BIOCRYST

PHARMACEUTICALS, INC.

BCX9930

PROTOCOL No. BCX9930-203

IND No. 142,217

EudraCT No. 2020-004403-14

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

Version 4.0: 01 August 2022

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SPONSOR SIGNATURE PAGE

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This protocol has been approved by BioCryst Pharmaceuticals, Inc.

Senior Clinical Development Physician:

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Signer Name: [redacted]
Signing Reason: I approve this document
Signing Time: 03-Aug-2022 | 13:58:57 EDT
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Sponsor's Authorized Signatory:

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Signer Name: [redacted]
Signing Reason: I approve this document
Signing Time: 03-Aug-2022 | 14:40:12 EDT
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BioCryst Pharmaceuticals, Inc.

INVESTIGATOR AGREEMENT

Protocol No. BCX9930-203

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Version (Date): Version 4.0: 01 August 2022

I have received and read the Investigator's Brochure (IB) for BCX9930.

I have carefully read this protocol and agree that it contains all of the necessary information required to conduct this study. I agree to conduct this study as described and according to the Declaration of Helsinki, International Council for Harmonisation guidelines for Good Clinical Practice, and all locally applicable regulations.

I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

STUDY INFORMATION

Protocol No.:	BCX9930-203
Study Title:	A Randomized, Double-Blind, Multicenter, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy, Safety, and Tolerability of Oral BCX9930 Monotherapy for the Treatment of Paroxysmal Nocturnal Hemoglobinuria
IND No.:	142,217
EudraCT No.:	2020-004403-14
Investigational Product:	BCX9930
Indication Studied:	Paroxysmal nocturnal hemoglobinuria (PNH)
Sponsor:	BioCryst Pharmaceuticals, Inc. 4505 Emperor Boulevard Nottingham Hall, Suite 200 Durham, North Carolina 27703, USA
Sponsor Medical Monitor:	[redacted] Office: [redacted] Mobile: [redacted] Email: [redacted] (Note: See Section 12.4.1 for contact information for SAE reporting.)
Sponsor Clinical Study Manager:	[redacted] Office: [redacted] Mobile: [redacted] Email: [redacted]
Lead or Coordinating Investigator:	[redacted]
Compliance Statement:	This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and clinical research guidelines established by the Code of Federal Regulations (Title 21, CFR Parts 50, 56, and 312), International Council for Harmonisation Guidelines, and all locally applicable regulations. Essential study documents are currently archived in accordance with applicable regulations.
Final Protocol Date:	Version 4.0: 01 August 2022 (Amendment 3)
Previous Version(s):	Version 3.0: 29 June 2022 (Amendment 2) Version 2.0: 27 May 2021 (Amendment 1) Version 1.0: 18 March 2021 (Original)

2. SYNOPSIS

Name of Sponsor/Company:
BioCryst Pharmaceuticals, Inc.

Name of Investigational Product:
BCX9930

Name of Active Ingredient:
[redacted]

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

BioCryst Protocol No.: BCX9930-203

Lead or Coordinating Investigator:
[redacted]

Study Centers:
This study will be conducted at study centers in multiple countries/regions

Phase of development: 2

Objectives:

Part 1 Primary Objective:

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

Part 1 Secondary Objectives:

- To evaluate the safety and tolerability of BCX9930 monotherapy administered for 12 weeks, as compared to placebo, in subjects with PNH
- To characterize the effects of BCX9930 monotherapy administered for 12 weeks, as compared to placebo, using clinical and laboratory measurements, including complement and thrombosis biomarkers, and PNH clone size, in subjects with PNH
- To evaluate the effects of BCX9930 monotherapy administered for 12 weeks, as compared to placebo, on the Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue scale and other patient-reported outcomes (PROs) in subjects with PNH
- To characterize BCX9930 plasma concentrations and pharmacokinetic (PK) parameters in subjects with PNH

In Part 1 of this study, unless indicated otherwise, all endpoints will be assessed at or to Week 12.

Part 1 Primary Endpoint:

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

Part 1 Key Secondary Endpoints:

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

Part 1 Other Secondary Endpoints:

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

Part 1 Exploratory Endpoints:

[redacted]

Part 1 Other Health-related Quality of Life (HRQoL) Endpoints:

- Proportion of subjects achieving a within-subject meaningful change for the FACIT-Fatigue scale [at Week 12]
- CFB in Quality of Life Questionnaire for patients with Aplastic Anemia/Paroxysmal Nocturnal Hemoglobinuria (QLQ-AA/PNH) Physical Functioning and other domain scores [at Week 12]
- Proportion of subjects with improvement on individual PNH symptom items (ie, frequency, severity, and/or interference) from baseline as assessed using the modified Patient-Reported Outcome Questionnaire for Aplastic Anemia/Paroxysmal Nocturnal Hemoglobinuria (PRO-AA/PNH) symptom collection tool [at Week 12]
- CFB in individual PNH symptom items on the modified PRO-AA/PNH [at Week 12]
- CFB in EuroQoL 5-dimension, 5-level (EQ-5D-5L) utility and visual analog scale (VAS) scores [at Week 12]
- Treatment Satisfaction Questionnaire for Medication (TSQM) scale score [at Week 12]

- Patient global impression of change in fatigue, impact of fatigue, and physical functioning as assessed using the Patient Global Impression of Change (PGIC)-Fatigue, PGIC-Impact of Fatigue, and PGIC-Physical Functioning scores, respectively [at Week 12]
- CFB in patient global impression of severity of fatigue, impact of fatigue, and physical functioning as assessed using the Patient Global Impression of Severity (PGIS)-Fatigue, PGIS-Impact of Fatigue, and PGIS-Physical Functioning scores, respectively [at Week 12]

Part 1 Safety Endpoints:

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

Part 2 Primary Objective:

- To evaluate the long-term safety and tolerability of oral BCX9930 monotherapy administered for up to 52 weeks in subjects with PNH

Part 2 Secondary Objectives:

- To assess the effectiveness of BCX9930 monotherapy administered for up to 52 weeks in subjects with PNH
- To characterize the effects of BCX9930 monotherapy administered for up to 52 weeks using clinical and laboratory measurements, including complement and thrombosis biomarkers, and PNH clone size, in subjects with PNH
- To evaluate the effects of BCX9930 monotherapy administered for up to 52 weeks on FACIT-Fatigue scale and other PROs
- To characterize BCX9930 plasma concentrations and PK parameters over time in subjects with PNH

In Part 2, unless indicated otherwise, all endpoints will be assessed at Week 52. For subjects who are switched from placebo to BCX9930 monotherapy at the end of Part 1, the baseline for treatment with BCX9930 will be defined as the last value prior to first dose of active treatment.

Part 2 Primary Endpoints:

- Number and proportion of subjects with a TEAE
- Number and proportion of subjects who discontinue due to a TEAE
- Number and proportion of subjects who experience a TESAE
- Number and proportion of subjects who experience a CTCAE Grade 3 or Grade 4 TEAE
- Number and proportion of subjects who experience a treatment-emergent CTCAE Grade 3 or Grade 4 laboratory abnormality

Part 2 Secondary Endpoints:

- CFB in Hb [mean of values from Weeks 12 to 52 for subjects randomized to BCX9930 in Part 1 and from Weeks 24 to 52 for subjects randomized to placebo]

- Proportion of subjects with Hb ≥ 12 g/dL [at Week 52]
- Proportion of subjects achieving Hb stabilization (avoidance of a > 2 g/dL decrease in the absence of transfusion) [from Weeks 12 to 52 for subjects randomized to BCX9930 in Part 1 and from Weeks 16 to 52 for subjects randomized to placebo in Part 1]
- Proportion of subjects who are transfusion-free [from Weeks 12 to 52 for subjects randomized to BCX9930 in Part 1 and from Weeks 16 to 52 for subjects randomized to placebo in Part 1]
- Number of units of pRBCs transfused [from Weeks 12 to 52 for subjects randomized to BCX9930 in Part 1 and from Weeks 16 to 52 for subjects randomized to placebo]
- Percent reduction in rate of pRBCs transfused [from Weeks 12 to 52 for subjects randomized to BCX9930 in Part 1 and from Weeks 16 to 52 for subjects randomized to placebo in Part 1 vs. prestudy transfusion rate]
- Percent CFB in LDH [mean of values from Weeks 12 to 52 for subjects randomized to BCX9930 in Part 1 and from Weeks 24 to 52 for subjects randomized to placebo]
- CFB in ARC [mean of values from Weeks 12 to 52 for subjects randomized to BCX9930 in Part 1 and from Weeks 24 to 52 for subjects randomized to placebo]
- Proportion of subjects with ARC in the normal range [at Week 52]
- CFB in haptoglobin [mean of values from Weeks 12 to 52 for subjects randomized to BCX9930 in Part 1 and from Weeks 24 to 52 for subjects randomized to placebo]
- Proportion of subjects with haptoglobin ≥ LLN [at Week 52]
- CFB in total PNH RBC clone size [mean of values from Weeks 12 to 52 for subjects randomized to BCX9930 in Part 1 and from Weeks 24 to 52 for subjects randomized to placebo]
- CFB in total PNH RBC clone size relative to PNH WBC clone size [mean of values from Weeks 12 to 52 for subjects randomized to BCX9930 in Part 1 and from Weeks 24 to 52 for subjects randomized to placebo]

Part 2 Exploratory Endpoints:

- [redacted]

Part 2 Health-related Quality of Life Endpoints:

- Durability of FACIT-Fatigue scale, QLQ-AA/PNH domain, modified PRO-AA/PNH, EQ-5D-5L utility and VAS, and TSQM scale scores
- Proportion of subjects achieving a within-subject meaningful change for FACIT-Fatigue scale
- Proportion of subjects with improvement in individual PNH symptom items (ie, frequency, severity, and/or interference) on the modified PRO-AA/PNH as compared to baseline
- Patient global impression of change in fatigue, impact of fatigue, and physical functioning since the start of open-label treatment as assessed using the PGIC-Fatigue, PGIC-Impact of Fatigue, and PGIC-Physical Functioning scores, respectively

- CFB in patient global impression of severity of fatigue, impact of fatigue, and physical functioning as assessed using the PGIS-Fatigue, PGIS-Impact of Fatigue, and PGIS-Physical Functioning scores, respectively

PK and Pharmacodynamic (PD) Endpoints – Parts 1 and 2:

- PK data will be used to estimate PK parameters using appropriate PK analyses based on the sampling collection approaches
- PD data will be used to estimate PD parameters as well as in combination with PK data to perform PKPD analyses
- CFB in PD and complement biomarker measurements, including constitutive complement levels and ex vivo stimulation assays

PK and PD data may be analyzed in combination with data from other clinical studies as appropriate.

Study Design:

This is a randomized, placebo-controlled, double-blind, multicenter, parallel-group, 2-part study. Parts 1 and 2 will be conducted in the same subjects. Part 1 of the study is designed to evaluate the efficacy, safety, and tolerability of treatment with oral BCX9930 monotherapy for 12 weeks versus placebo in subjects with PNH who are not currently receiving treatment with complement inhibitor therapy. Subjects will be randomized to receive BCX9930 monotherapy or to placebo under double-blind conditions for the 12-week randomized treatment period. The primary efficacy and safety analyses will be based on Part 1. Part 2 of the study is designed to evaluate the long-term safety, tolerability, and effectiveness of open-label BCX9930 monotherapy when administered through Week 52. All subjects in Part 2 will receive BCX9930. Subjects who are randomized to BCX9930 monotherapy in Part 1 will continue to receive BCX9930 in Part 2. Subjects who are randomized to placebo in Part 1 will discontinue that therapy at the Week 12 visit and receive BCX9930 in Part 2.

Methodology:

Part 1: Eligible subjects will be randomized in a 2:1 ratio to receive BCX9930 monotherapy or matched placebo twice-daily (BID) under double-blind conditions. Randomization will be stratified based on whether a pRBC transfusion was received within the 6 months prior to baseline (yes vs. no). All subjects will be required to return to the clinic for scheduled study visits at Weeks 1, 2, 4, 8, and 12. Additional safety assessments will be performed at Weeks 3, 5, 6, 7, and 10. At the Week 12 visit, the treatment assignment for Part 1 will be unblinded.

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

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

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

After completion of Part 2, all subjects continuing to derive clinical benefit will be allowed to continue treatment with BCX9930 through enrollment in a separate long-term extension study, or via another access mechanism, where available. Subjects who do not continue BCX9930 therapy after

Week 52, or who are prematurely discontinued from BCX9930 treatment prior to Week 52, will be monitored for potential hemolysis and may be required to return to the clinic for an additional visit(s) to assess for acute symptomatic hemolysis, if and when symptoms occur. Subsequently, they will return to the clinic approximately 3 weeks after the date of last dose of BCX9930 for end of study assessments.

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

Number of Subjects (Planned):

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

Diagnosis and Main Criteria for Inclusion:

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

1. Male or female, aged ≥ 18 years old.
2. Body weight ≥ 40 kg.
3. Documented diagnosis of PNH confirmed by flow cytometry with a PNH granulocyte or monocyte clone size of ≥ 10% during screening.
4. Are either: (a) naïve to treatment with a complement inhibitor, or (b) have received no treatment with a complement inhibitor for at least 12 months prior to the screening visit.
5. Do not have access to or have a contraindication (ie, have had a serious adverse reaction) to approved complement, C5 or C3, inhibitor therapies.
6. Recorded the following results during screening:
   a. Hb ≤ 105 g/L (≤ 10.5 g/dL).
   b. LDH ≥ 2 × upper limit of normal reference range (ULN)
   c. ARC of ≥ 100×10^9 cells/L (≥ 100,000 cells/µL; ≥ 100 G/L).
   d. Absolute neutrophil count (ANC) of ≥ 0.75×10^9 cells/L (≥ 750 cells/µL; ≥ 0.75 G/L).
   e. Platelet count of ≥ 30×10^9/L (≥ 30,000/µL; ≥ 30 G/L).
   f. Estimated glomerular filtration rate of ≥ 60 mL/min/1.73 m^2 using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (Levey and Stevens 2010) and no evidence of clinically relevant abnormal renal function unrelated to underlying PNH disease.
7. Contraception requirements:
   Female participants must meet at least one of the following requirements:
   a. Be a woman of nonchildbearing potential.
   b. Be a woman of childbearing potential who agrees to use a highly effective contraceptive method throughout the study and for a duration of 30 days after the last dose of study drug.

c. Alternatively, true abstinence is acceptable for women of childbearing potential when it is in line with the subject's preferred and usual lifestyle.

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

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

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

Additional details are provided in Section 11.2.1.

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

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

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

6. Current participation in any other investigational drug study or participation in an investigational drug study within 30 days prior to the screening visit, or 5.5 half-lives of the investigational drug, whichever is longer.
7. Treatment with anti-thymocyte globulin within 180 days prior to the screening visit.
8. Initiation of treatment with an erythropoiesis-stimulating agent (eg, erythropoietin), a thrombopoietin receptor agonist (eg, eltrombopag), or danazol within 28 days prior to the screening visit.
   (Note: Treatment with these medications initiated > 28 days prior to the screening visit is not exclusionary, if the dose is stable and there is a reasonable expectation that treatment will be continued.)
9. Receiving iron with an unstable dose in the 28 days prior to the screening visit.
10. Clinically significant abnormal electrocardiogram (ECG) at the screening visit.
    (Note: This includes, but is not limited to, a QT interval corrected using Fridericia's method [QTcF] of > 450 msec in males or > 470 msec in females, or ventricular and/or atrial premature contractions that are more frequent than occasional, and/or as couplets or higher in grouping.)
11. Subjects with any of the following results at the screening visit:
    a. Alanine aminotransferase (ALT; also serum glutamic-pyruvic transaminase [SGPT]) > 3 × ULN.
    b. AST (SGOT) > 3 × ULN.
       (Note: Subjects may be enrolled with AST > 3 × ULN if explained by hemolysis.)
    c. Total serum bilirubin > 2 × ULN.
       (Note: Subjects may be enrolled with total serum bilirubin > 2 × ULN if explained by hemolysis or Gilbert's syndrome. In the case of hemolysis, total serum bilirubin must be < 5 × ULN and in the case of Gilbert's syndrome, total serum bilirubin must be < 11 × ULN.)
12. Current use of a prohibited concomitant medication within 7 days prior to Day 1 as detailed in Section 9.8.1.
13. Positive serology for human immunodeficiency virus, or active infection with hepatitis B virus or hepatitis C virus, unless receiving antiviral therapy and viral load is undetectable.
14. Positive drugs of abuse screen, unless by prescription.
15. Pregnant, planning to become pregnant, or breastfeeding.
16. Known hypersensitivity to BCX9930 or any of its formulation excipients.
17. History of severe hypersensitivity to any medicinal product, which was associated with swelling, severe rash requiring treatment/hospitalization, or anaphylaxis.
18. Any other clinically significant medical or psychiatric condition that, in the opinion of the investigator or sponsor, would interfere with the subject's ability to participate in the study or increase the risk of participation for that subject.

Investigational Product, Dosage, and Mode of Administration:

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

Duration of Treatment:

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

Reference Therapy, Dosage and Mode of Administration:

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

Criteria for Evaluation:

Safety: TEAEs, laboratory analyses (clinical chemistry, hematology, coagulation, urinalysis including microscopy), vital signs, 12-lead ECGs, and physical examination findings.

Clinical and Laboratory Measurements of PNH: Hb, number of pRBC transfusions and number of pRBC units administered, LDH, ARC, haptoglobin, bilirubin, AST; assessment of PNH-associated clinical symptoms (eg, fatigue, dyspnea, chest pain/discomfort, dysphagia, abdominal pain, headache, erectile dysfunction, hemoglobinuria, and jaundice); acute symptomatic hemolysis; major adverse vascular events (MAVEs), including thrombotic events.

PROs: FACIT-Fatigue scale, QLQ-AA/PNH, modified PRO-AA/PNH, EQ-5D-5L, TSQM, and PGIC/PGIS items for fatigue, impact of fatigue, and physical functioning.

PK: Plasma BCX9930 concentrations (via sparse sampling in all subjects and via serial sampling for 0 to 6 hours post-first dose and at steady state in an optional PK/PD substudy) and PK parameter estimation. Urine for parent BCX9930/metabolite concentration.

PD: Blood samples for analysis of ex vivo AP Wieslab; alternative pathway (AP)-activated complement biomarkers Factor Bb, C3a, and C5a; and constitutive Factor D (as the pharmacologic target), Factor Bb, and sC5b-9. PNH clone size (ie, total PNH RBC, PNH WBC, and the ratio of total PNH RBC to PNH WBC) will be assessed. Acute symptomatic hemolysis will be evaluated, where possible, with analysis of ex vivo AP Wieslab, constitutive Factor D, Factor Bb, total C3, C3a, total C4, C4a, and sC5b-9, and ex vivo AP-activated (multiplex) Factor Bb, C3a, and C5a. [redacted]

Statistical Methods:

The primary study hypothesis is that the treatment effect, as measured by the CFB in Hb at Week 12 for BCX9930, will be superior to placebo. The primary efficacy endpoint is the CFB in Hb at Week 12 in the intent-to-treat (ITT) population, which includes all randomized subjects, regardless of whether study drug was administered. The difference between treatment groups in CFB in Hb at Week 12 will be analyzed using an analysis of covariance (ANCOVA) model. The model will include treatment and randomization stratum as categorical covariates and baseline Hb as a continuous covariate. Missing data will be imputed using the Jump-to-Reference (J2R) method (Carpenter, Roger, et al. 2013). Inferential testing for the primary endpoint of interest (CFB in Hb at Week 12)

will be conducted at the $\alpha = 0.05$ level of significance. The alpha level for tests of primary and key secondary endpoints will be adjusted for multiplicity using hierarchical testing in the order the endpoints are specified. All hypothesis tests will be 2-sided.

Sample Size: Assuming a common standard deviation for Hb of 2.3 g/dL from Lee and colleagues (Lee, Peffault de Latour, et al. 2019), and a randomization ratio of 2:1, a sample size of 57 subjects (approximately 38 subjects in the BCX9930 200/400 mg arm and approximately 19 subjects in the placebo arm) will provide 85.3% power to detect a treatment difference of 2.0 g/dL in change from baseline Hb for subjects randomized to BCX9930 200/400 mg compared to subjects randomized to placebo. Because missing data will be imputed for the primary analysis, enrollment has not been increased to account for drop-outs.

Safety assessments, data from PNH using clinical measurements, PK, clinical laboratory biomarkers, and quality-of-life measurements will be summarized in tables and figures.

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4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

Table 1: List of Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
AA	aplastic anemia
ACIP	Advisory Committee on Immunization Practices
ADL	Activities of Daily Living
AE	adverse event
aHUS	atypical hemolytic uremic syndrome
AKI	acute kidney injury
ALP	alkaline phosphatase
ALT	alanine aminotransferase (also SGPT)
ANC	absolute neutrophil count
ANCOVA	analysis of covariance
AP	alternative complement pathway
ARC	absolute reticulocyte count
AST	aspartate transferase (also SGOT)
BCRP	breast cancer resistance protein
BID	twice daily
BMF	bone marrow failure
BMI	body mass index
BQL	below the quantification level
BTH	breakthrough hemolysis
C3	complement component 3
C3b	end product of the alternative complement pathway
C3bB	Factor B in complex with C3b
C3G	complement 3 glomerulopathy
C4	complement component 4
C5	complement component 5
CAC	complement-activating condition
CDF	cumulative density function
CFB	change from baseline

Abbreviation or Specialist Term	Explanation
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration equation
COS	Clinical Outcomes Solutions
CMH	Cochran-Mantel-Haenszel
COVID-19	coronavirus disease 2019
CP	classical complement pathway
CSR	clinical study report
C_{tau}	trough concentration
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DDI	drug-drug interaction
DMC	Data Monitoring Committee
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
EOS	end of study
EOSM	events of special monitoring
EQ-5D-5L	EuroQoL 5-dimension, 5-level questionnaire
E-R	exposure-response
ET	early termination
EU	European Union
EVH	extravascular hemolysis
FACIT	Functional Assessment of Chronic Illness Therapy
FDA	US Food and Drug Administration
FIH	first in human
[redacted]	[redacted]
FSH	follicle-stimulating hormone
FXa	activated Factor X
FXIIa	activated Factor XII
GCP	Good Clinical Practice

Abbreviation or Specialist Term	Explanation
Hb	hemoglobin
HBV	hepatitis B virus
HCV	hepatitis C virus
Hib	*Haemophilus influenzae* type B
HIPAA	US Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HRQoL	health-related quality of life
IB	Investigator's Brochure
IC_{50}	50% of maximal inhibitory concentration
IC_{90}	90% of maximal inhibitory concentration
ICF	informed consent form
ICH	International Council for Harmonisation
IMP	investigational medicinal product
INR	international normalized ratio
ITT	intent-to-treat
IV	intravenous
IVH	intravascular hemolysis
IWRS	interactive web-based response system
J2R	Jump-to-Reference
LDH	lactate dehydrogenase
LLN	lower limit of normal (reference range)
LP	lectin complement pathway
LSM	least-squares mean
MAC	membrane attack complex
MAD	multiple ascending dose
MAVE	major adverse vascular event
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed model repeated measures
N, n	number of subjects or events (uppercase is total population; lowercase is subgroup population)
NCI	US National Cancer Institute
NRMWG	Nephrology Risk Mitigation Working Group

Abbreviation or Specialist Term	Explanation
NSAID	non-steroidal anti-inflammatory drug
PD	pharmacodynamic(s)
PDF	probability density function
P-gp	P-glycoprotein
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PK	pharmacokinetic(s)
PK/PD	pharmacokinetic/pharmacodynamic
PNH	paroxysmal nocturnal hemoglobinuria
PP	per-protocol
PPK	population pharmacokinetic(s)
pRBC	packed red blood cell
PRO-AA/PNH	Patient-Reported Outcome Questionnaire for Aplastic Anemia/Paroxysmal Nocturnal Hemoglobinuria
Q12h	every 12 hours
Q24h	every 24 hours
QLQ-AA/PNH	Quality of Life Questionnaire for patients with Aplastic Anemia and Paroxysmal Nocturnal Hemoglobinuria
QoL	quality-of-life
QTcF	QT interval corrected using Fridericia's method
RBC	red blood cell
SAD	single ascending dose
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
sC5b-9	soluble C5b-9
sCr	serum creatinine
SD	standard deviation
SGOT	serum glutamic-oxaloacetic transaminase (also AST)
SGPT	serum glutamic-pyruvic transaminase (also ALT)
SOC	system organ class
SUSAR	suspected unexpected serious adverse reaction

Abbreviation or Specialist Term	Explanation
$t_{1/2}$	half-life
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
TSQM	Treatment Satisfaction Questionnaire for Medication
uACR	urine albumin to creatinine ratio
ULN	upper limit of normal (reference range)
uNGAL	urine neutrophil gelatinase-associated lipocalin
US	United States
VAS	visual analog scale
VZV	varicella-zoster virus
WBC	white blood cell
WHO	World Health Organization

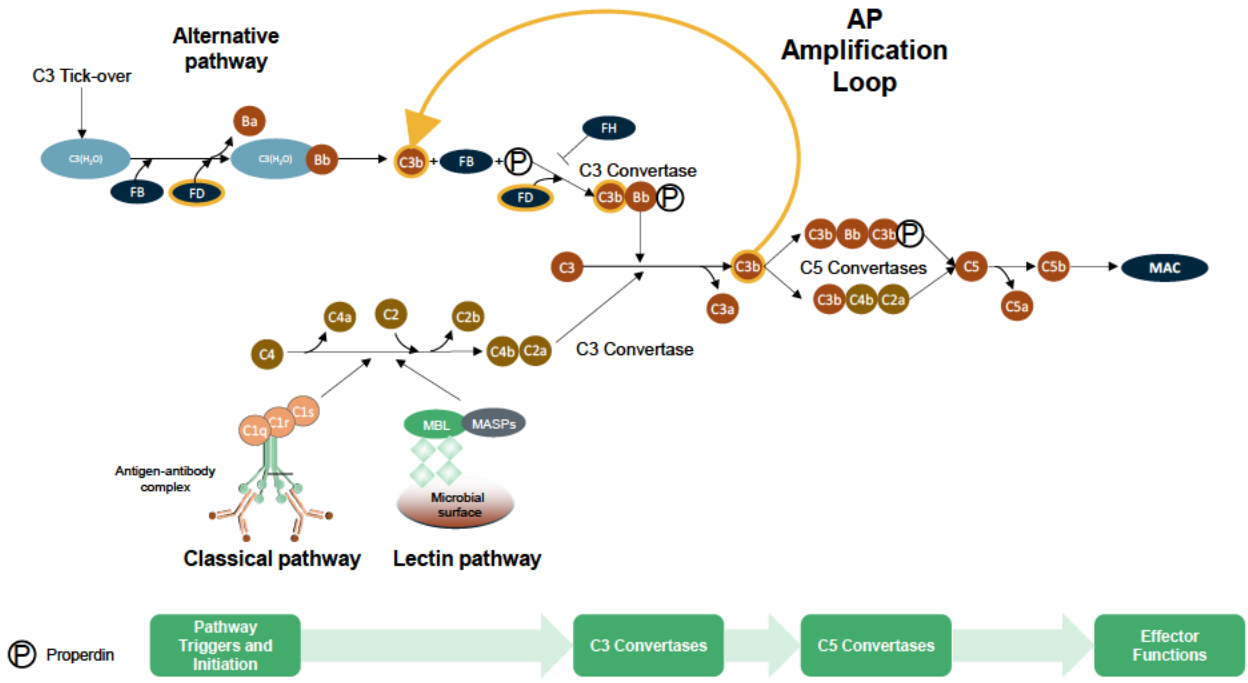
5. INTRODUCTION

5.1. Background

5.1.1. The Complement System

Complement activation is an innate defense mechanism that, when uncontrolled, leads to inflammation and local tissue damage. The complement system consists of 3 linked pathways: the classical pathway (CP), lectin pathway (LP), and alternative pathway (AP), as shown in Figure 1. Dysregulation of AP activity by germ line or somatic genetic mutations of complement regulatory proteins or enzymes, neutralizing antibodies to complement regulatory proteins, or stabilizing antibodies to complement enzyme complexes predisposes individuals to diverse disorders, including paroxysmal nocturnal hemoglobinuria (PNH), age-related macular degeneration, atypical hemolytic uremic syndrome (aHUS), and complement 3 glomerulopathy (C3G) (Holers 2008, Brodsky 2014, Zipfel, Skerka, et al. 2015, Ricklin, Reis, et al. 2016).

Figure 1: The Complement Pathways



Abbreviations: AP = alternative pathway; CP = classical pathway; FB = Factor B; FD = Factor D; LP = lectin pathway; P = properdin; MAC = membrane attack complex; MASP = MBL-associated serine proteases; MBL = mannose-binding lectin.
Source: Adapted from (Thurman and Holers 2006).

The complement system is constitutively active at low levels; the AP is continuously activated at low levels via "tickover", which is a slow spontaneous hydrolysis of an internal thioester within component 3 (C3), a key component of the complement cascade, thereby generating $C3(H_2O)$ at low concentrations. $C3(H_2O)$ pairs with Factor B and is then cleaved by serine protease Factor D to form $C3(H_2O)Bb$ (tickover C3 convertase) that eventually form low levels of C3b via the AP.

The complement system is activated to high levels by the 3 complement pathways (ie, the CP, the LP, or the AP) and amplified by the AP amplification loop. Activation of the complement system by any of the 3 pathways results in production of C3b fragments, which can covalently attach to available surfaces (ie, opsonization) (Holers 2008, Brodsky 2014, Zipfel, Skerka, et al. 2015, Ricklin, Reis, et al. 2016). Deposited C3b fragments trigger a positive feedback loop, called the AP amplification loop, by pairing with Factor B to form C3bB, which then is cleaved by Factor D to generate a second form of AP C3 convertase, C3bBb. Membrane-bound C3bBb then cleaves additional C3 to generate further C3b fragments, which bind additional Factor B molecules to repeat and amplify the cycle. Ultimately, activation of the AP amplification loop, whether initially by the AP, LP, or CP, leads to opsonization with C3b, release of the anaphylatoxins C3a and C5a, and assembly of the terminal membrane attack complex (MAC, also known as C5b-9) on the target surface, resulting in cell lysis (Ricklin, Reis, et al. 2016). Several studies have shown that the AP amplification loop may account for up to 80% of the C5a and MAC generated via CP or LP activation, substantially more than previously appreciated (Thurman and Holers 2006, Ekdahl, Mohlin, et al. 2019).

