

Subjects who have provided written informed consent and who have participated in a BCX9930 study will require a screening visit if they have interrupted study drug ≥ 31 days,

Subjects who have provided written informed consent and who have participated in a BCX9930 study will not require a screening visit if they have interrupted study drug for between 1 and 30 days. However, they will require a baseline visit.

For subjects who roll over directly from another BCX9930 study without treatment interruption, no screening visit will be required. The final on-study visit assessments in the prior BCX9930 study will serve as the baseline assessments for this study; however, additional relevant baseline assessments for this study may be performed at the final on-treatment visit for the prior study as needed to satisfy enrollment criteria. Enrollment without treatment interruption into the current study will obviate the requirement for a follow-up visit in the previous BCX9930 study.

A subject may be enrolled once all eligibility criteria and study requirements are met. On-treatment study visits will occur on Day 1, then every 4 weeks up to Week 96 and then every 8 weeks until Week 144. Subjects with sCr elevations will be required to complete additional assessments at the investigational site, at a laboratory local to the subject, or via a home health service (where permitted and available). An independent DMC will review the safety data from this study in concert with the accumulating safety information generated across the BCX9930 clinical development program. The DMC convened and reviewed safety data once the first 4 subjects enrolled completed 12 weeks of dosing. Subsequent DMC meetings were and will be convened as detailed in the DMC Charter.

3.5. Number of Subjects

No sample size calculations were conducted for this open-label, long-term safety study. Approximately 200 subjects will be enrolled. Subjects will be eligible to receive BCX9930 for up to 144 weeks or until the Sponsor discontinues development of the product; whichever comes first. Both males and females will be enrolled. As reproductive toxicology studies have not yet been conducted, women of childbearing potential may be enrolled in this trial only if they meet and maintain strict contraceptive and pregnancy test requirements as listed in this protocol.

3.6. Treatment

The active ingredient for this study is BCX9930, a small molecule inhibitor of Factor D supplied by BioCryst as 100, 200, and/or 250mg tablets. Earlier versions of this Protocol supplied a white or off-white powder in size 0 hard gelatin capsules. Additional details for the chemical and physical characteristics of BCX9930 may be found in the IB and investigational medical product (IMP) dossier (where applicable).

Subjects on earlier versions of the Protocol started treatment at the same dose level and regimen last administered to that subject in the prior study, and individually escalated their dose level as the physician felt appropriate. As of Protocol version 5, all subjects will receive 400 mg BID, and subjects on lower or higher doses will transition to 400 mg BID for continued participation. Where possible, the BCX9930 doses should be taken at the same times each day as close as possible to 12 hours apart (eg. 8:00 AM and 8:00 PM). If a subject does not take a BCX9930 dose at the scheduled time, the missed dose can be taken up to 6 hours after the scheduled dose time. Subjects will be instructed to bring all drug kits (both unused and used bottles) with them for each study visit.

3.7. Clinical Assessments

Planned study visits are Screening; Day 1; Weeks 4 through 96 at 4-week intervals, and Weeks 104 through 144 at 8-week intervals. Safety and tolerability will be evaluated through assessments of TEAEs, laboratory analyses (clinical chemistry, hematology, coagulation, and urinalysis), vital signs, ECGs, and physical examinations at the study visits indicated in the schedule of assessments (see Table 2).

- The questionnaires are to be administered first, then physical exam, then ECG and vital signs before lab samples, PNH clone sample, then PK, PD, concomitant medication and AE review, PNH symptoms assessment, transfusion review, and finally drug dispensing.
- A site is permitted to perform screening assessments over more than one screening visit. Rescreening of ineligible subjects will be approved or denied on a case-by-case basis by the Sponsor Medical Monitor. Retesting of specific assessments without entirely rescreening a subject may be permitted. A screening failure electronic case report form (eCRF) page will be completed for those subjects who do not proceed with study dosing.
- Subjects who dose escalate (under Protocol versions 1-3) will have an additional Dose Escalation visit 2 weeks (± 2 days) after each dose increase.
- Following discontinuation of study drug (either following completion of the treatment period or on premature discontinuation), subjects will return to the clinic for a minimum of 3 consecutive days for Hemolysis Monitoring visits. Following the 3 days of monitoring, if required, subjects may continue to be assessed every 2 days thereafter until the subject has stabilized to a new hemoglobin baseline.
- Subjects who permanently discontinue treatment will return to the clinic for Hemolysis Monitoring visits. Subsequently they will return to the clinic 3 weeks (21 ± 3 days) after the date of their last dose of BCX9930 for their End of Study assessments.

Table 2: Study Design and Schedule of Assessments

Assessment	***Screening Period*** [a]	***Baseline Visit*** [b]	***Treatment Period (Visit Schedule)***		***Unscheduled Visit Following BTH (within 48hrs or next working day)***	***Discontinuation of Study Drug***	***End of Study Assessment***
	Screening Visit (up to Day -28)	**(Day 1)**	**Week 4 and Every 4 Wks up to Wk 96** [c] **(± 3 days)**	**Week 96 and Every 8 wks Until Wk 144** [d] **(± 6 days)**		**Hemolysis Monitoring for at least 3 Consecutive Days** [e]	**3 Weeks (± 3 Days) After Last Dose of Study Drug**
Informed consent [f]	X	X					
Inclusion/exclusion criteria	X	X					
Medical and medication history [g]	X	X					
Weight/height/BMI [h]	X	X	X	X			X
Physical examination [i]	X	X	X	X	X	X	X
ECG [j]	X	X	X	X			X
Pregnancy test (women) [k]	X	X	X	X			X
FSH test (women) [l]	X	X					
Vital signs	X	X	X	X	X	X	X
Clinical chemistry [m]/ hematology/ coagulation/ urinalysis with microscopy [n]/ iron, folate, B12 status labs [o]	X	X	X	X	X [p]	X [p]	X
Urine for biomarkers [q]			X	X	X	X	X
PNH symptoms assessment	X	X	X	X	X	X	X
Assessment of blood transfusions	X	X	X	X			X
Assess AEs, concomitant medications	X	X	X	X	X	X	X
PNH RBC and WBC clone size	X	X	X	X			
FACIT-Fatigue Scale		X	X [r]	X			
QLQ-AA/PNH		X	X [s]	X			
TSQM		X	X [t]	X			
PK blood sample		X	X	X	X	X [u]	
PK urine collection [v]			X	X	X	X	
PD blood sample		X	X	X	X	X [u]	X
Study drug dosing [w]		←----------		----------→	X [x]		
Study drug accountability/ dispensing		X	X	X			X

Abbreviations: AE = adverse event; BID = twice daily; BTH = breakthrough hemolysis; BMI = body mass index; ECG = electrocardiogram; FSH = follicle-stimulating hormone; FACIT = Functional Assessment of Chronic Illness Therapy; IMP = investigational medicinal product; PD = pharmacodynamic; PK = pharmacokinetic; PNH = paroxysmal nocturnal hemoglobinuria; QLQ-AA/PNH = Quality of Life Questionnaire for Patients with Aplastic Anemia/PNH; RBC = red blood cell; TSQM = Treatment Satisfaction Questionnaire for Medication; WBC = white blood cell.

[a] Screening visit is required for subjects who have interrupted study drug for > 30 days.

[b] The baseline visit should be within 28 days of the screening visit. For subjects directly rolling over from another BCX9930 study without treatment interruption, the final on-treatment visit in the prior BCX9930 study will be considered the baseline visit for this study.

[c] Visits should be every 4 weeks until a subject has completed a total of 96 weeks on treatment with BCX9930 (ie, weeks in this study plus weeks in the previous study).

[d] Subjects with sCr elevations will be required to complete additional assessments to monitor for potential renal toxicity at the investigational site, at a remote laboratory more convenient for the subject, or via a home health service (where permitted and available) as indicated in Protocol Section 11.3.4.1 and Protocol Section 13.9.5.3.

[e] Monitoring for the onset of hemolysis will be conducted after each subject stops BCX9930 treatment. Depending on the results, additional hemolysis testing may continue.

[f] Informed consent will be signed at the screening visit for subjects requiring a screening visit and will be signed for all other subjects at the baseline visit or final on treatment visit in the prior study (which serves as the subject's baseline visit in this study).

