

BioCRYST

PHARMACEUTICALS, INC.

BCX9930

PROTOCOL No. BCX9930-202

IND No. 142,217

EudraCT No. 2020-004438-39

**A Randomized, Open-Label, Multicenter, Parallel-Group
Study to Evaluate the Efficacy, Safety, and Tolerability of
Oral BCX9930 Monotherapy for the Treatment of
Paroxysmal Nocturnal Hemoglobinuria in Subjects with
Inadequate Response to C5 Inhibitor Therapy**

Version 4.0: 01 August 2022

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Version 4.0: 01 August 2022

This protocol has been approved by BioCryst Pharmaceuticals, Inc.

Senior Clinical Development Physician:


DocuSigned by:

 Signer Name: 
Signing Reason: I approve this document
Signing Time: 03-Aug-2022 | 13:57:40 EDT
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BioCryst Pharmaceuticals, Inc.

Date

Sponsor's Authorized Signatory:

DocuSigned by:

 Signer Name: 
Signing Reason: I approve this document
Signing Time: 03-Aug-2022 | 14:41:01 EDT
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BioCryst Pharmaceuticals, Inc.

Date

INVESTIGATOR AGREEMENT

Protocol No. BCX9930-202

A Randomized, Open-Label, Multicenter, Parallel-Group Study to Evaluate the Efficacy, Safety, and Tolerability of Oral BCX9930 Monotherapy for the Treatment of Paroxysmal Nocturnal Hemoglobinuria in Subjects with Inadequate Response to C5 Inhibitor Therapy

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.:	BCX9930-202
Study Title:	A Randomized, Open-Label, Multicenter, Parallel-Group Study to Evaluate the Efficacy, Safety, and Tolerability of Oral BCX9930 Monotherapy for the Treatment of Paroxysmal Nocturnal Hemoglobinuria in Subjects with Inadequate Response to C5 Inhibitor Therapy
IND No.:	142,217
EudraCT No.:	2020-004438-39
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:	<div>████████████████████</div> <div>██</div> Office: <div>████████████████</div> Mobile: <div>████████████████</div> Email: <div>████████████████████</div> (Note: See Section 12.4.1 for contact information for SAE reporting.)
Sponsor Clinical Study Manager:	<div>████████████████</div> <div>████████████████████████████</div> Office: <div>████████████████</div> Mobile: <div>████████████████</div> Email: <div>████████████████████</div>
Lead or Coordinating Investigator:	<div>██</div> <div>██</div> <div>████</div>
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: <div style="background-color: black; height: 1.2em; width: 100%;"></div>
Title of Study: A Randomized, Open-Label, Multicenter, Parallel-Group Study to Evaluate the Efficacy, Safety, and Tolerability of Oral BCX9930 Monotherapy for the Treatment of Paroxysmal Nocturnal Hemoglobinuria in Subjects with Inadequate Response to C5 Inhibitor Therapy
BioCryst Protocol No.: BCX9930-202
Study Centers: This study will be conducted at study centers in multiple countries/regions
Lead or Coordinating Investigator: <div style="background-color: black; height: 1.2em; width: 100%;"></div> <div style="background-color: black; height: 1.2em; width: 100%;"></div>
Phase of development: 2
Objectives: Part 1 Primary Objective: <ul style="list-style-type: none"> To determine the efficacy of oral BCX9930 monotherapy administered for 24 weeks, compared to continued complement component 5 (C5) inhibitor therapy, in subjects with paroxysmal nocturnal hemoglobinuria (PNH) with an inadequate response to C5 inhibitor therapy Part 1 Secondary Objectives: <ul style="list-style-type: none"> To evaluate the safety and tolerability of BCX9930 monotherapy administered for 24 weeks, as compared to continued C5 inhibitor therapy, in subjects with PNH To characterize the effects of BCX9930 monotherapy, as compared to continued C5 inhibitor therapy, using clinical and laboratory measurements, including complement and thrombosis biomarkers, PNH clone size, and C3-opsonization of red blood cells (RBCs) in subjects with PNH To evaluate the effects of BCX9930 monotherapy, as compared to continued C5 inhibitor therapy, 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, endpoints will be assessed at or to Week 24.

Part 1 Primary Endpoint:

- Change from baseline (CFB) in hemoglobin (Hb) [mean of values at Weeks 12, 16, 20, and 24]

Part 1 Key Secondary Endpoints:

1. Proportion of subjects who are transfusion-free [from Week 4 to Week 24]
2. Number of units of packed red blood cells (pRBCs) transfused [from Week 4 to Week 24]
3. CFB in FACIT-Fatigue scale score [mean of values at Weeks 12, 16, 20, and 24]

Part 1 Other Secondary Endpoints:

- Percent CFB in lactate dehydrogenase (LDH) [mean of values at Weeks 12, 16, 20, and 24]
- Percent reduction in the rate of pRBC units transfused [from Week 4 to Week 24 vs. prestudy transfusion rate]
- Proportion of subjects with Hb \geq 12 g/dL [at Week 24]
- 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 24]
- CFB in C3-opsonized RBCs [mean of values at Weeks 12, 16, 20, and 24]
- CFB in total PNH RBC clone size [mean of values at Weeks 12, 16, 20, and 24]
- 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) [mean of values at Weeks 12, 16, 20, and 24]
- CFB in absolute reticulocyte count (ARC) [mean of values at Weeks 12, 16, 20, and 24]
- Proportion of subjects with ARC in the normal range [at Week 24]
- CFB in haptoglobin [mean of values at Weeks 12, 16, 20, and 24]
- Proportion of subjects with haptoglobin \geq lower limit of normal reference range (LLN) [at Week 24]
- CFB in total bilirubin [mean of values at Weeks 12, 16, 20, and 24]

Part 1 Exploratory Endpoints:

- [REDACTED]
- [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 24]
- 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 24]
- 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) [at Week 24]
- CFB in individual PNH symptom items on the modified PRO-AA/PNH [at Week 24]

- CFB in EuroQoL 5-dimension, 5-level (EQ-5D-5L) utility and visual analog scale (VAS) scores [at Week 24]
- Treatment Satisfaction Questionnaire for Medication (TSQM) scale score [at Week 24]
- 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 24]
- 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 24]

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 over a 28- to 52-week treatment period in subjects with PNH with an inadequate response to C5 inhibitor therapy

Part 2 Secondary Objectives:

- To assess the effectiveness of BCX9930 monotherapy in the treatment of PNH over a 28- to 52-week treatment period
- To characterize the effects of BCX9930 monotherapy using clinical and laboratory measurements, including complement and thrombosis biomarkers, PNH clone size, and C3-opsonization of RBCs, in subjects with PNH over a 28- to 52-week treatment period
- To evaluate the effects of BCX9930 monotherapy on FACIT-Fatigue scale and other PROs in subjects with PNH over a 28- to 52-week treatment period
- To characterize BCX9930 plasma concentrations and PK parameters over time in subjects with PNH

In Part 2, unless indicated otherwise, endpoints will be assessed at or to Week 52. For subjects who are switched from C5 inhibitor therapy to BCX9930 monotherapy at the end of Part 1, Part 2 endpoints will be assessed against Week 24 (ie, Week 52 vs. Week 24).

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 28 to 52 for subjects randomized to BCX9930 in Part 1 and from Weeks 36 to 52 for subjects randomized to continue C5 inhibitor]
- 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 24 to 52 for subjects randomized to BCX9930 in Part 1 and from Weeks 28 to 52 for subjects randomized to continue C5 inhibitor]
- Proportion of subjects who are transfusion-free [from Weeks 24 to 52 for subjects randomized to BCX9930 in Part 1 and from Weeks 28 to 52 for subjects randomized to continue C5 inhibitor]
- Number of units of pRBCs transfused [from Weeks 24 to 52 for subjects randomized to BCX9930 in Part 1 and from Weeks 28 to 52 for subjects randomized to continue C5 inhibitor]
- Percent reduction in the rate of pRBC units transfused [from Weeks 24 to 52 for subjects randomized to BCX9930 in Part 1 and from Weeks 28 to 52 for subjects randomized to continue C5 inhibitor vs. prestudy transfusion rate]
- Percent CFB in LDH [mean of values from Weeks 28 to 52 for subjects randomized to BCX9930 in Part 1 and from Weeks 36 to 52 for subjects randomized to continue C5 inhibitor]
- CFB in ARC [mean of values from Weeks 28 to 52 for subjects randomized to BCX9930 in Part 1 and from Weeks 36 to 52 for subjects randomized to continue C5 inhibitor]
- Proportion of subjects with ARC in the normal range [at Week 52]
- CFB in haptoglobin [mean of values from Weeks 28 to 52 for subjects randomized to BCX9930 in Part 1 and from Weeks 36 to 52 for subjects randomized to continue C5 inhibitor]
- Proportion of subjects with haptoglobin \geq LLN [at Week 52]
- CFB in C3-opsonized RBCs [mean of values from Weeks 28 to 52 for subjects randomized to BCX9930 in Part 1 and from Weeks 36 to 52 for subjects randomized to continue C5 inhibitor]
- CFB in total PNH RBC clone size [mean of values from Weeks 28 to 52 for subjects randomized to BCX9930 in Part 1 and from Weeks 36 to 52 for subjects randomized to continue C5 inhibitor]
- CFB in ratio of total PNH RBC clone size to PNH WBC clone size [mean of values from Weeks 28 to 52 for subjects randomized to BCX9930 in Part 1 and from Weeks 36 to 52 for subjects randomized to continue C5 inhibitor]

Part 2 Exploratory Endpoints:

- [REDACTED]

- [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 on the modified PRO-AA/PNH as compared to baseline
- 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
- 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 PK/PD 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, active-controlled, open-label, 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 24 weeks versus continuing C5 inhibitor therapy in subjects with PNH with inadequate response to their current C5 inhibitor therapy. Subjects will be randomized to either discontinue C5 inhibitor therapy and start BCX9930 monotherapy or to continue C5 inhibitor therapy for the 24-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 C5 inhibitor therapy in Part 1 will discontinue that therapy and start BCX9930 in Part 2.