In summary, regardless of whether complement is initially activated via the AP, CP, or LP, activation of the AP amplification loop results in opsonization of cell surfaces by C3b, formation of the C5 convertase C3bBb(3b)n, cleavage of C5, release of the anaphylatoxins C3a and C5a, and assembly of the terminal MAC on the target surface resulting in cell lysis (Ricklin, Reis, et al. 2016).

5.1.2. The Role of Factor D

Factor D is the rate-limiting enzyme of the AP (Volanakis and Narayana 1996) and the AP amplification loop and is made constitutively by adipocytes (White, Damm, et al. 1992). The only natural substrate for Factor D is complement Factor B bound to C3b (Volanakis and Narayana 1996). Factor D cleaves Factor B only after the latter is bound to C3b or C3(H_2O) at the bond between Factor B amino acid residues 259 and 260, releasing the 30kD N-terminal Ba fragment and retention of the 60kD C-terminal Bb fragment that is required for production of the C3 convertases of the AP [ie, C3bBb and C3(H_2O)Bb] (Torreira, Tortajada, et al. 2009). In addition, Factor D is essential for the AP amplification loop following generation of C3b by the AP, LP, or CP (Lesavre and Muller-Eberhard 1978, Volanakis and Narayana 1996, Xu, Narayana, et al. 2001). Based on in vitro studies using human serum, this AP amplification loop appears to account for up to 80% of the C5a and MAC generated from initial activation of complement by the CP or LP, or other proteolytic enzymes (eg, renin) in the plasma or other body fluids (Thurman and Holers 2006, Ekdahl, Mohlin, et al. 2019) (BioCryst internal data on file). As such, Factor D plays a central role in the activation and amplification of the AP, as well as in the amplification of the LP and the CP.

5.1.3. Paroxysmal Nocturnal Hemoglobinuria

PNH is an acquired, rare, serious, and potentially life-threatening disorder characterized by destruction of red blood cells (RBCs) resulting from uncontrolled activity of complement. PNH is caused by a somatic mutation in the phosphatidylinositol glycan anchor biosynthesis class A (PIG-A) gene in hematopoietic stem cells that leads to a deficiency of the membrane-displayed complement regulatory proteins CD55 and CD59 that normally protect RBCs from effective opsonization and lysis by the complement system. These deficiencies result in unrestrained

complement activity that attacks RBCs leading to episodes of intravascular hemolysis (IVH), extravascular hemolysis (EVH), chronic hemolytic anemia, bone marrow failure (BMF), and thrombosis (Parker 2009, Pu and Brodsky 2011, Parker 2012), and EVH in patients treated with C5 inhibitors (Risitano, Notaro, et al. 2009). PNH affects men and women equally, and is more common in people of Asian than Caucasian ethnicity (Hill, DeZern, et al. 2017, Jalbert, Chaudhari, et al. 2019). The onset of PNH can occur at any age. The median (interquartile range) age of patients with PNH at diagnosis reported in a large series was 44 years (30 to 60 years) (Curran, Kernan, et al. 2012, Ge, Shi, et al. 2015, Mercuri, Farruggia, et al. 2017, Narita, Muramatsu, et al. 2017, Cannizzo, Raia, et al. 2019, Griesser, Myskiw, et al. 2020).

IVH in PNH is associated with gastrointestinal, cardiovascular, pulmonary, neurological, and urogenital symptoms, as well as clotting disorders (Rother, Bell, et al. 2005, Savage and Brodsky 2007). A classic symptom experienced by patients with PNH is discoloration of the urine due to hemoglobinuria following hemolysis. Patients report attacks of abdominal pain, difficulty swallowing, and pain during swallowing, as well as erectile dysfunction in men (Borowitz, Craig, et al. 2010, Rachidi, Musallam, et al. 2010). Other common symptoms related to anemia of patients with PNH are those such as debilitating fatigue, shortness of breath, and palpitations (Parker, Omine, et al. 2005).

Patients with PNH have an increased risk for splanchnic, portal, and hepatic vein thrombosis, the latter leading to Budd-Chiari syndrome (Graham, Rosse, et al. 1996, Hauser, Brichta, et al. 2003, Yin, Liu, et al. 2009, Jain 2010, Torres, De Vroey, et al. 2010).

Other nonhematological clinical findings include acute or chronic renal failure (Sechi, Marigliano, et al. 1988, Jackson, Noble, et al. 1992, Chow, Lai, et al. 2001, Nair, Khaira, et al. 2008, Guasch 2010, Hillmen, Elebute, et al. 2010) and pulmonary hypertension (Heller, Grinberg, et al. 1992).

PNH is associated with significant morbidity and mortality (Harris, Koscick, et al. 1999, Rachidi, Musallam, et al. 2010). Median survival in the era prior to use of C5 inhibitors was reported in one study as 10 years (Hillmen, Lewis, et al. 1995); a retrospective analysis found that approximately 20% of patients with only supportive care died within 6 years of diagnosis (Loschi, Porcher, et al. 2016). Thrombosis was the leading cause of death in PNH patients, accounting for up to 67% of deaths (Loschi, Porcher, et al. 2016). While thrombosis is relatively rare as a presenting symptom, it has historically occurred in up to 40% of patients during the course of disease (Pu and Brodsky 2011); a history of major adverse vascular events (MAVEs), including thromboembolism, was reported in 19% of patients with PNH in a large series (Schrezenmeier, Roth, et al. 2020). Visceral thrombosis, cerebrovascular events, and pulmonary embolism predict a poor outcome (Ziakas, Poulou, et al. 2008).

5.1.3.1. Currently Licensed Treatments for PNH

There are currently three therapeutic agents approved for the treatment of PNH in various parts of the world: eculizumab, ravulizumab, and pegcetacoplan.

Eculizumab (approved in the United States [US] and European Union [EU] in 2007 and in Japan in 2010) and ravulizumab (approved in the US in 2018 and in the EU and Japan in 2019) were the only therapeutic agents approved for the treatment of PNH. Both eculizumab and ravulizumab are monoclonal antibodies directed against C5 and each is administered by

intravenous (IV) infusion (Alexion Pharmaceuticals Soliris PI 2020, Alexion Pharmaceuticals Ultomiris PI 2020).

Although survival has improved with the introduction of C5 inhibitors, significant unmet need remains (Marti-Carvajal, Anand, et al. 2014, Risitano, Marotta, et al. 2019). The hematological benefits among patients during C5 inhibitor treatment for PNH are heterogeneous. Complete normalization of hemoglobin (Hb) is seen in no more than one-third of patients, while the remaining patients continue to experience some degree of anemia, in some cases requiring regular RBC transfusions (Lee, Sicre de Fontbrune, et al. 2019). Different factors contribute to residual anemia during eculizumab treatment, including underlying bone marrow dysfunction, residual IVH, and C3-mediated EVH (Risitano, Marotta, et al. 2019). Therefore, there exists a significant unmet need for an efficacious and safe alternative therapeutic option that addresses the shortcomings of the available therapies, including dependence on lifelong IV infusion, ongoing EVH, and for those that do not respond adequately to available therapies, persistent anemia, PNH symptoms, and transfusion dependence.

On 14 May 2021, the US Food and Drug Administration (FDA) granted approval for pegcetacoplan for the treatment of PNH. In December 2021, the European Commission granted approval for pegcetacoplan for the treatment of adult patients with PNH who are anemic after treatment with a C5 inhibitor for at least 3 months. Pegcetacoplan, which is administered by subcutaneous administration twice a week, is a synthetic cyclic peptide conjugated to a polyethylene glycol polymer that binds specifically to C3 and C3b (Apellis Pharmaceutical Empaveli PI 2021).

5.2. BCX9930

BioCryst Pharmaceuticals, Inc. (“BioCryst”) is developing BCX9930, a potent and selective, orally bioavailable, small-molecule inhibitor of complement Factor D.

[redacted]

indicating that BCX9930 has the potential to inhibit both IVH and EVH.

Targeting Factor D with a pharmacologic inhibitor is expected to block the formation of MAC and also inhibit the formation of C3 fragments, opsonization and, therefore, prevent both IVH and EVH in patients with PNH.

Inhibiting Factor D with BCX9930 as a treatment strategy for PNH has at least 2 potential clinical advantages over C5 inhibitors: 1) C3b opsonization is blocked by Factor D inhibition, whereas it is not blocked by C5 inhibitors, with the result that opsonized PNH RBCs undergo EVH despite C5 inhibitor therapy; and 2) small molecule therapeutics inhibiting Factor D could be administered orally, abrogating the need for lifelong IV infusions of C5 inhibitors.

Therefore, targeting Factor D is a promising therapeutic strategy to inhibit AP activation for the treatment of AP-mediated diseases such as PNH.

[redacted]

5.2.1. Nonclinical Findings for BCX9930

The results of nonclinical pharmacology, pharmacokinetics (PK), and toxicology studies of BCX9930 are described briefly below; additional details can be found in the Investigator's Brochure (IB).

[redacted]

In rats and dogs, BCX9930 is rapidly absorbed. Increases in exposure of BCX9930 were approximately proportional to increases in dose in both species. [redacted]

The data from safety pharmacology studies indicate that BCX9930 has a low potential to affect the respiratory, cardiovascular, and central nervous systems. [redacted] BCX9930 has a low risk to prolong the QT interval. [redacted]

The weight of evidence suggests BCX9930 has a low risk for genotoxicity. BCX9930 is not fetotoxic and is not teratogenic in pregnant rats and rabbits. There is a low concern for phototoxicity.

5.2.2. Clinical Findings for BCX9930

5.2.2.1. Study BCX9930-101

The multipart first-in-human (FIH) study (Study 101) of single ascending dose (SAD) and multiple ascending dose (MAD) oral treatment with BCX9930 in 152 healthy subjects (Parts 1 and 2) and ascending doses in 16 PNH subjects (Part 3) commenced in 2019 and has fully enrolled.

Safety and tolerability were evaluated through assessments of treatment-emergent adverse events (TEAEs), laboratory analyses (clinical chemistry, hematology, and urinalysis), vital signs, electrocardiograms (ECGs; 12-lead and telemetry), and physical examinations.

5.2.2.1.1. Healthy Subjects (Study 101, Parts 1 and 2)

Part 1 of Study 101, a SAD study in 56 healthy subjects, has completed enrollment. No clinically significant dose-related trends in laboratory values, vital signs, or ECGs were noted in subjects receiving single doses ranging from 10 to 2000 mg. The most frequently reported TEAE assessed as possibly related to study drug was headache.

Part 2 of Study 101, a MAD study in 96 healthy subjects, has completed enrollment. No clinically significant dose-related trends in laboratory values, vital signs, or ECGs were noted in any cohort. BCX9930 was safe and generally well tolerated following multiple doses of BCX9930 50 to 500 mg administered every 12 hours (Q12h) and 1000 to 2000 mg every 24 hours (Q24h). The most frequently reported TEAE assessed as possibly related to study drug was rash that was self-limiting and not associated with mucosal involvement. No clinically significant dose-related trends in adverse events (AEs), laboratory values, vital signs, or ECGs were noted.

In healthy subjects, BCX9930 exposure was linear and dose-proportional, with no evidence of dose- or time-dependent PK. Food effect (of a high-fat meal) on exposure was modest with an approximate 30% increase in exposure. Steady state was reached within 48 hours after repeat dosing, with modest accumulation (approximately 1.5-fold for Q12h regimens). The effective half-life ($t_{1/2}$) was approximately 6 to 8 hours.

BCX9930 showed rapid and dose-related suppression of the AP. After multiple doses of BCX9930 at dose levels ≥ 100 mg Q12h and ≥ 1000 mg Q24h, AP Wieslab activity was inhibited by > 95%.

5.2.2.1.2. Subjects with PNH (Study 101, Part 3)

[redacted]

[redacted]

[redacted]

[redacted]

5.2.2.2. Study BCX9930-201

[redacted]

5.2.2.3. Study BCX9930-102

[redacted]

[redacted]

5.2.2.4. Other Clinical Studies

Four additional Phase 1 clinical studies in adult subjects have been initiated. Enrollment has completed for an absorption, distribution, metabolism, and excretion (ADME) study (Study BCX9930-103), a renal impairment study (Study BCX9930-104), an ethnobridging study to evaluate the safety, PK, and pharmacodynamics (PD) of SAD and MAD of BCX9930 in healthy subjects of Japanese origin (Study BCX9930-105), and a relative bioavailability study of BCX9930 tablet and capsule formulations in healthy subjects (Study 106). Results from these studies are described in the current version of the IB.

5.3. Rationale for Study

BCX9930 blocks the initiation of the AP and the C3 amplification loop via potent inhibition of Factor D, resulting in downstream inhibition of both proximal and terminal complement activity. Therefore, BCX9930 monotherapy has the potential to treat patients with PNH whether or not they have received treatment with C5 inhibitors and whether or not C3 opsonization associated with C5 inhibitor treatment is contributing to inadequate responses to those treatments. The clinical development plan for BCX9930 in PNH will evaluate BCX9930 in patients with PNH who have inadequate responses to C5 inhibitor treatment and patients who are not being treated with C5 inhibitor therapies in two complementary studies. Study BCX9930-202 will evaluate the efficacy, safety, and tolerability of BCX9930 monotherapy over a 24-week treatment period versus an active control of continued C5 inhibitor therapy in subjects with an inadequate response to that therapy, while the current study, BCX9930-203 (Study 203), will evaluate the efficacy, safety, and tolerability of BCX9930 monotherapy over a 12-week treatment versus placebo in subjects not currently receiving complement inhibitor therapy.

Study 203 is divided into two parts, conducted on the same population of subjects. Part 1 of the study is designed to evaluate the efficacy, safety, and tolerability of treatment with oral BCX9930 monotherapy for 12 weeks versus placebo in subjects with PNH who are not currently receiving treatment with complement inhibitor therapy. Subjects will be randomized to receive BCX9930 monotherapy or placebo under double-blind conditions for the 12-week randomized treatment period. The primary efficacy and safety analyses will be based on Part 1. Part 2 of the study is designed to evaluate the long-term safety, tolerability, and effectiveness of BCX9930 monotherapy when administered through Week 52. All subjects in Part 2 will receive BCX9930. Subjects who are randomized to BCX9930 monotherapy in Part 1 will continue to receive BCX9930 in Part 2. Subjects who are randomized to placebo in Part 1 will discontinue placebo at the Week 12 visit and receive BCX9930 in Part 2.

5.3.1. Rationale for Study Population

The current study will evaluate a single dose regimen of BCX9930 in subjects not currently receiving treatment with complement inhibitor therapy. For the purposes of this study,

"complement inhibitor therapy" includes both approved therapies and investigational medications, and both proximal complement inhibitors, such as C3 inhibitors and inhibitors of Factor B or Factor D, and terminal complement inhibitors such as C5 inhibitors. In addition to patients naïve to complement inhibitor therapy, who are expected to make up the majority of study participants, for reasons of equity, individuals who have previously received complement inhibitor therapy may also be allowed to enroll in the study. To avoid inadvertently biasing the results of the current study, any prior complement inhibitor therapy must have been stopped at least 12 months prior to screening for this study. This will include individuals whose prior treatment was for a prescribed period only, eg, women who were indicated for treatment with eculizumab during pregnancy only, or individuals who may have participated in a clinical trial with an investigational medication where treatment either was not continued after the study completed or access to the study or study drug was stopped for reasons not directly related to the study drug (eg, travel restrictions related to coronavirus disease [COVID-19]).

All participants must demonstrate ongoing IVH and anemia, as evidenced by an LDH of $\geq 2 \times$ ULN and a Hb ≤ 10.5 g/dL at screening. In addition to anemia, prospective subjects must show evidence of reticulocytosis (defined as an absolute reticulocyte count [ARC] of $\geq 100{,}000$ cells/μL) as further evidence of ongoing hemolysis and an ability to mount a hematopoietic response to treatment with BCX9930. To exclude patients with evidence of significant underlying aplastic anemia (AA) or BMF, who are unlikely to benefit from treatment with a complement inhibitor, and to minimize the risk of infection to participants, subjects will need to meet minimum thresholds at screening for platelet count ($\geq 30{,}000$ /μL) and absolute neutrophil counts (≥ 750 cells/μL).

5.3.2. Rationale for Placebo Comparator: Ethical Considerations for Study Design

Because PNH is such a rare disease, of necessity, the study is being conducted globally across multiple countries/regions, including in countries that have approved one or both of the commercially available C5 inhibitors and in other countries that have no approved PNH therapies beyond supportive care.

Randomized, controlled clinical trials are recognized as the gold standard, and as described in the 'International Ethical Guidelines for Health-related Research Involving Humans,' prepared by the Council for International Organizations of Medical Sciences (CIOMS) in collaboration with the World Health Organization (WHO) (CIOMS 2016), placebo is typically used as the comparator when there is no established effective intervention for the condition under study, or when the placebo is added on to an established effective intervention. For countries in which C5 inhibitor therapies are not currently approved, or approved but not accessible to patients, the inclusion of the placebo control is reasonable. Participants in both arms of the study will still be able to receive most of the treatments that currently constitute the local standard of care, including blood transfusions, growth factors and iron supplementation, and anticoagulant therapies for thrombosis prophylaxis. Thus, participants in the study randomized to placebo would be no worse off than if they did not participate in the study and will be able to access an investigational medicine at the end of the 12 weeks that would otherwise not be available to them.

The CIOMS/WHO guidelines also recognize that the inclusion of a placebo control can be considered ethical, even when there is an established effective intervention, if there are

"compelling scientific reasons for using placebo, and if delaying or withholding the established effective intervention, will result in no more than a minor increase above minimal risk to the participant and risks are minimized, including through the use of effective mitigation procedures". In this study, including a placebo control allows for the study to be blinded, which is not considered a practical option with a C5 inhibitor control, given the need for sham IV infusions, thereby reducing the potential bias from an open-label study. Importantly, the inclusion of the placebo control allows for an assessment of the absolute benefit-risk of BCX9930 therapy in this patient population.

Based on discussions with the US FDA at the End of Phase 1 meeting, a placebo control was considered acceptable if the following "mitigation procedures" are applied:

1. The duration of the placebo-controlled treatment period is kept short.
2. Placebo participants have the opportunity to receive active treatment after completing the placebo-controlled treatment period.
3. The study protocol includes prespecified objective criteria that, in the event that the participant's PNH disease was to worsen while receiving placebo, would allow a placebo recipient to be transitioned to active treatment early.

These considerations are addressed as follows:

1. The duration of blinded study treatment in this study is limited to 12 weeks. Based on review of the preliminary data from Study 101 and the results of Phase 2 studies performed with other investigational proximal complement inhibitors, including the C3 inhibitor, pegcetacoplan (APL-2), and orally administered inhibitors of Factor B, iptacopan (LNP 023) and Factor D, danicopan (ACH-0144471), a 12-week blinded treatment period is considered sufficient to be able to demonstrate the efficacy of treatment and sufficient to observe improvement in Hb after hemolysis is controlled (Kulasekararaj, Risitano, et al. 2019, Wong, Ignatova, et al. 2020, Risitano, Roth, et al. 2021).
2. At the end of the 12-week blinded treatment period, all placebo recipients are transitioned to BCX9930 monotherapy and will receive active treatment through Week 52. Thereafter, BioCryst has committed to provide access to BCX9930 to all study participants who are continuing to experience clinical benefit at the end of the current study.
3. Importantly, the study protocol allows for blinded treatment to be discontinued and treatment with open-label BCX9930 initiated in subjects who demonstrate an immediate therapeutic need for active treatment. These criteria are described in detail in Section 7.4 and include acute kidney injury (AKI) secondary to IVH and MAVEs, including thrombosis. Thrombotic events are recognized as the most significant cause of mortality in PNH patients (Hill, Kelly, et al. 2013). However, while serious and potentially life-threatening, these events are rare, and given the short 12-week duration of the placebo-controlled period, the actual risk from a thrombotic event is considered low. A cumulative thrombosis incidence of between 23% and 30% over an 8- to 10-year period is described by Griffin and Munir for the pre-eculizumab era, ie, representing untreated patients, in their 2017 paper [(Griffin and Munir 2017) based on original

reports (Socie, Mary, et al. 1996, Ray, Burows, et al. 2000, Hall, Richards, et al. 2003, de Latour, Mary, et al. 2008)]. All study participants will be allowed to continue anticoagulant therapy for thrombosis prophylaxis without interruption during the study.

Although eculizumab and ravulizumab are the current standard of care for the treatment of PNH in countries where one or both drugs have received regulatory approval, there are limitations on the availability of these drugs to clinicians treating PNH in many countries. It is recognized that these treatments represent some of the most expensive therapies available for the treatment of any disease. Because of the cost, the initiation of C5 inhibitor treatment is often limited to patients whose disease meets criteria specified by the relevant payers, whether the local health authorities and/or third-party healthcare insurers. Thus, there exists a patient population in these countries whose disease may not currently meet all of those criteria, who would derive benefit from an alternative complement inhibitor and who be willing to participate in this study. Similarly, in some jurisdictions, it is reported that the time needed to satisfy a healthcare insurer that a patient meets the criteria for treatment, absent a sudden deleterious worsening of the patient's health status, can be as long as or longer than the duration of the placebo control. There are also patients who are known to be waiting for alternatives to the established IV treatments, who would consider participation in a study of an all oral therapy.

In summary, there is scientific rationale for the inclusion of placebo to assess the true benefit-risk of BCX9930 and the design of the current study is intended to reduce the potential risk to participants by keeping the overall duration of placebo short, allowing all placebo patients to receive treatment with BCX9930 at the end of the placebo control period, and providing for a switch to open-label BCX9930 in the event that a subject should experience signs and symptoms consistent with the worsening of their disease.

5.3.3. Rationale for Study Endpoints

Patients with PNH who are not being treated with a C5 inhibitor or other complement inhibitor have uncontrolled IVH, resulting in anemia and fatigue (Risitano 2016). Therefore, the primary endpoint selected for this study is the change from baseline (CFB) in the Hb level, which is an objective biomarker that has generally been accepted as a surrogate for clinical benefit in this patient population, as reflected in its use as an endpoint in randomized controlled trials (Hillmen, Szer, et al. 2021) and in the draft hematological response categorization criteria proposed by the Severe Aplastic Anaemia Working Party of the European Bone Marrow Transplantation group (Risitano, Marotta, et al. 2019). This will be assessed though the end of the placebo-controlled treatment period at Week 12.

Key secondary endpoints include those that characterize the clinical benefit of treatment with BCX9930. Secondary endpoints include the proportion of subjects who are transfusion-free over the 12-week period and reductions in transfusions as reflected in the number of units of packed RBC units (pRBCs) transfused, the percent CFB in LDH, and improvement in subject health-related quality of life (HRQoL) as reported using the established Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue scale. Although RBC transfusion criteria vary, reductions in RBC transfusion burden, as reflected in the proportion of subjects who remain transfusion-free and the number of units of RBCs transfused, is an important benefit of treatment of PNH. Fatigue is a key symptom of PNH which is frequently, sometimes constantly, experienced by patients and significantly impacts their HRQoL (Escalante, Chisolm, et al. 2019).

The FACIT-Fatigue scale has been used in prior PNH clinical studies to assess self-reported fatigue and its impact upon daily activities and function, including pivotal clinical trials that supported the approvals of eculizumab and ravulizumab (Hillmen, Young, et al. 2006, Weitz, Meyers, et al. 2013, Kulasekararaj, Hill, et al. 2019, Lee, Sicre de Fontbrune, et al. 2019).

Additional secondary endpoints will characterize the effects of BCX9930 on IVH by measuring the CFB in the total PNH RBC clone size, as well as the change in the ratio of total PNH RBCs to PNH white blood cells (WBCs) (ie, percent PNH RBCs/percent PNH WBCs) after 12 weeks. Preventing complement-mediated destruction of PNH RBC cells will increase the size of the total PNH RBC clone, but not impact the PNH WBC clone size, as WBCs are not materially affected by complement, so the total PNH RBC clone size should increase to approximate the PNH WBC clone size, as the theoretical maximum.

Disease-specific instruments to measure HRQoL in patients with PNH are currently lacking and, as is often the case with ultra-rare diseases, evaluation of HRQoL is either incomplete or assessed using measures designed for other conditions. As a result, symptoms and impacts not relevant to patients with PNH are often measured and, most importantly, those that are of primary importance to patients are often not captured. The effect of BCX9930 monotherapy on HRQoL will be evaluated using a PNH-specific instrument, the Quality of Life Questionnaire for patients with Aplastic Anemia/Paroxysmal Nocturnal Hemoglobinuria (QLQ-AA/PNH). This instrument is currently being used in the International PNH Registry (Groth, Singer, et al. 2017, Niedeggen, Singer, et al. 2019). In addition, improvement on individual PNH symptom items (ie, frequency, severity, and/or interference) will be captured using a modified form of the PNH-specific symptom measure, the Patient-Reported Outcome Questionnaire for Aplastic Anemia and Paroxysmal Nocturnal Hemoglobinuria (PRO-AA/PNH) (Weisshaar, Ewald, et al. 2020). These disease-specific measures will be supplemented by established patient-reported outcome (PRO) measures, including the EuroQoL 5-dimension, 5-level (EQ-5D-5L) questionnaire and the Treatment Satisfaction Questionnaire for Medication (TSQM).

5.3.4. Rationale for Dose Selection

The dose regimen selected for this study is 400 mg BID, modified from 500 mg BID in previous versions of this protocol based on efficacy and safety considerations. The following observations support this dosing regimen:

- [redacted]

[redacted]

[redacted]

[redacted]

5.3.4.1. Summary of Hematologic Response at 400 and 500 mg BID – Studies 101 and 201

Available clinical efficacy data support the potential for lowering the target dose of BCX9930 from 500 to 400 mg BID in the ongoing clinical studies. As dosing of BCX9930 was titrated in the initial cohort of subjects with PNH enrolled in Study 101 Part 3, that study and the long-term extension study (Study 201) provide a comparison of efficacy during at least 6 weeks of initial treatment with 400 mg BID and with ongoing treatment at 500 mg BID (Table 2). Nine subjects in Studies 101/201 had at least 6 weeks of dosing at 400 mg BID prior to escalating to 500 mg BID; 7 of these subjects were naïve to C5 inhibitors and provide a meaningful comparative dataset. Mean Hb, CFB in Hb, PNH Type II+III RBC clone size, its CFB, and the CFB in the ratio of RBC clone size to WBC clone size were very similar at both dose levels. No subjects required red blood cell transfusions during treatment at either dose level. [redacted]

[redacted]

[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]

5.3.4.2. Summary of PPK and PK/PD Modeling

The primary efficacy consideration for the dose selection in this study was the development of PPK and PK/PD models using data from Studies 101 and 201.

PD endpoints in these models included AP Wieslab in healthy and PNH subjects, LDH in subjects with PNH naïve to C5 inhibitors, and C3 opsonization in PNH subjects with inadequate response to ongoing C5 inhibitor therapy. AP Wieslab was used as a real-time marker of overall complement activation. LDH was used as a marker of IVH (terminal complement inhibition) and C3 opsonization was used as a marker of the potential for EVH (proximal complement

inhibition) in PNH subjects. Target occupancy of Factor D is not expected to be affected by a terminal complement inhibitor, allowing for models of IVH and EVH to be extrapolated to all subjects with PNH regardless of C5 inhibitor status.

[redacted]

Separate PK/PD models were constructed for AP Wieslab, LDH, and C3 opsonization of RBCs. Overall, the models performed well and were able to describe trends in the observed data.

[redacted]

The LDH model in C5 inhibitor-naïve PNH subjects was characterized by indirect inhibition,

[redacted]

Outcomes of PK/PD modeling are summarized in Figure 2 (comparison of predicted inhibitory concentrations with PPK-predicted C_{tau}).

Figure 2: Comparison of PK/PD Model-Estimated IC Values (95% CI) for AP Wieslab, LDH, and C3 Opsonization with Median (10^{th} to 90^{th} percentile) PPK Model-Estimated C_{tau} at 200, 400, and 500 mg BID

Abbreviations: AP = alternative pathway; BID = twice daily; CI = confidence interval; IC = inhibitory concentration; LDH = lactate dehydrogenase; PK/PD = pharmacokinetic/pharmacodynamic; PPK = population pharmacokinetic(s).
Notes: Each simulation assumes perfect adherence and optimal spacing of BID doses (ie, every 12 hours).

Initially, a dose of 500 mg BID was selected due to a small potential benefit relative to 400 mg BID in PK/PD model predictions in the absence of any safety signal in humans. Given the available safety data and overlapping confidence intervals in model estimates vs. 500 mg BID, a BCX9930 dose of 400 mg BID is supported by PPK and PK/PD modeling predictions to reach a similar clinical efficacy in PNH subjects.

5.3.4.3. Clinical Safety and Tolerability

In Study 101 Part 3/Study 201, administration of BCX9930 50 to 500 mg has been generally well tolerated for up to 746 days (approximately 107 weeks) in subjects with PNH. There have been no discontinuations due to drug-related TEAEs. The most common TEAEs related to BCX9930 have been headache and events consistent with a drug rash. [redacted] As of the data cutoff, 11 of the 16 subjects with PNH enrolled in Study 101 Part 3 remain on treatment with BCX9930 at doses of 500 mg BID.

[redacted]

[redacted]

5.4. Benefit-Risk Assessment

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 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 LDH and C3 opsonization of RBC cells. Subjects participating in this study may similarly derive a benefit with BCX9930 in controlling the symptoms and/or improving laboratory parameters related to their PNH disease. Thorough monitoring and assessment of AEs will be performed for subjects enrolled in this study, and protocol-mandated safety assessments include vital sign measurements, physical examinations, 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 IB for BCX9930 and summarized below.

5.4.1. Potential Risks of Bacterial Infections

The most significant risk associated with complement inhibitor therapies is the risk of life-threatening or fatal meningococcal infections (Figueroa and Densen 1991, Hillmen, Young, et al. 2006). This risk is well-known and included as a warning in the relevant labels for both Soliris (eculizumab) and Ultomiris (ravulizumab) (Alexion Pharmaceuticals Soliris PI 2020, Alexion Pharmaceuticals Ultomiris PI 2020).