[g] Medical and medication history should include vaccination history status, assess risk of exposure, and arrange for any appropriate vaccinations to be administered based on local recommendations as well as individual subject considerations.

[h] BMI calculation and height at screening; weight is to be recorded at each in-clinic visit.

[i] Full physical examinations will be performed at screening and baseline; symptom-directed physical examinations will be performed at all post-baseline visits.

[j] All ECGs during the study will be single assessments. ECGs will be conducted every 12 weeks up to Week 96 (ie, Weeks 12, 24, 36, 48, 60, 72, 84, and 96) and every 24 weeks thereafter (ie, Weeks 120 and 144) during the treatment period.

[k] For women of childbearing potential, a serum pregnancy test will be administered at screening; urine pregnancy tests will be assessed at all subsequent visits. Starting at Week 100, women of childbearing potential will start performing urine pregnancy tests at home every 4 weeks (i.e., in between clinic visits). The results will be recorded by the site. If the urine pregnancy test is positive, the subject should contact the site immediately.

[l] FSH will be measured at screening for any woman post-menopausal ≤ 2 years (this may be omitted if menopausal status was demonstrated with elevated FSH in the prior study). For women who do not undergo a screening visit, FSH may be assessed at baseline. In this case, the subject must have a negative urine pregnancy test at baseline prior to receiving study drug.

[m] Cholesterol and triglycerides will be measured every 12 weeks up to Week 96 (ie, Weeks 36, 48, 60, 72, 84, and 96) and every 24 weeks thereafter (ie, Weeks 120 and 144).

[n] Urine microscopy will be performed on urine collected at investigative site visits (and, where possible, at remote visits where the lab has appropriate on-site testing capability). Urine microscopy should be performed using the site's local laboratory (assuming appropriate on-site testing capability exists) in lieu of the central laboratory.

[o] Weeks 48, 96, and 144 only.

[p] Only limited hematology and clinical chemistry parameters measured as per Protocol Section 11.3.5 and Protocol Section 11.3.6.

[q] Urine will be collected at investigative site visits (ie, excluding remote visits) and aliquots frozen for possible future analysis of urine biomarkers.

[r] Completed at all treatment visits through Week 96 only.

[s] Every 6 months through Week 96 only (ie, Weeks 24, 48, 72, and 96 only).
[t] Though Week 96 only (ie, at Weeks 12, 24, 48, 72, and 96 only).
[u] Single PK and PD sample collected 48 hours after treatment discontinuation.
[v] Spot urine samples will be collected for analysis of the concentration of BCX9930 and metabolites at investigational site visits (ie, excluding remote visits).
[w] The protocol-specified dosing regimen prior to this amendment was 500 mg BCX9930 BID. Under this amendment, subjects will take 400 mg BCX9930 BID. The IMP will be supplied by BioCryst as 100, 200, and/or 250 mg tablets to allow for dose adjustments if needed for the safety management of the subject.
[x] BCX9930 dosing should continue following BTH.

4. PLANNED ANALYSES

4.1. Interim Analyses

Interim analyses may be performed during the course of the study as needed to support regulatory filings and safety updates.

4.1.1. Data Monitoring Committee

An independent DMC has been formed to review data from subjects on a regular basis to ensure the continued benefit-risk profile is favorable for each subject. The DMC has convened and reviewed safety data once the first 4 subjects enrolled completed 12 weeks of dosing. Subsequent meetings were and will be convened as detailed in the DMC Charter. The DMC may meet at any time should a safety issue arise that requires DMC input or a partial or full data review. A separate DMC charter maintained in the trial master file describes membership, roles, timing of DMC review, and responsibilities of the DMC members.

4.2. Final Analysis

The final analysis will be performed when the last subject has completed the final study visit, the data are cleaned, and the database has been authorized for analysis.

5. GENERAL CONSIDERATIONS FOR DATA 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.

5.1. General Summary Table and Individual Subject Data Listing Considerations

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.

The BioCryst Style Guide for Tables, Figures, and Listings will be used to guide the appearance of output. 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.

5.2. General Post Text Summary Table and Individual Subject Data Listing Format Considerations

Tables and listings will be numbered to reflect main levels of unique tables and listings and sub-levels of replicate tables and listings with two digits per level (eg, Table XX.YY.ZZ. …).

1. The first level number should be consistent with the corresponding Clinical Study Report (CSR) appendix in which the tables or listings will appear. Following ICH-E3, all post text tables should have first level 14 and data listings should have 16.2.
2. For tabular presentations, subject accounting and final disposition, baseline, and demographic profile should appear as the first sub-level (Table 14.1 series). Efficacy should come next (Table 14.2 series), followed by safety, PK/PD, and other special-purpose sections. Similar conventions should be applied to the subject data listings (16.2.1 for discontinuation, 16.2.2 for protocol deviations, and so on).

The title should be complete, accurate, and concise. If convenient, the parameter and unit of measurement can appear in parentheses to conserve space in the body of the table. For example, a summary of orthostatic vital signs title could read "Summary of Sitting and Standing Blood Pressure (SBP) (mmHg) and Heart Rate (HR) (bpm)." Whether in the title or body of a table or listing, units must always be specified for all appropriate data. The last line of the title should provide the analysis group being summarized (eg, Intent-to-Treat Population or Per-Protocol Population).

In general, variables summarized and statistics reported should appear in the left-most column of a table. The columns for treatment groups should report the data from left to right for each treatment group (see Section 7), and (optional) all treated subjects, respectively. Any row with all zeros will not appear except

with reasons for disposition events or other similar lists of results (e.g. categorical urinalysis results). Summary tables clearly indicate the number of subjects to which the data apply, and unknown or not performed are distinguished from missing data.

In general, the listings should be sorted and presented by treatment group, subject number, parameter (where applicable), and date/time.

All tables and listings must have explanatory notes that give the definition of all derived variables and decodes for coded data. Footnotes will be in past tense for ease of incorporation into in-text tables in the CSR.

5.3. Data Management

The standard operating procedures (SOPs) of PharPoint, the selected data management and statistics vendor for this study, will be used. A data management plan was developed and approved prior to commencement of data entry. Data will be captured using the Medrio electronic data capture system. Electronic validation steps (edit checks) will be utilized, and data cleaning will occur in conjunction with each site. Prior to transfer of data provided by vendors (eg, laboratory data, PK 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 output. All analyses will be generated using SAS version 9.4 or above and in accordance with PharPoint SOPs.

5.4. Data Presentation Conventions

Continuous data will be summarized using the number of subjects with available data, mean, standard deviation (SD), standard error of the mean (SE), median, and minimum and maximum. Categorical data will be summarized using counts and percentages. Percentages are calculated using the total number of subjects per treatment group unless otherwise specified.

Unless otherwise specified, means and medians are formatted to one more decimal place than the measured value, SDs, SEs, confidence interval (CI) limits, and coefficient of variation (CV) to two more decimal places, and minimum and maximum values to the same number of decimal places. For categorical variables, the number and percentage of responses will be presented in the form XX (XX.X%) where the percentage is in the parentheses, except that 100% will be presented to three digits with no decimal. Dates will be formatted DDMMMYYYY and times will be formatted in 24-hour time as HH:MM. Partial dates will be handled as described in Sections 5.7.10 and 5.7.11. P-values and CIs will use a two-sided 0.05 significance level unless otherwise noted; p-values will be presented with three decimal places. Extreme p-values or CIs will be presented as “<0.001” and “>0.999” with the appropriate number of places.

All BCX9930 concentrations will be reported as provided by the concentration vendor.

Wherever possible, data will be decimal aligned.

A table of contents at the end of this SAP 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 will not necessitate a revision to the SAP, nor will it be considered a deviation from planned analyses. Additional data listings supporting the tables will not be considered a deviation from planned analyses.

5.5. Analysis Populations

5.5.1. Safety Population

The safety population will include all subjects who received at least 1 capsule or tablet of study drug. This population will be used for all analyses of accountability, demographics, BCX9930 drug concentrations, and safety. Subjects will be analyzed according to the treatment received.

5.5.2. Modified Intent-to-Treat (mITT) Population

The modified intent-to-treat (mITT) population will include all subjects who receive at least 1 capsule or tablet of study drug and have post baseline assessment of PNH symptoms and/or laboratory data. The mITT population will be the population for effectiveness analyses. Subjects will be analyzed according to the treatment intended.