Methodology:

Part 1: Eligible subjects will be randomized in a 2:1 ratio to either discontinue C5 inhibitor therapy and start BCX9930 monotherapy, or to continue C5 inhibitor therapy at the same dose and regimen as previously administered for 24 weeks. Randomization will be stratified based on C5 inhibitor (ravulizumab vs. eculizumab) and 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 at Weeks 1, 2, and 4, and every 4 weeks thereafter through Week 24. Subjects randomized to BCX9930 will be required to complete additional safety assessments at Weeks 3, 5, 6, 7, and 10.

Part 2: Subjects randomized to continue C5 inhibitor therapy during Part 1 will discontinue that therapy and be switched to BCX9930 monotherapy for Part 2. These subjects will be required to return to the clinic at Weeks 25, 26, 28, 32, and 36, and then every 4 weeks thereafter through Week 52. Additional safety assessments will be performed at Weeks 27, 29, 30, 31, and 34. Subjects randomized to BCX9930 monotherapy in Part 1 will continue with the every 4 weeks visit schedule through Week 52.

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 81 subjects with PNH and an inadequate response to C5 inhibitor therapy (ie, approximately 54 subjects in the BCX9930 200/400 mg BID arm and approximately 27 subjects in the control arm) will be enrolled.

Diagnosis and Main Criteria for Inclusion:

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

1. Male or female, aged ≥ 18 years old.
2. Body weight ≥ 40 kg.
3. Documented diagnosis of PNH confirmed by flow cytometry with a PNH granulocyte or monocyte clone size of $\geq 10\%$ during screening.
4. Treated with a stable regimen of eculizumab for ≥ 3 months prior to the screening visit or ravulizumab for ≥ 6 months prior to the screening visit.
5. Recorded the following results during screening:
 - a. Hb of ≤ 105 g/L (≤ 10.5 g/dL).
 - b. ARC of $\geq 100 \times 10^9$ cells/L ($\geq 100,000$ cells/ μ L; ≥ 100 G/L).
 - c. Absolute neutrophil count of $\geq 0.75 \times 10^9$ cells/L (≥ 750 cells/ μ L; $\geq 0.75 \times$ G/L).
 - d. Platelet count of $\geq 30 \times 10^9$ /L ($\geq 30,000$ / μ L; ≥ 30 G/L).
 - e. Adequate iron reserve based on ferritin \geq LLN or total iron binding capacity \leq upper limit of the normal reference range (ULN).

- f. Estimated glomerular filtration rate of ≥ 60 mL/min/1.73 m² using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation ([Levey and Stevens 2010](#)) and no evidence of clinically relevant abnormal renal function unrelated to underlying PNH disease.
6. Contraception requirements:
- Female participants must meet at least one of the following requirements:
- Be a woman of nonchildbearing potential.
 - 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.
 - 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:
- 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.
 - 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](#).
7. Documentation of current vaccinations against *Neisseria meningitidis* types A, C, W, and Y, and *Streptococcus pneumoniae*, or willingness to start vaccination series at least 14 days prior to Day 1.
(Note: Vaccination for *N. meningitidis* type B and for *Haemophilus influenzae* type B [Hib] is strongly encouraged where authorized and available.)
8. In the opinion of the investigator, the subject is expected to adequately comply with all required study procedures and restrictions for the study, including compliance with the twice daily (BID) dosing schedule for BCX9930.
9. Willing and able to provide written informed consent.

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

- Known history of or existing diagnosis of hereditary complement deficiency.
- History of hematopoietic cell transplant or solid organ transplant or anticipated candidate for transplantation during the study.
- 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.
- 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 supplementation 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. Aspartate aminotransferase (AST; also serum glutamic-oxaloacetic transaminase [SGOT]) > 3 × ULN.
(Note: Subjects may be enrolled with AST > 3 × ULN if explained by hemolysis.)
 - c. Total serum bilirubin > 2 × ULN.
(Note: Subjects may be enrolled with total serum bilirubin > 2 × ULN if explained by hemolysis or Gilbert's syndrome. In the case of hemolysis, total serum bilirubin must be < 5 × ULN and in the case of Gilbert's syndrome, total serum bilirubin must be < 11 × ULN.)
 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 be administered a dose of 200 mg BID for the first 14 days of treatment before increasing 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 continued C5 inhibitor therapy or BCX9930 monotherapy for 24 weeks. In Part 2, all subjects will receive BCX9930 monotherapy for 28 weeks.

Reference Therapy, Dosage and Mode of Administration:

Eculizumab or ravulizumab administered by intravenous infusion will be maintained at the same dose and posology received at screening.

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; 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 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. PK samples will not be collected from subjects randomized to continue C5 inhibitor therapy in Part 1.

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 (total PNH RBC, PNH WBC, and the ratio of total PNH RBC to PNH WBC) will be assessed, along with C3 deposition (ie, C3 RBC opsonization). 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]
[REDACTED]

Statistical Methods:

The primary study hypothesis is that the treatment effect, as measured by the CFB in Hb (mean of values at Weeks 12, 16, 20, and 24) for BCX9930 will be superior to continued C5 inhibitor therapy. The primary efficacy endpoint is the CFB in Hb (mean of values at Weeks 12, 16, 20, and 24) in the intent-to-treat (ITT) population, which includes all randomized subjects, regardless of whether study treatment was administered. The difference between treatment groups in CFB in Hb (mean of values at Weeks 12, 16, 20, and 24) 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. Inferential testing for the primary endpoint of interest (CFB in Hb) 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 66 subjects (44 subjects in the BCX9930 200/400 mg BID arm, 22 subjects in the control arm) will have 90% power to detect a treatment difference of 2.0 g/dL in Hb change from baseline for subjects randomized to BCX9930 compared to subjects randomized to continue C5 inhibitor therapy. To take account of potential dropouts, approximately 81 subjects (ie, approximately 54 subjects in the BCX9930 200/400 mg BID arm and approximately 27 subjects in the control arm) will be enrolled. Safety assessments, data from PNH using clinical measurements, PK, clinical laboratory biomarkers, and quality-of-life measurements will be summarized in tables and figures.

3. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF 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
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration equation
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
████	████████████████████
FSH	follicle-stimulating hormone
FXa	activated Factor X
FXIIa	activated Factor XII
GCP	Good Clinical Practice
Hb	Hemoglobin
HBV	hepatitis B virus

Abbreviation or Specialist Term	Explanation
HCV	hepatitis C virus
Hib	<i>Haemophilus influenzae</i> 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
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
NSAID	non-steroidal anti-inflammatory drug
PD	pharmacodynamic(s)
PDF	probability density function

Abbreviation or Specialist Term	Explanation
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
SGOT	serum glutamic-oxaloacetic transaminase (also AST)
SGPT	serum glutamic-pyruvic transaminase (also ALT)
SOC	system organ class
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	half-life
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
TSQM	Treatment Satisfaction Questionnaire for Medication

Abbreviation or Specialist Term	Explanation
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

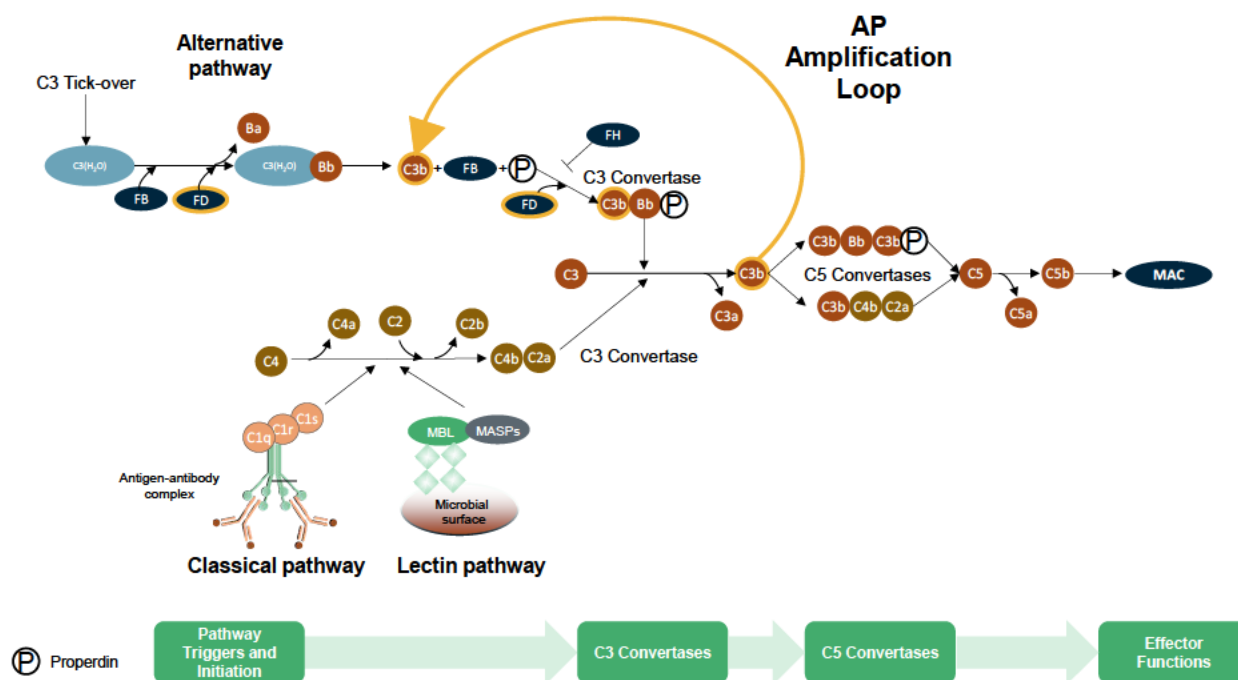
5. INTRODUCTION

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 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(H₂O) at low concentrations. C3(H₂O) pairs with Factor B and is then cleaved by serine protease Factor D to form C3(H₂O)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 C3bBb, 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(H₂O) 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(H₂O)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, Ma, 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, Hill, Rother, et al. 2010). 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 also 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, Kosciak, 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. After loading doses have been administered, eculizumab is label-indicated for administration once every 14 days and ravulizumab once every 8 weeks ([Alexion Pharmaceuticals Soliris PI 2020](#), [Alexion Pharmaceuticals Ultomiris PI 2020](#)).

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](#)).

5.1.3.2. Unmet Medical Need

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](#)).