As BCX9930 blocks the AP of complement, subjects may have increased susceptibility to bacterial infections, especially infections with encapsulated organisms, such as *Neisseria meningitidis, Streptococcus pneumoniae*, and *Haemophilus influenzae*, but also with unencapsulated strains of *N. meningitidis* and other bacteria such as *N. gonorrhoeae* (Ram, Lewis, et al. 2010). Study 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. If required on an individual basis, prophylactic antibiotic administration will be allowed.

5.4.2. Potential Risks of SARS-CoV-2 Infection and Vaccination While Receiving BCX9930 Therapy

Complement inhibitors do not inhibit cellular or humoral immunity. Therefore, BCX9930 is not expected to increase the risk of contracting 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.

All study activity will be conducted in accordance with relevant local, regional, and national guidance around COVID-19. In order to minimize the risk of COVID-19 transmission, additional procedures or assessments (which may include but are not limited to symptom assessment, temperature, viral ribonucleic acid [RNA] testing, and antibody testing) may be implemented at the discretion of the investigator and sponsor medical monitor beyond those required for this protocol.

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.

The sponsor's current risk assessment, relative to COVID-19 vaccination in clinical trials with BCX9930, is that authorized or available COVID-19 vaccinations are unlikely to have any potential interaction or added safety risk, if given in combination with BCX9930. Also, currently, there is no theoretical concern or data to suggest that complement inhibition with ongoing BCX9930 treatment would impact the potential efficacy of vaccinations against SARS-CoV-2. While there is a known or expected higher risk of some bacterial infections in patients treated with complement inhibition and in patients with certain hereditary complement deficiencies, there is no clear known increased or compounded risk with vaccinations in the setting of complement inhibition; however, there have been reports of hemolysis in patients with PNH after SARS-CoV-2 vaccination (Gerber, Yuan, et al. 2021).

5.4.3. Potential Risks for Hemolysis After Discontinuation or Interruption of Study Treatment

Similar to available complement inhibitors used to treat PNH (Alexion Pharmaceuticals Soliris PI 2020, Alexion Pharmaceuticals Ultomiris PI 2020), discontinuation of BCX9930 may result in increased risk of hemolysis of PNH RBCs. Subjects receiving blinded study drug or BCX9930 will be instructed to immediately contact the investigative site if they miss any doses of blinded study drug or BCX9930 and experience new or worsening symptoms of hemolysis. In addition, subjects who permanently discontinue blinded study drug or BCX9930 will be closely monitored for potential hemolysis. Assessments to detect hemolysis should be performed as described in Section 12.5.3 and Section 10.3.7.

5.4.4. Potential Risks of Adverse Events with BCX9930

5.4.4.1. Potential Risks for Headache

In Phase 3 studies of adult patients with PNH who received eculizumab or ravulizumab, headache was one of the most frequently reported adverse drug reactions (Alexion Pharmaceuticals Soliris PI 2020, Alexion Pharmaceuticals Ultomiris PI 2020). Headaches that were considered related to ravulizumab and eculizumab commonly occurred early after the initiation of treatment. These headaches may be associated with a transient surge

in plasma nitric oxide levels induced by the cessation of the depletion of nitric oxide by free hemoglobin (Hillmen, Young, et al. 2006, Brodsky 2008, Hillmen, Muus, et al. 2013, Roth, Rottinghaus, et al. 2018). In Study 101, early-onset headache was the most common TEAE in subjects with PNH treated with BCX9930, likely consistent with restoration of nitric oxide homeostasis due to improved control of hemolysis with BCX9930.

5.4.4.2. Potential Risks for Dermatologic Reactions

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. Clinical experience to date indicates that this rash resolves with no intervention while continuing dosing of BCX9930. Although there is no evidence for any systemic hypersensitivity, more severe reactions may be possible, and any subject with a rash believed to be related to BCX9930 should be evaluated, as deemed medically appropriate. Currently, the risk of discontinuing BCX9930 in PNH patients is greater than the potential risk of continuing with treatment; all PNH subjects with rash have recovered while continuing dosing and in the same timeframe as healthy subjects who stopped dosing of BCX9930.

5.4.4.3. Potential Risks for Renal or Hepatic Effects

Toxicities identified in nonclinical studies and detailed in the IB for BCX9930 are monitorable with standard blood and urine clinical chemistry tests.

Renal Effects

[redacted]

Monitoring of renal function will be undertaken in the study using standard measures (eg, sCr, estimated glomerular filtration rate [eGFR], and urinalysis including microscopy and biomarker analysis). Further information can be found in Section 11.7.5. Based on the timing of the early-onset sCr increases, the frequency of laboratory assessments is increased to monitor for any changes in renal function. Any renal events occurring on study should be evaluated as detailed in Section 12.5.2.

Hepatic Effects

Serum chemistries, including liver transaminases, bilirubin, and alkaline phosphatase (ALP), will be followed closely in this study to monitor for any hepatocellular and biliary system changes. Hepatic synthetic function will be monitored by prothrombin time, international normalized ratio (INR), albumin, and total protein levels in blood. The additional laboratory measurements performed through the first 12 weeks of BCX9930 treatment include monitoring for hepatic toxicities.

5.4.5. Overall Benefit-Risk Analysis

Treatment-emergent increases in [redacted] Based on the sponsor's preliminary investigations, reducing the BCX9930 dose to 400 mg BID and introducing a step-up regimen (ie, starting dosing at 200 mg BID for 2 weeks before escalating to 400 mg BID) is anticipated to mitigate the risk of [redacted] 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 IVH, but also by preventing C3-mediated EVH, thereby reducing symptom burden, reducing hemolysis, including EVH and breakthrough hemolysis (BTH), improving patient function, changing the administration route from IV to oral, and improving HRQoL. 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 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.

6. STUDY OBJECTIVES

6.1. Objectives

6.1.1. Part 1 Primary Objective

The primary objective of Part 1 of this study is:

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

6.1.2. Part 1 Secondary Objectives

The secondary objectives of Part 1 of this study are:

- To evaluate the safety and tolerability of BCX9930 monotherapy administered for 12 weeks, as compared to placebo, in subjects with PNH
- To characterize the effects of BCX9930 monotherapy administered for 12 weeks, as compared to placebo, using clinical and laboratory measurements, including complement and thrombosis biomarkers, and PNH clone size, in subjects with PNH
- To evaluate the effects of BCX9930 monotherapy administered for 12 weeks, as compared to placebo, on the FACIT-Fatigue scale and other PROs in subjects with PNH
- To characterize BCX9930 plasma concentrations and PK parameters in subjects with PNH

6.1.3. Part 2 Primary Objective

The primary objective of Part 2 of this study is:

- To evaluate the long-term safety and tolerability of oral BCX9930 monotherapy administered for up to 52 weeks in subjects with PNH

6.1.4. Part 2 Secondary Objectives

The secondary objectives of Part 2 of this study are:

- To assess the effectiveness of BCX9930 monotherapy administered for up to 52 weeks in subjects with PNH
- To characterize the effects of BCX9930 monotherapy administered for up to 52 weeks using clinical and laboratory measurements, including complement and thrombosis biomarkers, and PNH clone size, in subjects with PNH
- To evaluate the effects of BCX9930 monotherapy administered for up to 52 weeks on FACIT-Fatigue scale and other PROs
- To characterize BCX9930 plasma concentrations and PK parameters over time in subjects with PNH

6.2. Endpoints

In Part 1 of this study, unless indicated otherwise, all endpoints will be assessed at Week 12. In Part 2, unless indicated otherwise, all endpoints will be assessed at Week 52. For subjects who are switched from placebo to BCX9930 monotherapy at the end of Part 1, the baseline for treatment with BCX9930 will be defined as the last value prior to first dose of active treatment.

6.2.1. Part 1 Primary Endpoint

The primary endpoint of Part 1 of this study is:

- CFB in Hb [at Week 12]

6.2.2. Part 1 Key Secondary Endpoints

The key secondary endpoints of Part 1 of this study are:

1. Proportion of subjects who are transfusion-free [from Week 4 to Week 12]
2. Number of units of pRBCs transfused [from Week 4 to Week 12]
3. Percent CFB in LDH [at Week 12]
4. CFB in FACIT-Fatigue scale score [at Week 12]

6.2.3. Part 1 Other Secondary Endpoints

Other secondary endpoints for Part 1 of the study are:

- Percent reduction in the rate of pRBC units transfused [from Week 4 to Week 12 vs. prestudy transfusion rate]

- Proportion of subjects with Hb ≥ 12 g/dL [at Week 12]
- Hb stabilization, defined as avoidance of a > 2 g/dL decrease in the absence of transfusion [from Week 4 to Week 12]
- CFB in total PNH RBC clone size [at Week 12]
- CFB in ratio of total PNH RBC clone size to PNH WBC clone size (ie, percent PNH RBCs / percent PNH WBCs) [at Week 12]
- CFB in absolute reticulocyte count (ARC) [at Week 12]
- Proportion of subjects with ARC in the normal range [at Week 12]
- CFB in haptoglobin [at Week 12]
- Proportion of subjects with haptoglobin ≥ lower limit of normal reference range (LLN) [at Week 12]
- CFB in total bilirubin [at Week 12]
- CFB in aspartate aminotransferase (AST; also serum glutamic-oxaloacetic transaminase [SGOT]) [at Week 12]

6.2.4. Part 1 Exploratory Endpoints

The exploratory endpoints of Part 1 of this study are:

- [redacted]

[redacted]

6.2.5. Part 1 Other Health-related Quality of Life Endpoints

Other HRQoL endpoints for Part 1 of the study are:

- Proportion of subjects achieving a within-subject meaningful change for the FACIT-Fatigue scale [at Week 12]
- CFB in QLQ-AA/PNH Physical Functioning and other domain scores [at Week 12]
- Proportion of subjects with improvement on individual PNH symptom items (ie, frequency, severity, and/or interference) from baseline as assessed using the modified PRO-AA/PNH symptom collection tool [at Week 12]
- CFB in individual PNH symptom items on the modified PRO-AA/PNH scores [at Week 12]
- CFB in EQ-5D-5L utility and visual analog scale (VAS) scores [at Week 12]
- TSQM scale score [at Week 12]
- Patient global impression of change in fatigue, impact of fatigue, and physical functioning as assessed using the PGIC-Fatigue, PGIC-Impact of Fatigue, and PGIC-Physical Functioning scores, respectively [at Week 12]

- CFB in patient global impression of severity of fatigue, impact of fatigue, and physical functioning as assessed using the PGIS-Fatigue, PGIS-Impact of Fatigue, and PGIS-Physical Functioning scores, respectively [at Week 12]

6.2.6. Part 1 Safety Endpoints

The safety endpoints of Part 1 of this study are:

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

6.2.7. Part 2 Primary Endpoints

The primary endpoints of Part 2 of this study are:

- Number and proportion of subjects with a TEAE
- Number and proportion of subjects who discontinue due to a TEAE
- Number and proportion of subjects who experience a TESAE
- Number and proportion of subjects who experience a CTCAE Grade 3 or Grade 4 TEAE
- Number and proportion of subjects who experience a treatment-emergent CTCAE Grade 3 or Grade 4 laboratory abnormality

6.2.8. Part 2 Secondary Endpoints

The secondary endpoints in Part 2 of this study are:

- CFB in Hb [mean of values from Weeks 12 to 52 for subjects randomized to BCX9930 in Part 1 and from Weeks 24 to 52 for subjects randomized to placebo]
- Proportion of subjects with Hb ≥ 12 g/dL [at Week 52]
- Proportion of subjects with Hb stabilization (avoidance of a > 2 g/dL decrease in the absence of transfusion) [from Weeks 12 to 52 for subjects randomized to BCX9930 in Part 1 and from Weeks 16 to 52 for subjects randomized to placebo]
- Proportion of subjects who are transfusion-free [from Weeks 12 to 52 for subjects randomized to BCX9930 in Part 1 and from Weeks 16 to 52 for subjects randomized to placebo]

- Number of units of pRBCs transfused [from Weeks 12 to 52 for subjects randomized to BCX9930 in Part 1 and from Weeks 16 to 52 for subjects randomized to placebo]
- Percent reduction in the rate of pRBC units transfused [from Weeks 12 to 52 for subjects randomized to BCX9930 in Part 1 and from Weeks 16 to 52 for subjects randomized to placebo vs. prestudy transfusion rate]
- Percent CFB in LDH [mean of values from Weeks 12 to 52 for subjects randomized to BCX9930 in Part 1 and from Weeks 24 to 52 for subjects randomized to placebo]
- CFB in ARC [mean of values from Weeks 12 to 52 for subjects randomized to BCX9930 in Part 1 and from Weeks 24 to 52 for subjects randomized to placebo]
- Proportion of subjects with ARC in the normal range [at Week 52]
- CFB in haptoglobin [mean of values from Weeks 12 to 52 for subjects randomized to BCX9930 in Part 1 and from Weeks 24 to 52 for subjects randomized to placebo]
- Proportion of subjects with haptoglobin ≥ LLN [at Week 52]
- CFB in total PNH RBC clone size [mean of values from Weeks 12 to 52 for subjects randomized to BCX9930 in Part 1 and from Weeks 24 to 52 for subjects randomized to placebo]
- CFB in ratio of total PNH RBC clone size to PNH WBC clone size [mean of values from Weeks 12 to 52 for subjects randomized to BCX9930 in Part 1 and Weeks 24 to 52 for subjects randomized to placebo]

6.2.9. Part 2 Exploratory Endpoints

- [redacted]

6.2.10. Part 2 Health-related Quality of Life Endpoints

HRQoL endpoints in Part 2 of this study are:

- Durability of FACIT-Fatigue scale, QLQ-AA/PNH domain, modified PRO-AA/PNH, EQ-5D-5L utility and VAS, and TSQM scale scores
- Proportion of subjects achieving a within-subject meaningful change for FACIT-Fatigue scale
- Proportion of subjects with improvement in individual PNH symptom items (ie, frequency, severity, and/or interference) on the modified PRO-AA/PNH as compared to baseline
- Patient global impression of change in fatigue, impact of fatigue, and physical functioning since the start of open-label treatment as assessed using the

PGIC-Fatigue, PGIC-Impact of Fatigue, and PGIC-Physical Functioning scores, respectively

- CFB in patient global impression of severity of fatigue, impact of fatigue, and physical functioning as assessed using the PGIS-Fatigue, PGIS-Impact of Fatigue, and PGIS-Physical Functioning scores, respectively

6.2.11. Pharmacokinetic and Pharmacodynamic Endpoints – Parts 1 and 2

The PK and PD endpoints of Parts 1 and 2 of this study are:

- PK data will be used to estimate PK parameters using appropriate PK analyses based on the sampling collection approaches
- PD data will be used to estimate PD parameters as well as in combination with PK data to perform PKPD analyses
- CFB in PD and complement biomarker measurements, including constitutive complement levels and ex vivo stimulation assays

PK and PD data may be analyzed in combination with data from other clinical studies as appropriate.

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

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

Part 1: Evaluation of efficacy, safety, and tolerability of BCX9930 monotherapy vs. placebo

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

During the blinded treatment phase of the study, any subject who experiences a qualifying event reflecting a significant worsening of their PNH may be allowed to switch to open-label BCX9930. This is described in more detail in Section 7.4.

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

Part 2: Evaluation of the long-term safety, tolerability, and effectiveness of BCX9930 monotherapy

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

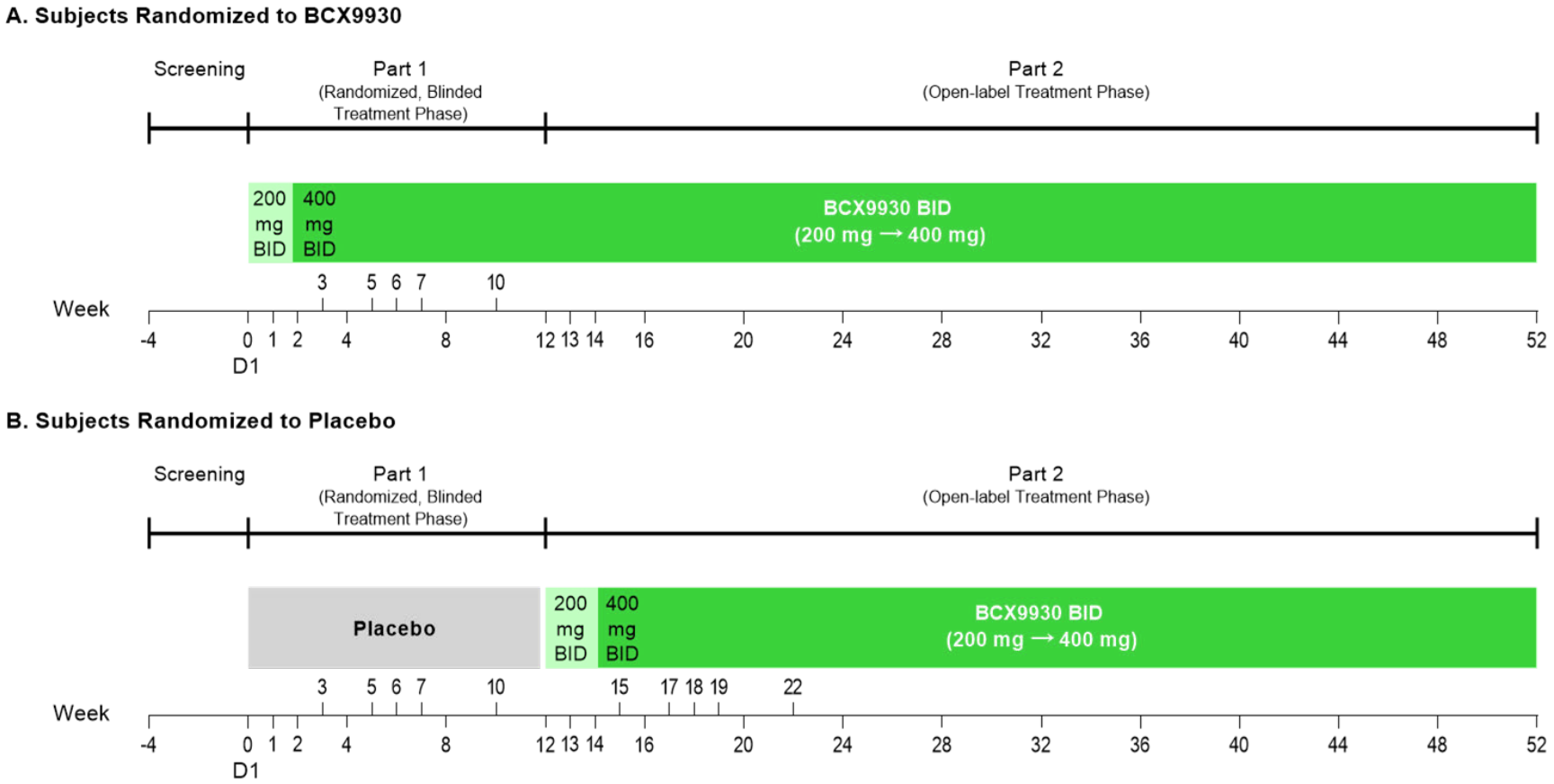
After completion of Part 2, all subjects continuing to derive clinical benefit will be allowed to continue treatment with BCX9930 through enrollment in a separate long-term extension study, or via another access mechanism, where available (see Section 8.5). Subjects who do not continue BCX9930 therapy after Week 52, or who are prematurely discontinued from BCX9930 treatment prior to Week 52, will be monitored for potential hemolysis and may be required to return to the clinic for an additional visit(s) to assess for acute symptomatic hemolysis, if and when symptoms occur, as described in Section 12.5.3. Subsequently, they will return to the clinic approximately 3 weeks after the date of last dose of BCX9930 for end of study assessments.

A study schema is shown in Figure 3.

7.2. Number of Subjects

This study will enroll approximately 57 subjects with PNH who are not currently receiving treatment with a complement inhibitor. In Part 1, approximately 38 subjects will be randomized to BCX9930 monotherapy and approximately 19 subjects will be randomized to placebo under double-blind conditions.

Figure 3: BCX9930-203 Study Schema (Parts 1 and 2)



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

7.3. Treatment Assignment

In Part 1, eligible subjects will be randomized in a 2:1 ratio through an interactive web-based response system (IWRS) to receive BCX9930 monotherapy or placebo through Week 12:

- BCX9930 to be administered orally BID (experimental arm)

  OR

- Matched placebo administered orally BID (control arm)

Randomization will be stratified based on receipt of a pRBC transfusion within the 6 months prior to baseline (yes vs. no).

In Part 2, all subjects will receive BCX9930 monotherapy through Week 52:

- BCX9930 to be administered orally BID (experimental arm)

7.4. Rescue Criteria for Part 1

In Part 1, subjects who meet either of the following criteria will be discontinued from blinded study drug, and at the investigator's discretion, may be switched to open-label BCX9930 for the remainder of the treatment period in Part 1:

- AKI, defined as an eGFR decrease of ≥ 50% or doubling of serum creatinine, secondary to IVH; or
- MAVE, defined as one of the following: deep vein thrombosis; pulmonary embolus; myocardial infarction; transient ischemic attack; unstable angina; renal vein thrombosis; acute peripheral vascular occlusion; mesenteric/visceral vein thrombosis or infarction; mesenteric/visceral arterial thrombosis or infarction; hepatic/portal vein thrombosis (Budd-Chiari syndrome); cerebral arterial occlusion/cerebrovascular accident; cerebral venous occlusion; renal arterial thrombosis; gangrene (nontraumatic; nondiabetic); amputation (nontraumatic; nondiabetic); dermal thrombosis.

Subjects should receive treatment with local standard of care appropriate for the event, as determined by the investigator or treating physician, based on available therapies.

The subject's treatment assignment will be unblinded after confirmation that the AKI or MAVE criterion has been met and prior to initiating treatment with open-label BCX9930. For subjects who were randomized to placebo, treatment with open-label BCX9930 should begin at 200 mg BID for the first 14 days before escalating to the 400 mg BID target dose. Subjects randomized to BCX9930 will continue on their current dose regimen.

7.5. Individual and Study Termination Criteria

7.5.1. Subject Withdrawal from Study Treatment

A subject will be permanently discontinued from study drug in either study part for any of the following reasons:

- Subject request to discontinue for any reason.

- Pregnancy in a female subject.
- Emergence of an AE, including a laboratory abnormality, or other unacceptable toxicity that, in the judgment of the investigator, compromises the ability of the subject to continue study-specific procedures or it is considered not to be in the subject's best interest to continue due to an altered benefit-risk profile.
- Intercurrent illness or the emergence of a new medical condition that would, in the judgment of the investigator, affect assessments of clinical status to a significant degree.
- Treatment-emergent ALT (also serum glutamic-pyruvic transaminase [SGPT]) > 3 × ULN (confirmed by repeat testing) combined with either:
  - laboratory abnormalities indicative of significant hepatic toxicity (ie, meeting Hy's law, total bilirubin > 2 × ULN OR with a new increase in INR > 1.5 in the absence of warfarin therapy)

    OR
  - symptomatology of acute hepatitis (ie, severe fatigue, nausea, vomiting, right upper quadrant pain and tenderness, fever, rash, and/or eosinophilia [> 5%] that has not been part of the subject's history of PNH symptomatology)

  AND
  - assessed as probably or definitely related to BCX9930

  AND
  - without clinical and/or laboratory evidence of hemolysis or any other potential alternative etiology.
- Treatment-emergent increase in sCr ≥ 3 × ULN (confirmed by repeat testing) without clinical and/or laboratory evidence of hemolysis or any other potential cause of renal dysfunction.
- Invasive meningococcal infection or invasive encapsulated bacterial infection. Discontinuation may occur after subject stabilization to prevent uncontrolled hemolysis.
- In the investigator's opinion it is in the best interest of the subject to discontinue from further dosing.
- Subject noncompliance (eg, protocol deviation), as assessed by the sponsor or investigator, to be detrimental to study or subject benefit-risk profile.
- Discontinuation at the request of the sponsor, relevant competent authority, or the governing institutional review board (IRB), research ethics board (REB), or independent ethics committee (IEC), collectively referred to as "ethics committee".

Whenever possible, the investigator will consult with the sponsor medical monitor (or designee) before discontinuing study treatment. The reason for discontinuation of study treatment will be recorded in the source documents and electronic case report form (eCRF).

Subjects who interrupt or discontinue study drug for any reason will be monitored for hemolysis as described in Section 12.5.3 and Section 10.3.7.

7.5.2. Criteria for Study Termination

The following study stopping criteria will be used to terminate either the study or the participation of a particular investigational site:

- Request of the relevant competent authority or ethics committee
- Emergence of unacceptable risk, toxicity, or negative change in the benefit-risk assessment
- Non-compliance with the study protocol, including inaccurate or incomplete recordkeeping, that jeopardizes the scientific integrity of the study or subject safety

BioCryst reserves the right to discontinue the study prior to inclusion of the planned number of subjects but intends only to exercise this right for valid scientific or administrative reasons. If BioCryst does discontinue the study, the investigator must contact all participating subjects immediately after notification of study termination.

If the study is halted due to safety concerns, re-start of the study will occur only following the appropriate authorization via a substantial amendment.

8. SELECTION AND WITHDRAWAL OF SUBJECTS

8.1. Subject Inclusion Criteria

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

1. Male or female, aged ≥ 18 years old.
2. Body weight ≥ 40 kg.
3. Documented diagnosis of PNH confirmed by flow cytometry with a PNH granulocyte or monocyte clone size of ≥ 10% during screening.
4. Are either: (a) naïve to treatment with a complement inhibitor, or (b) have received no treatment with a complement inhibitor for at least 12 months prior to the screening visit.
5. Do not have access to or have a contraindication (ie, have had a serious adverse reaction) to approved complement, C5 or C3, inhibitor therapies.
6. Recorded the following results during screening:
   a. Hb ≤ 105 g/L (≤ 10.5 g/dL).
   b. LDH ≥ 2 × ULN.
   c. ARC of ≥ 100×10^9 cells/L (≥ 100,000 cells/µL; ≥ 100 G/L).
   d. ANC of ≥ 0.75×10^9 cells/L (≥ 750 cells/µL; or ≥ 0.75 G/L).
   e. Platelet count of ≥ 30×10^9/L (≥ 30,000 /µL; or ≥ 30 G/L).

f. eGFR of ≥ 60 mL/min/1.73 m^2 using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (Levey and Stevens 2010) and no evidence of clinically relevant abnormal renal function unrelated to underlying PNH disease.

7. Contraception requirements:

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

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

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

   a. Males with a female partner of childbearing potential must use condoms throughout the study and for a duration of 90 days after the last dose of study drug unless their partner is using a highly effective contraceptive method independent of the study.
   b. Alternatively, true abstinence is acceptable when it is in line with the subject's preferred and usual lifestyle.

   Additional details are provided in Section 11.2.1.

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

8.2. Subject Exclusion Criteria

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

1. Known history of or existing diagnosis of hereditary complement deficiency.
2. History of hematopoietic cell transplant or solid organ transplant or anticipated candidate for transplantation during the study.
3. Myocardial infarction or cerebrovascular accident within 30 days prior to screening, or current and uncontrolled clinically significant cardiovascular or cerebrovascular condition, including unstable angina, severe congestive heart failure, unexplained syncope, arrhythmia, and critical aortic stenosis.
4. History of malignancy within 5 years prior to the screening visit, with exception of adequately treated non-melanoma skin or superficial bladder cancer, curatively treated

carcinoma in situ of the cervix, or other curatively treated solid tumor deemed by the investigator and medical monitor to be at low risk for recurrence.

5. Active bacterial, viral, or fungal infection or any other serious infection within 14 days prior to screening.
   (Note: Suspected or confirmed COVID-19; persistent or recurrent positive test(s) for SARS-CoV-2 nucleic acids or antigens; and worsening dyspnea not due to PNH, vasculitic rash, and persistent fever or other symptoms consistent with multisystem inflammatory syndrome in adults [MIS-A] are exclusionary.)
6. Current participation in any other investigational drug study or participation in an investigational drug study within 30 days prior to the screening visit, or 5.5 half-lives of the investigational drug, whichever is longer.
7. Treatment with anti-thymocyte globulin within 180 days prior to the screening visit.
8. Initiation of treatment with an erythropoiesis-stimulating agent (eg, erythropoietin), a thrombopoietin receptor agonist (eg, eltrombopag), or danazol within 28 days prior to the screening visit.
   (Note: Treatment with these medications initiated > 28 days prior to the screening visit is not exclusionary, if the dose is stable and there is a reasonable expectation that treatment will be continued.)
9. Receiving iron with an unstable dose in the 28 days prior to the screening visit.
10. Clinically significant abnormal ECG at the screening visit.
    (Note: This includes, but is not limited to, a QT interval corrected using Fridericia's method [QTcF] of > 450 msec in males or > 470 msec in females, or ventricular and/or atrial premature contractions that are more frequent than occasional, and/or as couplets or higher in grouping.)
11. Subjects with any of the following results at the screening visit:
    a. ALT (SGPT) > 3 × ULN.
    b. AST (SGOT) > 3 × ULN.
       (Note: Subjects may be enrolled with AST > 3 × ULN if explained by hemolysis.)
    c. Total serum bilirubin > 2 × ULN.
       (Note: Subjects may be enrolled with total serum bilirubin > 2 × ULN if explained by hemolysis or Gilbert's syndrome. In the case of hemolysis, total serum bilirubin must be < 5 × ULN and in the case of Gilbert's syndrome, total serum bilirubin must be < 11 × ULN.)
12. Current use of a prohibited concomitant medication within 7 days prior to Day 1 as detailed in Section 9.8.1.
13. Positive serology for human immunodeficiency virus (HIV), or active infection with hepatitis B virus (HBV) or hepatitis C virus (HCV), unless receiving antiviral therapy and viral load is undetectable.
14. Positive drugs of abuse screen, unless by prescription.
15. Pregnant, planning to become pregnant, or breastfeeding.

16. Known hypersensitivity to BCX9930 or any of its formulation excipients.
17. History of severe hypersensitivity to any medicinal product, which was associated with swelling, severe rash requiring treatment/hospitalization, or anaphylaxis.
18. Any other clinically significant medical or psychiatric condition that, in the opinion of the investigator or sponsor, would interfere with the subject's ability to participate in the study or increase the risk of participation for that subject.