5.5.3. Pharmacokinetic Population

The PK population will include all subjects included in the Safety population for whom a PK concentration was collected. The PK population will be the primary population for the PK listings. Subjects will be analyzed according to the treatment received.

5.5.4. Pharmacodynamic Population

The PD population will include all Safety population subjects for whom at least 1 PD or complement biomarker measurement can be obtained. This population will be used for all PD and complement biomarker analyses. Subjects will be analyzed according to the treatment received.

5.6. Baseline Definition

For a given subject and assessment, the baseline result generally will be the Day 1 value. For subjects who are directly rolling over from a previous study, the baseline ECG result will be obtained at the subject's final on-treatment visit in the previous study and recorded in the eCRF.

For determination of Hemoglobin (Hb) baseline, only preferred lab values that were not collected within 14 days after the subject received a packed red blood cell (pRBC) or whole blood transfusion will be used. For South African subjects, the local lab will be the preferred lab, and for all other subjects, the central lab will be the preferred lab. All Hb values that meet these criteria and were collected at any time from the preferred lab from the Screening visit up to Day 1 pre-dose will be averaged to determine a baseline value. Values from different labs will not be averaged together. If no preferred lab values are available but there are other lab values that were not collected within 14 days after the subject received any RBC or whole blood transfusion, lab values that meet the criteria will be used in place of the preferred lab values. If there are no baseline lab values that were collected outside the transfusion-

impacted period, the average of all (central and local labs) pre-treatment 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. This will lead to a conservative estimate of the baseline as the values could be impacted by transfusion and may be higher than expected as a result.

Derivation of the baseline for the following parameters: reticulocytes, PNH RBC (Type II and III red blood cells), the ratio of PNH RBC to PNH WBC (Type II and III granulocytes), haptoglobin, and FACIT-Fatigue will be as stated for Hb, above.

5.7. Derived and Transformed Data

5.7.1. Baseline Age

The subject's baseline age will be the age collected on the eCRF at time of consent. If this is missing, baseline age will be calculated as the number of complete years from date of birth through date of informed consent. In the case of a partial date, the lowest age consistent with available information will be used.

5.7.2. Study Day

Study Day 1 (or Day 1) is the date of first on-study dose of study drug and values captured on that day will generally be used as the baseline (see Section 5.6) If the date of interest occurs on or after the Study Day 1, then study day will be calculated as (date of interest – Study Day 1) + 1. If the date of interest occurs prior to the date of first dose, then study day will be calculated as (date of interest – Study Day 1). There is no Study Day 0.

5.7.3. Change from Baseline

Change from baseline is calculated as (post-baseline result – baseline result). Percent change from baseline is calculated as (100 x 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 are set to missing as well. If the baseline result is 0, then the percent change from baseline is set to missing.

5.7.4. Fold Change from Baseline

Fold change from baseline (also known as the ratio to baseline) is calculated as (post-baseline result / baseline result). If the baseline result is missing, the fold change is also set to missing.

5.7.5. Fold Change from ULN (Fold x ULN)

Fold change from the upper limit of normal (ULN) (also known as the ratio to ULN, fold x ULN, or fold above the ULN) is calculated as (post-baseline result / ULN). If the ULN is missing, the fold x ULN is also set to missing.

5.7.6. Total Time on Dose Level

The total time spent on any dose level will be calculated as the sum of the days on each dose level using the start and stop dates per dose period, including if another dose level was taken in between periods of the particular level in question.

5.7.7. End of Study

The end of the study is defined as the date when the last subject completes the last protocol-scheduled visit or terminates early.

5.7.8. 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 on-study dose of study drug. If the AE start date is missing and the AE stop date and time is after the start date and time of the first on-study dose of study drug (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 5.7.11 for incomplete dates or times.

5.7.9. Prior and Concomitant Medications

A medication will be classified as prior if its end date and time are before the date and time of the first on-study dose of study drug. 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 on-study dose of study drug, or its end date and time are on or after the start date and time of the first on-study dose of study drug, or the medication is flagged as ongoing. If either or both times are missing, then dates alone will be compared. See Section 5.7.10 for incomplete dates or times.

5.7.10. 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:

  If the year of trial termination is the same year or prior to the year the medication is reported, the end day and month will be set to the date of trial termination.

  Otherwise, the end day and month will be set to 31 December.

5.7.11. 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.

5.7.12. Windowing and Multiple Lab Values

Unscheduled and early termination visits will be assigned to an analysis window according to the study day of the actual visit date using visit windows described in Table 3 below:

Table 3: Visit Windows

Visit	Relative Target Day	Analysis Visit Window
Screening (optional)	-35 to -1	Prior to Day 1
Day 1 (Baseline)	1	1
Week 4	29	2 to 43
Weeks 8 to 92	Week * 7 +1	Target Day -13 to Target Day +14
Week 96	673	660 to 701
Week 104 to 136	Week * 7 +1	Target Day -27 to Target Day +28
Week 144	1009	982 and later

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. For South African sites: on days with multiple test results, results from the local lab will be used. For other sites: on days with multiple test results, results from the central lab 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; for these created median records, if applicable, the most frequent toxicity grade of the records used to calculate the median will be used.

5.7.13. Transfusion-impacted Period

The 14-day period following a transfusion of pRBCs or whole blood is defined as the transfusion-impacted period (ie, 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 (ie, the interval between the transfusion day and the current study day is ≤ 2 days and includes the day of transfusion). Transfusion-impacted periods will only be taken into account for effectiveness endpoints.

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)

5.7.13.1. Transfusion-impacted Period for South Africa

The algorithm as defined below aims to exclude transfusion impacted lab measurements when possible, and acts to select local lab measurements over central lab measurements (for South Africa subjects) or central lab measurements over local lab measurements (for subjects outside of South Africa), when possible. This is due to a lack of reliable data obtained from the central lab in South Africa.

For South African sites, the algorithm for determining which values should be used in effectiveness analysis are as follows:

The Hb value to use for a particular visit is provided below. The first item matching the description in the list should be used.

1. Local lab value for Hb at the visit of interest closest to the target day.
    a. If multiple results are equidistant from the target, use the latest.
    b. If multiple records exist on the same day, find the median of the results on that day (for grading, set to the most frequent grade or worst grade if two grade have the same frequency).
2. Central lab value for Hb at the visit of interest closest to the target day.
    a. If multiple results are equidistant from the target, use the latest.
    b. If multiple records exist on the same day, find the median of the results on that day (for grading, set to the most frequent grade or worst grade if two grade have the same frequency).

If the value at the visit of interest was taken during a transfusion-impacted period:

3. Local lab pre-transfusion value that itself was not within 14 days after the subject received a pRBC or whole blood transfusion.
    a. If multiple results are equidistant from the target, use the latest.
    b. If multiple records exist on the same day, find the median of the results on that day (for grading, set to the most frequent grade or worst grade if two grade have the same frequency).
4. Central lab pre-transfusion value that itself was not within 14 days after the subject received a pRBC or whole blood transfusion.
    a. If multiple results are equidistant from the target, use the latest.
    b. If multiple records exist on the same day, find the median of the results on that day (for grading, set to the most frequent grade or worst grade if two grade have the same frequency).

If no value meets the criteria listed, the Hb at the visit of interest will be set to missing and will not be summarized. This same algorithm will be used for all other transfusion-impacted parameters (Section 5.7.13), however haptoglobin will use a period of 3 days after transfusion instead of 14 days.

5.7.13.2. Transfusion-impacted Period for Other Countries

The Hb value to use for a particular visit is provided below. The first item matching the description in the list should be used.

5. Central lab value for Hb at the visit of interest closest to the target day.
    a. If multiple results are equidistant from the target, use the latest.
    b. If multiple records exist on the same day, find the median of the results on that day (for grading, set to the most frequent grade or worst grade if two grade have the same frequency).
6. Local lab value for Hb at the visit of interest closest to the target day.
    a. If multiple results are equidistant from the target, use the latest.
    b. If multiple records exist on the same day, find the median of the results on that day (for grading, set to the most frequent grade or worst grade if two grade have the same frequency).