C5 Inhibitors Do Not Control Extravascular Hemolysis

Blockade of the terminal complement pathway by eculizumab ([Rother, Rollins, et al. 2007](#)) reduces IVH, decreasing the levels of plasma lactate dehydrogenase (LDH), a sensitive biomarker for IVH. Eculizumab binds C5, blocks its cleavage to C5a and C5b, and thus protects PNH RBCs from MAC formation and lysis. However, due to the absence of CD55, the PNH RBCs in patients with PNH receiving eculizumab treatment continue to be opsonized by C3b and thus are susceptible to EVH ([Risitano, Notaro, et al. 2009](#)). With control of IVH, the PNH RBC Type III clone size increases, and patients administered eculizumab demonstrate selective, uncontrolled opsonization of PNH Type III RBCs, leading to EVH ([Risitano, Notaro, et al. 2009](#), [Hill, DeZern, et al. 2017](#)). Chronic EVH can result in a continued need for RBC transfusions ([Hillmen, Young, et al. 2006](#), [DeZern, Dorr, et al. 2013](#)). Ravulizumab has the same mechanism of action as eculizumab and patients receiving ravulizumab are similarly susceptible to EVH ([Kulasekararaj, Hill, et al. 2019](#), [Lee, Sicre de Fontbrune, et al. 2019](#)).

Continuing Hemolysis, Anemia, Need for Transfusions, and PNH Symptoms

The hematological benefits for patients receiving 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 ([Table 2](#)) ([Lee, Sicre de Fontbrune, et al. 2019](#)). Different factors contribute to residual anemia during eculizumab treatment, including underlying bone marrow dysfunction, C3-mediated EVH, and inadequate plasma levels of eculizumab with standard dose schedules in many patients associated with residual intravascular hemolysis ([Risitano, Marotta, et al. 2019](#), [Wijnsma, Ter Heine, et al. 2019](#)). Clinicians have been dosing eculizumab at levels higher than recommended by the drug label in an attempt to address this last issue with limited success ([McKinley, Richards, et al. 2017](#), [Cheng, Sarda, et al. 2020](#)).

Table 2: Anemia, Need for Transfusions, and PNH Symptoms Persist in Many Patients Despite C5 Inhibitor Treatment

C5 Inhibitor	RBC Transfusions	Hb not Stabilized	Fatigue	Hemoglobinuria	Dyspnea
Ravulizumab	26%	32%	29%	10%	14%
Eculizumab	33%	35%	30%	9%	14%

Abbreviations: C5 = complement component 5; Hb = hemoglobin; PNH = paroxysmal nocturnal hemoglobinuria; RBC = red blood cell.

Source: (Lee, Sicre de Fontbrune, et al. 2019)

Breakthrough Hemolysis

The reappearance of IVH symptoms during C5 inhibitor treatment for PNH is described as breakthrough hemolysis (BTH), which results in anemia and fatigue, dyspnea, and abdominal pain (Brodsky, Peffault de Latour, et al. 2021). Two types of BTH are recognized (Risitano, Marotta, et al. 2019). The first describes the regular reappearance of IVH symptoms towards the end of the dosing interval in about 10% to 15% of patients treated with eculizumab (Marti-Carvajal, Anand, et al. 2014, Risitano, Marotta, et al. 2019). This is associated with low trough concentrations of the drug and is referred to as “pharmacokinetic (PK) breakthrough”. In response, it has become commonplace to either increase the label-recommended maintenance dose of eculizumab to 1200 mg or 1500 mg, or to shorten the label-recommended dosing interval of eculizumab to 10 to 12 days (Marti-Carvajal, Anand, et al. 2014, Risitano, Marotta, et al. 2019, Bektas, Copley-Merriman, et al. 2020, Cheng, Sarda, et al. 2020). The second type of breakthrough hemolysis is less predictable and occurs in response to complement-activating conditions (CACs), including bacterial and viral infections, surgery, and other trauma. This has been referred to as “pharmacodynamic (PD) breakthrough”, since it occurs independently of C5 inhibitor concentrations, and is limited by resolution of the triggering event and does not usually require changes in the C5 inhibitor dose regimen.

Genetic Resistance

A small proportion of patients (up to 3.5% of patients, (Nishimura, Yamamoto, et al. 2014) have a disease with C5 polymorphisms that are resistant to eculizumab inhibition. The efficacy of a Factor D inhibitor would not be impacted by these polymorphisms in C5.

Burden of Therapy with Intravenous Treatments for PNH

The IV route of administration of current treatments and the frequency of infusions negatively impacts patients’ quality of life (QoL) (Fattizzo and Kulasekararaj 2020). A recent publication showed that a treatment with less frequent IV infusions (ravulizumab) is preferred over a treatment that has a treatment schedule with more frequent IV infusions (eculizumab) (Peipert and Hays 2019), inferring that patients’ preference leans towards the least amount of infusions possible, preferably none at all if they have a choice.

The challenges linked to current treatments in turn result in a significant burden on patient QoL (Acaster, Dickerhoof, et al. 2015), with persistent anemia leading to fatigue and subsequently impacting daily activities (Brodsky, Peffault de Latour, et al. 2021). Inadequate control of IVH and the appearance of EVH may require a continued need for RBC transfusions. In clinical

studies, 4.0% and 10.7% of patients with PNH treated with ravulizumab and eculizumab, respectively, experienced BTH ([Lee, Sicre de Fontbrune, et al. 2019](#)).

Based on the above considerations, 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.

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, PK, and toxicology studies of BCX9930 are described briefly below; additional details can be found in the Investigator’s Brochure (IB).

[REDACTED]

[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]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

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

[REDACTED] BCX9930 has a low risk to prolong the QT interval. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[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 (BCX9930-101; 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

[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 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 BCX9930-106). Results from these studies are described in the current version of the IB.

5.3. Rationale for Study

The current study, BCX9930-202 (Study 202) will evaluate the efficacy, safety, and tolerability of BCX9930 monotherapy versus continued C5 inhibitor therapy in subjects with PNH with inadequate response to C5 inhibitor therapy.

5.3.1. Rationale for Study Design

Study 202 is divided into two parts, conducted on the same population of subjects. Part 1 will include BCX9930 monotherapy administered for 24 weeks in comparison to continued complement C5 inhibitor therapy. Data collected through Week 24 will constitute the primary efficacy data set for the study. Subjects randomized to continue C5 inhibitor therapy in Part 1 will discontinue that therapy in Part 2 and switch to BCX9930 monotherapy, so that all subjects will receive BCX9930 in Part 2. The second part of the study will evaluate the long-term safety and effectiveness of BCX9930 monotherapy.

Evidence from other studies of complement inhibitors in PNH supports the conclusion that 24 weeks of dosing is an ample duration to demonstrate the efficacy of BCX9930 versus continued C5 inhibitor therapy. The 24-week duration of the randomized treatment phase of Study 202 is consistent with the 26-week duration of the pivotal studies for eculizumab and ravulizumab ([Hillmen, Young, et al. 2006](#), [Kulasekararaj, Hill, et al. 2019](#), [Lee, Sicre de Fontbrune, et al. 2019](#)). A 24-week duration rather than 26 weeks was chosen for practical reasons because of the every 8-week dose schedule of ravulizumab and the convenience of a monthly (4-week) visit schedule for participants. The 28-week duration of Part 2, with subjects dosed through Week 52, will allow for evaluation of the long-term safety, tolerability, and effectiveness of BCX9930 monotherapy as a potential treatment for PNH.

5.3.2. Rationale for Study Population

The current study is designed to evaluate the superiority of a BCX9930 monotherapy compared to continued C5 inhibitor therapy in subjects with an inadequate response to C5 inhibitors. For the purposes of this study, determination of an “inadequate response” will be based on residual anemia, defined as a Hb value of ≤ 10.5 g/dL at screening. Prospective subjects must have been treated with a stable regimen of eculizumab for at least 3 months or a stable regimen of ravulizumab for 6 months prior to the screening visit to allow adequate time to assess their response to that therapy. In addition to residual anemia, prospective subjects must show evidence of reticulocytosis (absolute reticulocyte count [ARC] of $\geq 100,000$ cells/ μ L) 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 additionally need to meet minimum thresholds at screening for platelet count ($\geq 30,000$ μ L) and absolute neutrophil counts (≥ 750 cells/ μ L).

LDH was not included in the definition of an inadequate responder because blockade of the terminal complement pathway by the C5 inhibitor is expected to have abrogated IVH and decreased LDH in this population.

This population of patients currently has no approved treatment alternatives other than continuing C5 inhibitor therapy and, therefore, is a population of unmet medical need. In clinical practice, these patients would not be characterized as non-responders and would remain on C5 inhibitor therapy. As such, it is considered clinically and ethically acceptable to continue C5 inhibitor therapy in this population of patients, as these inadequate responders derive some benefit from the C5 inhibitor therapy in controlling IVH, but continue to have an unmet need regarding control of EVH. Inhibition of Factor D by BCX9930 should control both IVH and EVH, and should result in a superior treatment effect, compared to C5 inhibitor therapy.

5.3.3. Rationale for Comparator

This is an active-controlled study. Eculizumab and ravulizumab represent the current standard of care for the treatment of PNH in jurisdictions where these drugs have received regulatory approval and are commercially available. To encompass as broad a patient population as possible, prospective subjects with an inadequate response to either eculizumab or ravulizumab may be enrolled in this study. The dose of C5 inhibitor must have been stable for a minimum of 3 months prior to the screening visit for eculizumab and 6 months prior to the screening visit for ravulizumab to ensure that adequate time has been allowed to assess the subject's response to C5 inhibitor therapy. Enrollment will not be limited only to inadequate responders who are being treated with the label-indicated regimen of eculizumab. Instead, patients with an inadequate response to eculizumab therapy despite dose or dose interval adjustment ([Brodsky 2021](#)), representing a subgroup with clear unmet medical need, will be allowed to enroll in the current study. However, they must still meet the 3-month requirements for dose stability. In addition, the same dose regimen of eculizumab or ravulizumab that the study subject was receiving at screening will be maintained during Part 1 of the study.

5.3.4. Rationale for Study Endpoints

Patients with an inadequate response to C5 inhibitors present with fatigue from low Hb levels and may be transfusion-dependent, but due to control of IVH by the C5 inhibitor, may have normal or only modestly elevated LDH and aspartate aminotransferase (AST, also serum glutamic-oxaloacetic transaminase [SGOT]) concentrations ([Risitano 2016](#)). Therefore, the primary endpoint selected for this study is the change from baseline (CFB) in Hb, which is a direct measure of the correction of anemia and 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](#)).