8.3. Subject Withdrawal

Participation in the study is strictly voluntary; a subject may withdraw consent to contribute additional study information at any point. Subjects have the right to withdraw from the study at any time and for any reason. In addition, a subject's participation may be terminated for any of the reasons described in Section 7.5.1. Whenever possible, the investigator will consult with the sponsor medical monitor before halting a subject's participation in the study.

Although a subject may withdraw from the study at any time without specifying a reason for withdrawal, the reason for withdrawal, if provided by the subject, will be recorded in the subject's medical records (source documents) and also in the eCRF. If the reason for subject withdrawal is not known, attempts to contact the subject must be documented to establish whether the reason was due to an AE, and if so, this must be reported in accordance with the procedures outlined in Section 12.4.1. Vigorous attempts will be made for follow-up of all subjects who miss a study visit, given the potential for acute symptomatic hemolysis if BCX9930 dosing is interrupted. If at any point in the study the clinic is unable to contact the subject after appropriate attempts have been made, the subject will be considered lost to follow-up. If a subject's participation in this study is terminated, the responsible investigator/clinical staff member will document termination in the source documents.

Unless consent is withdrawn, subjects who discontinue study treatment in Parts 1 or 2 will be monitored for potential hemolysis and may be required to return to the clinic for an additional visit(s) to assess for acute symptomatic hemolysis, if and when symptoms occur. An early termination (ET) visit will be completed approximately 3 weeks after the date of last dose of BCX9930. See Section 10.3.7 and Section 10.3.8, respectively.

Once subjects have withdrawn from the study, the sponsor will no longer provide treatment with BCX9930 through the study.

Subjects are not eligible for treatment with BCX9930 in Part 2 if they discontinue study treatment in Part 1 unless they meet the criteria for discontinuation of blinded treatment described in Section 7.4.

8.4. End of Study Definition

The end of the study will be defined as the date when the last subject completes the last protocol-scheduled visit.

8.5. BCX9930 Access at Study Completion

Subjects who are assessed as deriving clinical benefit from BCX9930 will be offered continued access to BCX9930 through participation in a separate long-term extension study, or via another

treatment access mechanism, where available and approved by the relevant competent authority. Assuming continued approval of the competent authority, it is anticipated that BCX9930 will continue to be made available in each country until such time as BCX9930 is available through another means (eg, commercial approval) or until BioCryst discontinues development of the product for this indication.

9. TREATMENT OF SUBJECTS

9.1. Description of Study Drug and Study Drug Product

The investigational medicinal product (IMP) for this study consists of BCX9930 and matched placebo tablets.

BCX9930 is a small-molecule inhibitor of Factor D and will be supplied by BioCryst as tablets for oral administration. The active ingredient is BCX9930 drug substance.

[redacted]

Dosage forms include BCX9930 tablets of 100-, 200-, and 250-mg strength, which are all from a dose-proportional blend compressed into tablets of the desired weight.

The matching placebo will also be provided as tablets to match the BCX9930 tablets. The matching placebo tablets contain microcrystalline cellulose, mannitol, and magnesium stearate, and are film-coated with Opadry white.

Additional details of the chemical and physical characteristics of BCX9930 may be found in the IB for BCX9930 and the IMP manual for the study.

9.2. Description of Study Drug Packaging, Labelling, and Storage

The study drug (BCX9930 tablets or matched placebo) will be packaged in bottles.

Each bottle of study drug will be labeled with the information required per local law, which may include sponsor name, study protocol number, description of the contents, a statement regarding the investigational (clinical study) use of the study drug and expiry date.

The bottles of study drug should be stored at 15°C to 25°C (59ºF to 77ºF).

Details on the study drug packaging, labeling, shipment, storage, and dispensing will be provided in the IMP manual for the study.

9.3. Randomization and Blinding of Study Drug

9.3.1. Blinding

In Part 1 of the study, the study drug assignment (BCX9930 or placebo) will be double-blinded (ie, the investigator, study staff, study subjects, and clinical research organization staff will be blinded). Sponsor employees will also be blinded to the treatment allocation of individual

subjects, with the exception of sponsor staff responsible for managing study drug/IMP supplies. Other exceptions are described in the separate Blinding and Unblinding Plan for the study.

Part 2 of the study will be open-label (ie, no blinding will be used). At the Week 12 visit, all subjects will be unblinded as to Part 1 treatment assignment and dispensed open-label BCX9930 for Part 2.

Information on unblinding in the event of an SAE is provided in Section 12.4.3.

9.3.2. Randomization

In Part 1 of the study, approximately 57 subjects will be randomized in a 2:1 ratio to the following treatments using a computer-generated randomization schedule prepared by an unblinded statistician:

- Treatment 1: BCX9930 administered orally BID for 12 weeks (n = 38)
- Treatment 2: Matched placebo administered orally BID for 12 weeks (n = 19)

Details on the processes to be followed for randomization will be provided in a separate manual.

Day 1 for purposes of analysis in Part 1 is defined as the day on which subjects take their first dose of study drug. Randomization will be scheduled such that it occurs on the same day that the subject is scheduled to receive the first dose of study drug, after completion of all baseline study procedures and confirmation of subject eligibility. If required by site procedures (ie, dispensing of randomized study drug must occur through a pharmacy), the subject may be randomized on the business day prior to the planned baseline (Day 1) visit.

Randomization will be stratified based on whether a subject has received a pRBC transfusion within the 6 months prior to baseline (yes vs. no). There will be 2 strata as shown below.

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

9.4. Study Drug Administration

Subjects who previously received 500 mg BID and remain on study treatment will be dose adjusted to 400 mg BID.

For newly enrolled subjects randomized to BCX9930 in Part 1, and subjects switched to BCX9930 for Part 2, BCX9930 will be taken at a dose of 200 mg BID for the first 14 days of treatment before increasing to 400 mg BID. For subjects randomized to placebo in Part 1, an equivalent number of matched placebo tablets will be taken. Subjects will be instructed to take the BCX9930 or matched placebo tablets orally, twice a day at approximately the same times each day (ie, at intervals of approximately 12 hours) without regard to food. Adequate hydration should be maintained to prevent the formation of highly concentrated urine.

No additional study drug preparation is required. BCX9930 or matched tablets will be taken from the provided bottles.

Subjects will be dispensed a sufficient number of bottles of BCX9930 or matched tablets to cover the dosing period until the next study visit.

Drug dispensation will occur in-clinic but may be delivered to subjects by other means (eg, traceable courier) if warranted due to extenuating circumstances (eg, COVID-19 restrictions) which will be determined individually for each site and/or subject taking into account applicable local law or regulation.

Subjects will be instructed to bring all bottles of study drug (both unused and used bottles) with them for each study visit, including any unscheduled visits, where possible. Accountability and adherence will be reviewed at these visits.

9.4.1. Treatment Interruption or Dose Reduction

Treatment interruption or dose reduction as a result of investigator management of AEs potentially related to study drug is permissible with appropriate monitoring for potential hemolysis as described in Section 12.5.3. Any treatment interruption or dose reduction will be recorded in the eCRF and source documents, including the reason for the interruption or reduction. Resumption of study drug administration is also permissible upon resolution of the event, as assessed by the investigator, with a plan for monitoring of the subject for recurrence of the AE, as appropriate. See Section 9.4.2 for potential dose reduction options.

9.4.2. Dose Tapering

In the event of permanent discontinuation of BCX9930, [redacted]

The decision to taper the dose and duration of any taper should be based on the investigator's medical judgement, taking into account the reason for discontinuation of the drug, the severity of any reported signs or symptoms, and/or any reported worsening of signs or symptoms. The tapering schedule should be discussed with the sponsor medical monitor (or designee), ideally prior to implementation, and adjusted, as appropriate, for the individual subject.

9.5. Treatment Compliance

The first dose of study drug will be administered in the clinic on Day 1 under supervision. All subsequent doses can be taken at home; subjects do not need to withhold any doses on clinic days or take a dose at the clinic, unless the clinic visit falls during the subject's normal time of dosing, or the subject is participating in the optional PK/PD substudy on a given visit. Subjects will be provided instructions for taking the twice-daily doses of BCX9930 at home, including frequency and time of administration. 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).

It is anticipated that subject compliance with the BID dosing schedule for BCX9930 is critical to the success of this study. Missing more than 2 consecutive doses of BCX9930 increases the risk of subjects experiencing a hemolytic episode. Therefore, participants must be educated about and understand the importance of compliance with the dosing schedule, be reminded about the risks associated with breakthrough hemolysis, and the need to promptly report new or worsening signs and symptoms of potential hemolysis to staff, especially when associated with missed doses. Once enrolled in this study, each participant will need to be responsible for taking the study drug or BCX9930 doses twice a day, at approximately the same times and as close as possible to 12 hours apart. Investigators are requested to meet with each participant and discuss with them the importance of treatment compliance prior to qualifying the participant for the study. Consideration should be given to strategies that will help reinforce these behaviors, such as asking subjects to voluntarily set up reminder alarms on their mobile phones or at their homes to remind them to take their doses, at least until they become adjusted to their new treatment regimen. BioCryst will provide materials that can be used to communicate the importance of compliance. Subjects will be asked to report new or worsening signs or symptoms of hemolysis to staff. Subjects will be required to bring the bottles of study drug or BCX9930 to clinic visits, including any unscheduled visit to assess for potential hemolysis, when possible. Investigators should remind participants who regularly miss doses about the importance of treatment compliance.

9.6. Missed Doses and Special Considerations for Dosing

If study drug needs to be withheld (eg, to assess a potentially drug-related TEAE), consideration for potential hemolysis as described in Section 12.5.3 should be given.

9.6.1. Missed Doses

Ideally, BCX9930 doses should be taken 12 hours apart at the same times each day without missing doses. 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. If more than 6 hours has passed, the missed dose should not be taken. Regardless of whether the missed dose was made up, dosing should resume with the next dose taken at the scheduled time. For example, a subject who normally takes the BCX9930 doses at 8:00 AM/PM each day can take a missed morning dose as late as 2:00 PM with the evening dose administered on schedule at 8:00 PM. A missed evening dose can be taken as late as 2:00 AM the next day, with the next dose taken on schedule at 8:00 AM.

Subjects should be instructed to immediately contact the investigator if they miss any BCX9930 doses and have new or worsening signs or symptoms consistent with acute symptomatic hemolysis (see Section 12.5.3).

9.6.2. Special Considerations for Dosing, Including Inability to Take Medications Orally

It is imperative that study subjects take study medication as scheduled without missing doses. Under certain circumstances, when a subject cannot take or absorb BCX9930 (including acute illness with vomiting, dysphagia due to symptomatic hemolysis, and unplanned circumstances requiring hospitalization), there are provisions that can be taken.

For acute vomiting, treatment of nausea and/or vomiting with an oral, orally dissolving, or rectal suppository anti-emetic 30 minutes to an hour (as a suggestion) before attempting to swallow the BCX9930 tablets could be attempted. If a subject vomits after receiving a dose of BCX9930, the subject may be re-dosed (take two new tablets) if the intact tablets or pieces of the tablets are seen in the vomitus.

Please refer also to the IMP manual for specific instructions.

9.7. Study Drug Accountability

Accountability of study drug dispensed and returned (as applicable) will be performed at Day 1 and at each subsequent study visit (including at unscheduled visits, where possible). Returned study drug bottles must be retained and reviewed during monitoring visits by the study monitor.

The investigator or designee (eg, pharmacist) must maintain accurate records of the disposition of all study drugs received from the sponsor, directly administered to the subject (including date and time) or dispensed to the subject. At the end of the study, information describing study drug accountability must be maintained at the site.

All study drug not administered and any returned study drug (including empty bottles) will be returned to the sponsor or destroyed on site as instructed by the sponsor following IMP accountability by the study monitor, abiding by appropriate standard operating procedure(s) at the participating institution.

9.8. Prior and Concomitant Medications

Details of all prior treatments for PNH (ie, C5 and other complement inhibitors) will be recorded in the source documentation and eCRF, where known; all other medications will be documented beginning 30 days prior to the screening visit. All concomitant medication use, beginning with the screening visit, will be recorded in the source documentation and eCRF.

Prior to enrollment, the investigator should review the subject's medication list for potentially nephrotoxic medications and consider, when medically feasible, whether these medications may be stopped or substituted with non- or less nephrotoxic medications. Caution should be exercised with the chronic use of non-steroidal anti-inflammatory drugs (NSAIDs) while taking BCX9930.

With the exception of any changes to nephrotoxic medications and prohibited and restricted medications detailed below (Section 9.8.1), subjects should continue their normal medications. Medications that increase infection risk (including oral corticosteroids and other immunosuppressants) and erythropoietin (and analogs) should remain stable until at least the Week 12 visit, and then tapered as per the investigator's judgement, unless taper or discontinuation during Part 1 needs to be done for safety reasons (eg, hemosiderosis).

Prophylactic use of antibacterial and antiviral medications, other than those expressly prohibited on the prohibited medication list, may be considered if clinically indicated (eg, acyclovir for varicella-zoster virus [VZV]) and after discussion with the sponsor medical monitor (or designee), with consideration of the list of prohibited and restricted medications separate from this protocol (Section 9.8.1).

Please refer to inclusion criterion 7 and Section 9.9 for vaccination requirements.

9.8.1. Prohibited and Restricted Medications

Drug interactions with concomitant medications (including supplements) may affect plasma concentrations of that medication or of BCX9930. Adjustments in the dosing regimen of concomitant medications and/or increased safety monitoring may be necessary based on the potential for interaction. Additional detail regarding potential for interaction with specific medications may be found in the prohibited and restricted medications list.

All subjects should observe the prohibitions and restrictions on concomitant use described in Section 8.2 and in the following text for the appropriate window prior to screening or Day 1. All subjects must have discontinued all prohibited medications for a minimum of 7 days prior to Day 1 and have an agreed plan in place for monitoring any restricted medications that will be continued. Similarly, dose adjustments to restricted medications that are necessary for enrollment should be completed at least 7 days prior to Day 1.

Use of the following medications is currently excluded while subjects are receiving treatment with study drug or BCX9930, beginning 7 days prior to Day 1, as is the planned initiation of treatment with such medications during the study:

- [redacted]

[redacted]

- [redacted]

[redacted]

The sponsor will provide a list separate from the protocol of prohibited and restricted medications for which there may be a drug interaction with BCX9930 based upon regulatory labeling for individual medications, regulatory guidances, peer-reviewed literature, and regularly updated drug interaction reference databases (eg, University of Washington School of Pharmacy Drug Interaction Database, Pharmapendium). The sponsor may modify this list of prohibited

medications based upon available PK and safety data on concomitant medications, ongoing clinical findings, and continued review of labeling, regulatory guidances, literature, and reference databases. A memorandum of any such changes to this list will be provided to all clinical sites.

Phase 1 DDI studies may be conducted and resulted during the conduct of this study. Should the guidance for individual medications change, the use of currently prohibited medications may be subsequently allowed based upon the quantitative data generated in the DDI study. A summary and justification of the updated allowance/guidance will be provided to all clinical sites along with a revised list of prohibited medications.

[redacted]

Throughout the course of the study, investigators should inquire about newly initiated, daily chronic-use medications; the investigator should compare these medications to the prohibited medication list.

Similarly, subjects should be aware that there may be restricted medications in this study and should inform all treating physicians of their participation in this study and the possibility of potential interactions with BCX9930.

Please contact the sponsor medical monitor for specific questions regarding prohibited and restricted medications if needed.

9.9. Vaccination Requirements, Vaccinations During Study, and Prophylactic Antibiotic Coverage

BCX9930 blocks the alternative pathway of complement activation; therefore, subjects may have increased susceptibility to bacterial infections, especially infections with encapsulated organisms such as *N. meningitidis*, *S. pneumoniae*, and *H. influenzae*, but also with unencapsulated strains of *N. meningitidis* and other bacteria such as *N. gonorrhoeae* (Ram, Lewis, et al. 2010). Effective and current vaccination coverage must be documented for *N. meningitidis* types A, C, W, and Y, and for *S. pneumoniae*. Vaccination for *N. meningitidis* type B and for *H. influenzae* type B (Hib) is strongly encouraged where authorized and available.

For those who have not received all of the required vaccines (including boosters) or vaccine series, administration of any needed vaccines should start no later than 14 days prior to Day 1. If the recommended vaccination coverage requires more than a single dose, then the additional dose(s) may be administered after Day 1 to complete the recommended vaccination coverage. If a vaccine is not available, the sponsor medical monitor (or designee) should be contacted to discuss potential options in order to satisfy eligibility requirement prior to completing the Day 1 visit.

Antibiotic prophylaxis must be given from Day 1 until a subject is considered fully vaccinated (ie 2 weeks after a booster and 2 weeks after the last vaccination in a series) for those who receive a *N. meningitidis* vaccine less than 14 days before the first dose of study drug. Local treatment guidelines should be followed for prophylactic antibiotic therapy for patients with PNH at the discretion of the investigator for those receiving treatment with complement

inhibition. The screening window can be extended for required vaccinations as per Section 10.3.2.

Unless local guidelines are more stringent, the US Centers for Disease Control and Prevention Advisory Committee on Immunization Practices (ACIP) recommendations for meningococcal vaccination and ACIP guidance for altered immunocompetence (including complement inhibition therapy) should be followed (Mbaeyi 2020, Kroger, Bahta, et al. 2021). For vaccines against serogroups A, C, W, and Y, a booster vaccine should be given every 5 years while on complement inhibitor therapy; the available vaccines are interchangeable. For vaccines against serogroup B, a booster vaccine should be given 1 year after the series completion and every 2 to 3 years thereafter; the available vaccines are not interchangeable (Mbaeyi 2020).

S. pneumoniae vaccination is also required; vaccination with both conjugate and polysaccharide vaccines is preferred.

Vaccination or a booster vaccine against Hib is strongly encouraged for all study participants where authorized and available.

Prior to randomization, each study participant's vaccination record will be reviewed by the sponsor medical monitor or designee, and a plan for required vaccinations will be made based on ACIP guidelines, any national guidance, local practice, authorized vaccines, and vaccine availability. Investigators will also review each subject's vaccination status at periodic intervals to ensure that any needed booster vaccinations are administered at the optimal timing during the study. Please contact the sponsor medical monitor or designee for any questions.

If a live vaccine needs to be given during the study, please contact the sponsor medical monitor or designee.

10. STUDY CONDUCT

10.1. Overview

Prospective subjects will be qualified for the study during a screening period of up to 28 days prior to Day 1 (baseline). Once randomized, subjects will complete 2 consecutive treatment periods with a total duration of approximately 52 weeks. In the first, 12-week treatment period, subjects will be randomized to receive BCX9930 or placebo under double-blind conditions through Week 12. In the second, 40-week treatment period, subjects who are randomized to BCX9930 in Part 1 will continue to receive BCX9930, while those subjects who are randomized to placebo will discontinue placebo and receive BCX9930 through Week 52. At the end of the study, it is anticipated that subjects who have completed treatment with BCX9930 and, in the opinion of the investigator, would benefit from continued treatment with BCX9930 will be allowed to do so. Subjects who do not qualify for continued treatment with BCX9930, or who choose not to continue treatment, will be required to complete an end-of-study (EOS) visit approximately 3 weeks after the last dose of BCX9930.

During the combined 52-week treatment period, all subjects will be required to attend at least 18 in-clinic study visits: Day 1 (Baseline), Week 1 (Day 8), Week 2 (Day 15), Week 4 (Day 29), Week 8 (Day 57), Week 12 (Day 85), Week 13 (Day 92), Week 14 (Day 99), Week 16 (Day 113), Week 20 (Day 141), Week 24 (Day 169), Week 28 (Day 197), Week 32 (Day 225),

Week 36 (Day 253), Week 40 (Day 281), Week 44 (Day 309), Week 48 (Day 337), and Week 52 (Day 365). Additional visits will be required for subjects who experience acute symptomatic hemolysis on-study and/or require additional post-treatment hemolysis assessment at the end of treatment, or who require unscheduled visits for additional or repeat evaluations.

Additional safety assessments will also be required as part of the renal and hepatic safety monitoring program for all subjects at Weeks 3, 5, 6, 7, and 10 during the blinded treatment phase and at Weeks 15, 17, 18, 19, and 22 for subjects randomized to placebo after switching to BCX9930 for Part 2. These additional assessments may be performed at the investigational site, at a laboratory local to the subject, or via a home health service (where permitted and available) and will be continued until sufficient data are available to allow for reduction or elimination of the additional assessments.

Inclusive of the screening and potential post-treatment follow-up periods, each subject's participation in this study is expected to span up to approximately 59 weeks.

10.2. Schedule of Assessments

The schedule of study assessments/procedures for Part 1 of this study is presented in Table 3 and for Part 2 in Table 4.

Assessments in the study are intended to be conducted in clinic; they may be conducted remotely under extenuating circumstances (eg, COVID-19 restrictions), which will be determined individually for each site and/or subject.

Table 3: Study BCX9930-203: Part 1 Schedule of Study Assessments/Procedures (Screening to Week 12)

Assessment/Procedure	Screening (D-28 to D-1)	Baseline D1	Part 1 Treatment (Study Week/Day[a])										Unscheduled Visit (including for hemolysis assessment)[b]	ET[c]
			Wk1 / D8	Wk2 / D15	Wk3 / D22	Wk4 / D29	Wk5 / D36	Wk6 / D43	Wk7 / D50	Wk8 / D57	Wk10 / D71	Wk12 / D85		
Site visit	X	X	X	X		X				X		X		X
Site visit or remote assessment[d]					X		X	X	X		X		X	
Written informed consent[e]	X													
Review eligibility criteria	X	X												
Demographics	X													
Medical & medication history[f]	X	X												
Height, body weight & BMI[g]	X	X				X				X		X		X
Physical examination[h]	X	X	X	X		X				X		X	X	X
12-lead ECG[i]	X	X	X	X		X				X		X		X
Vital signs[j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology	X	X	X	X		X				X		X	X	X
Clinical chemistry	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis including microscopy[k]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Coagulation & haptoglobin	X	X	X	X		X				X		X	X	X
[redacted]														
Drugs of abuse screen	X													
Pregnancy test[l]	X	X				X				X		X		X
FSH[m]	X													

Assessment/Procedure	Screening (D-28 to D-1)	Baseline D1	Part 1 Treatment (Study Week/Day[a])										Unscheduled Visit (including for hemolysis assessment)[b]	ET[c]
			Wk1 / D8	Wk2 / D15	Wk3 / D22	Wk4 / D29	Wk5 / D36	Wk6 / D43	Wk7 / D50	Wk8 / D57	Wk10 / D71	Wk12 / D85		
HBV, HCV, HIV, VZV testing[n]	X													
Urine for biomarkers[o]		X	X	X	X	X	X	X	X	X	X	X	X	X
Optional exit interview[p]												X		
PRO questionnaire[q]														
FACIT-Fatigue scale		X		X		X				X		X		
QLQ-AA/PNH		X				X				X		X		
Modified PRO-AA/PNH		X	X	X		X				X		X		
TSQM						X						X		
EQ-5D-5L		X										X		
PGIS-Fatigue/Impact of Fatigue/Physical Functioning		X										X		
PGIC-Fatigue/Impact of Fatigue/Physical Functioning												X		
PK blood sample collection[r]			X	X	X	X	X	X	X	X	X	X	X	
PD blood sample collection[s]	X	X	X	X		X				X		X	X	X
Optional PK/PD substudy[t]		X												
PK urine collection[u]			X	X	X	X	X	X	X	X	X	X	X	
Iron assessments[v]	X	X										X		X
Subject randomization[w]		X												
Study drug dispensing[x]		X		X		X				X		X[y]		

Assessment/Procedure	Screening (D-28 to D-1)	Baseline D1	Part 1 Treatment (Study Week/Day[a])										Unscheduled Visit (including for hemolysis assessment)[b]	ET[c]
			Wk1 / D8	Wk2 / D15	Wk3 / D22	Wk4 / D29	Wk5 / D36	Wk6 / D43	Wk7 / D50	Wk8 / D57	Wk10 / D71	Wk12 / D85		
Drug accountability			X	X		X				X		X	X	X
Record AEs, concomitant medications & transfusions[z]	←													→

Abbreviations: AE = adverse event; BMI = body mass index; ECG = electrocardiogram; EQ-5D-5L = EuroQoL 5-dimension, 5-level; ET = early termination; [redacted]; FACIT = Functional Assessment of Chronic Illness Therapy; FSH = follicle-stimulating hormone; Hb = hemoglobin; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; ICF = informed consent form; IWRS = interactive web response system; PD = pharmacodynamic(s); PGIC = Patient Global Impression of Change; PGIS = Patient Global Impression of Severity; PK = pharmacokinetic(s); pRBC = packed red blood cells; PRO = patient-reported outcome; PRO-AA/PNH = Patient-Reported Outcome Questionnaire for Aplastic Anemia/Paroxysmal Nocturnal Hemoglobinuria symptom collection tool; QLQ-AA/PNH = Quality of Life Questionnaire for patients with Aplastic Anemia/Paroxysmal Nocturnal Hemoglobinuria; TSQM = Treatment Satisfaction Questionnaire for Medication; VZV = varicella-zoster virus.

Note: X = procedure to be performed only at visits to investigational site.

[a] Visits may be performed within a window of ± 1 days for Week 1 and Week 2, and ± 3 days thereafter.

[b] Subjects should be instructed to immediately contact the investigator if they have new or worsening symptoms of hemolysis. Following the permanent discontinuation of BCX9930, subjects may be required to complete an additional visit(s) to assess for acute symptomatic hemolysis if and when symptoms occur.

[c] Subjects who discontinue the study for any reason will be asked to complete an early termination visit approximately3 weeks (± 3 days) after their last dose of study drug.

[d] For subjects required to complete additional assessments for enhanced renal and hepatic safety monitoring purposes. These assessments may be performed at the investigational site or remotely using a laboratory more convenient for the subject or via a home health service (where permitted and available); results from local laboratory testing must be provided to the investigational site.

[e] Signing of the written ICF may occur in advance of the screening visit and must be obtained from the subject as required by national or local law and institutional practice, prior to conducting any study-related assessments/procedures.

[f] Medical history will include baseline PNH clinical characteristics and disease burden and review of current and prior renal health. Medication history will include all medications administered specifically for PNH (including C5 and other complement inhibitors) and within 30 days prior to screening visit for all other medications taken.

[g] Body weight will be captured at all assessments; height will be measured and BMI calculated at screening only.

[h] A full physical examination will be completed at screening; all other physical examinations may be abbreviated (ie, symptom-driven) examinations, targeted to new or worsening signs and symptoms.

[i] Bedside 12-lead ECGs will be conducted in triplicate pre-dose on Day 1 and Week 12; all other ECGs may be single assessments. Subjects should rest quietly for 10 minutes in a supine position prior to the ECGs being performed. Any blood draws scheduled at the same time should occur after obtaining the ECG.

[j] Vital signs (to include blood pressure, pulse rate, and temperature) will be performed at investigational site visits only (ie, excluding remote visits). Prior to obtaining blood pressure and pulse rate, subjects should rest quietly for a brief period.

[k] Urine microscopy will be performed on urine collected at investigational site visits (and, where possible, at remote visits where the laboratory 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.

[l] A serum pregnancy test will be administered to women of childbearing potential or who are postmenopausal for ≤ 2 years at screening. All other pregnancy tests performed during the study may be urine pregnancy tests (for women of childbearing potential only, or as required by normal institutional practice). The subject's continued use of contraception should be reviewed throughout the study.

[m] FSH will be measured at screening to confirm postmenopausal state in women who report being postmenopausal for< 2 years.

[n] Tests for HIV serology and active HBV and HCV infection – to include hepatitis B surface antigen, hepatitis B core antibody, hepatitis C antibody, HIV antibody – and VZV immunoglobulin G titer.

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

[p] Optional one-on-one qualitative exit interviews will be conducted by Clinical Outcomes Solutions or a third-party vendor over the telephone or by videoconference in a subset of subjects. The exit interview will be conducted for individual subjects as soon as possible (ideally within 2 weeks) after the end of blinded treatment (ie, Week 12 visit). A separate consent for the exit interview will be obtained at the screening or later visit.

[q] All PRO instruments will be administered electronically using a tablet or equivalent device; QLQ-AA/PNH will be administered in paper form.

[r] Single venous blood samples for analysis of plasma BCX9930 concentration will be collected from all subjects at each scheduled study visit, beginning at Week 1, and at any unscheduled visits to the investigational site to assess for acute symptomatic hemolysis or perform additional safety assessments. The blood sample may be drawn without regard to study drug dosing.

[s] Blood samples for analysis of PD and clinical laboratory biomarkers will be collected at each study visit (including screening and Day 1) from all subjects regardless of treatment, including any unscheduled visit to assess for acute symptomatic hemolysis. On Day 1, the samples will be collected prior to administration of the first dose of study drug; at all other visits the blood sample may be drawn without regard to study drug dosing.

[t] For subjects who participate in the optional PK/PD substudy, 4 blood samples for analysis of plasma BCX9930 concentration will be collected on Day 1 at 0.5 (± 0.25), 1.5 (± 0.5), 3.5 (± 0.5), and 6 (± 1) hours post-dose. In addition, where possible, 5 blood samples for analysis of PD and clinical laboratory biomarkers will be collected on Day 1; the first sample will be collected prior to study drug dosing (≤ 2 hours) with subsequent samples collected at 0.5 (± 0.25), 1.5 (± 0.5), 3.5 (± 0.5), and 6 (± 1) hours post-dose. As applicable, PD blood samples will be collected at the same time as the corresponding PK blood sample (ie, excluding the pre-dose sample).

[u] Spot urine samples will be collected for analysis of the concentration of BCX9930 and metabolites at investigational site visits only (ie, excluding remote visits).

[v] Iron, vitamin B_{12}, and folate levels will be measured at screening. At baseline (Day 1), Week 12, and any ET visit performed, blood will be collected for assessment of iron, total iron binding capacity, transferrin, ferritin, hepcidin, and erythroferrone; urine will be collected for hemosiderin.

[w] Subjects will be randomized on Day 1 to receive BCX9930 or placebo using an interactive web-based response system (IWRS). If required by site procedures (ie, dispensing of randomized study drug must occur through a pharmacy), the subject may be randomized on the business day prior to the planned baseline (Day 1) visit.