If the value at the visit of interest was taken during the transfusion-impacted period:

1. Central lab pre-transfusion value that itself was not within 14 days after the subject received a pRBC or whole blood transfusion closest to the target day.
    a. If multiple results are equidistant from the target, use the latest.
    b. If multiple records exist on the same day, find the median of the results on that day (for grading, set to the most frequent grade or worst grade if two grade have the same frequency).
2. Local lab pre-transfusion value that itself was not within 14 days after the subject received a pRBC or whole blood transfusion
    a. If multiple results are equidistant from the target, use the latest.
    b. If multiple records exist on the same day, find the median of the results on that day (for grading, set to the most frequent grade or worst grade if two grade have the same frequency).

If no value meets the criteria listed, the Hb at the visit of interest will be set to missing and will not be summarized. This same algorithm will be used for all other transfusion-impacted parameters, however haptoglobin will use a period of 3 days after transfusion instead of 14 days.

For FACIT-Fatigue, since the scale is not captured at unscheduled visits, any FACIT-Fatigue occurring within a transfusion-impacted period will not be summarized on the tables but will be presented in the listings.

5.8. Multicenter Studies

No adjustment for multiple centers is planned.

5.9. Stratification

No stratification is planned.

5.10. Examination of Subgroups

No subgroups are planned.

5.11. Multiple Comparisons and Multiplicity

No adjustment for multiple comparisons is planned.

5.12. Data Handling Conventions

5.12.1. Premature Withdrawal and Missing Data

No missing data will be imputed, except dates and times as mentioned above.

5.12.2. Dropouts

Subjects will not be replaced if they discontinue study drug.

5.13. Values of Clinical Concern

Values of clinical concern include events of special monitoring (EOSMs), which are AEs or safety topics for which special monitoring, additional data collection activities, and/or enhanced signal detection activities within BioCryst are considered appropriate for this population and study. EOSMs for this study include hemolysis, SARS-CoV-2 infections (asymptomatic and symptomatic), [redacted]

5.14. Events of Special Interest

For this study, severe infections will be considered events of special interest (EOSIs).

6. TREATMENT COMPARISONS

6.1. Data Display Treatment and Other Sub-Group Descriptors

Planned treatment categories to be displayed on the summary tables are defined by whether the subject was naïve to both eculizumab and ravulizumab (C5 inhibitor [C5-INH] naïve) or had an inadequate response to either eculizumab or ravulizumab (C5-INH inadequate response). Subjects who have not taken either eculizumab or ravulizumab within the previous calendar year are considered naïve. Subjects whose parent study is BCX9930-202 are considered inadequate response subjects, and subjects whose parent study is BCX9930-203 are considered naïve subjects. These categories may be changed; if so, the final treatment categories will be used in the data displays.

Table 4: Planned Treatment Categories

C5-INH Naïve
C5-INH Inadequate Response

6.2. Significance Tests

If performed, unless otherwise specified, by-treatment significance tests will use a two-sided 0.05 significance level for p-values and confidence intervals (CIs).

7. STUDY POPULATION

7.1. Disposition of Subjects

Subject disposition will be presented for all subjects. The number and percentage of subjects who completed the study and discontinued from the study will be provided. The reasons for early discontinuation at any point also will be presented by planned treatment category. These data will also be listed by treatment and subject. Duration on study treatment during Study 201 and from the beginning of the previous study will also be provided.

The number and percentage of subjects included in the Safety, PK, and PD populations will be presented by treatment category.

7.2. Protocol Deviations

Protocol deviations will be identified and displayed in data listings by treatment, subject, and (where applicable) date of deviation. Deviation category, major or minor status, and importance will be listed if included in the received deviation data.

7.3. Demographic and Baseline Characteristics

Demographic data and baseline characteristics including age, race, ethnicity, sex, height (if available), weight, and body mass index (BMI) (if available) will be summarized using descriptive statistics for the Safety population, presented by treatment category. If not collected, baseline BMI will be calculated as BMI = weight (kg)/[height $(m)^2$] to one decimal place. Time from last BCX9930 dose to baseline will be summarized and listed as applicable.

7.4. Medical History

Medical history will be coded using the Medical Dictionary for Regulatory Affairs (MedDRA) version 24.0 and listed.

7.5. Prior and Concomitant Medications

Medications will be classified as prior or concomitant and coded using the World Health Organization (WHO) drug dictionary version B3 March 2021. Concomitant medications will be summarized, and prior medications may be summarized, by descending frequency of Class 4 term, preferred term (PT), and treatment. Medications will be listed by treatment category and subject.

7.6. Exposure and Compliance

Subjects will receive kits containing BCX9930 per the schedule of assessments for self-administration at home. The number and percentage of subjects exposed to BCX9930, and the number of days of exposure to BCX9930 in Study 201 and including the parent study will be summarized by treatment category. Individual kit data will be listed by treatment, subject, and date issued.

Compliance will be determined from the Study 201 Study Drug Accountability form kit data as tablets dispensed minus tablets returned, multiplied by 100, divided by the total number of tablets of study drug which should have been taken according to the Protocol and dose escalation and reduction records. Compliance data will be summarized by treatment and listed by treatment and subject.

8. EFFECTIVENESS

The following effectiveness endpoints will be summarized and listed:

- Durability of response
- Hematological response (categorization of response according to criteria in Table 5)
- PROs: QLQ-AA/PNH, FACIT fatigue scale, TSQM scores
- Clinical measurements of PNH (LDH, hemoglobin, haptoglobin, reticulocytes, transfusions)
- Subjects with dose escalation
- Discontinuations due to lack of efficacy
- Disease severity as recorded by the PNH symptoms assessment

8.1.1. Durability of Response

Durability of response will be summarized using absolute and change from baseline in hemoglobin measures throughout the study. Plots of mean change from baseline hemoglobin by treatment category and time point will be produced.

8.1.2. Hematological Response

Hemoglobin and RBC transfusions will be primarily used to assess hematological response. Additionally, LDH and absolute reticulocyte count (ARC) will be used to distinguish between complete and major response (Table 5). Hematological response will be determined and summarized using counts and percentages by treatment category and study visit at 6-month intervals (i.e. Weeks 24, 48, 72, 96, 120, and 144). Bar charts of response by treatment category and time point will be produced.

Table 5: Hematological Response Categories

Response Category	RBC Transfusions	Hemoglobin (g/dL) [a]	LDH x ULN [a]	ARC (/uL) [a]
Complete response	None	≥ 12	≤ 1.5	≤ 150,000
Major response	None	≥ 12	>1.5	Or >150,000
Good response	None	≥ 10 and <12		
Partial response	≤ 2 every 6 months	≥ 8 and <10		
Minor response	≤ 2 every 6 months	< 8		
Minor response	3 to 6 every 6 months, or reduction of ≥ 50% [b]	< 10		
No response	> 6 every 6 months and not reduction ≥ 50% [b]	< 10		

ARC = absolute reticulocyte count; LDH = lactate dehydrogenase; RBC = red blood cell; ULN = upper limit of normal

[a] Hemoglobin, LDH, and ARC values should be median over 6-month period.

[b] 50% reduction compared with at least 6 months pre-study data.

8.1.3. Patient Reported Outcomes

8.1.3.1. Treatment Satisfaction Questionnaire for Medication

The TSQM questionnaire will be completed at Baseline and at the Week 12, 24, 48, 72, and 96 visits. The individual question data from the TSQM will be listed. Domain scores will not be calculated.

8.1.3.2. Quality of Life Questionnaire for Patients with Aplastic Anemia/PNH

The QLQ-AA/PNH will be completed at Baseline and at the Week 24, 48, 72, and 96 visits. It has 54 items in 12 domains: body image (BI), cognitive functioning (CF), emotional functioning (EF), fatigue (FA), illness intrusiveness (II), fear of progression (PAF), infections (IN), other symptoms (OS), physical functioning (PF), role functioning (RF), social support (SS), and stigmatization (ST). The individual question data from the QLQ-AA/PNH will be listed. Domain scores will not be calculated.