Key secondary endpoints have been selected to characterize the clinical benefit of treatment with BCX9930. In particular, secondary endpoints include the proportion of subjects who are transfusion-free over the 24-week treatment period and reductions in transfusions as reflected in the number of units of packed RBC units (pRBCs) transfused, 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 EVH by measuring the CFB in C3-opsonized RBCs, the CFB in the total PNH RBC clone size, and the change in the ratio of total PNH RBCs to PNH white blood cells (WBCs) (ie, percent PNH RBCs/percent PNH WBCs) after 24 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).

Because of the potential adverse effects of coronavirus disease (COVID-19) and other unpredictable CACs on otherwise well-controlled IVH and EVH, the primary and relevant secondary endpoints will be assessed as the average of values obtained at visits from Weeks 12 through 24. Preliminary data from PNH patients treated with BCX9930 in Study 101 (Section 5.2.2), supported by data reported for other proximal complement inhibitors, including the C3 inhibitor, pegcetacoplan, and orally administered inhibitors of Factor B, iptacopan (LNP 023) and Factor D, danicopan (ACH-0144471), suggests that treatment through 12 weeks is sufficient to show maximal or close to maximal responses in Hb, C3 opsonization of RBCs, PNH clone size, and the FACIT-Fatigue scale (Kulasekararaj, Hill, et al. 2019, Wong, Ignatova, et al. 2020, Risitano, Roth, et al. 2021). In addition, transfusion avoidance and related endpoints will be assessed over an effective treatment period from Week 4 through Week 24 to account for the initial 2-week BCX9930 200 mg BID dose titration and turnover of PNH RBCs (Ninomiya, Sato, et al. 2008, Risitano, Notaro, et al. 2009).

[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]

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.

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]

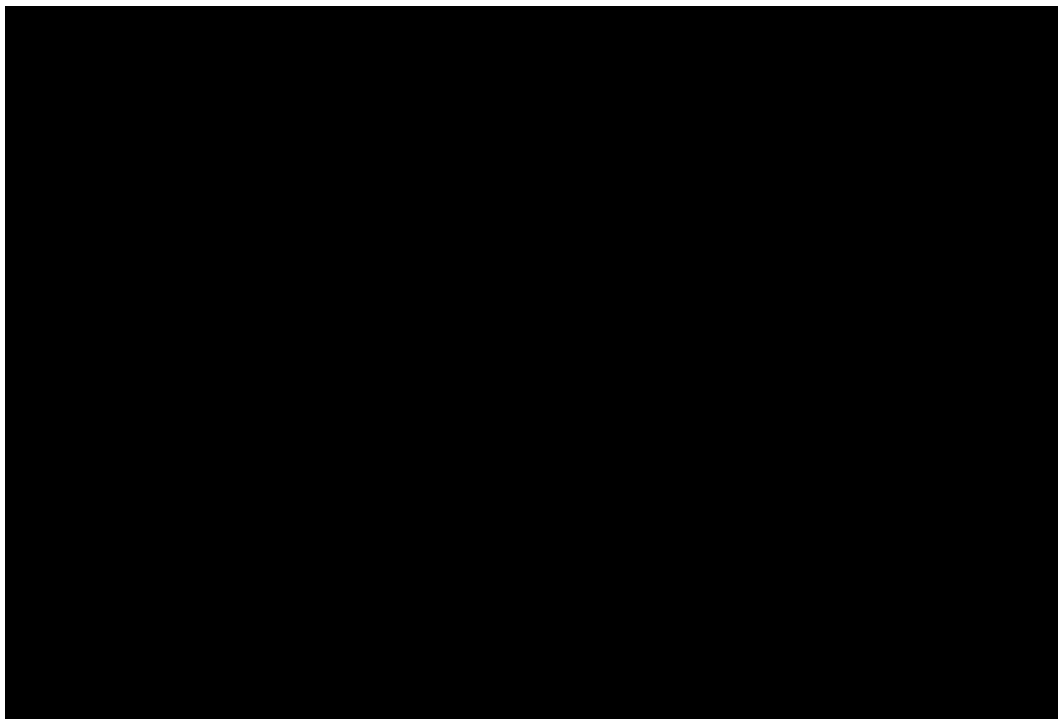
The LDH model in C5 inhibitor-naïve PNH subjects was characterized by indirect inhibition,

[REDACTED]

[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 (10th to 90th percentile) PPK Model-Estimated C_{tau} at 200, 400, and 500 mg BID



Abbreviations: AP = alternative pathway; BID = twice daily; CI = confidence interval; C_{tau} = trough concentration; IC = inhibitory concentration; LDH = lactate dehydrogenase; PK/PD = pharmacokinetic/pharmacodynamic; PPK = population pharmacokinetic(s).

Note: 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.

5.3.5.3. 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]

[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.

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 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 examination, 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, discontinuation of BCX9930 may result in increased risk of hemolysis of PNH RBCs ([Alexion Pharmaceuticals Soliris PI 2020](#), [Alexion Pharmaceuticals Ultomiris PI 2020](#)). Accordingly, subjects who discontinue or interrupt study treatment, whether BCX9930 or C5 inhibitor, may be at increased risk of hemolysis. Subjects should be instructed to immediately contact the investigative site if they miss any BCX9930 (or C5 inhibitor) doses and experience new or worsening symptoms of hemolysis. In addition, subjects who discontinue permanently BCX9930 (or C5 inhibitor therapy) will be monitored for potential hemolysis. Assessments to detect hemolysis should be performed as described in Section [12.5.3.1](#) and Section [10.3.6](#).

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]

[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 conducted 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] [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 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 24 weeks, compared to continued C5 inhibitor therapy, in subjects with PNH with an inadequate response to C5 inhibitor therapy

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 24 weeks, as compared to continued C5 inhibitor therapy, in subjects with PNH
- To characterize the effects of BCX9930 monotherapy, as compared to continued C5 inhibitor therapy, using clinical and laboratory measurements, including complement and thrombosis biomarkers, PNH clone size, and C3-opsonization of RBCs, in subjects with PNH
- To evaluate the effects of BCX9930 monotherapy, as compared to continued C5 inhibitor therapy, 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 over a 28- to 52-week treatment period in subjects with PNH with inadequate response to C5 inhibitor therapy

6.1.4. Part 2 Secondary Objectives

The secondary objectives of Part 2 of this study are:

- To assess the effectiveness of BCX9930 monotherapy in the treatment of PNH over a 28- to 52-week treatment period
- To characterize the effects of BCX9930 monotherapy using clinical and laboratory measurements, including complement and thrombosis biomarkers, PNH clone size, and C3-opsonization of RBCs, in subjects with PNH over a 28- to 52-week treatment period
- To evaluate the effects of BCX9930 monotherapy on FACIT-Fatigue scale and other PROs in subjects with PNH over a 28- to 52-week treatment period

- 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, endpoints will be assessed at or to Week 24. In Part 2, unless indicated otherwise, endpoints will be assessed at or to Week 52. For subjects who are switched from C5 inhibitor therapy to BCX9930 monotherapy at the end of Part 1, Part 2 endpoints will be assessed against Week 24 (ie, Week 52 vs. Week 24).

6.2.1. Part 1 Primary Endpoint

The primary endpoint of Part 1 of this study is:

- CFB in Hb [mean of values at Weeks 12, 16, 20, and 24]

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 24]
2. Number of units of pRBCs transfused [from Week 4 to Week 24]
3. CFB in FACIT-Fatigue scale score [mean of values at Weeks 12, 16, 20, and 24]

6.2.3. Part 1 Other Secondary Endpoints

Other secondary endpoints of Part 1 of this study are:

- Percent CFB in LDH [mean of values at Weeks 12, 16, 20, and 24]
- Percent reduction in the rate of pRBC units transfused [from Week 4 to Week 24 vs. prestudy transfusion rate]
- Proportion of subjects with Hb \geq 12 g/dL [at Week 24]
- 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 24]
- CFB in C3-opsonized RBCs [mean of values at Weeks 12, 16, 20, and 24]
- CFB in total PNH RBC clone size [mean of values at Weeks 12, 16, 20, and 24]
- CFB in ratio of total PNH RBC clone size to PNH WBC clone size (ie, ratio of percent PNH RBCs / percent PNH WBCs) [mean of values at Weeks 12, 16, 20, and 24]
- CFB in absolute reticulocyte count (ARC) [mean of values at Weeks 12, 16, 20, and 24]
- Proportion of subjects with ARC in the normal range [at Week 24]
- CFB in haptoglobin [mean of values at Weeks 12, 16, 20, and 24]

- Proportion of subjects with haptoglobin \geq lower limit of normal reference range (LLN) [at Week 24]
- CFB in total bilirubin [mean of values at Weeks 12, 16, 20, and 24]

6.2.4. Part 1 Exploratory Endpoints

The exploratory endpoints of Part 1 of this study are:

- [REDACTED]
- [REDACTED]
- [REDACTED]

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

Other HRQoL endpoints of Part 1 of this study are:

- Proportion of subjects achieving a within-subject meaningful change for the FACIT-Fatigue scale [at Week 24]
- CFB in QLQ-AA/PNH Physical Functioning and other domain scores [at Week 24]
- 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 [at Week 24]
- CFB in individual PNH symptom items on the modified PRO-AA/PNH [at Week 24]
- CFB in EQ-5D-5L utility and visual analog scale (VAS) scores [at Week 24]
- TSQM scale score [at Week 24]
- 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 24]
- 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 24]

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 28 to 52 for subjects randomized to BCX9930 in Part 1 and mean of values from Weeks 36 to 52 for subjects randomized to continue C5 inhibitor]
- 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 24 to 52 for subjects randomized to BCX9930 in Part 1 and from Weeks 28 to 52 for subjects randomized to continue C5 inhibitor]
- Proportion of subjects who are transfusion-free [from Weeks 24 to 52 for subjects randomized to BCX9930 in Part 1 and from Weeks 28 to 52 for subjects randomized to continue C5 inhibitor]
- Number of units of pRBCs transfused [from Weeks 24 to 52 for subjects randomized to BCX9930 in Part 1 and from Weeks 28 to 52 for subjects randomized to continue C5 inhibitor]
- Percent reduction in the rate of pRBC units transfused [from Weeks 24 to 52 for subjects randomized to BCX9930 in Part 1 and from Weeks 28 to 52 for subjects randomized to continue C5 inhibitor vs. prestudy transfusion rate]
- Percent CFB in LDH [mean of values from Weeks 28 to 52 for subjects randomized to BCX9930 in Part 1 and from Weeks 36 to 52 for subjects randomized to continue C5 inhibitor]