[x] Study drug (BCX9930 or matched placebo) will be taken orally twice-daily, approximately 12 hours apart and at approximately the same times each day, without regard to food.

[y] At the Week 12 visit, all subjects will be subjects will be unblinded as to Part 1 treatment assignment and dispensed open-label BCX9930 for Part 2.

[z] AEs will be assessed and recorded from the time of signing of the ICF through the appropriate follow-up period. At each visit, subjects should be assessed for new or worsening signs and symptoms of PNH, including acute symptomatic hemolysis. Starting at randomization, subjects will be assessed for possible pRBC transfusion as described in Section 11.4.2.

Table 4: Study BCX9930-203: Part 2 Schedule of Study Assessments/Procedures (Weeks 13 to 52)

Assessment/Procedure	Part 2 Treatment (Study Week/Day[a])																	Unscheduled Visit (including for hemolysis assessment)[b]	EOS/ ET[c]
	Wk13 / D92	Wk14 / D99	Wk15 / D106	Wk16 / D113	Wk17 / D120	Wk18 / D127	Wk19 / D134	Wk20 / D141	Wk22 / D155	Wk24 / D169	Wk28 / D197	Wk32 / D225	Wk36 / D253	Wk40 / D281	Wk44 / D309	Wk48 / D337	Wk52 / D365		
Site visit	X	X		X				X		X	X	X	X	X	X	X	X		X
Site visit or remote assessment[d]			X		X	X	X		X									X	
Body weight				X				X		X	X	X	X	X	X	X	X		X
Physical examination[e]	X	X		X				X		X	X	X	X	X	X	X	X	X	X
12-lead ECG[f]	X	X		X				X		X	X	X	X	X	X	X	X		X
Vital signs[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology	X	X		X				X		X	X	X	X	X	X	X	X	X	X
Clinical chemistry	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis including microscopy[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Coagulation & haptoglobin	X	X		X				X		X	X	X	X	X	X	X	X	X	X
Pregnancy test[i]				X				X		X	X	X	X	X	X	X	X		X
Urine for biomarker testing[j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PRO questionnaires[k]																			
FACIT-Fatigue scale		X		X				X		X			X				X		
QLQ-AA/PNH				X				X		X			X				X		
Modified PRO-AA/PNH	X	X		X				X		X			X				X		
TSQM				X						X			X				X		
EQ-5D-5L										X							X		

Assessment/Procedure	Part 2 Treatment (Study Week/Day[a])																Unscheduled Visit (including for hemolysis assessment)[b]	EOS/ ET[c]
	Wk13 / D92	Wk14 / D99	Wk15 / D106	Wk16 / D113	Wk17 / D120	Wk18 / D127	Wk19 / D134	Wk20 / D141	Wk22 / D155	Wk24 / D169	Wk28 / D197	Wk32 / D225	Wk36 / D253	Wk40 / D281	Wk44 / D309	Wk48 / D337	Wk52 / D365		
PGIS-Fatigue/Impact of Fatigue/Physical Functioning																X		
PGIC-Fatigue/Impact of Fatigue/Physical Functioning																X		
PK blood sample collection[l]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
PD blood sample collection[m]	X	X		X				X		X	X	X	X	X	X	X	X	X
Optional PK/PD substudy[n]		←	—	—	—	—	—	—	—	—	—	—	—	—	—	→		
PK urine collection[o]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Iron assessments[p]										X						X		X
BCX9930 Dispensing[q]		X		X				X		X	X	X	X	X	X	X		
Drug accountability	X	X		X				X		X	X	X	X	X	X	X		X
Record AEs, concomitant medications, transfusions[r]	←	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	→	

Abbreviations: AE = adverse event; BID = twice daily; ECG = electrocardiogram; EOS/ET = end-of-study/early termination; EQ-5D-5L = EuroQoL 5-dimension, 5-level; [redacted]; FACIT = Functional Assessment of Chronic Illness Therapy; Hb = hemoglobin; PD = pharmacodynamic(s); PGIC = Patient Global Impression of Change; PGIS = Patient Global Impression of Severity; PK = pharmacokinetic(s); PNH = paroxysmal nocturnal hemoglobinuria; pRBC = packed red blood cells; PRO = patient-reported outcome; PRO-AA/PNH = Patient-Reported Outcome Questionnaire for Aplastic Anemia/Paroxysmal Nocturnal Hemoglobinuria symptom collection tool; QLQ-AA/PNH = Quality of Life Questionnaire for patients with Aplastic Anemia/Paroxysmal Nocturnal Hemoglobinuria; TSQM = Treatment Satisfaction Questionnaire for Medication.
Note: X = procedure to be performed at visits to investigational site.

[a] Visits may be performed within a window of ± 1 day for Week 13 and Week 14, and ± 3 days thereafter.

[b] Subjects should be instructed to immediately contact the investigator if they have new or worsening symptoms of hemolysis. Following the permanent discontinuation of BCX9930, subjects may be required to complete an additional visit(s) to assess for acute symptomatic hemolysis if and when symptoms occur.

[c] Subjects who complete the study through Week 52 and who do not continue into the long-term extension study, and any subject who discontinues the study prior to Week 52 (for any reason), will be asked to complete an end-of-study or early termination visit, as applicable, approximately3 weeks (± 3 days) after last dose of BCX9930.

[d] For subjects randomized to placebo who are newly switched to BCX9930 for Part 2 and who are required to complete additional assessments for enhanced renal and hepatic safety monitoring purposes. These assessments may be performed at the investigational site or remotely using a laboratory more convenient for the subject or via a home health service (where permitted and available); results from local laboratory testing must be provided to the investigational site.

[e] Abbreviated (ie, symptom-driven) physical examinations, targeted to new or worsening signs and symptoms.

[f] Subjects should rest quietly for 10 minutes in a supine position prior to the ECGs being performed. Any blood draws scheduled at the same time should occur after obtaining the ECG.

[g] Vital signs (to include blood pressure, pulse rate, and temperature) will be performed at investigational site visits only (ie, excluding remote visits). Prior to obtaining blood pressure and pulse rate, subjects should rest quietly for a brief period.

[h] Urine microscopy will be performed on urine collected at investigational site visits (and, where possible, at remote visits where the laboratory 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.

[i] Urine pregnancy tests (for women of childbearing potential only, or as required by normal institutional practice). The subject's continued use of contraception should be reviewed throughout the study.

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

[k] All PRO instruments except QLQ-AA/PNH will be administered electronically using a tablet or equivalent device; QLQ-AA/PNH will be administered in paper form.

[l] Single venous blood samples for analysis of plasma BCX9930 concentration will be collected at each scheduled study visit, and at any unscheduled visits to the investigational site to assess for acute symptomatic hemolysis or perform additional safety assessments.

[m] Blood samples for analysis of clinical laboratory biomarkers will be collected at each scheduled study visit and any unscheduled visit to assess for acute symptomatic hemolysis. In addition, for subjects participating in the optional PK/PD substudy, time-matched blood samples for analysis of PD and clinical laboratory biomarkers will be collected at the same timepoints as the PK samples.

[n] For subjects who participate in the optional PK/PD substudy, 5 blood samples for analysis of plasma BCX9930 concentration will be collected at Week 14 or a later visit, beginning prior to BCX9930 dosing (≤ 15 minutes) and continuing at 0.5 (± 0.25), 1.5 (± 0.5), 3.5 (± 0.5), and 6 (± 1) hours post-dose. In addition, where possible, 5 blood samples for analysis of PD and clinical laboratory biomarkers will be collected at the same time as the corresponding PK blood samples.

[o] Spot urine samples will be collected for analysis of the concentration of BCX9930 and metabolites at investigational site visits (ie, excluding remote visits).

[p] At Week 24, Week 52, and at any EOS/ET visit performed, blood will be collected for assessment of iron, total iron binding capacity, transferrin, ferritin, hepcidin, and erythroferrone; urine will be collected for hemosiderin.

[q] BCX9930 doses will be taken orally, approximately 12 hours apart and at approximately the same times each day, without regard to food.

[r] At each visit, the investigator (or designee) will assess the subject for new or worsening signs and symptoms of PNH, including acute symptomatic hemolysis. The need for pRBC transfusion will be assessed as described in Section 11.4.2.

10.3. Study Visits

10.3.1. Screening

Subjects who are either naïve to complement inhibitor treatment or have not been treated with a complement inhibitor in the past ≥ 12 months may be screened for this study.

Written informed consent must be obtained from each subject before initiation of any screening assessments or procedures. Signing of the informed consent form (ICF) may occur prior to the first on-study visit, which is defined as the visit where site-conducted procedures are first performed.

A 28-day window is provided to qualify subjects for the study. All screening procedures do not need to be completed on the same day, but all screening procedures must be completed and the results reviewed and approved by the investigator (or designee) prior to randomizing a subject. An important consideration for the timing of the screening visit is the collection of blood for hematological testing relative to any pRBC transfusion that may have been administered or is planned to be administered. Where possible, the screening visit should be scheduled such that the hematology sample is drawn prior to any planned pRBC transfusion, or at least 14 days after the subject's last pRBC transfusion, as applicable.

The following assessments will be performed at the screening visit(s):

- Obtain written informed consent
- Discuss optional Exit Interview (by Clinical Outcomes Solutions [COS] or a third-party vendor) and obtain written informed consent for exit interview, if applicable. Note: A Subject Contact Form must be completed and sent to COS or the third-party vendor upon receipt of an executed informed consent.
- Obtain demographic information
- Review of inclusion-exclusion criteria
- Medical history, including collection of PNH history, current and prior renal health, and confirmation of adequate vaccination status and either providing any protocol-required vaccinations and/or scheduling with local health care provider to have the subject vaccinated, as needed, where vaccination status cannot be confirmed; see Section 11.3.
- Review medication history, including prohibited and restricted medications (see Section 9.8.1). All medications administered specifically for PNH (including C5 and other complement inhibitors) and within 30 days prior to screening visit for all other medications will be recorded.
- Record all blood transfusions administered in at least the 12 months prior to the screening visit
- Full physical examination
- 12-lead ECG

- Height, weight, and body mass index (BMI) estimation
- Vital signs (resting blood pressure and pulse rate, and temperature)
- Blood collection for clinical laboratory evaluations (see Table 3 and Table 6):
  - Blood for hematology, clinical chemistry (including haptoglobin), coagulation testing, and iron, folate, and vitamin B_{12}
  - Blood for HBV, HCV, HIV, and VZV testing
  - Serum pregnancy test for female subjects of childbearing potential or who are postmenopausal for ≤ 2 years at screening
  - Blood collection for follicle-stimulating hormone (FSH) to confirm postmenopausal state in women who are postmenopausal for ≤ 2 years at screening
- Blood collection for PD and clinical laboratory biomarkers
- Blood collection for [redacted]
- Urine collection for clinical laboratory evaluations (see Table 3 and Table 6):
  - Urinalysis including microscopy
  - Urine drug screen

A screening failure eCRF page will be completed for those subjects who do not proceed with study dosing, recording the reason for screening failure.

10.3.2. Rescreening/Retesting

Rescreening of ineligible subjects, where there is a reasonable expectation that the subject will become eligible, is permitted up to 2 times. If a subject is unable to be qualified in the 28-day window, eg, due to recent pRBC transfusion or acute illness, the screening window may be extended up to 14 additional days. Retesting of specific assessments without entirely rescreening a subject may be permitted with the approval of the sponsor medical monitor (or designee).

10.3.3. Baseline Visit (Day 1)

Where possible, the baseline (Day 1) visit should be scheduled such that the hematology sample is drawn prior to any planned pRBC transfusion, or at least 14 days after the subject's last pRBC transfusion, as applicable.

Before any study drug is administered, the following assessments will be completed:

- Administer PRO questionnaires; where possible, the questionnaires should be completed by the subject prior to other assessments to prevent influencing subject perceptions:
  - FACIT-Fatigue scale
  - QLQ-AA/PNH
  - Modified PRO-AA/PNH

  - EQ-5D-5L
  - PGIS-Fatigue, PGIS-Impact of Fatigue, and PGIS-Physical Functioning
- Review and update medical history, including PNH history, as needed
- Review and update medication history, including prohibited and restricted medications. Record all medications administered specifically for PNH and all other medications since screening visit.
- 12-lead ECG (triplicate ECGs)
- Targeted physical examination
- Body weight
- Vital signs (resting blood pressure and pulse rate, and temperature)
- Blood collection for clinical laboratory evaluations (see Table 3 and Table 6):
  - Blood for hematology, clinical chemistry (including haptoglobin), and coagulation testing
  - Blood for iron, total iron binding capacity, transferrin, ferritin, hepcidin, and erythroferrone
- Blood collection for PK if participating in the optional PK/PD substudy, a total 4 samples will be drawn through 6 hours post-dose as described in Section 11.5.1.1.
- Blood collection for PD and clinical laboratory biomarkers (all subjects).
  Note: If participating in the optional PK substudy, where possible, a total of 5 samples will be drawn through 6 hours post-dose as described in Section 11.5.1.1.
- Blood collection for [redacted]
- Urine collection for clinical laboratory evaluations (see Table 3 and Table 6):
  - Urinalysis including microscopy
  - Urine collection for biomarker testing
  - Urine collection for hemosiderin
- Urine pregnancy test for female subjects of childbearing potential (or as required by local or institutional practice). A negative pregnancy test result must be recorded in order for the subject to receive study drug.
- Review of inclusion-exclusion criteria (to confirm study eligibility)
- Randomization (if not done previously).
  Note: If required by site procedures (eg, dispensing of randomized study drug must occur through a pharmacy), the subject may be randomized on the business day prior to the planned baseline (Day 1) visit.
- Review/record AEs since screening visit
- Record any blood transfusions administered since the screening visit

After completion of all baseline procedures, subjects will receive the first dose of blinded study drug administered under the supervision of clinic staff. Subjects participating in the optional PK/PD substudy will remain in the clinic for approximately 6 hours post-dose to allow for the collection of the additional post-dose PK and PD blood samples as described in Section 11.5.1.1.

10.3.4. On-study Visits for Part 1: Weeks 1, 2, 4, 8, and 12

In Part 1, all subjects will return to the clinic during Week 1 (Day 8 ± 1 day), Week 2 (Day 15 ± 1 day), Week 4 (Day 29 ± 3 days), Week 8 (Day 57 ± 3 days), and Week 12 (Day 85 ± 3 days). [Note: If the subject attends the clinic for an unscheduled visit, including for pRBC transfusion, at any time within the 14-day period prior to the scheduled Week 12 visit, where possible, a blood sample for hematology should be collected for analysis by the designated central laboratory.]

Subjects do not need to withhold any doses on clinic days or take a dose in the clinic unless the clinic visit falls during the subject's normal time of dosing.

The following assessments will be performed at each visit unless otherwise indicated:

- Administer PRO questionnaires; where possible, the questionnaires should be completed by the subject prior to other assessments to prevent influencing subject perceptions:
  - FACIT-Fatigue scale at Weeks 2, 4, 8, and 12
  - QLQ-AA/PNH at Weeks 4, 8 and 12
  - Modified PRO-AA/PNH at Weeks 1, 2, 4, 8, and 12
  - TSQM at Weeks 4 and 12
  - EQ-5D-5L at Week 12
  - PGIS-Fatigue, PGIS-Impact of Fatigue, and PGIS-Physical Functioning at Week 12
  - PGIC-Fatigue, PGIC-Impact of Fatigue, and PGIC-Physical Functioning at Week 12
- 12-lead ECG (single ECGs, except at Week 12 when triplicate ECGs are required)
- Targeted physical examination
- Body weight at Weeks 4, 8, and 12
- Vital signs (resting blood pressure and pulse rate, and temperature)
- Blood collection for clinical laboratory evaluations (see Table 3 and Table 6):
  - Blood for hematology, clinical chemistry (including haptoglobin), and coagulation testing
  - Blood for iron, total iron binding capacity, transferrin, ferritin, hepcidin, and erythroferrone at Week 12
- Blood collection for PK

- Blood collection for PD and clinical laboratory biomarkers
- Blood collection for [redacted]
- Urine collection for clinical laboratory evaluations (see Table 3 and Table 6):
  - Urinalysis including microscopy
  - Urine collection for biomarker testing
  - Urine collection for hemosiderin at Week 12
- Urine collection for PK
- Urine pregnancy test for female subjects of childbearing potential (or as required by local or institutional practice) at Weeks 4, 8, and 12. A negative pregnancy test result must be recorded in order for the subject to continue receiving study drug.
- Study drug dispensing and drug accountability review
- Review/record AEs, concomitant medication use, including prohibited and restricted medications, and blood transfusions

At Week 8, subjects participating in the optional Exit Interview should be reminded that they will be contacted by COS or a third-party vendor about scheduling the interview.

At Week 12, all subjects will receive a new treatment allocation, reflecting the transition to open-label BCX9930. After completion of all Week 12 procedures, subjects will be unblinded so staff can advise participants of the need to complete additional safety assessments if previously randomized to placebo. Subjects will receive the first dose of open-label BCX9930 administered under the supervision of clinic staff. Where appropriate, subjects will be reminded about the optional Exit Interview.

10.3.5. On-study Visits for Part 2: Weeks 13, 14, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52

In Part 2, all subjects will return to the clinic during Week 13 (Day 92 ± 1 day), Week 14 (Day 99 ± 1 day), Week 16 (Day 113 ± 3 days), Week 20 (Day 141 ± 3 days), Week 24 (Day 169 ± 3 days), Week 28 (Day 197 ± 3 days), Week 32 (Day 225 ± 3 days), Week 36 (Day 253 ± 3 days), Week 40 (Day 281 ± 3 days), Week 44 (Day 309 ± 3 days), Week 48 (Day 337 ± 3 days), and Week 52 (Day 365 ± 3 days).

Subjects do not need to withhold any BCX9930 doses on clinic days or take a dose in the clinic, unless the clinic visit falls during the subject's normal time of dosing or the subject is participating on the optional PK/PD substudy on that day.

The following assessments will be performed at each visit unless otherwise indicated:

- Administer PRO questionnaires; where possible, the questionnaires should be completed by the subject prior to other assessments to prevent influencing subject perceptions:
  - FACIT-Fatigue scale at Weeks 14, 16, 20, 24, 36, and 52
  - QLQ-AA/PNH at Weeks 16, 20, 24, 36, and 52
  - Modified PRO-AA/PNH at Weeks 13, 14, 16, 20, 24, 36, and 52

  - TSQM at Weeks 16, 24, 36, and 52
  - EQ-5D-5L at Weeks 24 and 52
  - PGIS-Fatigue, PGIS-Impact of Fatigue, and PGIS-Physical Functioning at Week 52
  - PGIC-Fatigue, PGIC-Impact of Fatigue, and PGIC-Physical Functioning at Week 52
- 12-lead ECG
- Targeted physical examination
- Body weight at Weeks 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52
- Vital signs (resting blood pressure and pulse rate, and temperature)
- Blood collection for clinical laboratory evaluations (see Table 4 and Table 6):
  - Blood for hematology, clinical chemistry (including haptoglobin), and coagulation testing
  - Blood for iron, total iron binding capacity, transferrin, ferritin, hepcidin, and erythroferrone at Weeks 24 and 52
- Blood collection for PK. A single sample will be collected on each visit unless the subject is participating in the optional PK/PD substudy. If participating in the optional PK/PD substudy, a total of 5 samples will be drawn over an approximately 6-hour period at the optional substudy visit as described in Section 11.5.1.1 (Week 14 or later).
- Blood collection for PD and clinical laboratory biomarkers. If participating in the optional PK/PD substudy, where possible, a total of 5 samples will be drawn over an approximately 6-hour period at the optional PK/PD substudy visit as described in Section 11.5.1.1 (Week 14 or later).
- Urine collection for clinical laboratory evaluations (see Table 4 and Table 6):
  - Urinalysis including microscopy
  - Urine collection for biomarker testing
  - Urine collection for hemosiderin at Weeks 24 and 52
- Urine collection for PK
- Urine pregnancy test for female subjects of childbearing potential (or as required by local or institutional practice) at Weeks 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52. A negative pregnancy test result must be recorded in order for the subject to continue receiving BCX9930.
- BCX9930 dispensing and drug accountability
- Review/record AEs, concomitant medication use, including prohibited and restricted medications, and blood transfusions

10.3.6. Additional Assessments for Renal and Hepatic Safety Monitoring

Additional assessments to monitor for potential renal and hepatic toxicity will be performed during the first 12 weeks of study treatment for all subjects in Part 1 and for subjects newly switched to BCX9930 for Part 2 as specified in the schedule of events specified in Table 3 for Part 1 and Table 4 for Part 2. The assessments may be performed at the investigational site, at a remote laboratory more convenient for the subject, or via a home health service (where permitted and available) and will be continued until sufficient data are available to allow for reduction or elimination of the additional assessments.

The minimum procedures to be completed at each assessment will depend on whether the subject is assessed at the investigational site or assessed remotely.

For subjects assessed at the investigational site:

- Review/record AEs, concomitant medication use, and blood transfusions
- Vital signs (resting blood pressure, pulse rate, and temperature)
- Blood collection for clinical laboratory evaluations:
  - Clinical chemistry
- Blood collection for PK
- Urine collection for clinical laboratory evaluations:
  - Urinalysis including microscopy
  - Urine collection for biomarker testing
- Urine collection for PK

These assessments will also be performed for subjects identified with potential renal events and required to return to the investigational site on a weekly basis (see Section 12.5.2).

For subjects assessed remotely:

- Blood collection for clinical laboratory evaluations:
  - Clinical chemistry (to include at a minimum: sCr, eGFR, blood urea nitrogen, ALT, AST, ALP, and bilirubin [total and direct])
- Urine collection for clinical laboratory evaluations:
  - Urinalysis (to include at a minimum specific gravity, pH, protein, and blood)
  - Urine microscopy (only if the facility is deemed sufficiently qualified to perform this analysis)
  - Urine albumin to creatinine ratio (uACR)

The enhanced safety assessments described in this amendment (ie, the additional assessments to be completed during the first 12 weeks of BCX9930 therapy) will be revisited and reviewed with the DMC after an additional approximately 15 subjects with PNH have completed through the first 8 weeks of monitoring between the current study and Study 202.

10.3.7. Unscheduled Visits (Including for Assessment of Acute Symptomatic Hemolysis)

At the investigator's discretion, an unscheduled visit may be completed at any time during the study prior to the EOS visit. Depending on the reason for the visit, any of the below assessments may be performed, as appropriate.

Following the discontinuation of study treatment in Part 1 or BCX9930 in Part 2, subjects may be required to complete an additional visit(s) to assess for acute symptomatic hemolysis if and when symptoms occur (see Section 12.5.3).

If subjects attend an unscheduled visit to assess acute symptomatic hemolysis, all of the following assessments should be performed. If applicable, dosing compliance should also be reviewed to ensure that the subject is taking the drug correctly. Any missed doses should be recorded.

- Review/record AEs, concomitant medication use, including prohibited and restricted medications, and blood transfusions since the most recent visit
- Vital signs (resting blood pressure, pulse rate, and temperature)
- Targeted physical examination
- Blood collection for clinical laboratory evaluations (see Table 3 [Part 1] or Table 4 [Part 2] and Table 6):
  - Blood for hematology, clinical chemistry (including haptoglobin), and coagulation testing
- Blood collection for PK
- Blood collection for PD and clinical laboratory biomarkers
- Urine collection for clinical laboratory evaluations (see Table 3 [Part 1] or Table 4 [Part 2] and Table 6):
  - Urinalysis including microscopy
  - Urine collection for biomarker testing
- Urine collection for PK
- Any additional testing needed to evaluate for etiology of hemolysis (including acute symptomatic hemolysis), if applicable. This should include review of recent complement-activating conditions (CACs) (eg, infection, trauma, or surgery) that could have contributed to the hemolytic event. Consider testing for acute SARS-CoV-2 infection (the causative agent of COVID-19) in the correct setting.

10.3.8. End-of-Study Visit/Early Termination Visit

All subjects who complete the Week 52 visit, and either do not qualify for or choose not to continue treatment with BCX9930, will be asked to return to the clinic approximately 3 weeks (21 ± 3 days) after the date of the last dose of BCX9930 for an EOS visit. In addition, any subject who discontinues study treatment prior to Week 52 will be asked to complete the same procedures at an ET visit approximately 3 weeks (21 ± 3 days) after the date of the last dose of blinded study drug or BCX9930.

The following assessments will be performed at the EOS/ET visit:

- 12-lead ECG
- Targeted physical examination
- Body weight
- Vital signs (resting blood pressure and pulse rate, and temperature)
- Blood collection for clinical laboratory evaluations (see Table 3 [Part 1] or Table 4 [Part 2] and Table 6):
- Blood collection for clinical laboratory evaluations (see Table 4 and Table 6):
  - Blood for hematology, clinical chemistry (including haptoglobin), and coagulation testing
  - Blood for iron, total iron binding capacity, transferrin, ferritin, hepcidin, and erythroferrone
- Blood collection for [redacted]
- Blood collection for PD and clinical laboratory biomarkers
- Urine collection for clinical laboratory evaluations (see Table 3 [Part 1] or Table 4 [Part 2] and Table 6):
  - Urinalysis including microscopy
  - Urine collection for biomarker testing
  - Urine collection for hemosiderin
- Urine pregnancy test for female subjects of childbearing potential (or as required by local or institutional practice)
- Drug accountability (if not completed earlier)
- Review/record AEs, concomitant medication use, and blood transfusions

If an AE, including a clinically significant laboratory abnormality, is ongoing at the end of study visit, additional clinic visit(s) or telephone contact(s) may be warranted (see Section 12.4).

11. STUDY ASSESSMENTS

11.1. Chronology of Assessments

It is preferred that the PRO questionnaires be administered prior to other study procedures and clinic procedures, such as ECGs, physical examinations, and vital signs measurements, should be completed prior to specimen collection.

11.2. Demographic Information, Medical and Medication History

Demographic information, and medical and medication history will be captured for each subject participating in the study at the screening visit. The medical and medication history review

should include review of the subject's current and prior renal health, and potential risk factors, including pre-existing chronic kidney disease, renal complications of PNH, inter-current illness, including the potential for renal tuberculosis in areas where the disease is endemic, vaccinations, and the use of potentially nephrotoxic medications. Medical history, medication review, and review of inclusion and exclusion criteria, potentially nephrotoxic medications, and prohibited and restricted medications will also be updated and rechecked at baseline (Day 1) as outlined in Section 10.

A PNH history will be taken to document PNH clinical characteristics and disease burden, including time since diagnosis and history of MAVEs (including thrombotic events), bone marrow failure, pRBC transfusions, and PNH-related symptoms. Medication history will include details of all treatments administered specifically for PNH (including any prior complement inhibitor therapies); all other medications will be documented beginning 30 days prior to screening.

11.2.1. Contraception Requirements

The following represents the minimum contraception that should be used by study participants and their partners. Additional contraceptive requirements (eg, requiring the female partners of male subjects to additionally use highly effective contraception) may be required by local site practice and/or the governing ethics committee. It is anticipated that that not all contraceptive methods may be available in all countries/regions, so the list should be modified accordingly.

For the purposes of this study, females are considered fertile following menarche and until becoming postmenopausal, unless permanently sterile (ie, premenopausal with one of the following: documented hysterectomy, documented bilateral salpingectomy, or documented bilateral oophorectomy). Documentation can come from site personnel's review of the subject's medical records, medical examination, or medical history interview.

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

1. Be a woman of nonchildbearing potential, either postmenopausal (defined as without menses for ≥ 12 months without an alternative medical cause with an FSH > 40 mIU/mL) or had a hysterectomy, bilateral salpingectomy, or bilateral oophorectomy.
2. Be a woman of childbearing potential (defined as a female following menarche and prior to becoming post-menopausal who has not had a hysterectomy, bilateral salpingectomy, or bilateral oophorectomy) who agrees to use a highly effective contraceptive method while enrolled in the study and for a duration of 30 days after last dose of study drug. The following methods are acceptable:
   - surgical sterilization (ie, bilateral tubal occlusion or vasectomy of the sole male partner and the vasectomized partner has received medical assessment of surgical success)
   - intrauterine device (IUD) or intrauterine system (IUS)
   - combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal)

- progestogen only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable)

Women of childbearing potential who declare themselves sexually abstinent or exclusively having female sexual partners do not need to use highly effective contraception. Abstinence in this study is defined as true abstinence when it is in line with the subject's preferred and usual lifestyle. If a subject is usually not sexually active but becomes active, she, with her partner, must meet the requirements listed above.

Female subjects must abstain from egg donation throughout the study and for a duration of 30 days after last dose of study drug.

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

1. Males with a female partner of childbearing potential (as defined above) must agree to use condoms while enrolled in the study and for at least 90 days after the last dose of study drug unless their partner is using a highly effective contraceptive method as defined above independent of the study.
2. Males who declare themselves sexually abstinent or having exclusively male partners are not required to use contraception. Abstinence in this study is defined as true abstinence when it is in line with the subject's preferred and usual lifestyle. If a subject is usually not sexually active but becomes active, the criteria listed above must be met.

Male subjects must abstain from sperm donation throughout the study and for a duration of 90 days after last dose of study drug.

Methods of contraception, as applicable, for both male and female participants should be documented in the source documentation.

11.3. Immunity Assessment

In Study 101, a subject with PNH and multiple risk factors including occupation, concomitant corticosteroids, and additional immunosuppression developed disseminated varicella infection as an unrelated SAE. Antibodies to VZV will be tested in all subjects at screening. If an exposure to VZV occurs during the study, this will help the investigator assess the risk for developing primary varicella for non-immune subjects. Any subject who has an exposure to someone with primary varicella (chickenpox) or herpes-zoster (shingles), or who has recently received a live varicella vaccine should contact the investigator, and administration of varicella zoster immune globulin or other medications should be considered, where available.

11.4. Efficacy/Effectiveness Assessments

11.4.1. Clinical and Laboratory Measurements of PNH

Clinical measurements of PNH include clinical laboratory testing for Hb, LDH, ARC, haptoglobin, bilirubin, and AST; number of pRBC transfusions and number of pRBC units administered; assessment of PNH-associated clinical symptoms (eg, fatigue, dyspnea, chest pain/discomfort, dysphagia, abdominal pain, headache, erectile dysfunction, hemoglobinuria, and jaundice); and the incidence of acute symptomatic hemolysis and MAVEs, including thrombotic events.