8.1.3.3. FACIT-Fatigue Scale

The Functional Assessment of Chronic Illness Therapy (FACIT) Fatigue scale will be administered at Baseline and each clinic visit through Week 96. The FACIT-Fatigue scale has 13 items scored 0-4. A total score will be calculated with range 0 to 52 where 52 indicates complete functionality. See Section 12.4 for the scoring algorithm. The FACIT-Fatigue scale score and change from baseline will be summarized by treatment category and visit. Note that assessments within a transfusion-impacted period will not be summarized but will be presented on the listings.

8.1.4. Other Effectiveness Assessments

8.1.4.1. Clinical Measurements of PNH

Assessment of clinical measurements of PNH are described in Section 10.1.2.

8.1.4.2. Subjects with Dose Escalation

The number of subjects who were on each dose level at any time during the study and the total length of time on each dose level will be summarized using descriptive statistics by treatment category. Changes in subject dosing will be listed.

8.1.4.3. Discontinuation Due to Lack of Efficacy

Discontinuation due to lack of efficacy was not captured in the eCRF and so cannot be summarized specifically. Captured discontinuation reasons will be summarized on the disposition table.

8.1.4.4. Disease Severity

Disease severity will be summarized by treatment category, visit, and by PNH symptom category (fatigue, dyspnea, chest pain/discomfort, difficulty swallowing, abdominal pain, headache, erectile dysfunction, hemoglobinuria, jaundice). The number of subjects with a symptom at each visit will be presented, along with a summary of the number of days with symptoms and the severity.

9. SAFETY ANALYSES

Safety endpoints that will be summarized, include the proportion of subjects 1) with TEAEs; 2) who discontinue BCX9930 due to TEAEs; 3) with treatment-emergent serious adverse events (SAEs); 4) with treatment-emergent Grade 3 or 4 AEs; and 5) with treatment-emergent Grade 3 or 4 laboratory abnormalities.

9.1. Adverse Events

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 a MedDRA version 24.0 PT and system organ class (SOC). Relationship to study drug will be assessed as not related, unlikely related, possibly related, probably related, or definitely related. AEs will be graded according to the Division of Microbiology and Infectious Diseases (DMID) Adult Toxicity Table (draft version November 2007, see Protocol Appendix 1). AEs not covered by DMID criteria will be assessed for severity as mild, moderate, severe, or life-threatening, corresponding to toxicity Grades 1 through 4. EOSIs include severe infections that will be identified using the SOC "Infections and infestations" and a reported severity of grade 3 or higher (or missing). In this study the disease related events of BTH and thromboembolic events will be reported as AEs, even if deemed related to the disease under investigation.

If the relationship between the AE or SAE and the study drug is determined to be 'possibly', 'probably', or 'definitely' related, the event will be considered related to the study drug for the purposes of expedited regulatory reporting. Conversely, both events deemed 'unlikely' and those judged 'not related' will be considered not related for regulatory reporting purposes.

TEAEs will be summarized by SOC, PT, and treatment category. TEAEs will also be summarized by SOC, PT, severity, and treatment category. SAEs will be summarized by SOC, PT, and treatment. TEAEs deemed related to study drug, grade 3 and 4 TEAEs, TEAEs leading to treatment interruption or treatment discontinuation, EOSIs, and major adverse vascular events (MAVEs) will be summarized separately by SOC, PT, and treatment category. Summaries will be sorted by descending frequency of SOC and PT. Summaries will be presented chiefly by subject counts, and event counts will also be provided.

AEs, SAEs, MAVEs, and EOSIs will be listed separately by treatment, subject, and start date, showing SOC, PT, and verbatim term.

The duration of AEs in days will be derived and presented in all listings; this value is calculated as (AE stop date/time – AE start date/time). Both start and stop dates must be present to calculate a duration. If an AE start time or end time is missing then include the entire day, but if the AE start date is the treatment start date, then the treatment start time will be used.

Time to first dose reduction either associated with an AE or otherwise, time to discontinuation due to a TEAE, and time to development of drug-related rash will be estimated using the Kaplan-Meier method. Subjects who do not experience a particular event will be censored at the date of the last study visit.

Clinical findings for cutaneous eruptions requiring assessment will be listed.

9.1.1. Events of Special Monitoring

EOSMs for this study include hemolysis, SARS-CoV-2 infections (asymptomatic and symptomatic), [redacted]

Time to each subject's first SARS-CoV-2 infection, [redacted] will be estimated separately using the Kaplan-Meier method. The results will be displayed in summary tables as well as in a Kaplan-Meier plot. Subjects who do not experience the event will be censored at the date of the most recent dose of BCX9930. [redacted]

Duration of SARS-CoV-2 infection will be summarized as well as displayed in a Kaplan-Meier plot, with the event as the unit of interest rather than the subject. Ongoing durations will be censored at the most recent examination date. The summary display will provide the median duration of event by treatment category.

These summaries and plots will be presented by treatment category.

9.2. Clinical Laboratory Evaluations

Non-PK/PD blood and urine samples will be obtained per the schedule of assessments in Table 2.

Laboratory test results and change from baseline will be summarized by panel, parameter, time point, and treatment. Laboratory results, including lab normal ranges, will be listed by treatment category, subject, parameter, and time point.

For continuous laboratory data that are reported using "<" or "≤", a value of the number presented less one level of precision will be used for tables and figures. If the resulting value is equal to zero, the value will be adjusted by an additional level of precision. Similarly, ">" or "≥" will result in adding one at the level of precision for use in tables and figures. Actual results will be presented in the data listings. Table 6 provides example imputations.

Table 6: Example Imputation of Inequalities

Reported Value	Imputed Values
< 23	22
< 2.3	2.2
< 2	1
< 1	0.9*

< 0.23	0.22
< 0.1	0.09*
< 0.10	0.09
< 0.0200	0.0199
> 1.030	1.031
> 8	9

*value precision adjusted

Hemoglobin and other transfusion-impacted parameters will be summarized using the rules for transfusion-impacted periods as described in Section 5.7.13.

Select lab parameters including but not limited to serum creatinine and urine albumin/creatinine ratio will be plotted versus time from Day 1 to last visit.

9.2.1. Analysis of Abnormal Laboratory Values

Laboratory abnormalities will be graded according to DMID Adult Toxicity Table (draft version November 2007, see Protocol Appendix 1), with the exception of creatinine clearance and glomerular filtration rate, which will be graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

Any graded abnormality that occurs following the initiation of study drug and represents at least 1-grade increase from the baseline assessment is defined as treatment emergent. The number and percentage of subjects who experience treatment-emergent graded toxicities will be summarized by panel, parameter, time point, and treatment category. Laboratory toxicity shifts from baseline to worst post-baseline grade will be summarized by panel, parameter, toxicity grade, and treatment.

9.2.2. Liver Enzymes

The number and percentage of subjects having elevations in liver enzyme abnormalities (alanine aminotransferase [ALT] or aspartate aminotransferase [AST], or bilirubin) in relation to fold above the ULN will be summarized according to the FDA's Premarketing Clinical Evaluation on Drug-Induced Liver Injury Guidance for Industry (DHHS 2009).

Both fold change from ULN and fold change from baseline will be summarized by visit for ALT, ALP, AST, and bilirubin.

The following categories of abnormal hepatic laboratory values will be evaluated for any occurrence among all post-baseline assessments (where "and" indicates elevations occurring at the same visit). Treatment-emergent elevations will also be summarized. Within each treatment group and laboratory parameter grouping, a subject may be counted once per elevation criteria using the worst-case result. That is, a subject with a worst-case ALT elevation >3 × ULN for a given treatment group would be counted once in the ALT > 1.5 × ULN category and once in the ALT > 3 × ULN category, regardless of how many ALT elevations the subject had that met the > 3 × ULN and > 1.5 × ULN elevation criteria.

- ALT or AST and total bilirubin
  - ALT > 3 × ULN and bilirubin > 1.5 × ULN
  - ALT > 3 × ULN and bilirubin > 2 × ULN
  - AST > 3 × ULN and bilirubin > 1.5 × ULN
  - AST > 3 × ULN and bilirubin > 2 × ULN
  - (ALT > 3 × ULN or AST > 3 × ULN) and bilirubin > 1.5 × ULN
  - (ALT > 3 × ULN or AST > 3 × ULN) and bilirubin > 2 × ULN
- AST > 1.5, 3, 5, 10, or 20 × ULN
- ALT > 1.5, 3, 5, 10, or 20 × ULN
- Total bilirubin > 1, 1.5, or 2 × ULN
- ALP > 1.5 × ULN

Profiles of hemoglobin, liver enzymes (ALT, ALP, AST) and bilirubin over time will be graphically displayed for subjects with any Grade 3 or 4 abnormality in ALT, ALP, AST, or total bilirubin. In addition, a listing of all liver function test (ALT, AST, bilirubin, ALP) results for subjects experiencing a treatment-emergent Grade 3 or 4 liver function test will be provided.