- CFB in ARC [mean of values from Weeks 28 to 52 for subjects randomized to BCX9930 in Part 1 and mean of values from Weeks 36 to 52 for subjects randomized to continue C5 inhibitor]
- Proportion of subjects with ARC in the normal range [at Week 52]
- CFB in haptoglobin [mean of values from Weeks 28 to 52 for subjects randomized to BCX9930 in Part 1 and from Weeks 36 to 52 for subjects randomized to continue C5 inhibitor]
- Proportion of subjects with haptoglobin \geq LLN [at Week 52]
- CFB in C3-opsonized RBCs [mean of values from Weeks 28 to 52 for subjects randomized to BCX9930 in Part 1 and mean of values from Weeks 36 to 52 for subjects randomized to continue C5 inhibitor]
- CFB in total PNH RBC clone size [mean of values from Weeks 28 to 52 for subjects randomized to BCX9930 in Part 1 and mean of values from Weeks 36 to 52 for subjects randomized to continue C5 inhibitor]
- CFB in ratio of total PNH RBC clone size to PNH WBC clone size [mean of values from Weeks 28 to 52 for subjects randomized to BCX9930 in Part 1 and mean of values from Weeks 36 to 52 for subjects randomized to continue C5 inhibitor]

6.2.9. Part 2 Exploratory Endpoints

- [REDACTED]

6.2.10. 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 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 PK/PD 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, active-controlled, open-label, multicenter, parallel-group, 2-part study. Part 1 of the study is designed to evaluate the efficacy, safety, and tolerability of treatment with oral BCX9930 monotherapy for 24 weeks versus continued C5 inhibitor therapy in subjects with PNH with an inadequate response to the C5 inhibitor. Subjects will be randomized to either discontinue C5 inhibitor therapy and start BCX9930 monotherapy or to continue C5 inhibitor therapy for the 24-week randomized treatment period. Part 2 of the study is designed to evaluate the long-term safety and tolerability and effectiveness of BCX9930 monotherapy when administered through Week 52. Subjects who are randomized to BCX9930 monotherapy in Part 1 will continue to receive BCX9930 in Part 2. Subjects who are randomized to C5 inhibitor therapy in Part 1 will discontinue that therapy at the Week 24 visit and start BCX9930 in Part 2.

Data collected through Week 24 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 24.

Part 1: 24-week, randomized, open-label evaluation of efficacy, safety, and tolerability of BCX9930 monotherapy versus continued C5 inhibitor therapy

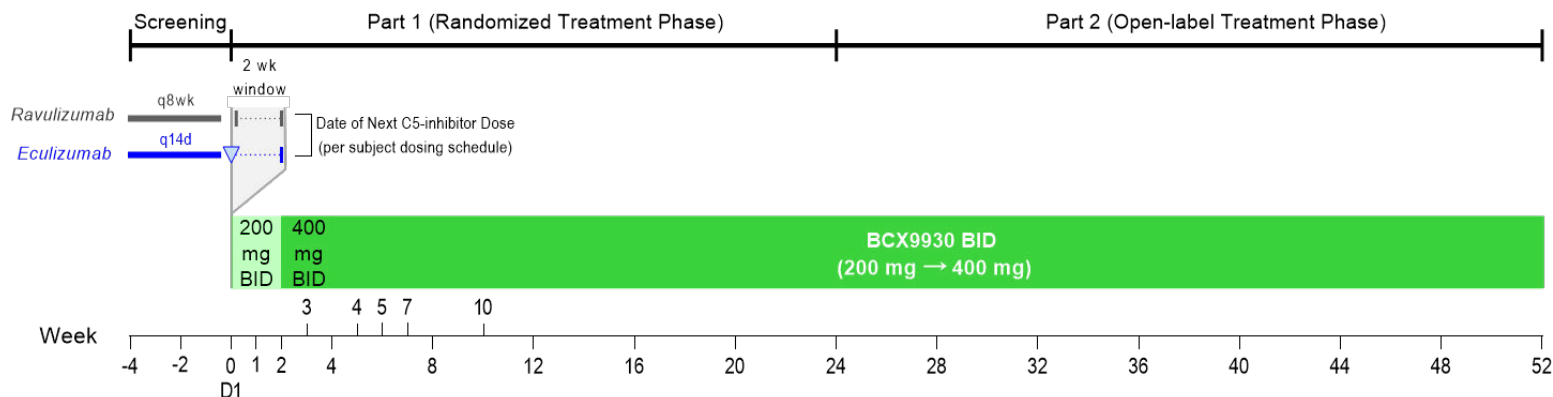
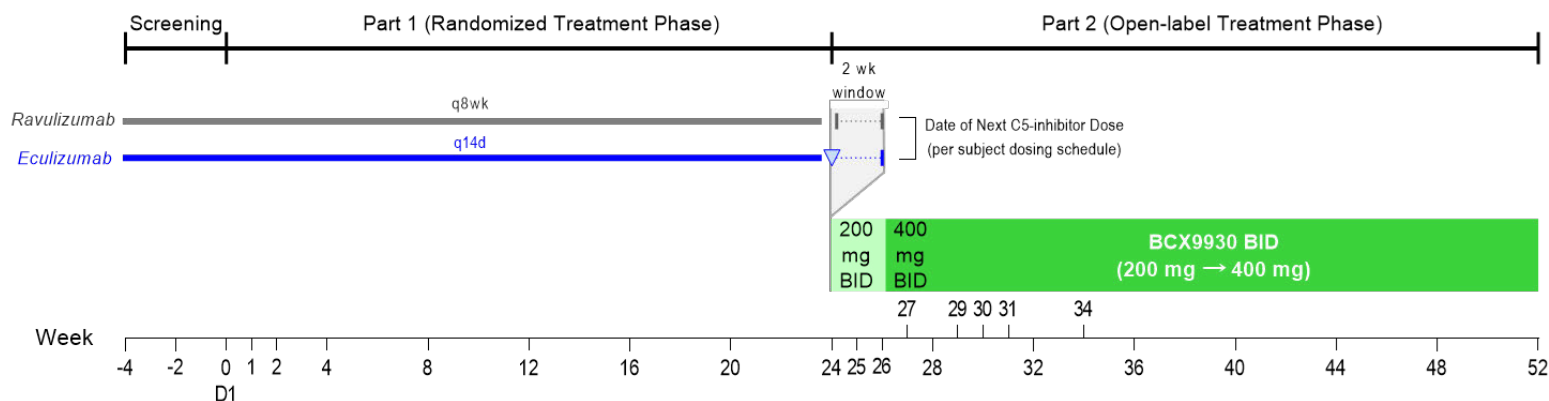
Patients with PNH who have been treated with a stable regimen of eculizumab for ≥ 3 months or ravulizumab for ≥ 6 months and who have had an inadequate response to that therapy may be screened for this study. Following confirmation of study eligibility, Day 1 will be scheduled such that it occurs on or within 2 weeks prior to the date that the subject is scheduled to receive the next dose of eculizumab, or within 2 weeks prior to the date on which the subject is scheduled to receive the next dose of ravulizumab, as applicable (see the study schema shown in [Figure 3](#)). On that day, after completion of all baseline procedures, subjects randomized to BCX9930 monotherapy will receive the first dose of BCX9930 administered under the supervision of clinic staff, with the second dose administered later that day. Subsequent doses of BCX9930 are taken BID, approximately 12 hours apart, through Week 24. For subjects randomized to continue C5 inhibitor therapy, Day 1 may be scheduled at any time within the 2 weeks prior to the next dose of the C5 inhibitor. All subjects will be required to return to the clinic at Weeks 1, 2, and 4,

and every 4 weeks thereafter through Week 24. Subjects randomized to BCX9930 will be required to complete additional safety assessments at Weeks 3, 5, 6, 7, and 10.

Part 2: 28-week open-label evaluation of the long-term safety, tolerability, and effectiveness of BCX9930 monotherapy

Subjects randomized to continue C5 inhibitor therapy during Part 1 will be switched to BCX9930 monotherapy in Part 2. The timing of the final dose of the C5 inhibitor on or prior to Week 24 will be determined by the dose schedule for each individual subject. These subjects will be required to return to the clinic at Weeks 25, 26, 28, 32, and 36, and every 4 weeks thereafter through Week 52. Additional safety assessments will be performed at Weeks 27, 29, 30, 31, and 34. Subjects randomized to BCX9930 monotherapy in Part 1 will continue with the every 4 weeks visit schedule, ie, omitting the visits at Weeks 25 and 26, returning to the clinic at Week 28 and every 4 weeks thereafter through Week 52.

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. Subsequently, they will return to the clinic approximately 3 weeks after the date of last dose of BCX9930 for end of study assessments.

Figure 3: BCX9930-202 Study Schema (Parts 1 and 2)**A. Subjects Randomized to BCX9930****B. Subjects Randomized to Continue C5 Inhibitor Therapy**

Abbreviations: BID = twice daily; D1 = Day 1; q8wk = every 8 weeks; q14d = every 14 days.

Note: First dose of BCX9930 administered (1) within 2 weeks prior to the next scheduled dose of ravulizumab, or (2) on or within 2 weeks prior to the next scheduled dose of eculizumab. Subjects will not receive their next scheduled dose of C5 inhibitor (exception: subjects receiving eculizumab may receive their final dose on the day they initiate BCX9930 if scheduled for that day (blue triangle). 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) for as long as enhanced safety monitoring procedures are required.

7.2. Number of Subjects

This study will enroll approximately 81 subjects with PNH and an inadequate response to C5 inhibitor therapy. In Part 1 of this study, approximately 54 subjects will be randomized to discontinue C5 inhibitor therapy and start BCX9930 200/400 mg monotherapy and approximately 27 subjects will be randomized to continue C5 inhibitor therapy.