At each visit, the investigator (or designee) will assess the subject for new or worsening signs and symptoms of PNH, including acute symptomatic hemolysis. Starting at randomization, subjects will be assessed for possible pRBC transfusion as described in Section 11.4.2.

11.4.2. Blood Transfusions

At screening, the number and type of blood transfusions administered within at least the prior 12 months will be recorded. During the study, all blood transfusions will be documented, including the number of units and the type of blood product administered.

In order to standardize the approach to transfusions on-study, beginning at randomization through completion of the Week 52 visit, it is recommended that pRBC transfusion be administered to subjects who meet either of the following criteria:

- Hb value of ≤ 9 g/dL and, in the opinion of the investigator, with symptoms warranting transfusion, or
- Hb value of ≤ 7 g/dL regardless of symptoms

Transfusions will be administered based on the results of local laboratory testing of Hb (or central laboratory testing if local laboratory results are not available) and, as applicable, the investigator's assessment of the subject's PNH symptoms. The investigator (or designee) will determine the appropriate number of units of pRBCs to be transfused. Administration of each pRBC transfusion, including the date of transfusion, the Hb result and source (ie, local or central laboratory, as applicable) and associated symptoms warranting transfusion (if applicable) that triggered the transfusion and the number of units transfused, will be documented in the eCRF.

11.4.3. Clinical Measurements of Iron, Folate, and Vitamin B_{12}

Most patients with PNH who are not receiving C5 inhibitor therapy are iron-depleted due to IVH and loss through the kidneys. When treated with eculizumab, C5 blockade results in increased C3 levels upstream in the complement cascade. The resulting increase in EVH, in combination with chronic blood transfusion, is reported to contribute to iron load in some patients over time (Risitano, Notaro, et al. 2012, Roth, Rottinghaus, et al. 2018).

All subjects will have blood samples drawn for assessment of iron, total iron binding capacity, transferrin, ferritin, hepcidin, and erythroferrone at baseline, Weeks 12, 24, and 52, and the EOS/ET visit; urine collected at these visits will be analyzed for hemosiderin. Iron, vitamin B_{12}, and folate levels will also be measured at screening to assess the status of these analytes.

11.4.4. Patient-reported Outcomes

The following PRO instruments will be used during this study, where translations into the local language are available:

- FACIT-Fatigue scale
- QLQ-AA/PNH
- Modified PRO-AA/PNH
- TSQM

- EQ-5D-5L
- PGIS-Fatigue, PGIS-Impact of Fatigue, and PGIS-Physical Functioning
- PGIC-Fatigue, PGIC-Impact of Fatigue, and PGIC-Physical Functioning

With the exception of the QLQ-AA/PNH, the available PRO instruments will be administered electronically using a tablet or equivalent device; the QLQ-AA/PNH will be administered in paper form. For all subject-completed forms, clinic staff should ensure the subject reads the instructions and completes the questionnaire in full. The investigator and clinic staff are not permitted to provide any assistance, interpretation, or clarification of information or questions contained in the questionnaires. Where possible, the questionnaires should be completed by the subject prior to other assessments for that visit to prevent assessments from influencing subject perceptions (Section 11.1).

11.4.4.1. FACIT-Fatigue

The FACIT-Fatigue scale was derived from instrument development work conducted in 1994 and 1995 to evaluate fatigue associated with anemia in cancer patients (Yellen, Cella, et al. 1997). It contains 13 items which assess self-reported tiredness, weakness, and difficulty conducting usual activities due to fatigue. Items are measured on a 5-point Likert-type scale of 0 to 4 from "Not at all" to "Very much", respectively. The FACIT-Fatigue total score is derived by summing all items and ranges from 0 to 52; items are reverse scored, when appropriate, to provide a scale in which a higher score indicates better functioning or less fatigue (Cella, Lai, et al. 2002). Experience and Impact scores may also be obtained by aggregating the 5 Experience items and the 8 Impact items separately (Cella, Lai, et al. 2011). The recall period for each question is the past 7 days. Content validation of the FACIT-Fatigue scale was examined in a cross-sectional validation study involving cognitive debrief interviews with patients with PNH (Weitz, Meyers, et al. 2013). The FACIT-Fatigue scale total score has been shown to be responsive to change in both clinical and observational studies. Using both anchor- and distribution-based methods, the minimal important difference (MID) for the FACIT-Fatigue scale total score is 3 points. Currently, there are no published interpretation thresholds for the FACIT-Fatigue Experience and Impact scores (Cella, Lai, et al. 2002).

The FACIT-Fatigue scale will be administered at baseline (Day 1) and at Weeks 2, 4, 8, 12, 14, 16, 20, 24, 36, and 52.

11.4.4.2. QLQ-AA/PNH

The QLQ-AA/PNH is a 54-item patient-reported instrument developed to assess symptom burden and HRQoL in patients with AA and/or PNH (Groth, Singer, et al. 2017, Niedeggen, Singer, et al. 2019). It consists of 10 preliminary hypothesized domains including: 1) Social Support, 2) Fear of Progression and Illness Intrusiveness, 3) Fatigue, 4) Other Symptoms, 5) Infections, 6) Physical Functioning, 7) Role Functioning, 8) Emotional Functioning, 9) Stigmatization, and 10) Body Image. The recall period varies by items with a recall of 7 days for items 1 to 52, and a recall period of 6 months for items 53 and 54. Response options for all items are "Not at all", "A little", "Moderately", and "Very" or "A lot".

The QLQ-AA/PNH will be administered at baseline (Day 1) and at Weeks 4, 8, 12, 16, 20, 24, 36, and 52.

11.4.4.3. Modified PRO-AA/PNH

The PRO-AA/PNH is modified from the patient-centered version of the PRO-AA/PNH questionnaire developed by Weisshaar and colleagues (Weisshaar, Ewald, et al. 2020). As modified, the questionnaire includes the 11 PNH symptom questions from the original PRO-AA/PNH patient-centered questionnaire (ie, excluding the 3 AA-specific questions): 1) Fatigue, 2) Bleeding, 3) Shortness of Breath, 4) Mood, 5) Memory and Concentration, 6) Heart Palpitations, 7) Gastrointestinal Problems, 8) Pain, 9) Dark Urine [Hemoglobinuria], 10) Difficulty Swallowing [Dysphagia], and 11) Itching) plus the Erectile Dysfunction question from the physician-centered version of the PRO-AA/PNH questionnaire. For symptoms other than Bleeding and Dark Urine, additional questions assess the frequency, severity and/or impact of the symptoms on the subject's usual or daily activities. The bleeding-related questions follow the modified WHO bleeding scale for locations and severity grading. The recall period is the last 7 days.

The modified PRO-AA/PNH will be administered at baseline (Day 1) and at Weeks 1, 2, 4, 8, 12, 13, 14, 16, 20, 24, 36, and 52.

11.4.4.4. TSQM

The TSQM (version 1.4) consists of 14 items of which 13 items are made up of 3 specific scales (effectiveness, side effects, and convenience) and a global satisfaction scale (global satisfaction). In addition, 1 item (Item 4) questions whether the subject experienced any side effects at all as a result of taking this medication, which can be answered by yes or no. Scale scores are calculated for each scale and are transformed into scores ranging from 0 to 100, with higher scores indicating higher satisfaction. The recall period is the last 2 to 3 weeks, or since the medication was last used.

The TSQM will be administered at Weeks 4, 12, 16, 24, 36, and 52.

11.4.4.5. EQ-5D-5L

The EQ-5D-5L consists of the EQ-5D descriptive system and the EQ visual analogue scale (EQ VAS). The descriptive system (EQ-5D-5L) comprises five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. The patient is asked to indicate his/her health state by ticking the box next to the most appropriate statement in each of the 5 dimensions. This decision results in a 1-digit number that expresses the level selected for that dimension. The digits for the five dimensions can be combined into a 5-digit number that describes the patient's health state. There is no recall period; the health status captured by EQ-5D-5L reflects the respondent's status at the time of completion.

The EQ VAS records the respondent's self-rated health on a 20-cm vertical VAS. The VAS is numbered from 0 to 100 with 0 meaning "the worst health you can imagine" and 100 meaning "the best health you can imagine". This information can be used as a quantitative measure of health as judged by the individual respondents. The EQ VAS asks respondents to simply "mark an X on the scale to indicate how your health is TODAY" and then to "write the number you marked on the scale in the box below".

The EQ-5D-5L will be administered at baseline (Day 1) and at Weeks 12, 24, and 52.

11.4.4.6. PGIS-Fatigue, PGIS-Impact of Fatigue, and PGIS-Physical Functioning

Subjects will be asked to rate the severity of their fatigue, the impact of their fatigue on their usual activities, and how much their PNH symptoms interfere with physical functioning (eg, walking, climbing stairs, standing) using the PGIS-Fatigue, PGIS-Impact of Fatigue, and PGIS-Physical Functioning, respectively. The recall period is the past 7 days. The severity and impact of fatigue will both be assessed on a 4-point scale with responses ranging from 1 = "None" to 4 = "Severe". Interference will be assessed using a 5-point scale with responses ranging from 1 = "Not at all" to 5 = "Very much".

The PGIS-Fatigue, PGIS-Impact of Fatigue, and PGIS-Physical Functioning will be administered at baseline (Day 1) and at Weeks 12 and 52.

11.4.4.7. PGIC-Fatigue, PGIC-Impact of Fatigue, and PGIC-Physical Functioning

Subjects will be asked to rate changes in the severity of their fatigue, the impact of their fatigue on their usual activities, and how much their PNH symptoms interfere with physical functioning using the PGIC-Fatigue, PGIC-Impact of Fatigue, and PGIC-Physical Functioning, respectively. At Week 12, all subjects will be asked to assess how the severity and impact of their fatigue, and interference of their PNH symptoms with physical functioning have changed since the start of the study. At Week 52, subjects will be asked how the severity and impact of their fatigue, and interference of their PNH symptoms with physical functioning have changed since the start of the open-label study (ie, since being told they were on active drug). All changes will be assessed on a 7-point Likert scale ranging from 1 = "Very much improved" to 7 = "Very much worse".

The PGIC-Fatigue, PGIC-Impact of Fatigue, and PGIC-Physical Functioning will be administered at Weeks 12 and 52.

11.4.5. Optional Exit Interviews

One-on-one qualitative exit interviews will be conducted by COS or a third-party vendor over the telephone or by videoconference in a subset of approximately 15 subjects. The exit interviews will be conducted to explore participants' overall experience with the study drug and what constitutes a meaningful change in terms of symptoms to better understand the relevance of the FACIT-Fatigue items and cognitive debriefing of the Physical Function domain of the QLQ-AA/PNH. Participants will also be asked to rate and explain their perception of meaningful change in fatigue and physical function. The interviews will be conducted for individual subjects as soon as possible (ideally within 2 weeks) after the end of blinded treatment (ie, Week 12 visit) using a semi-structured interview guide. Subjects will sign a separate ICF, which provides further information about the exit interviews. A separate communication will be provided to sites about the exit interviews.

11.5. Pharmacokinetic and Pharmacodynamic Assessments

Detailed instructions for collection, processing, storage, and shipment of PK and PD samples will be provided in a separate laboratory manual.

11.5.1. Blood Sampling for Pharmacokinetic Analysis

Single venous blood samples for measurement of plasma BCX9930 concentrations ("sparse sampling" to support PPK and PK/PD modeling) will be collected from all subjects receiving study drug at each scheduled study visit to the investigational site, beginning at Week 1, and at any visits to the investigational site to assess for acute symptomatic hemolysis or perform additional safety assessments. PK samples will not be collected at the baseline (Day 1) visit unless subjects participate in the optional PK/PD substudy.

Sparse PK blood samples may be drawn at any time without regard to study drug/BCX9930 dosing. However, where feasible, investigators are requested to vary the timing of non-PK/PD substudy visits to facilitate PK sampling at different times relative to the previous dose. It is preferred that the cumulative sparse PK data for each subject will contain samples drawn within each of the following intervals (all relative to the previous dose for BID dosing): 0.5 to 2 hours, 2 to 5 hours, and 10 to 12 hours post-dose.

Subjects do not need to withhold any study drug/BCX9930 doses on clinic days or take a dose in the clinic, unless the clinic visit falls during the subject's normal time of dosing or the subject is participating in the optional PK/PD substudy on that day (see Section 11.5.1.1).

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

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

PK samples collected from subjects receiving placebo will not be analyzed except if required.

Any unused portion of the plasma samples collected for PK purposes will be retained for possible repeat or future PK analysis of BCX9930 and/or identified metabolites. Subjects can request for these samples to be destroyed at the end of the study, but any data previously collected will be retained.

11.5.1.1. Optional Pharmacokinetic/Pharmacodynamic Substudy

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

At these centers, subjects consenting to participate in the optional PK/PD substudy will be asked to complete up to two serial PK sample collections. The first sample collection will assess the single-dose PK of BCX9930, with samples collected on Day 1 in Part 1. The second sample collection will assess the PK of BCX9930 at steady state, with samples collected during the Week 14 or any later visit in Part 2. Four blood samples will be collected on Day 1, and 5 blood samples will be collected during the Week 14 or later visit. On Day 1, samples will be collected at 0.5 (± 0.25), 1.5 (± 0.5), 3.5 (± 0.5), and 6 (± 1) hours post-dose. At the Week 14 or later visit, samples will be collected immediately (≤ 15 minutes) prior to dosing and at 0.5 (± 0.25), 1.5 (± 0.5), 3.5 (± 0.5), and 6 (± 1) hours post-dose. For the second sample collection (on or after

Week 14), the subject's scheduled dose of BCX9930 should not be taken at home, but administered in the clinic after collection of the pre-dose sample, as close as possible to the subject's regularly scheduled dose time (and as close as possible to 12 hours after the previous dose). On both occasions, the actual date and time of each blood sample collection and the observed BCX9930 dose will be recorded in the eCRF. In addition, for the steady-state collection on Week 14 or later, the actual date and time of the last two BCX9930 doses taken prior to the pre-dose blood collection (assumed to be the two doses taken the previous day), and whether those doses were administered with or without food will also be recorded in the eCRF.

In addition, where possible, taking into account blood volume requirements, subjects will have 5 PD samples collected at each substudy visit; the first sample will be collected prior to study drug/BCX9930 dosing (≤ 2 hours on Day 1 or ≤ 15 minutes at the Week 14 or later visit), with subsequent samples collected at 0.5 (± 0.25), 1.5 (± 0.5), 3.5 (± 0.5), and 6 (± 1) hours post-dose. As applicable, PD blood samples will be collected at the same time as the corresponding PK blood sample applicable (ie, excluding the pre-dose sample on Day 1). Additional guidance on prioritizing sample collections where there are blood volume concerns will be provided in the separate laboratory manual.

Ideally, subjects will participate in both serial PK/PD sample collections. However, subjects who do not participate at the Day 1 serial PK/PD sample collection can still participate in the later steady-state PK/PD collection in Part 2.

Plasma concentration and PK parameters of BCX9930 metabolites may also be assessed using these samples. Samples collected from subjects receiving placebo on Day 1 will not be analyzed.

11.5.2. Urine Collection for Measurement of Parent-Metabolite Concentration

Spot urine samples will be collected for analysis of the concentration of BCX9930 and metabolites. Because of the study blind, samples will be collected from all subjects during Part 1; samples collected from subjects randomized to placebo will not be analyzed.

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

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

11.5.3. Blood Sampling for Analysis of Pharmacodynamic and Complement Biomarkers

Blood samples will be analyzed for concentrations of complement cleavage products (eg, Factor Bb and sC5b-9). The capacity of the complement system will be assessed by measuring these analytes or the activity of the AP using ex vivo stimulation assays, such as AP Wieslab, that activate the AP in blood samples using a specific stimulus. Additional exploratory assays (eg, for chemokines or cytokines) may be evaluated. Samples collected may be run in more than one assay to elucidate the PD effects of BCX9930. The analyses variously need serum, plasma, and whole blood.

Blood samples for analysis of PD and complement biomarkers will be collected at each study visit (including screening and baseline [prior to dosing on Day 1]) from all subjects regardless of treatment, including any visit to assess for acute symptomatic hemolysis or hemolysis monitoring following discontinuation of therapy. Where feasible, and as applicable, blood samples for PD analyses should be collected at the same time as sparse PK samples.

The plasma PD and complement biomarkers for assessment may include, but are not limited to:

- Ex vivo AP activity (as assessed by AP Wieslab assay)
- Ex vivo AP-activated complement biomarkers: Factor Bb, C3a, and C5a
- Constitutive complement biomarkers: Factor D (as the pharmacologic target), Factor Bb, and sC5b-9

Acute symptomatic hemolysis will be evaluated, where possible. The PD and complement biomarkers for assessment of acute symptomatic hemolysis may include, but are not limited to:

- Ex vivo AP activity (as assessed by AP Wieslab)
- Ex vivo AP-activated complement biomarkers: Factor Bb, C3a, and C5a
- Constitutive complement biomarkers: Factor D (as the pharmacologic target), Factor Bb, total C3*, C3a*, total C4*, C4a*, and sC5b-9

* In subjects experiencing acute symptomatic hemolysis, as applicable, these additional analytes will also be evaluated in previously collected samples to provide internal reference values for the acute symptomatic hemolysis values.

The following are considered key clinical laboratory blood biomarkers of AP activity: AP Wieslab and constitutive levels of Factor Bb and sC5b-9. Not all PD and complement biomarkers will be assessed at all timepoints. The plans for analysis of other biomarkers may be modified based on emerging data, eg, if data show that a particular biomarker is redundant or the assay is of poor quality.

PNH clone size (total PNH RBC [Type II plus Type III], PNH WBC, and the ratio of total PNH RBC to PNH WBC) will be assessed at each visit.

[redacted]

Any unused portion of the whole blood, plasma, or serum collected for PD purposes will be retained for possible repeat or future analysis of biomarkers related to PNH and other complement-mediated disease. Subject can request for these samples to be destroyed at the end of the study, but any data previously collected will be retained.

A tabular summary of the PD sampling is provided in Table 5.

(Note: Some PD and complement biomarkers may not be analyzed, depending on the availability of validated assays at the designated regional bioanalytical laboratory.)

Table 5: Summary of Pharmacokinetic and Pharmacodynamic Blood Sampling

PK or PD Sampling	Screening	Day 1	Study Week																Hemolysis Assessment/ Monitoring
			Wk1	Wk2	Wk4	Wk8	Wk12	Wk13	Wk14	Wk16	Wk20	Wk24	Wk28	Wk32	Wk36	Wk40	Wk44	Wk48	Wk52	
All Subjects																				
PK[a]	-	-	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PD[b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Optional PK/PD substudy[c]																				
PK	-	4[d]	-	-	-	-	-	-	< ---------- 5[e] ---------- >											-
PD	-	5[e]	-	-	-	-	-	-	< ---------- 5[e] ---------- >											-

Abbreviations: PD = pharmacodynamic; PK = pharmacokinetic.

[a] Single venous blood samples for measurement of plasma BCX9930 concentrations will be collected at each scheduled study visit, beginning at Week 1, and at any visit to the investigational site to assess for acute symptomatic hemolysis (if and when symptoms occur) or to perform additional safety assessments (not shown).

[b] Blood samples for analysis of PD and complement biomarkers will be collected at each study visit (including screening and Day 1) from all subjects regardless of treatment, including at any visit to assess for acute symptomatic hemolysis or hemolysis monitoring following discontinuation of therapy.

[c] The first sample collection will be performed on Day 1 and the second sample collection during the Week 14 or any later visit.

[d] Four blood samples will be collected at 0.5 (± 0.25), 1.5 (± 0.5), 3.5 (± 0.5), and 6 (±1) hours after administration of the first dose of study drug/BCX9930.

[e] Five blood samples will be collected, where possible; the first sample will be collected prior to study drug/BCX9930 dosing (either ≤ 2 hours on Day 1 or ≤ 15 minutes at the Week 14 or later visit), with subsequent samples collected at 0.5 (± 0.25), 1.5 (± 0.5), 3.5 (± 0.5), and 6 (±1) hours post-dose. As applicable, PD blood samples will be collected at the same time as the corresponding PK blood samples.

11.6. Optional Pharmacodynamic Analyses

All study participants will be asked to consent to the storage of unused and/or residual PD samples collected in the study for possible additional research. The stored PD samples may be used for exploratory PD assays to evaluate the PD or PK of BCX9930. If a participant does not agree to have his or her PD samples stored, he or she can still participate in this study; all PD samples collected during the study will be destroyed upon completion of the study and all protocol-mandated analyses. All PD samples for which consent has been obtained will be stored for up to 10 years after completion of the study (or according to local regulations) for possible additional research. Stored samples will be coded throughout the sample storage and analysis process and will not be linked to any personal identifiers. Analysis of these samples is not intended for diagnostic or prognostic purposes and results will not be communicated back to the investigator or subjects. The research may begin at any time during the study or following completion of the study during the post-study storage period.

11.7. Safety Assessments

11.7.1. Vital Signs

Vital signs comprising blood pressure, pulse rate, and temperature will be obtained per the schedule of assessments specified in Table 3 for Part 1 and Table 4 for Part 2.

Measurements of vital signs should be obtained after the subject has rested for at least 5 minutes in a quiet room at a comfortable temperature, with the subject's arm unconstrained by clothing or other material. Blood pressure measurements will be obtained with the appropriate cuff size, with the subject's arm supported at the level of the heart, while the subject is resting in a semi-supine position. It is acceptable to obtain a pulse rate from the blood pressure or ECG machine.

11.7.2. Body Weight, Height, and Body Mass Index

Body weight will be recorded per the schedule of assessments specified in Table 3 for Part 1 and Table 4 for Part 2; height and BMI will be recorded at screening only. For determination of height and body weight, subjects should be clothed with shoes removed.

11.7.3. Physical Examination

Subjects will undergo a physical examination per the schedule of assessments specified in Table 3 for Part 1 and Table 4 for Part 2.

A full physical examination should be performed per normal site practice as part of the screening evaluation (eg, genitourinary and breast examinations may be omitted when not required by normal site practice). A targeted (ie, symptom driven) physical examination will be performed at subsequent study visits to assess for any changes from the previous examination, including, at a minimum, evaluation of new or worsening signs or symptoms.

11.7.4. Electrocardiogram

A 12-lead ECG will be obtained per the schedule of assessments specified in Table 3 for Part 1 and Table 4 for Part 2.

A standard bedside 12-lead ECG machine system that calculates heart rate and measures the PR, QRS, QT, RR, and corrected QT (QTc) intervals will be utilized. Twelve-lead ECGs will be measured after the subject has rested quietly in the supine position for a minimum of 10 minutes. All ECGs will be single assessments, with the exception of the baseline (Day 1) ECG, which will be recorded in triplicate. Triplicate ECGs will also be collected at the Week 12 visit.

Qualified site personnel should review the ECGs and automated findings in real time for gross abnormalities and interval measurements of concern (absolute readings and change from baseline). An ECG should be repeated after at least an additional 10-minute rest in a supine position in the event of a CFB (mean of pre-dose triplicate values on Day 1) in QTcF ($QT / \sqrt[3]{RR}$) of > 60 msec or an absolute QTcF interval of > 500 msec.

For all ECGs, the clinical interpretation of the ECG should be recorded (including re-adjudication of any automatic findings) directly on a hard copy of the ECGs. Copies of the subject identifier-redacted ECGs may be requested by the sponsor.

11.7.5. Clinical Chemistry, Hematology, Urinalysis, and Other Laboratory Assessments

Blood and urine samples will be obtained per the schedule of assessments specified in Table 3 for Part 1 and Table 4 for Part 2. Individual laboratory tests are specified in Table 6.

In general, laboratory samples collected at visits to the investigational site should be collected using kits provided by the designated central laboratory. However, at the investigator's discretion, local laboratories may be used in place of the central laboratory (eg, for logistical reasons such as delays in transport due to COVID-19) or for analysis of samples collected for assessment of possible AEs (eg, when emergent safety concerns require expedited turnaround times for safety laboratory assessments). Urine microscopy for samples collected at the investigational site will be performed at the site's local laboratory, where appropriate on-site testing capability exists (see Section 11.7.5.1). The additional renal and hepatic safety assessments may be performed at the investigational site or remotely at a location more convenient for the subject or via a home health service. If the use of a home health service is permitted, testing may be performed at the central laboratory or at a remote laboratory. The results from laboratory testing performed at a local or remote must be provided to the investigational site. The use of a local or remote laboratory in this manner, and any differences in analyte panels with the central laboratory, based on the availability of testing at the local or remote laboratory, will not be considered protocol deviations for the purposes of this protocol. Reference ranges for each local or remote laboratory used will be provided to the sponsor and included in data listings.

Results from laboratories should be reviewed as received by the investigator. Evidence of this review should be provided in the source records and may include printing of the laboratory reports with a signature attesting to a review. For out-of-range laboratory findings, the interpretation of clinically significant or not clinically significant should be denoted in the source records. Clinically significant laboratory findings, as assessed by the investigator, should be recorded as AEs as described in the protocol (Section 12.1).

Table 6: Clinical Laboratory Evaluations

Serum Chemistry	**Urinalysis**[a]
Albumin Alanine aminotransferase (ALT) (SGPT) Alkaline phosphatase (ALP) Amylase[b] Aspartate aminotransferase (AST) (SGOT) Bicarbonate or carbon dioxide[c] Bilirubin (total and direct) Blood urea nitrogen (BUN) Calcium Chloride Cholesterol (total, high- and low-density lipoprotein) Creatine (phospho)kinase (C[P]K) Creatinine (sCr) Glucose Haptoglobin Lactate dehydrogenase (LDH) Magnesium Potassium Sodium Protein (total) Triglycerides Uric acid	Albumin Bilirubin Blood Creatinine Glucose Ketones Leukocytes Nitrites pH Protein Specific gravity Urobilinogen
	Urine Drug Screen
	Amphetamines Barbiturates Benzodiazepines Ecstasy Methamphetamine Opiates
	Pregnancy/Menopause
	Follicle-stimulating hormone (FSH) β-human chorionic gonadotropin (hCG)[d] Urine pregnancy test[e]
Hematology	**Iron, Folate, and Vitamin B_{12}**
Hemoglobin (Hb) Hematocrit (Hct) Mean corpuscular hemoglobin (MCH) Mean corpuscular hemoglobin concentration (MCHC) Mean corpuscular volume (MCV) Platelet count (PLT) Red blood cell (erythrocyte) count (RBC) Reticulocyte count White blood cell count (WBC) with differential	Erythroferrone Ferritin Folate Hepcidin Hemosiderin (urine) Iron Total iron binding capacity) Transferrin Vitamin B_{12}
	Other Testing
	C-reactive protein

Coagulation/Fibrinolysis	Cystatin C (in blood)
Activated partial thromboplastin time (aPTT)	Estimated glomerular filtration rate(eGFR)[f]
[redacted]	HBV surface antigen (HBsAg)
Prothrombin time (PT)	HBV core antibody (HBcAb)[g,h]
International normalized ratio (INR)	HCV antibody (HCVAb)[i,h]
[redacted]	HIV antibody[j,h]
Thrombin time	PNH RBC clone size (total)
Urine Biomarkers[k]	PNH WBC clone size
β-2-microglobulin	VZV immunoglobulin G (IgG) titer
Cystatin C	
Kidney injury molecule 1 (KIM-1)	
Liver-type fatty acid-binding protein (L-FABP)	
Urine albumin to creatinine ratio (uACR)	
Urine neutrophil gelatinase-associated lipocalin (uNGAL)	
Urine aliquots for storage[l]	

Note: Some analytes may not be analyzed, depending on the availability of validated assays at the designated regional central laboratory.

Abbreviations: DNA = deoxyribonucleic acid; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; PNH = paroxysmal nocturnal hemoglobinuria; RNA = ribonucleic acid; SGOT = serum glutamic-oxaloacetic transaminase; SGPT = serum glutamic-pyruvic transaminase; VZV = varicella-zoster virus.

[a] For local laboratory testing, urinalysis analytes may be different.

[b] If amylase is elevated, reflex to lipase.

[c] In those regions where bicarbonate or carbon dioxide is analyzed and reported.

[d] Serum (screening) or urine (all other scheduled visits) for women of childbearing potential or post-menopausal for ≤ 2 years (or as required by institutional practice).

[e] For women of childbearing potential (or as required by local or institutional practice).

[f] To be calculated by the designated central reference laboratory using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation using the serum creatinine method (Levey and Stevens 2010).

[g] Subjects with a positive HBV core antibody (HBcAb) test at screening will be reflexed to confirmatory HBV DNA viral load and excluded for a positive viral titer.

[h] Confirmatory sample for serology may be collected at screening visit in some regions but analysis will be performed only if serology result is positive. Otherwise, confirmatory sample will be discarded.

[i] Subjects with a positive HCV antibody test at screening will be reflexed to confirmatory HCV RNA viral load and excluded from the study for a positive viral titer.

[j] Subjects with a positive HIV antibody test will be reflexed to confirmatory HIV RNA viral load.

[k] KIM-1 and L-FABP will not be tested at screening.

[l] Urine will be aliquoted, frozen, and sent to the central laboratory for possible future analysis of urine biomarkers. Additional biomarkers may be recommended by the Nephrology Risk Mitigation Working Group.

11.7.5.1. Urine Collections for Urinalysis, Microscopy, and Biomarker Testing

Investigators should emphasize to staff and the subjects the importance of collecting fresh, high-quality urine specimens (clean-catch, mid-void, etc.) and ensuring appropriate handling and prompt analysis of the samples for urinalysis. Urine microscopy will be performed on all urine samples collected for urinalysis at investigational site visits. Because of the potential for extended transit times to the central laboratory, where possible, the urine microscopy should be

performed using the site's local laboratory (where appropriate on-site testing capability exists) in lieu of the designated central laboratory. Urine microscopy should also be performed at any remote laboratory where appropriate on-site testing capability exists. If the local or remote laboratory does not have on-site testing capability, the sample may be sent to the designated central laboratory.

Urine will be collected at all investigational site visits for analysis of uACR, β-2-microglobulin, cystatin C, urine neutrophil gelatinase-associated lipocalin (uNGAL), kidney injury molecule 1 (KIM-1), and liver-type fatty acid-binding protein (L-FABP). In addition, aliquots of urine will be frozen and shipped to the central laboratory for storage for possible future analysis of urine biomarkers.