In addition, a Hy's law plot, a shift plot showing liver safety panel tests over time (baseline vs. on-study), and distribution plots of ALT, AST, ALP, bilirubin, cholesterol, and triglycerides over time will be produced using the format recommended by the FDA/Industry/Academia Safety Graphics working group (https://www.ctspedia.org/do/view/CTSpedia/StatGraphHome). The plots to be included are the scatter plot of maximum transaminase versus maximum bilirubin, the liver test safety panel over time, and the distribution of ALT by time and treatment. Distribution plots for AST, ALP, bilirubin, cholesterol, and triglycerides will use the same format as is used for ALT.

9.3. Bedside ECGs

Bedside ECGs are obtained as scheduled in Table 2.

Descriptive summaries of bedside ECG parameters (PR, QRS, QT, RR, and QTcF) and change from baseline will be presented by parameter, time point, and treatment category. ECG interpretation (normal, abnormal, abnormal clinically significant) will be presented by time point and treatment including "worst post baseline" (defined as Abnormal if ever Abnormal post-baseline, and otherwise Normal if always Normal post-baseline).

The number and percentage of subjects with QTcF ≤ 450, > 450 to ≤ 480, > 480 to ≤ 500, and > 500 msec; or changes of ≤ 30, > 30 to ≤ 60, or > 60 msec will be summarized by treatment category and visit along with worst post-baseline result. Unscheduled ECG results will be included in this summary table.

ECG results will be listed by treatment category, subject, parameter, and time point.

9.4. Other Safety Measures

Descriptive summaries of vital signs and change from baseline in vital signs will be presented by parameter, time point, and treatment category. Vital signs and physical examination results will each be listed by treatment, subject, and time point.

10. CLINICAL MEASUREMENTS AND SYMPTOMS OF PNH

10.1.1. Clinical PNH Symptoms

The following clinical parameters will be summarized with counts and percentages by treatment category and study visit: fatigue, dyspnea, chest pain/discomfort, difficulty swallowing (esophageal pain, dysphagia), abdominal pain, headache, erectile dysfunction, hemoglobinuria, and jaundice.

10.1.2. Clinical Measurements of PNH

Continuous clinical measurements of PNH (LDH, hemoglobin, haptoglobin levels, absolute reticulocyte count, AST, total bilirubin, and direct bilirubin) will be summarized by summary statistics including change from baseline and percent change from baseline, by treatment category and study visit. Note that LDH, hemoglobin, haptoglobin, and absolute reticulocyte count that occur within a transfusion-impacted period will not be included in summaries but will be presented in respective listings. Categorical clinical measurements of PNH (number of blood transfusions, incidence of major thromboses) will be summarized with counts and percentages by treatment category (see Section 12.3 for a list of thrombosis events). Incidence of breakthrough hemolysis will be analyzed by the sponsor.

11. CLINICAL PHARMACOLOGY DATA ANALYSES

11.1. Pharmacokinetic Analyses

Sparse plasma and spot urine samples for determination of BCX9930 concentrations are planned to be collected at each study visit to the investigative site and 48 hours after evidence of BTH.

Plasma and urine concentrations of BCX9930 and BCX13559—a metabolite of BCX9930—will be listed with the time of sample collection and time of prior dose along with other available information. Any analysis of PK data including the calculation and assessment of PK parameters will be performed under a separate analysis plan.

11.2. Pharmacodynamic Analyses

In this study, PD assessments include PNH clone size (RBC and WBC), Factor Bb, serum AP activity as assessed by AP Wieslab, and additional exploratory assays.

Descriptive summaries of the above assessments including change from baseline will be presented by treatment category, dose regimen, and study visit. AP Wieslab (and other similar assays, if applicable) will be reported only as percent of baseline, not as actual value or percent change from baseline. Data values will be listed.

If PD assessments are reported with inequalities ($<$, $\leq$, $>$, or $\geq$), the same conventions used for laboratory values as described in Section 9.2 will be used.

Any further analysis of PD data including the relationship to PK concentrations will be performed under a separate analysis plan.

12. ATTACHMENTS

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.

Table 7: Data Displays

Table Number	Title	Population
14.1.1	Subject Disposition	All
14.1.2	Analysis Populations	All
14.1.3.1	Demographic and Baseline Characteristics	mITT
14.1.3.2	Demographic and Baseline Characteristics	Safety
14.1.4.1	Prior Medication	Safety
14.1.4.2	Concomitant Medication	Safety
14.1.5	Treatment Exposure and Compliance	Safety
14.2.1	Durability of Response – Hemoglobin (g/dL)	mITT
14.2.2.1	Hematological Response	mITT
14.2.3	Functional Assessment of Chronic Illness Therapy (FACIT) Fatigue Scale	mITT
14.2.4	Total Time on Dose Level	mITT
14.2.5	Disease Severity	mITT
14.3.1	Overall Summary of Treatment-emergent Adverse Events	Safety
14.3.2.1	Treatment-emergent Adverse Events by MedDRA System Organ Class and Preferred Term	Safety
14.3.2.2	Treatment-emergent Adverse Events by MedDRA System Organ Class, Preferred Term, and Severity	Safety
14.3.2.3	Serious Treatment-emergent Adverse Events by MedDRA System Organ Class and Preferred Term	Safety
14.3.2.4	Treatment-emergent Adverse Events Related to Study Drug by MedDRA System Organ Class and Preferred Term	Safety
14.3.2.5	Grade 3 or 4 Treatment-emergent Adverse Events by MedDRA System Organ Class and Preferred Term	Safety
14.3.2.6	Treatment-emergent Adverse Events Leading to Treatment Discontinuation by MedDRA System Organ Class and Preferred Term	Safety
14.3.2.7	Treatment-emergent Adverse Events Leading to Treatment Interruption by MedDRA System Organ Class and Preferred Term	Safety
14.3.2.8	Treatment-emergent Major Adverse Vascular Events (MAVEs) by MedDRA System Organ Class and Preferred Term	Safety
14.3.2.9	Treatment-emergent Events of Special Interest (EOSIs) by MedDRA System Organ Class and Preferred Term	Safety
14.3.2.10.1	Time to First Dose Reduction – Kaplan-Meier	Safety
14.3.2.11.1	Time to Discontinuation Due to a Treatment-Emergent Adverse Event – Kaplan-Meier	Safety