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 either discontinue C5 inhibitor therapy and start BCX9930 monotherapy or to continue C5 inhibitor therapy through Week 24:

- BCX9930 to be administered orally BID (experimental arm)
- OR
- Continuation of current C5 inhibitor therapy (control arm)

Randomization will be stratified based on each subject's current C5 inhibitor (ravulizumab vs. eculizumab) and receipt of a pRBC transfusion within the 6 months prior to baseline (yes vs. no).

In Part 2, all subjects will receive BCX9930 monotherapy:

- BCX9930 to be administered orally BID (experimental arm)

7.4. Individual and Study Termination Criteria

7.4.1. Subject Withdrawal from Study Treatment

Subjects randomized to continue C5 inhibitor therapy will be managed according to local or institutional practice guidelines, and which the investigator prescribes as being in the best interests of the subject.

A subject will be permanently discontinued from BCX9930 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 (serum glutamic-pyruvic transaminase [SGPT]) $> 3 \times \text{ULN}$ (confirmed by repeat testing) combined with either:
 - laboratory abnormalities indicative of significant hepatic toxicity (ie, meeting Hy's law, total bilirubin $> 2 \times \text{ULN}$ 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 BCX9930AND
 - without clinical and/or laboratory evidence of hemolysis or any other potential alternative etiology.- Treatment-emergent increase in sCr $\geq 3 \times \text{ULN}$ (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 of BCX9930 (or C5 inhibitor) 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 discontinue complement inhibition (ie, BCX9930 or C5 inhibitor) for any reason (other than protocol-mandated cessation of C5 inhibitor on Day 1 or Week 24, as applicable) will be monitored for hemolysis as described in Section 12.5.3 and Section 10.3.6.

7.4.2. 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 $\geq 10\%$ during screening.
4. Treated with a stable regimen of eculizumab for ≥ 3 months prior to the screening visit or ravulizumab for ≥ 6 months prior to the screening visit.
5. Recorded the following results during screening:
 - a. Hb of ≤ 105 g/L (≤ 10.5 g/dL).
 - b. ARC of $\geq 100 \times 10^9$ cells/L ($\geq 100,000$ cells/ μ L; ≥ 100 G/L).
 - c. Absolute neutrophil count of $\geq 0.75 \times 10^9$ cells/L (≥ 750 cells/ μ L; ≥ 0.75 G/L).
 - d. Platelet count of $\geq 30 \times 10^9$ /L ($\geq 30,000$ / μ L; ≥ 30 G/L).
 - e. Adequate iron reserve based on ferritin \geq LLN or total iron binding capacity \leq ULN.
 - f. eGFR of ≥ 60 mL/min/1.73 m² using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation ([Levey and Stevens 2010](#)) and no evidence of clinically relevant abnormal renal function unrelated to underlying PNH disease.
6. Contraception requirements:

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

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

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

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

Additional details are provided in Section 11.2.1.

7. 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.)
8. In the opinion of the investigator, the subject is expected to adequately comply with all required study procedures and restrictions for the study, including compliance with the BID dosing schedule for BCX9930.
9. 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 supplementation 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 of QTcF > 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 7.4.1. 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 (or C5 inhibitor) 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 10.3.6 and Section 10.3.8, respectively.

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

Subjects are not eligible for treatment with BCX9930 in Part 2 if they discontinue study treatment in Part 1.

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 other 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

9.1.1. BCX9930

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.

BCX9930 tablets contain the active ingredient blended with the [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.

Additional details of the chemical and physical characteristics of BCX9930 may be found in the IB for BCX9930 and the investigational medicinal product (IMP) manual for the study.

9.1.2. Eculizumab or Ravulizumab

Eculizumab and ravulizumab are humanized, anti-C5 monoclonal antibodies.

Eculizumab is an IgG2/4 kappa immunoglobulin consisting of human constant regions, and murine complementarity-determining regions grafted onto human framework light- and heavy-chain variable regions. Eculizumab is composed of two 448 amino acid heavy chains and two 214 amino acid light chains.

Ravulizumab was designed through minimal targeted engineering of eculizumab by introducing 4 unique amino acid substitutions to its heavy chain to extend antibody half-life.

See the relevant prescribing information, product monograph, or summary of product characteristics for a more detailed description of Soliris (eculizumab) or Ultomiris (ravulizumab) ([Alexion Pharmaceuticals Soliris PI 2020](#), [Alexion Pharmaceuticals Ultomiris PI 2020](#)).

Where required by local regulation, provision of C5 inhibitor therapies will be coordinated by the sponsor in accordance with local practice.

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

9.2.1. BCX9930

BCX9930 tablets will be packaged in an appropriate size bottle. Each bottle 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 BCX9930 tablets should be stored at 15°C to 25°C (59°F to 77°F).

Additional details on the packaging, labeling, shipment, storage, and dispensing of BCX9930 tablets will be provided in the IMP manual for the study.

9.2.2. Eculizumab

Soliris (eculizumab) drug product is supplied as 300 mg single-use vials containing 30 mL of 10 mg/mL solution per vial.

Soliris vials must be stored in the original carton until time of use under refrigerated conditions at 2°C to 8°C (36°F to 46°F).

See the relevant prescribing information, product monograph, or summary of product characteristics for any updates.

9.2.3. Ravulizumab

Ultomiris (ravulizumab-cwvz) drug product is supplied as single-use vials containing 300 mg/30 mL (10 mg/mL), 300 mg/3 mL (100 mg/mL), or 1,100 mg/11 mL (100 mg/mL) solution per vial.

Ultomiris vials should be refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light. Do not freeze. Do not shake.

See the relevant prescribing information, product monograph, or summary of product characteristics for any updates.

9.3. Randomization and Blinding of Study Treatment**9.3.1. Blinding**

This is an open-label study; no study treatments (ie, BCX9930 or C5 inhibitor in Part 1 and BCX9930 in Part 2) will be blinded or masked.

9.3.2. Randomization

In Part 1 of the study, approximately 81 subjects will be randomized in a 2:1 ratio to either discontinue C5 inhibitor therapy and start BCX9930 monotherapy or to continue C5 inhibitor therapy through Week 24. Randomization for individual subjects will occur prior to Day 1 after completion of all screening procedures and confirmation of study eligibility.

Randomization will be stratified based on C5 inhibitor (ravulizumab vs. eculizumab) and whether a pRBC transfusion was received within the 6 months prior to baseline (yes vs. no). Thus, there will be 4 strata as shown below.

Stratum No.	Stratum Description
1	Treated with eculizumab, received pRBC transfusion within previous 6 months
2	Treated with eculizumab, did not receive pRBC transfusion within previous 6 months
3	Treated with ravulizumab, received pRBC transfusion within previous 6 months
4	Treated with ravulizumab, did not receive pRBC transfusion within previous 6 months

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

9.4. Study Drug Administration

9.4.1. BCX9930

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 who are 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. The appropriate quantity of BCX9930 tablets will be taken orally, twice a day, at approximately the same times (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 tablets will be taken from the provided bottles.

Subjects will be dispensed a sufficient number of bottles and BCX9930 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, when possible). Accountability and adherence will be reviewed at these visits.

9.4.2. Continued C5 Inhibitor Therapy

Soliris (eculizumab) for injection and Ultomiris (ravulizumab) for injection are each administered via continuous IV infusion after dilution to a final admixture concentration in an appropriate diluent; see the relevant prescribing information, product monograph, or summary of product characteristics for additional details.

For subjects randomized to continue C5 inhibitor therapy, the same prescribed dose regimen of eculizumab or ravulizumab that the subject was receiving at screening will be maintained during Part 1 of the study.

Administration of the C5 inhibitor infusions may be scheduled to occur during study visits if consistent with the subject's regular infusion schedule. However, subjects who receive their infusions outside of the clinic, eg, at an infusion center or at home, may continue to do so. Additional clinic visits needed to accommodate an individual's C5 inhibitor infusion schedule that fall outside of the time window for a scheduled study visit will not be considered a study visit. In this case, subjects will need to return to the clinic to complete the study visit within the indicated time window.

While continuing therapy with eculizumab or ravulizumab in Part 1, subjects should be managed according to local or institutional practice guidelines, and which are in the best interests of the subject.

9.4.3. 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 12.5.3.1. 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 9.4.4 for potential dose reduction options.

9.4.4. Dose Tapering

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

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[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

For subjects randomized to discontinue C5 inhibitor therapy and initiate treatment with BCX9930, the first dose of BCX9930 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 overall 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. Participants are expected to have become accustomed to life receiving IV infusions administered by others at approximately 2- or 8-week intervals. Once enrolled in this study and randomized to BCX9930 in Part 1, or after transitioning to BCX9930 therapy in Part 2, each participant will need to be responsible for taking BCX9930 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 BCX9930 to clinic visits, including any unscheduled visit to assess for potential hemolysis, when possible. Investigators should remind participants who regularly miss doses of BCX9930 about the importance of treatment compliance.

9.6. Missed Doses and Special Considerations for Dosing

If BCX9930 needs to be withheld (eg, to assess a potentially drug-related TEAE), consideration for potential hemolysis as described in Section 12.5.3.1 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 12.5.3.1).

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

It is imperative that study subjects take study drug 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 redosed (ie, take two new tablets) if the intact tablets or pieces of the tablets are seen in the vomitus (vomit contents).

Please refer also to the IMP manual for specific instructions.

9.7. Study Drug Accountability

Accountability of BCX9930 dispensed and returned (as applicable) will be performed at Day 1 and at each subsequent study visit (including at unscheduled visits, when 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.

9.7.1. C5 Inhibitors

In jurisdictions in which the sponsor is required to supply or reimburse for the C5 inhibitor, appropriate drug accountability requirements will be performed.

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 24 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 (see 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.

9.8.1.1. Prohibited and Restricted Medications for Subjects Receiving BCX9930

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 in anticipation of potential randomization to the BCX9930 treatment arm. In addition, 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. Subjects randomized to continue C5 therapy may restart any prohibited medications after randomization. The same process will need to be repeated for subjects randomized to continue C5 therapy prior to the transition to treatment with BCX9930 at the Week 24 visit.

Use of the following medications is currently excluded while subjects are receiving treatment with BCX9930, beginning 7 days prior to Day 1 (or the Week 24 visit for subjects randomized to continue C5 inhibitor therapy), as is the planned initiation of treatment with such medications during the study:

- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]

- [REDACTED]
- [REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[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 guidance, 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 guidance, 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]
[REDACTED]
[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.