11.7.6. Menopause and Pregnancy Testing

FSH will be measured at screening in women declaring themselves postmenopausal ≤ 2 years to confirm non-childbearing status if above the reference range. At screening, a serum pregnancy test should also be drawn in the event that a female subject who is postmenopausal ≤ 2 years is found to be of childbearing potential.

For all women of childbearing potential, a serum β-human chorionic gonadotropin (β-hCG) test will be performed at screening. Urine pregnancy tests will be assessed at baseline (Day 1) and every 4 weeks thereafter as specified in the schedule of events presented in Table 3 for Part 1 and Table 4 for Part 2, or as required per normal site practice. Urine pregnancy tests will be provided by the central laboratory, but will be administered and read at the clinical site. A serum pregnancy test should immediately be drawn and sent for analysis for any positive urine pregnancy test. Where required, pregnancy testing may be performed using the local laboratory, and using serum testing in lieu of the supplied urine pregnancy tests.

For female participants who meet the criteria for postmenopausal status, an FSH can be measured during the study; pregnancy testing will continue until postmenopausal status by the above definition is met.

12. ADVERSE EVENTS

In this section, "study drug/IMP" is intended to refer to BCX9930 and/or placebo, unless otherwise noted.

12.1. Definition of Adverse Events

12.1.1. Adverse Event

An AE is any untoward medical occurrence in a clinical study subject. No causal relationship with the study drug/IMP or with the clinical study itself is implied. An AE may be an unfavorable and unintended sign, symptom, syndrome, or illness that develops or worsens during the clinical study. Clinically relevant abnormal results of diagnostic procedures including abnormal laboratory findings (eg, requiring unscheduled diagnostic procedures or treatment measures, or resulting in withdrawal from the study) are considered to be AEs. Abnormal results of diagnostic procedures that are incidental or not clinically relevant are not reportable as AEs. If

the diagnostic procedure prompts no additional treatment, visits, or monitoring, it will not meet the definition of an AE.

This includes the following:

- AEs not previously observed in the subject that emerge during the protocol-specified AE reporting period (see Section 12.4.1).
- Findings from protocol-mandated interventions. This can include laboratory assessments performed in the course of the clinical study. AEs should be reported only if the abnormalities are changes from baseline and are clinically significant as described above.
- Pre-existing medical conditions (other than the condition being studied) judged by the investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period. When recording such events on an AE/SAE eCRF page, it is important to convey the concept that the pre-existing condition has changed by including applicable descriptors (eg, “more frequent headaches”).
- In addition, for this study, the disease-related events of acute symptomatic hemolysis and MAVEs (including thromboembolic events) will be reported as AEs, even if deemed related to the disease under investigation.

An adverse reaction is defined in International Council for Harmonisation (ICH) E6 guideline as follows: all untoward and unintended responses to a study drug/IMP related to any dose administered. The definition covers also medication errors and uses outside what is foreseen in the protocol, including misuse and abuse of the product. The definition implies a reasonable possibility of a causal relationship between the event and the study drug/IMP. This means that there are facts (evidence) or arguments to suggest a causal relationship.

Hospitalization scenarios do not require reporting as an SAE where there is no occurrence of an AE. These scenarios include a planned hospitalization or prolonged hospitalization to:

- Perform a routine control screening for a pre-existing illness or to diagnose a suspected illness. In the case of the latter, the symptomatology should be reported as an AE and amended if a diagnosis is confirmed.
- Undergo a diagnostic or elective surgical procedure for a pre-existing medical condition that has not changed (eg, a joint replacement for which the subject was on a waiting list).
- Undergo medical observation without the occurrence of an AE due to standard of care in the region or hospital.

Surgical procedures should not be reported as AEs. The condition for which the surgery is required should be reported as the AE if it occurs or is detected during the study period. Planned surgical measures permitted by the clinical study protocol and the conditions(s) leading to these measures are not AEs if the condition(s) was (were) known before the start of study treatment. In the latter case, the condition should be reported as medical history.

AEs are designated as “nonserious” or “serious”.

12.1.2. Serious Adverse Event

An SAE is an adverse event/reaction that results in any of the following outcomes:

- Death
- Is life-threatening (subject is at immediate risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe)
- Requires subject hospitalization (formal admission to a hospital for medical reasons) or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity (ie, there is a substantial disruption of a person's ability to carry out normal life functions)
- Is a congenital anomaly/birth defect

Important medical events that may not result in death, are not life-threatening, or do not require hospitalization may be considered SAEs when, based upon appropriate medical judgment, they may jeopardize the subject's health or may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such events may include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias, or convulsions that do not result in subject hospitalization.

In addition, the sponsor considers any abortions (elective or spontaneous), fetal demise, and still birth to be SAEs for reporting purposes (see Section 12.4.2).

Some hospitalization scenarios, as outlined in Section 12.1.1 do not require reporting as SAEs.

Overdose will be considered an SAE only if any of the seriousness criteria are met. Any clinical complication in association with the overdose should be reported as an AE or SAE (as applicable) along with the overdose (see Section 12.6). Details of signs or symptoms, clinical management, and outcome should be reported, if available. Overdose without associated signs or symptoms should not be recorded as AEs but should be recorded as protocol deviations.

12.1.3. Events of Special Monitoring

Events of special monitoring (EOSM) 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. Identified EOSMs can be of particular concern based on findings from the IMP clinical program to date, potential and/or known risks generally associated with the underlying disease, or comorbidities and risk factors prevalent in the study population.

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

12.2. Definition of Severity

All AEs will be assessed (graded) for severity by the investigator and classified using the US NCI CTCAE (version 5.0, published 27 November 2017). The NCI CTCAE is a descriptive terminology that can be used for AE reporting. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on the following general guideline:

Mild:	(Grade 1): Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Moderate:	(Grade 2): Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL[a].
Severe:	(Grade 3): Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL[b].
Life-threatening:	(Grade 4): Life-threatening consequences; urgent intervention indicated.
Death	(Grade 5): Death related to AE[c].

Abbreviations: ADL = activities of daily living; AE = adverse event.

[a] Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] Self-care ADL refer to bathing, dressing, and undressing, feeding self, using the toilet, taking medications, and not bedridden.

[c] Grade 5 (Death) is not appropriate for some AEs and therefore is not an option.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity, as defined above, whereas seriousness is defined by the criteria under Section 12.1.2. An AE of severe intensity may or may not be considered serious.

12.3. Relationship to Study Drug

An investigator who is qualified in medicine must make the determination of relationship to the study drug/IMP for each AE (not related, unlikely related, possibly related, probably related, definitely related). The investigator should decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the investigational product. If no valid reason exists for suggesting a relationship, then the AE should be classified as “not related”. If there is any valid reason, even if undetermined, for suspecting a possible cause-and-effect relationship between the study drug/IMP and the occurrence of the AE, then the AE should be considered “related”.

Not Related:	The event can be readily explained by other factors such as the subject’s underlying medical condition, concomitant therapy, or accident, and no temporal relationship exists between the study drug/IMP and the event.
Unlikely Related:	The event does not follow a reasonable temporal sequence from drug administration and is readily explained by the subject’s clinical state or by other modes of therapy administered to the subject.

Possibly Related:	There is some temporal relationship between the event and the administration of the study drug/IMP and the event is unlikely to be explained by the subject's medical condition, other therapies, or accident.
Probably Related:	The event follows a reasonable temporal sequence from study drug/IMP administration, abates upon discontinuation of the study drug/IMP, and cannot be reasonably explained by the known characteristics of the subject's clinical state.
Definitely Related:	The event follows a reasonable temporal sequence from study drug/IMP administration, follows a known or suspected response pattern to the study drug/IMP, is confirmed by improvement upon stopping the study drug/IMP (dechallenge), and reappears upon repeated exposure (rechallenge, if rechallenge is medically appropriate).

If the relationship between the (S)AE and the investigational product is determined to be "possible", "probable", or "definite", the event will be considered to be related to the study drug/IMP for the purposes of expedited regulatory reporting (as applicable per country-specific regulatory requirements).

The sponsor may upgrade causality if deemed appropriate.

12.4. Method, Frequency, and Time Period for Detecting Adverse Events and Reporting Serious Adverse Events

Reports of all AEs and SAEs, regardless of investigator attribution, are to be collected from the time of signing of the ICF through to the last study visit (ie, through the post-treatment follow-up visit). All AEs and SAEs are to be reported on the AE eCRF.

AEs should be documented on the eCRFs as investigators become aware of them. AEs are to be followed until the event resolves. If an event is ongoing at the last follow-up visit, Grade 1 and Grade 2 events do not need to be followed if the event is deemed unlikely to be related or not related to study drug/IMP (see Section 12.2 for AE grading). For all Grade 3 and Grade 4 events or events deemed possibly, probably, or definitely related to use of study drug/IMP, the event should be followed until the AE is resolved or the subject is in a clinically stable condition with regards to the AE.

The investigator shall report all SAEs immediately and no later than 24 hours of their knowledge of the event to the sponsor by communicating with the medical monitor (phone or email) and by entering the event into the AE eCRF and by completion of the SAE eCRF. The SAE eCRF is an additional form to the AE eCRF that provides important details on the SAE. The investigator should follow all unresolved SAEs observed during the study until they are resolved, or are judged medically stable, or are otherwise medically explained.

The investigator should attempt, if possible, to establish a diagnosis based on the presenting signs and symptoms. In such cases, the diagnosis should be documented as the AE and not the individual sign/symptom. If a clear diagnosis cannot be established, each sign and symptom must be recorded individually. Once a diagnosis is made during evaluation or treatment, the investigator will update the AE record with this diagnosis and delete the previously reported signs and symptoms. The rapid reporting of SAEs ensures that the sponsor shall have the

necessary information to continuously assess the benefit-risk profile of the study drug in clinical studies.

12.4.1. Serious Adverse Events and Suspected Unexpected Serious Adverse Reactions

The investigator must report all SAEs immediately and in no case later than within 24 hours of their knowledge of the event. Investigators should adhere to their country or region requirements for the reporting timeframe, which may not allow any delay. SAEs should be reported to the sponsor medical monitor and via the AE and SAE eCRFs. All additional follow-up evaluations of the SAE must be reported to BioCryst or its designee as soon as they are available by amending these eCRFs. The eCRF system automatically sends SAE notifications to the following email address:

[redacted]

Email: safety@biocryst.com

In the event the eCRF system is not functioning, the reporting of an SAE must not be delayed. Sites will have SAE report forms (electronic Word document) that can be completed and emailed to the above recipient. As soon as the eCRF system is functioning, that particular SAE must be entered into the AE eCRF.

Immediate reporting should allow BioCryst to take the appropriate measures to address potential new risks in a clinical study. Therefore, the initial report should be submitted by the investigator within a very short period of time and under no circumstances should this period exceed 24 hours following awareness of the SAE.

The follow-up report should allow BioCryst to determine whether the SAE requires a reassessment of the benefit-risk profile of the study drug/IMP in clinical study, if the relevant information was not already available and provided in the initial report.

Country-specific rules and requirements for safety management will be described in the Safety Management Plan prepared for this study.

Investigators or designees at each site are responsible for retaining copies of all suspected unexpected serious adverse reaction (SUSAR) reports (initial and follow-up) and other safety information (eg, revised IB) in the investigator site files.

BioCryst shall ensure that all relevant information about SUSARs that are fatal or life-threatening is recorded and reported as soon as possible to all competent authorities, and to the applicable ethics committee in any case no later than 7 calendar days after knowledge by BioCryst of such a case, and that relevant follow-up information is subsequently communicated within an additional 8 days. All other SUSARs shall be reported to the competent authorities concerned and to the ethics committees, as applicable, according to local regulations, as soon as possible but in no case later than 15 calendar days of first knowledge by BioCryst. BioCryst or designee shall also inform the investigator. Although acute kidney injury is considered an expected event (see Section 6.11 of the IB), the event will be reported in an expedited manner.

12.4.2. Pregnancy

Any female subject who becomes pregnant during the course of the study should have BCX9930 discontinued immediately and must be followed through the end of the pregnancy. While pregnancy is not considered an AE, all cases of fetal drug exposure via the parent as a study participant (including partners of study participants) are to be reported immediately to BioCryst or its designee. Consent from study partners who become pregnant will be obtained prior to reporting any details of the pregnancy. Information related to the pregnancy must be given on a "Pregnancy Notification and Outcome" form that will be provided by the sponsor or its designee so that the pregnancy may be followed, and an outcome determined. Any AEs or SAEs experienced by a pregnant subject are to be reported as directed in Section 12.4.1. Any complications reported in a subject's pregnant partner should be reported on the Pregnancy Notification and Outcome form. All pregnancies must be followed to outcome, which occurs when an infant is delivered (live or still born), there is fetal demise, or there is an abortion (spontaneous or induced). Abortion (spontaneous or induced), fetal demise, and still birth, along with congenital abnormalities in the newborn, should be reported as separate SAEs.

12.4.3. Emergency Unblinding Procedures

Access to study drug/IMP assignment will be available immediately through the IWRS system if the investigator deems it necessary to break the study blind in the interest of a subject's medical safety, in case of a medical emergency, to meet regulatory reporting obligations, or if warranted during scheduled safety reviews. Where medically appropriate, the investigator will contact the sponsor medical monitor to discuss the situation that has arisen and resulted in the need for unblinding of the subject. The sponsor medical monitor will not be involved in the decision to unblind or the actual unblinding.

12.5. Adverse Event Management

The investigator (or qualified designee) will grade clinically significant events and laboratory abnormalities (if considered AEs) as detailed in Section 12.2. Grade 3 and Grade 4 clinically significant laboratory abnormalities should be confirmed by repeat testing and before any contemplated study drug/IMP discontinuation, unless such a delay is not consistent with good medical practice.

12.5.1. Potential Drug-induced Liver Injury: Monitoring, Evaluation, and Discontinuation Criteria

All treatment-emergent ALT elevations > 3 × ULN should be confirmed, preferably within 72 hours, with repeat assessment of ALT, AST, total bilirubin, ALP, prothrombin time/INR, and complete blood count with differential. These may be repeated at a local laboratory as long as the results are reported to the investigator when available and the investigative site contacts the subject to ascertain any symptoms.

Subjects with ALT elevation > 3 × ULN must be assessed to determine whether study drug must be withheld or discontinued. In addition, any potentially contributing medications, supplements, or over-the-counter medications that are not medically necessary should be discontinued if medically feasible.

Discontinuation of treatment should be considered for any of the following, and should be discussed with the sponsor medical monitor prior to BCX9930 discontinuation, considering the benefit-risk of discontinuing BCX9930:

- ALT or AST > 8 × ULN
- ALT or AST > 5 × ULN for more than 2 weeks
- ALT or AST > 3 × ULN and (total bilirubin > 2 × ULN [unless there is evidence that the increase in bilirubin is due to hemolysis or Gilbert's syndrome] or INR > 1.5 × ULN in the absence of warfarin therapy)
- ALT or AST > 3 × ULN with the appearance of fatigue (over baseline fatigue), nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%)

If subjects are asymptomatic with no other pertinent laboratory abnormality, study drug may be continued under close observation. Transaminases, total bilirubin, ALP, and INR should be repeated at least twice weekly. Frequency of retesting can decrease to once per week or less if abnormalities stabilize or the study drug has been discontinued and the subject is asymptomatic. Additionally, several other items should be considered, including obtaining a more detailed history of symptoms and prior or concurrent diseases; obtaining a history of concomitant use of nonprescriptive medications, herbal and dietary supplements, alcohol intake, recreational drug use, or special diets; evaluation for acute viral hepatitis A, B, C, D, and E and potentially other serologies; evaluation for others as clinically indicated including alcoholic and autoimmune hepatitis, non-alcoholic steatohepatitis (NASH), and biliary tract disease.

The above criteria will be applied to increases in AST unless there is evidence that the increase is due to hemolysis. If both ALT and AST are elevated, subjects will be managed based on their ALT level, regardless of whether their AST increase is thought to be due to hemolysis.

If Hy's Law criterion is met and is assessed as probably or definitely related per treatment discontinuation criterion in Section 7.5.1, then study drug must be discontinued. Prior to discontinuation from study drug/BCX9930, the investigator should contact the sponsor medical monitor for a discussion regarding the event and assessment. If medically indicated, the investigator can discontinue the subject immediately and follow up with the sponsor within 24 hours.

12.5.2. Renal Events

12.5.2.1. Monitoring, Evaluation, and Subject Discontinuation Criteria

There are multiple potential reasons that sCr can increase in those with PNH, including hemolysis. For subjects who have a confirmed treatment-emergent increase in sCr, evaluations to investigate potential etiology should be chosen considering baseline renal function, history of prior renal events including those due to PNH, other comorbidities, concomitant medications, and other relevant factors. In addition:

- For all subjects, ensure adequate hydration, stop or substitute potentially nephrotoxic medications, and evaluate for tuberculosis if sterile pyuria is present if potential exposure

- For treatment-emergent increases in sCr > ULN or ≥ 0.3 mg/dL (≥ 26.5 µmol/L) from baseline confirmed by repeat testing, notify sponsor medical monitor
- A renal ultrasound with doppler should be considered to exclude renal vein thrombosis or other incidental causes
- Subject data may be reviewed by a Nephrology Risk Mitigation Working Group (NRMWG) for additional recommendations, including dose reduction, interruption of dosing, and permanent discontinuation
- If a biopsy is performed, a redacted copy of the biopsy report and available images (whole slide images of light microscopy or electron microscopy specimens, immunofluorescence, immunohistochemistry, etc.) should be made available

The following table gives additional actions based on sCr:

sCr > ULN but ≤ 1.5 × ULN	• Assessment frequency as per the schedule specified in Table 3 (Part 1) or Table 4 (Part 2) (ie, every 1 to 4 weeks, as applicable) until sCr is ≤ ULN • Consider evaluation by nephrologist
sCr > 1.5 × ULN but < 3 × ULN	• Assessment frequency weekly until sCr is ≤ ULN • Evaluation by nephrologist
sCr ≥ 3 × ULN	• BCX9930 should be discontinued, with taper (see Section 9.4.2), after confirmation • If hemolysis or any other potentially reversible cause is suspected, contact sponsor medical monitor

12.5.2.2. Study Stopping Rule

The NRMWG will be notified promptly of and review any instances of subjects experiencing increased sCr ≥ 3 × ULN, and the DMC will be notified of each confirmed case, regardless of causality.

In the event that 3 subjects are determined by the NRMWG to have confirmed elevations of sCr ≥ 3 × ULN considered related to BCX9930, the study will be stopped. This will apply only to newly enrolled subjects treated at a dose of 400 mg BID.

12.5.3. Risk of Hemolysis After Missed Doses, Treatment Interruption, or Permanent Discontinuation of BCX9930

Subjects must be warned of the potential risk of hemolysis following missed doses (particularly multiple consecutive missed doses) and treatment interruption, and the definite risk after permanent discontinuation of BCX9930. By inhibiting the AP of complement, BCX9930 may improve Hb levels and increase circulating RBC clone size by reducing the hemolysis of PNH RBCs. Missed doses and treatment interruption of BCX9930 may lead to hemolysis. Subjects are at risk of severe hemolysis when BCX9930 is permanently discontinued. Based on available data regarding the PK and PD of BCX9930, severe hemolysis, if it occurs, would be expected to present within days after discontinuation of therapy.

Therefore, when subjects permanently discontinue blinded study drug in Part 1 or BCX9930 in Part 2 (either at the end of the study for those who do not continue treatment or those who permanently discontinue BCX9930 treatment prematurely at any time during the study), they must be monitored for hemolysis. When an investigator is made aware that a subject has permanently discontinued study drug or BCX9930, if the subject is asymptomatic, contact with the subject should occur at least daily for a minimum of 7 days. Contact may be conducted by telephone, email, or other means, including in person, if preferred. When any sign or symptom of hemolysis occurs, the subject should be promptly evaluated (refer to Section 10.3.7 for a list of minimum laboratory testing). Additional monitoring following the first contact after permanent discontinuation should be guided by the medical judgement of the investigator. For subjects who are already symptomatic when treatment is discontinued, whether the subject should be assessed in person or can be followed with daily contact will be based on the investigator's medical judgement taking into account the severity of the reported signs or symptoms and/or any reported worsening of the signs or symptoms. When possible, subjects should return to the investigative center; however, when this is not possible, arrangements may be made for the subject to be assessed by his or her local hematologist and a local laboratory used for clinical laboratory testing. When hemolysis occurs after the permanent discontinuation of BCX9930, supportive treatment should be provided according to the judgement of the investigator.

Treatment with study drug/BCX9930 should not be interrupted or withheld unless there is an absolute contraindication for continued dosing. Suggestions for anti-emetic therapy for subject with active nausea and vomiting when tablet contents are vomited are given in Section 9.6.2. The sponsor medical monitor should be contacted for guidance in both cases as soon as possible after the investigator is made aware of the event.

The sponsor medical monitor should be notified in the event of hemolysis symptoms, any planned treatment interruption, and permanent discontinuation of study drug/BCX9930. Any missed doses, treatment interruption, or permanent discontinuation must be recorded in the eCRF and source documents, including the reason for the interruption, missed doses, or discontinuation.

Study assessments for monitoring of potential hemolysis for missed doses, treatment interruption, and permanent discontinuation of blinded study drug or BCX9930 for subjects who experience signs or symptoms of hemolysis are in Section 10.3.7.

12.5.4. Acute Symptomatic Hemolysis

Subjects should contact the investigator if they experience any new or worsening signs or symptoms of hemolysis, including increased fatigue over baseline, abdominal pain, dysphagia, shortness of breath over baseline, hemoglobinuria, new signs and/or symptoms suggestive of thrombosis, or new or worsening erectile dysfunction, upon first awareness. Subjects should be evaluated per the investigator's medical judgement. In person evaluation is preferred, but can include phone or telemedicine contact with documentation, if in-person evaluation is not possible.

For subjects receiving blinded study drug in Part 1 or BCX9930 in Part 2, a review of dosing compliance to ensure that the subject is taking the drug correctly must be performed, regardless of the method used to evaluate the subject (ie, in-person or remote assessment), and any missed

doses should be recorded. It should also be determined whether the subject has had any recent CACs (eg, infection, trauma, or surgery) that may have contributed to the hemolytic event.

For this study, the term "acute symptomatic hemolysis" is defined by the following:

- ≥ 1 new or worsening acute sign or symptom of IVH, such as fatigue, hemoglobinuria, abdominal pain, dyspnea, MAVE (including thrombosis), dysphagia, erectile dysfunction, or acute kidney injury [AKI; defined as eGFR decrease of ≥ 50% or doubling of serum creatinine])

  AND

- acute reduction in Hb of > 2 g/dL and a 2-fold increase (ie, doubling) in LDH, as compared to the most recent Hb and LDH values (ie, while not experiencing symptoms of acute symptomatic hemolysis).

The sponsor medical monitor should be notified when the investigator first becomes aware of a potential acute symptomatic hemolysis event. Treatment with blinded study drug in Part 1, and BCX9930 for all subjects in Part 2, should continue in addition to any other treatments.

12.6. Overdose

To date, there is no experience with overdose of BCX9930. Healthy subjects received BCX9930 at a dose of 2000 mg administered as single doses and as multiple once-daily doses for 3 days in Study 101 with no clinically significant safety concerns. In the event that study personnel become aware of an overdose of BCX9930 that is associated with an AE, both the overdose and the resultant event should be reported as AEs. Overdose without any symptoms (ie, AEs) does not need to be reported as an AE. If overdose occurs with or without associated AEs, subjects should undergo clinical and laboratory monitoring, as appropriate, for their clinical condition and, if indicated, should receive clinically indicated supportive therapy. See also Section 12.1.2.

12.7. Data Monitoring Committees

A DMC will be established for interim safety monitoring. The specific responsibilities and composition of the DMC are outlined in a separate DMC charter. In addition, the details of outputs provided for the meetings will be referenced in this charter.

A NRMWG will review and advise on subjects with treatment-emergent increases in sCr and other renal events. The specific responsibilities and composition of the NRMWG are outlined in a separate charter.

13. STATISTICS

13.1. Hypotheses

The primary study hypothesis is the differential effect on the mean CFB in Hb at Week 12 in Hb between BCX9930 and placebo.

The primary null and alternative hypotheses are:

- CFB in Hb at Week 12.

- H_o: $Hb_B = Hb_P$; BCX9930 does not have a differential effect on the mean CFB in Hb at Week 12 as compared to placebo
- H_A: $Hb_B \neq Hb_P$; BCX9930 does have a differential effect on the mean CFB in Hb at Week 12 as compared to placebo

where Hb_B is the mean CFB in Hb at Week 12 for BCX9930 and Hb_P is the mean CFB in Hb at Week 12 for placebo.

Key secondary hypotheses comparing BCX9930 to placebo are as follows:

- Proportion of subjects who are transfusion-free from Week 4 to Week 12
  - H_o: $TA_B = TA_P$; BCX9930 does not have a differential effect on the proportion of subjects who are transfusion-free from Week 4 to Week 12
  - H_A: $TA_B \neq TA_P$; BCX9930 does have a differential effect on the proportion of subjects who are transfusion-free from Week 4 to Week 12

  where TA_B is the proportion of subjects who are transfusion-free from Week 4 to Week 12 for BCX9930 and TA_P is the proportion of subjects who are transfusion-free for placebo.
- Number of units of pRBCs transfused from Week 4 to Week 12
  - H_o: $pRBC_B = pRBC_P$; BCX9930 does not have a differential effect on the number of units of pRBCs transfused from Week 4 to Week 12
  - H_A: $pRBC_B \neq pRBC_P$; BCX9930 does have a differential effect on the number of units of pRBCs transfused from Week 4 to Week 12

  where $pRBC_B$ is the number of units of pRBCs administered from Week 4 to Week 12 for BCX9930 and $pRBC_P$ is the number of units of pRBCs administered for placebo.
- Percent CFB in LDH at Week 12
  - H_o: $LDH_B = LDH_P$; BCX9930 does not have a differential effect on the mean percent CFB in LDH at Week 12 as compared to placebo
  - H_A: $LDH_B \neq LDH_P$; BCX9930 does have a differential effect on the mean percent CFB in LDH at Week 12 as compared to placebo

  where LDH_B is the mean percent CFB in LDH at Week 12 for BCX9930 and LDH_P is the mean percent CFB for placebo.
- Change from baseline in FACIT-Fatigue scale score at Week 12
  - H_o: $FACIT_B = FACIT_P$; BCX9930 does not have a differential effect on the mean CFB in FACIT-Fatigue scale score at Week 12
  - H_A: $FACIT_B \neq FACIT_P$; BCX9930 does have a differential effect on the mean CFB in FACIT-Fatigue scale score at Week 12

  where $FACIT_B$ is the mean CFB in FACIT-Fatigue scale score at Week 12 for BCX9930 and $FACIT_P$ is the mean CFB in FACIT-Fatigue scale score for placebo.

Inferential testing for the primary endpoint of interest (CFB in Hb at Week 12) will be conducted at the $\alpha = 0.05$ level of significance. The alpha level for tests of primary and key secondary endpoints will be adjusted for multiplicity using hierarchical testing in the order the endpoints are specified as described in Section 13.1.1. All hypothesis tests will be 2-sided.

13.1.1. Controlling for Multiplicity

Five endpoints are being tested: the primary endpoint and 4 secondary endpoints. The Type I error rate will be controlled at the study level using a hierarchical testing procedure.

Statistical testing for the primary hypothesis will be performed using an alpha of 0.05. All hypothesis tests will be two-sided. If the null hypothesis associated with the primary endpoint is rejected, the key secondary endpoints for Part 1 will be tested in the following order using an alpha of 0.05. Testing will stop when an endpoint has an associated p-value ≥ 0.05 or when all endpoints have been tested (ie, all p-values are < 0.05):

1. Proportion of subjects who are transfusion-free [from Week 4 to Week 12]
2. Number of units of pRBCs transfused [from Week 4 to Week 12]
3. Percent CFB in LDH [at Week 12]
4. CFB in FACIT-Fatigue scale score [at Week 12]

13.2. Sample Size Considerations

Assuming a common standard deviation (SD) for Hb of 2.3 g/dL from Lee and colleagues (Lee, Peffault de Latour, et al. 2019) and a randomization ratio of 2:1, a sample size of 57 subjects (approximately 38 subjects in the BCX9930 200/400 mg arm and approximately 19 subjects in the placebo arm) will provide 85.3% power to detect a treatment difference of 2.0 g/dL in change from baseline Hb for subjects randomized to BCX9930 200/400 mg compared to subjects randomized to placebo. Because missing data will be imputed for the primary analysis, enrollment has not been increased to account for drop-outs.

13.3. Sample Size Re-estimation

No sample size re-estimation is planned.

13.4. Stratification

Randomization will be stratified based on whether a pRBC transfusion was received within the 6 months prior to baseline (yes vs. no).

13.5. Statistical Methods

A detailed statistical analysis plan (SAP) will be developed to describe the methods of analyses and summaries, including all endpoints, time points, populations, missing data, etc. Deviations from the analyses outlined in the SAP will be described in the clinical study report (CSR).

13.5.1. Analysis Populations

The analysis populations for the study are defined below.

13.5.1.1. Screen Failures

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

13.5.1.2. Intent-to-Treat Population

The intent-to-treat (ITT) population is defined as all randomized subjects, regardless of whether study treatment was administered. This population will be the primary population for efficacy analyses. Subjects will be analyzed according to the treatment randomized.

13.5.1.3. Safety Population

The safety population is defined as all subjects who receive at least 1 dose of study drug, whether BCX9930 or placebo. This population will be used for all analyses of accountability, demographics, and safety. Data will be analyzed according to the actual treatment received at first dose for all subjects or at first dose of Part 2 for subjects originally randomized to placebo.

13.5.1.4. Per Protocol Population

The per-protocol (PP) population is defined as all subjects who did not violate key protocol inclusion or exclusion criteria, received only the study drug to which they were randomized, and did not have any protocol deviations or violations that would affect analysis, as determined by the sponsor. This population will be used for a sensitivity analysis of the primary efficacy analysis. Analyses based on the PP population will be produced for Part 1 only. Subjects will be analyzed according to the treatment randomized.