14.3.2.12.1	Time to First Drug-Related Rash – Kaplan-Meier	Safety
14.3.2.13.1	Time to First SARS-CoV-2 Infection – Kaplan-Meier	Safety
14.3.2.13.3	Duration of SARS-CoV-2 Infection – Kaplan-Meier	Safety
14.3.2.14.1	Time to First Potential Drug-Induced Liver Injury (pDILI) Event – Kaplan-Meier	Safety
14.3.2.15.1	Time to First Increase in Serum Creatinine > ULN – Kaplan-Meier	Safety
14.3.3.1.1	Laboratory Results by Visit – Clinical Chemistry	Safety
14.3.3.2	Laboratory Results by Visit – Hematology, PNH Clone Size, and Coagulation	Safety
14.3.3.3.1	Laboratory Results by Visit – Continuous Urinalysis Parameters	Safety
14.3.3.3.2	Laboratory Results by Visit – Categorical Urinalysis Parameters	Safety
14.3.3.4	Laboratory Results by Visit – Complement Factors	Safety
14.3.3.5	Laboratory Results by Visit – Iron Assessments	Safety
14.3.3.6	Treatment-emergent Graded Laboratory Abnormalities by Visit	Safety
14.3.3.7	Treatment-emergent Grade 3 or 4 Laboratory Abnormalities by Visit	Safety
14.3.3.8	Treatment-emergent Graded Laboratory Toxicity Grade Increases from Baseline	Safety
14.3.3.9	Shift from Baseline to Worst Post-baseline Assessment: Clinical Chemistry	Safety
14.3.3.10	Shift from Baseline to Worst Post-baseline Assessment: Hematology	Safety
14.3.3.11	Shift from Baseline to Worst Post-baseline Assessment: Urinalysis	Safety
14.3.3.12	Fold x ULN for Liver Function Tests	Safety
14.3.3.13	Fold Change from Baseline for Liver Function Tests	Safety
14.3.3.14.1	Post-baseline Elevations in Liver Function Tests	Safety
14.3.3.15	Treatment-emergent Elevations in Liver Function Tests	Safety
14.3.4	Vital Signs by Visit	Safety
14.3.5.1	12-Lead ECG Results by Visit	Safety
14.3.5.2	12-Lead ECG Findings by Visit	Safety
14.3.5.3	12-Lead ECG QTcF Interval Abnormalities (Categorical) by Visit	Safety
14.4.1.1	Clinical PNH Symptoms	mITT
14.4.1.2	Clinical Measurements of PNH: Blood Transfusions and Major Thromboses	mITT
14.4.1.3	Continuous Clinical Measurements of PNH	mITT
14.5.1	PD Assessment Summary Statistics	PD
Figure Number	**Title**	**Population**
14.2.2.2	Bar Chart of Hematological Response over Time (Note to programmers: Present each time point on its own page.)	
14.3.2.10.2	Kaplan-Meier Plot of First Dose Reduction	Safety
14.3.2.11.2	Kaplan-Meier Plot of Discontinuation Due to a Treatment-Emergent Adverse Event	Safety
14.3.2.12.2	Kaplan-Meier Plot of First Drug-Related Rash	Safety
14.3.2.13.2	Kaplan-Meier Plot of First SARS-CoV-2 Infection	Safety

14.3.2.13.4	Kaplan-Meier Plot of Duration of SARS-CoV-2 Infection	Safety
14.3.2.14.2	Kaplan-Meier Plot of First Potential Drug-Induced Liver Injury (pDILI) Event	Safety
14.3.2.15.2	Kaplan-Meier Plot of First Increase in Serum Creatinine > ULN	Safety
14.3.3.1.2	Distribution of Cholesterol and Triglycerides over Time	Safety
14.3.3.1.3	Selected Laboratory Parameters by Time	Safety
14.3.3.14.2	Hy's Law Plot of Maximum Total Bilirubin vs. Maximum ALT	Safety
14.3.3.14.3	Liver Test Safety Panel over Time, Baseline vs. On-study	Safety
14.3.3.14.4	Individual Patient Profile of ALT, ALP, AST, Hemoglobin, and Total Bilirubin (Note to programmers: display ALT, ALP, AST, and total bilirubin as the fold x ULN on a semi-log axis (left-hand y-axis). Display hemoglobin on a linear scale using the right-hand axis and display lines and symbols in red)	Safety: Subjects with Treatment-Emergent Grade 3 or 4 ALT, ALP, AST, or Total Bilirubin
14.3.3.14.5	Distribution of Liver Tests over Time: ALT, AST, ALP, and Bilirubin	Safety
14.4.3.2	Plot of Clinical Measurements of PNH (Note to programmers: display LDH, hemoglobin, haptoglobin, absolute reticulocyte count, AST, total bilirubin, and direct bilirubin on the same plot if possible. Display hemoglobin on a linear scale (on each page, if multiple pages are needed) using the right-hand axis and display lines and symbols in red.)	mITT
14.4.3.3	Plot of Clinical Measurements of PNH Change from Baseline (Note to programmers: display LDH, hemoglobin, haptoglobin, absolute reticulocyte count, AST, total bilirubin, and direct bilirubin on the same plot if possible. Display hemoglobin on a linear scale (on each page, if multiple pages are needed) using the right-hand axis and display lines and symbols in red.)	mITT
14.4.3.4	Plot of Clinical Measurements of PNH Percent Change from Baseline (Note to programmers: display LDH, hemoglobin, haptoglobin, absolute reticulocyte count, AST, total bilirubin, and direct bilirubin on the same plot if possible. Display hemoglobin on a linear scale (on each page, if multiple pages are needed) using the right-hand axis and display lines and symbols in red.)	mITT
Listing Number	**Title**	**Population**
16.2.1.1	Informed Consent	All
16.2.1.2	Subject Registry	
16.2.1.3	Subject Disposition	All
16.2.2	Protocol Deviations	All
16.2.3	Analysis Populations	All

16.2.4.1	Demographic and Baseline Characteristics	All
16.2.4.2	Medical History	All
16.2.4.3	Prior and Concomitant Medications	All
16.2.5.1	Study Drug Accountability	Safety
16.2.5.2	Overall Compliance	Safety
16.2.6.1	PNH Characteristics and Symptoms	All
16.2.6.2	Clinical Measurements of PNH	All
16.2.7	QLQ-AA/PNH Individual Question Responses	All
16.2.8.1	FACIT-Fatigue Scale Individual Question Responses	All
16.2.8.2	FACIT-Fatigue Scale Score	All
16.2.9	TSQM Individual Question Responses	All
16.2.10.1	Hemolysis Monitoring	All
16.2.10.2	Renal Events	All
16.2.10.3	Transfusions	All
16.2.11.1	Adverse Events	All
16.2.11.2	Serious Adverse Events	All
16.2.11.3	Adverse Events Leading to Study Discontinuation	All
16.2.11.4	Adverse Events Related to Study Drug	All
16.2.11.5	Adverse Events with Grade 3 or Grade 4 Severity	All
16.2.11.6	Major Adverse Vascular Events (MAVEs)	All
16.2.11.7	Events of Special Interest (EOSIs)	All
16.2.11.8	Hemolysis Adverse Events	All
16.2.11.9	Rash-related Adverse Events	All
16.2.11.10	Acute Kidney Injuries	All
16.2.12	Cutaneous Eruption Assessments	All
16.2.13.1	Laboratory Results - Clinical Chemistry	All
16.2.13.2	Laboratory Results - Hematology	All
16.2.13.3	Laboratory Results - Coagulation	All
16.2.13.4	Laboratory Results - Urinalysis	All
16.2.13.5	Laboratory Results - Other Laboratory Tests	All
16.2.14	Bedside 12-lead Electrocardiogram	All
16.2.15	Vital Signs, Height, and Weight	All
16.2.16	Physical Examinations	All
16.2.17.1	Plasma BCX9930 Pharmacokinetic Concentrations	All
16.2.17.2	Urine BCX9930 Pharmacokinetic Concentrations	All
16.2.18.1	Plasma BCX13559 Pharmacokinetic Concentrations	All
16.2.18.2	Urine BCX13559 Pharmacokinetic Concentrations	All
16.2.19	Individual PD Assessments and Biomarkers	All

12.2. Data Display Specifications

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

12.3. Preferred Terms that Qualify as MAVEs and Thrombotic Events

MAVE Term	PT	SOC	Thrombotic Event?
deep vein thrombosis	Deep vein thrombosis	Vascular disorders	YES
	Deep vein thrombosis postoperative	Injury, poisoning and procedural complications	YES
	Deep vein thrombosis postoperative	Vascular disorders	YES
	Pelvic venous thrombosis	Vascular disorders	YES
pulmonary embolus	Pulmonary embolism	Respiratory, thoracic and mediastinal disorders	YES
	Pulmonary embolism	Vascular disorders	YES
myocardial infarction	Myocardial infarction	Cardiac disorders	YES
	Myocardial infarction	Vascular disorders	YES
	Acute myocardial infarction	Cardiac disorders	YES
	Acute myocardial infarction	Vascular disorders	YES
	ECG signs of myocardial infarction	Investigations	NO
	Periprocedural myocardial infarction	Injury, poisoning and procedural complications	YES
	Periprocedural myocardial infarction	Cardiac disorders	YES
	Dressler's syndrome	Cardiac disorders	NO
	Dressler's syndrome	Immune system disorders	NO
	Dressler's syndrome	Respiratory, thoracic and mediastinal disorders	NO
	Post procedural myocardial infarction	Injury, poisoning and procedural complications	YES