9.8.1.2. Prohibited and Restricted Medications for Subjects Randomized to Continue C5 Inhibitor Therapy in Part 1

Subjects randomized to continue C5 inhibitor therapy should follow any restrictions or prohibitions per the relevant prescribing information for that product.

For Part 2, the same prohibitions and restrictions on the use of concomitant medications described above for subjects randomized to BCX9930 must be followed, with prohibited

medications discontinued beginning 7 days prior to planned administration of the first dose of BCX9930, and have an agreed plan in place for monitoring and/or dose adjustment of any restricted medications that will be continued post Week 24.

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, 24-week treatment period, subjects will be randomized to either discontinue C5 inhibitor therapy and start BCX9930 monotherapy or to continue that C5 inhibitor therapy through Week 24. In the second, 28-week treatment period, subjects who are randomized to BCX9930 monotherapy in Part 1 will continue to receive BCX9930, while those subjects who are randomized to continue C5 inhibitor therapy in Part 1 will discontinue that therapy at the end of the first 24 weeks and start BCX9930 monotherapy 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 16 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 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). Subjects who are randomized to continue C5 inhibitor treatment will complete two additional visits at Week 25 (Day 176) and Week 26 (Day 183). Additional visits will be required for subjects who experience acute symptomatic hemolysis on-study and/or who require additional post-treatment hemolysis assessment, or who require unscheduled visits for additional or repeat evaluations.

Additional safety assessments will be required as part of the renal and hepatic safety monitoring program for all subjects when they initiate treatment with BCX9930, ie, Weeks 3, 5, 6, 7, and 10 for subjects randomized to BCX9930 and Weeks 27, 29, 30, 31, and 34 for subjects randomized to continue C5 inhibitor therapy 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 4](#) and for Part 2 in [Table 5](#).

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 4: Study BCX9930-202: Part 1 Schedule of Study Assessments/Procedures (Screening to Week 24)

Assessment/ Procedure	Screening (D-28 to D-1) ^a	Baseline ^b D1	Part 1 Treatment (Study Week/Day ^c)													Unscheduled Visit (including for hemolysis assessment) ^d	ET ^e
			Wk1 / D8	Wk2 / D15	Wk3 / D22	Wk4 / D29	Wk5 / D36	Wk6 / D43	Wk7 / D50	Wk8 / D57	Wk10 / D71	Wk12 / D85	Wk16 / D113	Wk20 / D141	Wk24 / D169		
Site visit	X	X	X	X		X				X		X	X	X	X		X
Site visit or remote assessment ^f					X		X	X	X		X					X	
Written informed consent ^g	X																
Review eligibility criteria	X	X															
Demographics	X																
Medical & medication history ^h	X	X															
Height, body weight & BMI ⁱ	X	X				X				X		X	X	X	X		X
Physical examination ^j	X	X	X	X		X				X		X	X	X	X	X	X
12-lead ECG ^k	X	X	X	X		X				X		X	X	X	X		X
Vital signs ^l	X	X	X	X	<u>X</u>	X	<u>X</u>	<u>X</u>	<u>X</u>	X	<u>X</u>	X	X	X	X	X	X
Hematology	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
Urinalysis including microscopy ^m	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
Drugs of abuse screen	X																
Pregnancy test ⁿ	X	X				X				X		X	X	X	X		X
FSH ^o	X																
HBV, HCV, HIV, VZV testing ^p	X																

Assessment/ Procedure	Screening (D-28 to D-1) ^a	Baseline ^b D1	Part 1 Treatment (Study Week/Day ^c)													Unscheduled Visit (including for hemolysis assessment) ^d	ET ^e
			Wk1 / D8	Wk2 / D15	Wk3 / D22	Wk4 / D29	Wk5 / D36	Wk6 / D43	Wk7 / D50	Wk8 / D57	Wk10 / D71	Wk12 / D85	Wk16 / D113	Wk20 / D141	Wk24 / D169		
Urine for urinary biomarkers ^q		X	X	X	<u>X</u>	X	<u>X</u>	<u>X</u>	<u>X</u>	X	<u>X</u>	X	X	X	X	X	X
PRO questionnaires ^r																	
FACIT-Fatigue scale		X		X		X				X		X	X	X	X		
QLQ-AA/PNH		X				X				X		X	X	X	X		
Modified PRO-AA/PNH		X	X	X		X				X		X			X		
TSQM						X						X			X		
EQ-5D-5L		X													X		
PGIS-Fatigue/Impact of Fatigue/ Physical Functioning		X													X		
PGIC-Fatigue/Impact of Fatigue/ Physical Functioning															X		
Iron assessments ^s	X	X													X		X
PK blood sample collection ^t			X	X	<u>X</u>	X	<u>X</u>	<u>X</u>	<u>X</u>	X	<u>X</u>	X	X	X	X	X	X
PD blood sample collection ^u	X	X	X	X		X				X		X	X	X	X	X	X
Optional PK/PD substudy ^v		X															
PK urine collection ^w			X	X	<u>X</u>	X	<u>X</u>	<u>X</u>	<u>X</u>	X	<u>X</u>	X	X	X	X	X	X
Randomization ^x		X															
BCX9930 dispensing ^y		X		X		X				X		X	X	X	X		
Drug accountability			X	X		X				X		X	X	X	X	X	X
Record AEs, concomitant medications & transfusions ^z																	

Abbreviations: AE = adverse event; BID = twice daily; BMI = body mass index; C5 = complement component 5; 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); 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; 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 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.
- ^b The baseline visit will be scheduled on or within 2 weeks prior to the date that the subject is scheduled to receive the next dose of eculizumab or within 2 weeks prior to the date on which the subject is scheduled to receive the next dose of ravulizumab, as applicable.
- ^c Visits may be performed within a window of ± 1 day for Week 1 and Week 2, and ± 3 days thereafter.
- ^d 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.
- ^e Subjects who discontinue the study for any reason will be asked to complete an ET visit approximately 3 weeks (± 3 days) after last dose of BCX9930 (or the decision to discontinue the study for subjects randomized to continue C5 inhibitor therapy).
- ^f Subjects randomized to BCX9930 will be 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.
- ^g 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.
- ^h 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.
- ⁱ Body weight will be captured at all assessments; height will be measured and BMI calculated at screening only.
- ^j 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.
- ^k Bedside 12-lead ECGs will be conducted in triplicate pre-dose on Day 1 for all subjects, and at Week 24 for subjects randomized to continue C5 inhibitor before the first dose of BCX9930 is administered; 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.
- ^l 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.
- ^m Urine microscopy will be performed on urine collected at investigational site visits (and, where possible, at remote visits where the lab has appropriate on-site testing capability). Urine microscopy should be performed using the site's local laboratory (assuming appropriate on-site testing capability exists) in lieu of the central laboratory.

- ⁿ 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.
- ^o FSH will be measured at screening to confirm postmenopausal state in women who report being postmenopausal for < 2 years.
- ^p 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.
- ^q Urine will be collected at investigational site visits (ie, excluding remote visits) and aliquots frozen for possible future analysis of urine biomarkers.
- ^r 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.
- ^s Iron, ferritin, iron binding capacity, vitamin B₁₂, and folate levels will be measured at screening. At baseline (Day 1), Week 24, and any ET visit performed, blood samples will be drawn for assessment of iron, total iron binding capacity, transferrin, ferritin, hepcidin, and erythroferrone at baseline and Week 24; urine collected at baseline and Week 24 will be analyzed for hemosiderin.
- ^t Single venous blood samples for analysis of plasma BCX9930 concentration will be collected from all subjects randomized to BCX9930 at each scheduled study visit, beginning Week 1, and at any unscheduled visits to the investigational site to assess for acute symptomatic hemolysis or perform additional safety assessments. The blood sample may be drawn without regard to BCX9930 dosing. PK samples will not be collected from subjects randomized to continue C5 inhibitor therapy, unless participating in the optional PK/PD substudy.
- ^u 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.
- ^v For subjects randomized to BCX9930 who participate in the optional PK/PD substudy, additional blood samples for analysis of plasma BCX9930 concentration will be drawn on Day 1 and at Week 2 or a later visit. For subjects randomized to continue C5 inhibitor therapy, additional blood samples will be collected at Week 24 only. In addition, where possible, additional blood samples for analysis of PD and clinical laboratory biomarkers will be drawn at each substudy visit. See Section 11.5.1.1 for additional details of the PK/PD substudy.
- ^w Spot urine samples will be collected for analysis of the concentration of BCX9930 and metabolites at investigational site visits (ie, excluding remote visits). PK samples will not be collected from subjects randomized to continue C5 inhibitor therapy.
- ^x Subjects will be randomized to receive BCX9930 or continue C5 inhibitor therapy using an IWRS prior to the planned baseline (Day 1) visit.
- ^y For subjects randomized to BCX9930 monotherapy, the first dose of BCX9930 will be administered in the clinic under the supervision of staff after completion of all pre-dose procedures. At the initiation of BCX9930 dosing, subjects will be administered a dose of 200 mg BID for the first 14 days of treatment before increasing to 400 mg BID. BCX9930 doses will be administered orally, approximately 12 hours apart and at approximately the same times each day, without regard to food. Subjects randomized to continue C5 inhibitor therapy will continue on that therapy at the same dosing regimen through the Week 24 visit. At the Week 24 visit, subjects will be transitioned to BCX9930 monotherapy.
- ^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 5: Study BCX9930-202: Part 2 Schedule of Study Assessments/Procedures (Weeks 25 to 52)