13.5.1.5. Completers Population

The subset of subjects in the ITT population who complete Part 1 of the study and 12 weeks of blinded study drug will compose the completers population. This population will be used for a sensitivity analysis of the primary efficacy analysis for Part 1 only. Subjects will be analyzed according to the treatment randomized.

13.5.1.6. Pharmacokinetic Population

The PK population will comprise the subset of subjects in the safety population for whom BCX9930 concentration data are available. The PK substudy population will include all subjects who participate in the optional PK/PD substudy and have 1 post-dose concentration collected during a substudy visit.

13.5.1.7. Pharmacodynamic Population

The PD population will include all safety population subjects for whom at least 1 pre-dose and 1 post-dose PD or complement biomarker measurement can be obtained. This population will be used for all PD and complement biomarker analyses and for correlation with BCX9930 PK parameters or BCX9930 concentrations. Subpopulations including subjects for whom at least 1 pre-dose and 1 post-dose measurement for each PD or complement biomarker may be used for analysis. Subjects will be analyzed according to the treatment received.

13.5.2. General Considerations for Data Analysis

In general, descriptive summaries will include n, mean, standard deviation, median, minimum, and maximum for continuous variables and n and percent for categorical variables. Summaries will be presented by treatment and study visit.

All individual subject data will be listed as measured. All statistical summaries and analyses will be performed using SAS® software (SAS Institute, Cary, North Carolina, USA).

13.5.3. Subject Demographic and Disposition Data

Demographic data and baseline characteristics including age, gender, race or ethnicity, height, body weight, BMI, and PNH history will be summarized by treatment and overall.

The following baseline measures will be summarized using descriptive statistics: Hb levels, LDH levels, and FACIT-Fatigue scale score.

Subject disposition will be presented by treatment and overall. The number of subjects who completed the study and those that discontinued from the study will be provided. The reasons for early discontinuation will be presented. A tabulation of the number of subjects exposed to study drug and duration of exposure will also be presented for each treatment and overall. Treatment adherence, dose interruptions, and reason for dose interruptions will be provided as summaries or listed as appropriate.

13.5.4. Analysis of Efficacy Variables

The primary efficacy analyses will be based on Part 1 of the study. The efficacy analyses will be based on the ITT population. The analyses of the PP population and completers population will be used to support the primary efficacy analyses.

Efficacy data will be summarized by treatment in Part 1.

13.5.4.1. Primary Efficacy Analysis

The primary endpoint is the CFB in Hb at Week 12. The analysis of the primary endpoint will be conducted using Part 1 data.

The primary efficacy analysis will be produced using the ITT population. The estimand will be based on data from subjects while taking study treatment and prior to any rescue, if applicable, with data missing not at random imputed to be similar to what would have been observed on the reference treatment (ie, placebo) and data missing at random imputed to be similar to that of the randomized treatment of the subject. Statistical testing will be two-sided.

CFB in Hb will be summarized by treatment and visit. The difference between treatment groups in CFB Hb at Week 12 will be analyzed using an analysis of covariance (ANCOVA) model. The model will include treatment and randomization stratum as categorical covariates and baseline Hb as a continuous covariate. Observed data will be included up to the time of discontinuation of study treatment or to start of rescue treatment, if applicable. In addition, CFB Hb values that occur within 14 days after the subjects receives a pRBC transfusion (ie, the interval between the transfusion day and the current study day is ≤ 13 days) will be replaced with an unscheduled CFB Hb if one is available within the 14-day period prior to Week 12 and it was not obtained within 14 days after pRBC transfusion or, if an unscheduled value is not available, will be

censored unless the CFB Hb value is ≤ 0. Central laboratory values will be used. If a central laboratory value is missing but a local laboratory value is available, the local laboratory value will be used in place of the censored lab value. Missing data will be imputed using the method of Jump-to-Reference (J2R) (Carpenter, Roger, et al. 2013). The estimated treatment difference comparing BCX9930 to placebo at Week 12 will be displayed together with the 95% CI and the associated p-value. Least-squares means (LSM) will also be presented with the standard error (SE).

Sensitivity analyses will be conducted to support the primary analysis. This will include the following analyses:

1) Analyses based on data from subjects who are in the completers population using the same analysis methodology as for the primary analysis.
2) Analyses based on data from subjects in the PP population using the same analysis methodology as for the primary analysis.
3) An ITT analysis will also be conducted using observed data up to the time of discontinuation of study treatment or to start of rescue treatment, if applicable, without imputation of missing data.
4) A tipping point analysis will be conducted to further examine the effect of missingness.
5) A Mixed Models Repeated Measures (MMRM) analysis will be conducted using the ITT population and observed data to look at trends over time by treatment.

Details of sensitivity analyses will be provided in the SAP.

Subgroup analyses will be conducted by geographical region and by race. Additional subgroup analyses will be described in the SAP.

Plots of mean Hb and mean CFB Hb by visit and treatment will be produced for Part 1, using a different color for each treatment. Plots will be updated to include Part 2 data at the final analysis.

13.5.4.2. Analyses of Key Secondary, Other Secondary, and Exploratory Efficacy Endpoints

13.5.4.2.1. Part 1

Key secondary hypotheses comparing BCX9930 to placebo for Part 1 will be analyzed as follows:

1. Proportion of subjects who are transfusion-free [from Week 4 to Week 12]
2. Number of units of pRBCs transfused [from Week 4 to Week 12]
3. Percent CFB in LDH [at Week 12]
4. CFB in FACIT-Fatigue scale score [at Week 12]

The proportion of subjects who are transfusion-free from Week 4 to Week 12 will be summarized by treatment. Subjects who either (1) discontinue treatment prior to Week 12, or (2) do not receive a transfusion during the Week 4 to Week 12 time period despite recording a Hb value ≤ 9 g/dL with symptoms warranting transfusion or a Hb value ≤ 7 g/dL regardless of

symptoms will not be considered transfusion-free. A Cochran-Mantel-Haenszel (CMH) chi-squared analysis will be conducted to test the hypothesis of interest and to compute an odds ratio and 95% CI comparing the odds of being transfusion-free for BCX9930 treatment as opposed to treatment with placebo. As a supportive analysis, a logistic regression analysis will be conducted with a fixed effect for treatment and an indicator variable for the randomization stratum. A sensitivity analysis using CMH will be conducted in which subjects who discontinue treatment prior to Week 12 will not be considered transfusion-free, but subjects who do not receive a transfusion despite a Hb value ≤ 9 g/dL with symptoms warranting transfusion or a Hb value ≤ 7 g/dL regardless of symptoms will be considered as transfusion-free.

The number of units of pRBCs transfused from Week 4 to Week 12 will be summarized by treatment. The van Elteren test will be used to compare the two treatments with respect to the number of pRBCs transfused from Week 4 to Week 12. As a supportive analysis, the rate of pRBCs units transfused per 28 days will be derived using a negative binomial model. The negative binomial model will include the number of units of pRBCs from Week 4 to Week 12 as the dependent variable, the treatment and an indicator variable for the randomization factor as independent variables, and the logarithm of duration on treatment included as an offset variable. The model-estimated rate of pRBCs per 28 days from Week 4 to Week 12 will be reported for each treatment group. A rate ratio (with 95% CI) comparing BCX9930 to placebo will be obtained as well as a percent reduction in rate (with 95% CI) for BCX9930 as compared to placebo.

The actual and change from baseline in the endpoints of LDH and FACIT-Fatigue scale score will be summarized by treatment group and visit. The difference between treatment groups in percent CFB LDH at Week 12 and CFB FACIT-Fatigue score at Week 12 will be separately analyzed using an ANCOVA model. The model will include the CFB endpoint at Week 12 as the dependent variable with the treatment, an indicator variable for the randomization stratum, and baseline endpoint value as independent variables. Values obtained after treatment discontinuation or after rescue treatment, if applicable, will not be included. FACIT-Fatigue values occurring within a 14-day window after transfusion (ie, the interval between the transfusion day and the current study day is ≤ 13 days) will be censored. As such, the J2R method for handling of missing data will be used for the CFB FACIT-Fatigue analysis. Percent CFB LDH values will not be censored following a transfusion and the analysis for that endpoint will use observed data prior to study discontinuation or rescue treatment without imputation of missing data. For percent CFB in LDH and CFB in FACIT-Fatigue scale score, a supportive analysis using observed data will be conducted using MMRM with fixed effects for randomization stratum, treatment, baseline endpoint, visit, a visit-by-treatment interaction, and a random effect for subject. An unstructured covariance structure will be used. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom. The estimated treatment difference comparing BCX9930 to placebo at each post-baseline visit will be displayed together with the 95% CI and the associated p-value. LSM for each visit will also be presented with the SE. Plots of the mean endpoint and change from baseline by visit and treatment group will be produced for Part 1. Cumulative density function (CDF) and probability density function (PDF) plots of observed data for CFB FACIT-Fatigue at Week 12 will be produced. As an additional sensitivity analysis for CFB in FACIT-Fatigue scale score at Week 12, an ANCOVA analysis will be conducted using observed data with censoring due to transfusion within a 14-day window but without imputation of missing data. For percent CFB in

LDH at Week 12, a sensitivity analysis will be conducted using ANCOVA with missing data imputed using the J2R method.

Nominal p-values will be provided for other secondary and exploratory endpoints.

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

[redacted]

CFB in the continuous endpoints will be summarized by treatment group and visit. An ANCOVA analysis will be conducted with CFB value at Week 12 as the dependent variable, treatment, an indicator variable for randomization stratum, and the value of the endpoint at baseline included as independent variables. Missing data will not be imputed. CFB in ARC, CFB total PNH RBC clone size, CFB ratio of total PNH RBC clone size to PNH WBC clone size, and CFB in haptoglobin will be censored if the subject had a transfusion within 14 days prior to measurement of the endpoint (ie, the interval between the transfusion day and the current study day is ≤ 13 days).

The rate of pRBC units transfused from Week 4 to Week 12 will be calculated and compared to the rate of pRBC units transfused during the 12 months prior to screening. The percent reduction in rate of pRBC units transfused is the percent difference in rate relative to the retrospective rate, calculated as: (current rate – retrospective rate)/retrospective rate * 100%. Summary statistics will be provided for the percent reduction in rate of pRBC units transfused. In addition, the proportion of subjects with ≥ 50%/70%/90% reduction in rate will be reported.

Proportions of subjects with Hb ≥ 12 g/dL, with ARC in the normal range, and with haptoglobin ≥ LLN will be summarized by treatment and visit. Subjects will not be considered to meet the criteria for the endpoint of Hb ≥ 12 g/dL, ARC in the normal range, or haptoglobin ≥ LLN if they had a transfusion within 14 days of the endpoint measurement. The proportion of subjects with Hb stabilization from Week 4 to Week 12 will also be summarized. The proportion of

subjects with Hb ≥ 12 g/dL at Week 12, Hb stabilization from Week 4 to Week 12, Week 12 ARC in the normal range, and Week 12 haptoglobin ≥ LLN will be separately analyzed using the CMH chi-squared analysis method. For proportion of subjects with Hb ≥ 12 g/dL, proportion of subjects with ARC in the normal range, and proportion of subjects with haptoglobin ≥ LLN, subjects will be considered as not meeting these endpoints if they have had a transfusion within 14 days prior to the Week 12 visit (ie, the interval between the transfusion day and the Week 12 visit is ≤ 13 days)

Nominal p-values for other HRQoL endpoints for Part 1 will be provided for:

- Proportion of subjects achieving a within-subject meaningful change for the FACIT-Fatigue scale [at Week 12]
- CFB in QLQ-AA/PNH Physical Functioning and other domain scores [at Week 12]
- Proportion of subjects with improvement on individual PNH symptom items (ie, frequency, severity, and/or interference) from baseline as assessed using the modified PRO-AA/PNH symptom collection tool [at Week 12]
- CFB in individual PNH symptom items on the modified PRO-AA/PNH scores [at Week 12]
- CFB in EQ-5D-5L utility and VAS scores [at Week 12]
- TSQM scale score [at Week 12]
- Patient global impression of change in fatigue, impact of fatigue, and physical functioning as assessed using the PGIC-Fatigue, PGIC-Impact of Fatigue, and PGIC-Physical Functioning scores, respectively [at Week 12]
- CFB in patient global impression of severity of fatigue, impact of fatigue, and physical functioning as assessed using the PGIS-Fatigue, PGIS-Impact of Fatigue, and PGIS-Physical Functioning scores, respectively [at Week 12]

The proportion of subjects achieving a within-subject meaningful change for the FACIT-Fatigue scale at Week 12 and the proportion of subjects with improvement on individual PNH symptom items as assessed using the modified PRO-AA/PNH at Week 12 will be analyzed using the CMH chi-squared analysis method. The level required for meaningful within-person change will be determined for the FACIT-Fatigue scale using anchor-based analyses. These analyses will be described in the SAP.

QLQ-AA/PNH Physical Functioning and other domain scores, the PNH symptom items on the modified PRO-AA/PNH, EQ-5D-5L utility and VAS scores, and PGIS-Fatigue, PGIS-Impact of Fatigue, and PGIS-Physical Functioning scores will be summarized by visit for both actual and CFB values and the Week 12 CFB result will be analyzed using ANCOVA with effects for treatment, randomization stratum, and baseline value. Note that for TSQM scale scores, a similar analysis will be conducted but with the actual Week 12 value rather than the CFB Week 12 value as the dependent variable. For the QLQ-AA/PNH Physical Functioning domain score, CDF and PDF plots will be provided for the CFB score at Week 12.

PGIC for fatigue, impact of fatigue, and physical functioning scores will be summarized using descriptive statistics by treatment group and study visit. For ease of interpretation and

comparison, the PGIC items will be mapped to the values -3 to 3, from the worst outcome to the best outcome, respectively. PGIC items at Week 12 will be summarized by treatment group and study visit and analyzed using an ANCOVA model. The model will include effects for treatment, randomization stratum, and baseline score.

13.5.4.2.2. Part 2

The baseline for Part 2 for subjects who switch from placebo to BCX9930 at the end of Part 1 will be the last value prior to the first dose of BCX9930 in Part 2. The baseline value for subjects randomized to BCX9930 treatment will be the same as for Part 1.

Analysis of Part 2 secondary endpoints will generally be descriptive with summaries of actual and CFB values provided by visit for Hb, ARC, haptoglobin, total PNH RBC clone size, and ratio of total PNH RBC clone size to PNH WBC clone size. The mean (SD) of CFB values at Weeks 12 to 52 for subjects randomized to BCX9930 in Part 1 and for Weeks 24 to 52 for subjects randomized to placebo will be provided. Similar summaries will be provided for percent CFB in LDH.

The proportion of subjects with Hb ≥ 12 g/dL at Week 52, with haptoglobin ≥ LLN at Week 52, with Hb stabilization during the relevant Part 2 period, and who are transfusion-free during the relevant Part 2 period will be presented by randomized treatment in Part 1.

The number of units of pRBCs will be summarized using summary statistics. The rate of pRBC units transfused during the relevant period in Part 2 will be calculated along with the percent reduction in the rate of pRBCs transfused as compared to the rate of pRBC units transfused prestudy during the 12 months prior to screening. Summary statistics will be provided along with a summary of the number of subjects with a ≥ 50%/70%/90% reduction in rate of pRBC units transfused.

Summaries of actual and CFB values will be provided by visit for [redacted]

Analysis of Part 2 HRQoL endpoints will generally be descriptive with summaries of actual and CFB values provided by visit for FACIT-Fatigue scale, QLQ-AA/PNH domain, modified PRO-AA/PNH, EQ-5D-5L utility and VAS, and TSQM scale scores. Summaries of individual PNH symptom items at each visit will also be produced.

Summaries of FACIT-Fatigue scale scores and PNH symptom items by Part 1 treatment group and study visit will be provided. The proportion of subjects achieving a within-subject meaningful change for FACIT-Fatigue and with improvement in individual PNH symptoms items as compared to baseline will be summarized by visit.

For PGIC and PGIS for fatigue, impact of fatigue, and physical functioning, descriptive summaries by treatment group and study visit will show the number and percentage of subjects with each choice of response as well as summary statistics for PGIC items, PGIS items, and CFB PGIS items. For ease of interpretation, PGIC items will be mapped to the values -3 to 3, from the worst outcome to the best outcome, respectively.

13.5.5. Analysis of Safety Variables

Separate safety analyses will be produced for the analysis at the end of Part 1 and again at the end of Part 2, based on actual exposure. Subjects enrolled at a starting dose of 500 mg BID will be reported separately.

Safety endpoints that will be summarized include, at a minimum, the number and proportion of subjects 1) with a TEAE; 2) who discontinue BCX9930 due to a TEAE; 3) who experience a TESAE; 4) who experience a treatment-emergent CTCAE Grade 3 or Grade 4 AE; and 5) who experience a treatment-emergent CTCAE Grade 3 or Grade 4 laboratory abnormality.

AEs will be assessed and recorded from the time of signing of the ICF through the appropriate follow-up period. AEs will be mapped to a Medical Dictionary for Regulatory Activities (MedDRA) preferred term and system organ class (SOC). The occurrence of TEAEs will be summarized using MedDRA preferred terms, SOCs, and severity. Separate summaries of TEAEs, TESAEs and AEs considered to be related to study drug, and AEs leading to study drug interruption will be generated. All AEs will be listed for individual subjects showing both verbatim and preferred terms.

Clinical laboratory assessments and corresponding changes from baseline will be summarized for each laboratory panel by treatment and study visit.

Descriptive summaries (actual and CFB) of vital signs, body weight, 12-lead ECG parameters, and clinical laboratory results will be presented. Laboratory abnormalities will be graded according to the CTCAE scales (Version 5.0, 27 November 2017).

Any graded abnormality that occurs following the initiation of study drug and represents at least a 1-grade increase from the baseline assessment is defined as treatment emergent. The number and percentage of subjects experiencing treatment-emergent graded toxicities will be summarized. Laboratory toxicity shifts from baseline to worst post-baseline assessments will be summarized.

Vital signs (systolic and diastolic blood pressure, pulse rate, and temperature) and body weight and corresponding changes from baseline will be summarized by treatment and study visit using descriptive statistics. These data will be listed by subject, treatment, and study visit.

At each time point ECGs are analyzed, an individual subject's change from baseline will be calculated using the average of the triplicate ECGs performed at baseline (Day 1) and single values at each post-dose time point. The number and proportion of subjects with QTcF $\leq$ 450, $>$ 450 to $\leq$ 480, $>$ 480 to $\leq$ 500, and $>$ 500 msec; or CFB of $\leq$ 30, $>$ 30 to $\leq$ 60, or $>$ 60 msec will be summarized. Clinically significant abnormal morphological ECG findings will be summarized.

Physical examination findings will be listed.

A listing of pregnancy test results will be provided. Other pregnancy data captured in the eCRF will also be listed if necessary.

Concomitant medications will be coded using the WHO drug dictionary and summarized.

As applicable, safety data will be summarized by treatment and overall.

No tests of hypothesis are planned for safety data.

13.5.6. Acute Symptomatic Hemolysis

Acute symptomatic hemolysis is defined as: ≥ 1 new or worsening acute sign or symptom of IVH (fatigue, hemoglobinuria, abdominal pain, dyspnea, MAVE [including thrombosis], dysphagia, erectile dysfunction, or AKI [defined as an eGFR decrease of ≥ 50% or ≥ doubling of serum creatinine]) associated with an acute reduction in Hb of > 2 g/dL and a 2-fold increase (ie, doubling) in LDH, as compared to the most recent Hb and LDH values while not experiencing symptoms of acute symptomatic hemolysis. The sites will complete the Acute Symptomatic Hemolysis eCRF module for each episode of acute symptomatic hemolysis; these will be summarized by treatment group.

13.5.7. Breakthrough Hemolysis

BTH is defined as: ≥ 1 new or worsening sign or symptom of IVH (fatigue, hemoglobinuria, abdominal pain, dyspnea, anemia [Hb < 10 g/dL], MAVE [including thrombosis], dysphagia, or erectile dysfunction) in the presence of LDH ≥ 2 × ULN after prior LDH reduction to ≤ 1.5 × ULN on therapy. The number of subjects experiencing BTH with and without AKI and the number of BTH episodes will be summarized by treatment group.

13.5.8. Major Adverse Vascular Events

MAVEs are defined as: deep vein thrombosis; pulmonary embolus; myocardial infarction; transient ischemic attack; unstable angina; renal vein thrombosis; acute peripheral vascular occlusion; mesenteric/visceral vein thrombosis or infarction; mesenteric/visceral arterial thrombosis or infarction; hepatic/portal vein thrombosis (Budd-Chiari syndrome); cerebral arterial occlusion/cerebrovascular accident; cerebral venous occlusion; renal arterial thrombosis; gangrene (nontraumatic; nondiabetic); amputation (nontraumatic; nondiabetic); and dermal thrombosis.

All MAVEs and will be summarized by treatment group; thrombosis events will also be summarized separately.

13.5.9. Pharmacokinetic Analyses

All subjects who are included in the safety population and have available BCX9930 concentration data will be included in the PK population.

Plasma and urine samples for analysis of BCX9930 concentration will be collected according to the schedules presented in Table 3 to Table 5. Plasma PK sampling will include both sparse (all subjects) and serial (subjects participating in the PK/PD substudy only) collection. Urine sampling will include spot collections only.

Sparse plasma and spot urine concentration data will be listed.

For subjects enrolled in the PK/PD substudy, the plasma concentration data for BCX9930 will be summarized by visit (first dose vs. steady state) and nominal timepoint.

Metabolites of BCX9930 may also be included in PK analyses if deemed appropriate.

Plasma PK data collected from this study may be pooled with other clinical studies to develop population PK models. These analyses will be reported separately from the CSR.

Further details of the plasma PK analyses for this study will be included in a specific analysis plan.

13.5.10. Pharmacodynamic and Biomarker Analyses

PD assessments include plasma Factor Bb, C3a, and C5a, and serum AP activity (AP Wieslab assay), as well as plasma Factor D as the pharmacologic target of BCX9930. Additionally, total PNH RBC clone size, PNH WBC clone size, and the ratio of total PNH RBC clone size to PNH WBC clone size will be assessed. Biomarkers that would be indicative of disease state such as LDH levels, Hb and RBC counts, ARC, and haptoglobin will be assessed. Additional PD markers may also be analyzed.

Descriptive summaries of the above assessments (actual, CFB, and percent CFB) will be presented by parameter, time point, treatment, and study part.

Exposure-response (E-R) analyses of the relationships between BCX9930 plasma concentrations and PD endpoints, such as complement biomarkers, may be explored using quantitative, model-based techniques. Model-based analyses will possibly incorporate data from other clinical studies and will be reported separately from the CSR.

Further details of the PK/PD and E-R analyses for this study will be included in a specific analysis plan.

14. STUDY ADMINISTRATION

14.1. Study Monitoring

Before an investigational site can enter a patient into the study, a representative(s) of BioCryst or its designee will assess the investigational study site to:

- Determine the adequacy of the facilities
- Discuss with the investigator(s) and other personnel their responsibilities with regard to protocol adherence, and the responsibilities of BioCryst or its designee. This will be documented in a Clinical Study Agreement between BioCryst and the investigator.

During study conduct, BioCryst or its designee will conduct periodic monitoring visits to ensure that the protocol and Good Clinical Practice (GCP) are being followed. The monitor(s) will review source documents to confirm that the data recorded on eCRFs are accurate. The investigator and institution will allow the representative(s) of BioCryst or its designee direct access to source documents to perform this verification.

It is important that the investigator(s) and relevant personnel are available during the monitoring visits and that sufficient time is devoted to the process.

During the study, a representative(s) from BioCryst or its designee will have regular contacts with the investigational site personnel for the following:

- Provide information and support to the investigator(s)
- Confirm that facilities remain acceptable

- Confirm that the investigational team is adhering to the protocol, that data are being accurately recorded in the eCRFs, and that investigational product accountability checks are being performed
- Perform source data verification. This includes a comparison of the data in the eCRFs with the subject's medical records at the hospital or practice, and other records relevant to the study. This will require direct access to all original records for each subject (eg, clinic charts).
- Record and report any protocol deviations not previously sent to BioCryst or its designee
- Confirm AEs and SAEs have been properly documented on the eCRFs and confirm any SAEs have been forwarded to BioCryst or its designee and those SAEs that met criteria for reporting have been forwarded to the ethics committee

The representative(s) of BioCryst or its designee will be available between visits if the investigator(s) or other staff needs information or advice.

14.2. Audits and Inspections

Authorized representatives of BioCryst or its designee, US Food and Drug Administration (FDA) and other regulatory authorities, and/or ethics committee may visit the site to perform audits or inspections, including source data verification. The purpose of a BioCryst audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, standard operating procedures, ICH GCP guidelines, and any applicable regulatory requirements. The investigator should contact BioCryst immediately if contacted by a regulatory agency about an inspection.

It is important that the investigator and relevant personnel are available during the possible audits or inspections and that sufficient time is devoted to the process.

14.3. Ethics Committee

The investigator must obtain ethics approval for the investigation. Initial ethics approval, and all materials approved by the ethics committee, including the ICF and any recruitment materials, must be maintained by the investigator and made available for inspection.

14.4. Serious Breaches of GCP

It is the responsibility of the sponsor to notify the competent authority of any serious breach of GCP that is likely to affect, to a significant degree, the safety or mental integrity of the subjects of the study or the scientific value of the study. All serious breaches will be notified to the relevant competent authority in accordance with locally applicable regulations. The reporting to the sponsor will be performed by the party who suspects the serious breach.

15. QUALITY CONTROL AND QUALITY ASSURANCE

During study conduct, BioCryst or its designee will conduct periodic monitoring visits to ensure that the protocol and GCP are being followed as described in Section 14.1.

To ensure compliance with GCP and all applicable regulatory requirements, BioCryst or its designee may conduct a quality assurance audit. Please see Section 14.2 for more details regarding the audit process. The investigator agrees to allow the auditors to inspect the drug storage area, study drug stocks, drug accountability records, subject charts and study source documents, and other records relative to study conduct.

16. ETHICS

16.1. Ethics Review

The final study protocol and the final version of the ICF must be approved or given a favorable opinion in writing by an ethics committee, as appropriate. The investigator must submit written approval from the ethics committee to BioCryst before he or she can enroll any subject into the study.

The ethics committee will be informed of any amendment to the protocol in accordance with local requirements. In addition, the ethics committee must approve any advertising used to recruit subjects for the study. The protocol must be re-approved by the ethics committee upon receipt of amendments and annually, as local regulations require.

The ethics committee will be provided with reports of any reportable serious adverse drug reactions from any other study conducted with the investigational product, in accordance with local regulations. BioCryst will provide this information to the investigator.

Progress reports and notifications of serious adverse drug reactions will be provided to the ethics committee according to local regulations and guidelines.

16.2. Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH GCP, applicable regulatory requirements, and BioCryst's policies.

16.3. Written Informed Consent

In accordance with applicable national or local law, and current institutional practice, written informed consent to participate in the study will be obtained from each subject prior to conducting any study-related assessments/procedures.

A signed ICF must be obtained from each subject prior to performing any study-related procedures. Each subject should be given both oral and written information describing the nature, purpose, and duration of the study. Subjects will be informed that they are free not to participate in the study and that they may withdraw consent to participate at any time. They will be told that refusal to participate in the study will not prejudice future treatment. They will also be told that their records may be examined by competent authorities and authorized persons, but that personal information will be treated as strictly confidential and will not be publicly available. The informed consent process should take place under conditions where the subject has adequate time to consider the risks and benefits associated with participation in the study.

Subjects must be given the opportunity to ask questions. Subjects will not be screened or treated until the subject has signed an approved ICF written in a language in which the subject is fluent.

The ICF that is used must be approved both by BioCryst and by the governing ethics committee. The ICF should be in accordance with the current revision of the Declaration of Helsinki, current ICH and GCP guidelines, and BioCryst policies.

The subject should receive a signed and dated copy of the ICF. The original signed ICF should be retained in the study files.

The investigator shall maintain a log of all subjects for whom consent was signed and indicate if the subject was enrolled into the study or reason for non-enrollment.

17. DATA HANDLING AND RECORDKEEPING

17.1. Inspection of Records

BioCryst or designee will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The investigator agrees to allow the monitor to inspect the drug storage area, study drug stocks, drug accountability records, subject charts, and study source documents, and other records relative to study conduct.

17.2. Retention of Records

To enable evaluations and/or audits from regulatory authorities or BioCryst, the investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, eCRFs, and medical/hospital records), all original signed ICFs, all eCRFs, and detailed records of study drug accountability and treatment disposition. The records should be retained by the investigator according to local regulations or as specified in the Clinical Study Agreement, whichever is longer.

If the investigator relocates, retires, or for any reason withdraws from the study, the study records may be transferred to an acceptable designee, such as another investigator, another institution, or to BioCryst. The investigator must obtain BioCryst's written permission before disposing of any records and must notify BioCryst before transferring any records to another facility.

All correspondence related to records retention, destruction, or transfer of study documents, should be sent directly to BioCryst study personnel, copying the email archives@biocryst.com.

17.3. Confidentiality of Information and Data

BioCryst affirms the subject's right to protection against invasion of privacy and secure maintenance of the confidential nature of his/her personal data. Only a subject identification number and subject identifiers permitted by local regulation will identify subject data retrieved by BioCryst. However, in compliance with federal regulations, BioCryst requires the investigator to permit BioCryst's representatives and, when necessary, representatives of the FDA or other regulatory authorities to review and/or copy any medical records relevant to the study, maintaining pseudo-anonymity.

All parties will abide by all applicable laws and regulations regarding subject privacy and confidentiality, including the Health Insurance Portability and Accountability Act (HIPAA), where this rule is applicable, and the requirements of the General Data Protection Regulation (GDPR) in the EU, where applicable. A valid authorization and consent must meet the specifications of the applicable laws and regulations relating to such personal data and health information. It is the responsibility of the investigator and institution to obtain such waiver/authorization in writing from the appropriate individual. HIPAA authorizations are required for US sites only.

18. PUBLICATION POLICY

All data generated from this study are the property of BioCryst and shall be held in strict confidence along with all information furnished by BioCryst. Except as provided through written agreement between BioCryst, independent analysis and/or publication of these data by the investigator or any member of his/her staff is not permitted without prior written consent of BioCryst. Such consent will not be withheld unreasonably. BioCryst is in agreement with the principle of full disclosure of clinical study results.

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