MAVE Term	PT	SOC	Thrombotic Event?
	Post procedural myocardial infarction	Cardiac disorders	YES
	Silent myocardial infarction	Cardiac disorders	YES
	Silent myocardial infarction	Vascular disorders	YES
transient ischemic attack	Transient ischaemic attack	Nervous system disorders	YES
	Transient ischaemic attack	Vascular disorders	YES
unstable angina	Angina unstable	Cardiac disorders	YES
	Angina unstable	Vascular disorders	YES
renal vein thrombosis	Renal vein thrombosis	Renal and urinary disorders	YES
	Renal vein thrombosis	Vascular disorders	YES
	Renal vein embolism	Renal and urinary disorders	YES
	Renal vein embolism	Vascular disorders	YES
acute peripheral vascular occlusion	Vascular occlusion	Vascular disorders	YES
	Cerebral vascular occlusion	Nervous system disorders	YES
	Cerebral vascular occlusion	Vascular disorders	YES
	Coronary vascular graft occlusion	Injury, poisoning and procedural complications	YES
	Coronary vascular graft occlusion	Cardiac disorders	YES
	Coronary vascular graft occlusion	Vascular disorders	YES
	Mesenteric vascular occlusion	Gastrointestinal disorders	YES

MAVE Term	PT	SOC	Thrombotic Event?
	Mesenteric vascular occlusion	Vascular disorders	YES
	Retinal vascular occlusion	Eye disorders	YES
	Retinal vascular occlusion	Vascular disorders	YES
	Vascular access site occlusion	Injury, poisoning and procedural complications	YES
	Vascular access site occlusion	Vascular disorders	YES
	Vascular access site occlusion	General disorders and administration site conditions	YES
	Vascular device occlusion	General disorders and administration site conditions	NO
	Vascular device occlusion	Vascular disorders	YES
	Vascular graft occlusion	Injury, poisoning and procedural complications	NO
	Vascular graft occlusion	Vascular disorders	YES
	Vascular stent occlusion	General disorders and administration site conditions	YES
	Vascular stent occlusion	Vascular disorders	YES
mesenteric/visceral vein thrombosis or infarction	Mesenteric vein thrombosis	Gastrointestinal disorders	YES
	Mesenteric vein thrombosis	Vascular disorders	YES
	Portosplenomesenteric venous thrombosis	Hepatobiliary disorders	YES

MAVE Term	PT	SOC	Thrombotic Event?
	Portosplenomesenteric venous thrombosis	Gastrointestinal disorders	YES
	Portosplenomesenteric venous thrombosis	Vascular disorders	YES
	Intestinal infarction	Gastrointestinal disorders	YES
	Intestinal infarction	Vascular disorders	YES
	Visceral venous thrombosis	Gastrointestinal disorders	YES
	Visceral venous thrombosis	Vascular disorders	YES
mesenteric/visceral arterial thrombosis or infarction	Mesenteric artery thrombosis	Gastrointestinal disorders	YES
	Mesenteric artery thrombosis	Vascular disorders	YES
	Intestinal infarction	Gastrointestinal disorders	YES
	Intestinal infarction	Vascular disorders	YES
hepatic/portal vein thrombosis (Budd-Chiari syndrome)	Budd-Chiari syndrome	Hepatobiliary disorders	YES
	Budd-Chiari syndrome	Vascular disorders	YES
cerebral arterial occlusion/cerebrovascular accident	Cerebral artery occlusion	Nervous system disorders	YES
	Cerebral artery occlusion	Vascular disorders	YES
	Intraoperative cerebral artery occlusion	Injury, poisoning and procedural complications	YES
	Intraoperative cerebral artery occlusion	Nervous system disorders	YES
	Intraoperative cerebral artery occlusion	Vascular disorders	YES

MAVE Term	PT	SOC	Thrombotic Event?
	Precerebral artery occlusion	Nervous system disorders	YES
	Precerebral artery occlusion	Vascular disorders	YES
	Cerebrovascular accident	Nervous system disorders	YES
	Cerebrovascular accident	Vascular disorders	YES
	Cerebrovascular accident prophylaxis	Surgical and medical procedures	NO
cerebral venous occlusion	Cerebral venous thrombosis	Nervous system disorders	YES
	Cerebral venous thrombosis	Vascular disorders	YES
renal arterial thrombosis	Renal artery thrombosis	Renal and urinary disorders	YES
	Renal artery thrombosis	Vascular disorders	YES
gangrene (nontraumatic; nondiabetic)	Gangrene	Infections and infestations	NO
	Gangrene	Vascular disorders	YES
	Gangrene	Skin and subcutaneous tissue disorders	NO
	Arteriosclerotic gangrene	Infections and infestations	YES
	Arteriosclerotic gangrene	Vascular disorders	YES
	Arteriosclerotic gangrene	Skin and subcutaneous tissue disorders	YES
	Peripheral arterial occlusive disease	Vascular disorders	YES
	Femoral hernia gangrenous	Infections and infestations	NO
	Femoral hernia gangrenous	Gastrointestinal disorders	NO

MAVE Term	PT	SOC	Thrombotic Event?
	Femoral hernia gangrenous	Vascular disorders	YES
	Inguinal hernia gangrenous	Infections and infestations	NO
	Inguinal hernia gangrenous	Vascular disorders	YES
	Inguinal hernia gangrenous	Gastrointestinal disorders	NO
	Dry gangrene	Vascular disorders	YES
	Dry gangrene	Skin and subcutaneous tissue disorders	NO
	Gas gangrene	Infections and infestations	NO
	Gas gangrene	Vascular disorders	YES
	Gas gangrene	Skin and subcutaneous tissue disorders	NO
	Fournier's gangrene	Infections and infestations	NO
	Fournier's gangrene	Musculoskeletal and connective tissue disorders	NO
	Fournier's gangrene	Reproductive system and breast disorders	NO
	Penile gangrene	Infections and infestations	NO
	Penile gangrene	Reproductive system and breast disorders	NO
	Penile gangrene	Vascular disorders	YES
	Scrotal gangrene	Infections and infestations	NO
	Scrotal gangrene	Vascular disorders	YES
	Scrotal gangrene	Reproductive system and breast disorders	NO

MAVE Term	PT	SOC	Thrombotic Event?
	Scrotal gangrene	Skin and subcutaneous tissue disorders	NO
	Umbilical hernia gangrenous	Infections and infestations	NO
	Umbilical hernia gangrenous	Vascular disorders	YES
	Umbilical hernia gangrenous	Gastrointestinal disorders	NO
	Abdominal hernia gangrenous	Infections and infestations	NO
	Abdominal hernia gangrenous	Gastrointestinal disorders	NO
	Incisional hernia gangrenous	Infections and infestations	NO
	Incisional hernia gangrenous	Vascular disorders	YES
	Incisional hernia gangrenous	Gastrointestinal disorders	NO
amputation (nontraumatic; nondiabetic)	Amputation	Surgical and medical procedures	NO
	Hemipelvectomy	Surgical and medical procedures	NO
	Leg amputation	Surgical and medical procedures	NO
	Amputation of penis	Surgical and medical procedures	NO
	Arm amputation	Surgical and medical procedures	NO
	Foot amputation	Surgical and medical procedures	NO
	Cervix colporrhaphy with amputation	Surgical and medical procedures	NO
	Finger amputation	Surgical and medical procedures	NO
	Interscapulothoracic amputation	Surgical and medical procedures	NO

MAVE Term	PT	SOC	Thrombotic Event?
	Hand amputation	Surgical and medical procedures	NO
	Limb amputation	Surgical and medical procedures	NO
	Spontaneous amputation	Vascular disorders	NO
	Spontaneous amputation	Skin and subcutaneous tissue disorders	NO
	Toe amputation	Surgical and medical procedures	NO
dermal thrombosis	Thrombophlebitis superficial	Vascular disorders	YES
	Vascular skin disorder	Skin and subcutaneous tissue disorders	NO
	Vascular skin disorder	Vascular disorders	YES

12.4. FACIT-Fatigue Questionnaire Scoring

The FACIT-Fatigue scale is portrayed in Table 8 below.

Table 8: 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 past 7 days.**

		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 starting things because I am tired	0	1	2	3	4
An4	I have trouble finishing things because I am tired	0	1	2	3	4
An5	I have energy	0	1	2	3	4

		Not at all	A little bit	Some-what	Quite a bit	Very much
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.