Assessment/Procedure	Part 2 Treatment (Study Week/Day ^a)														Unscheduled Visit (including for hemolysis assessment) ^b	EOS/ ET ^c
	Wk25 / D176 ^d	Wk26 / D183 ^d	Wk27 / D190	Wk28 / D197	Wk29 / D204	Wk30 / D211	Wk31 / D218	Wk32 / D225	Wk34 / D239	Wk36 / D253	Wk40 / D281	Wk44 / D309	Wk48 / D337	Wk52 / D365		
Site visit	X	X		X				X		X	X	X	X	X		X
Site visit or remote assessment ^e			X		X	X	X		X						X	
Body weight				X				X		X	X	X	X	X		X
Physical examination ^f	X	X		X				X		X	X	X	X	X	X	X
12-lead ECG ^g	X	X		X				X		X	X	X	X	X		X
Vital signs ^h	X	X	<u>X</u>	X	<u>X</u>	<u>X</u>	<u>X</u>	X	<u>X</u>	X	X	X	X	X	X	X
Hematology	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
Urinalysis including microscopy ⁱ	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
Pregnancy test ^j				X				X		X	X	X	X	X		X
Urine for biomarkers ^k	X	X	<u>X</u>	X	<u>X</u>	<u>X</u>	<u>X</u>	X	<u>X</u>	X	X	X	X	X	X	X
PRO questionnaires ^l																
FACIT-Fatigue scale		X		X				X		X	X	X	X	X		
QLQ-AA/PNH				X				X		X	X	X	X	X		
Modified PRO-AA/PNH	X	X		X				X		X			X	X		
TSQM				X						X				X		

Assessment/Procedure	Part 2 Treatment (Study Week/Day ^a)														Unscheduled Visit (including for hemolysis assessment) ^b	EOS/ ET ^c
	Wk25 / D176 ^d	Wk26 / D183 ^d	Wk27 / D190	Wk28 / D197	Wk29 / D204	Wk30 / D211	Wk31 / D218	Wk32 / D225	Wk34 / D239	Wk36 / D253	Wk40 / D281	Wk44 / D309	Wk48 / D337	Wk52 / D365		
EQ-5D-5L														X		
PGIS-Fatigue/Impact of Fatigue/ Physical Functioning														X		
PGIC-Fatigue/Impact of Fatigue/ Physical Functioning														X		
Iron assessments ^m														X		X
PK blood collection ⁿ	X	X	<u>X</u>	X	<u>X</u>	<u>X</u>	<u>X</u>	X	<u>X</u>	X	X	X	X	X	X	
PK urine collection ^o	X	X	<u>X</u>	X	<u>X</u>	<u>X</u>	<u>X</u>	X	<u>X</u>	X	X	X	X	X	X	
PD blood collection ^p	X	X		X				X		X	X	X	X	X	X	X
Optional PK/PD study ^q																
BCX9930 dispensing ^r	X	X		X				X		X	X	X	X	X		
Drug accountability	X	X		X				X		X	X	X	X	X	X	X
Record AEs, concomitant medications & transfusions ^s																

Abbreviations: AE = adverse event; BID = twice daily; ECG = electrocardiogram; EOS/ET = end-of-study/early termination; EQ-5D-5L = EuroQoL 5-dimension, 5-level; 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; 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 only at visits to investigational site.

^a Visits may be performed within a window of ± 1 day for Week 25 and Week 26, 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, approximately 3 weeks (\pm 3 days) after last dose of BCX9930.
- ^d Subjects switched to BCX9930 for Part 2 will be required to complete additional investigational site visits at Weeks 25 and 26.
- ^e Subjects switched to BCX9930 for Part 2 will be required to complete additional laboratory assessments for enhanced 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.
- ^f Abbreviated (ie, symptom-driven) physical examinations, targeted to new or worsening signs and symptoms.
- ^g 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.
- ^h 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.
- ⁱ Urine microscopy will be performed on urine collected at investigational site visits (and, where possible, at remote visits where the lab has appropriate on-site testing capability). Urine microscopy should be performed using the site's local laboratory (assuming appropriate on-site testing capability exists) in lieu of the central laboratory.
- ^j 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.
- ^k Urine will be collected at investigational site visits and aliquots frozen for possible future analysis of urine biomarkers.
- ^l 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.
- ^m At Week 52, and at any EOS/ET visit performed, blood samples will be drawn for assessment of iron, total iron binding capacity, transferrin, ferritin, hepcidin, and erythroferrone; urine will be analyzed for hemosiderin.
- ⁿ 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.
- ^o Spot urine samples will be collected for analysis of the concentration of BCX9930 and metabolites at investigational site visits only (ie, excluding remote visits).
- ^p Blood samples for analysis of clinical laboratory biomarkers will be collected at each study visit from all subjects, including any visit to assess for acute symptomatic hemolysis.
- ^q For subjects previously randomized to continue C5 inhibitor therapy who participate in the optional PK/PD substudy, additional blood samples for analysis of plasma BCX9930 concentration will be drawn during the Week 26 or any later visit. In addition, where possible, time-matched blood samples for analysis of PD and clinical laboratory biomarkers will be collected at the same timepoints as the PK samples. See Section 11.5.1.1 for additional details of the PK/PD substudy.
- ^r For subjects randomized to continue C5 inhibitor therapy in Part 1 and newly switched to BCX9930 for Part 2, BCX9930 will be administered a dose of 200 mg BID for the first 14 days of treatment before increasing to 400 mg BID. Subjects randomized to BCX9930 in Part 1 will continue BCX9930 400 mg BID. BCX9930 doses will be administered orally, approximately 12 hours apart and at approximately the same times each day, without regard to food.

^s 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

Unless indicated otherwise, all subjects are expected to complete all scheduled study assessments/procedures, regardless of treatment assignment.

10.3.1. Screening

Subjects with PNH who have been treated with C5 inhibitor therapy and who have had an inadequate response to that therapy, based on ongoing residual anemia, 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.

For subjects who are being treated with ravulizumab, which requires infusions to be administered at approximately 8-week intervals, screening and randomization should be scheduled to allow the baseline (Day 1) visit to be performed in the 2 weeks prior to administration of the next scheduled ravulizumab dose. For subjects who are being treated with eculizumab, with infusions administered at approximately 2-week intervals, screening and randomization should be timed to allow the baseline (Day 1) visit to be performed on or within 2 weeks prior to the date that the subject is scheduled to receive the next dose of eculizumab. It is acceptable for subjects to receive another dose of eculizumab before randomization to avoid limiting the screening window to 14 days.

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

- Obtain written 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 4](#) and [Table 7](#)):
 - Blood for hematology, clinical chemistry (including haptoglobin), coagulation testing, and iron, ferritin, total iron binding capacity, folate, and vitamin B₁₂
 - 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 4](#) and [Table 7](#)):
 - 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)

Subjects should be qualified for the study in time to allow the Day 1 visit to be scheduled no earlier than 2 weeks prior to the date on which the subject is due to receive the next scheduled dose of his or her current C5 inhibitor treatment. 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, 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 (including C5 and other complement inhibitors) 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 4](#) and [Table 7](#)):
 - 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 for subjects randomized to BCX9930 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/PD 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 4](#) and [Table 7](#)):
 - 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)
- Review/record AEs since screening visit
- Record any blood transfusions administered since the screening visit

After completion of all baseline procedures, subjects randomized to BCX9930 monotherapy will receive the first dose of BCX9930 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, 12, 16, 20, and 24

In Part 1, all subjects will return to the clinic during Week 1 (Day 8 \pm 1 day), Week 2 (Day 15 \pm 1 day), Week 4 (Day 29 \pm 3 days), Week 8 (Day 57 \pm 3 days), Week 12 (Day 85 \pm 3 days), Week 16 (Day 113 \pm 3 days), Week 20 (Day 141 \pm 3 days), and Week 24 (Day 169 \pm 3 days).

Subjects randomized to BCX9930 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 or the subject is participating in 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 2, 4, 8, 12, 16, 20, and 24
 - QLQ-AA/PNH at Weeks 4, 8, 12, 16, 20, and 24
 - Modified PRO-AA/PNH at Weeks 1, 2, 4, 8, 12, and 24
 - TSQM at Weeks 4, 12, and 24
 - EQ-5D-5L at Week 24
 - PGIS-Fatigue, PGIS-Impact of Fatigue, PGIS-Physical Functioning at Week 24
 - PGIC-Fatigue, PGIC-Impact of Fatigue, PGIC-Physical Functioning at Week 24
- 12-lead ECG (single ECGs, except at Week 24 for subjects randomized to continue C5 inhibitor for Part 1, when triplicate ECGs are required)
- Targeted physical examination
- Body weight at Weeks 4, 8, 12, 16, 20, and 24
- Vital signs (resting blood pressure and pulse rate, and temperature)

- Blood collection for clinical laboratory evaluations (see [Table 4](#) and [Table 7](#)):
 - Blood for hematology, clinical chemistry (including haptoglobin), and coagulation testing
 - Blood for iron, total iron binding capacity, transferrin, ferritin, hepcidin, and erythroferrone at Week 24
- Blood collection for PK. A single sample will be collected on each visit for subjects receiving BCX9930 unless the subject is participating in the optional PK/PD substudy. If participating in the PK substudy, a total of 4 or 5 samples will be drawn over an approximately 6-hour period at the selected substudy visit as described in [Section 11.5.1.1](#) (Week 2 or later for subjects randomized to BCX9930 or at Week 24 for subjects randomized to continue C5 inhibitor).
- 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 PK/PD substudy visit as described in [Section 11.5.1.1](#) (Week 2 or later for subjects randomized to BCX9930 or at Week 24 for subjects randomized to continue C5 inhibitor).
- Blood collection for [REDACTED]
- Urine collection for clinical laboratory evaluations (see [Table 4](#) and [Table 7](#)):
 - Urinalysis including microscopy
 - Urine collection for biomarker testing
 - Urine collection for hemosiderin at Week 24
- Urine collection for PK for subjects randomized to BCX9930
- Urine pregnancy test for female subjects of childbearing potential (or as required by local or institutional practice) at Weeks 4, 8, 12, 16, 20, and 24. A negative pregnancy test result must be recorded in order for the subject to continue receiving BCX9930.
- Study drug dispensing and drug accountability review (all visits for subjects randomized to BCX9930 and at Week 24 only for subjects randomized to continue C5 inhibitor therapy)
- Review/record AEs, concomitant medication use, including prohibited and restricted medications, and blood transfusions

At Week 24, subjects who were randomized to continue C5 therapy will receive the first dose of BCX9930 administered under the supervision of clinic staff. The timing of the final dose of the C5 inhibitor on or prior to Week 24 will be determined by the dose schedule for each individual subject. Subjects participating in the optional PK substudy will remain in the clinic for approximately 6 hours post-dose to allow for the collection of the additional post-dose PK blood samples as described in [Section 11.5.1.1](#).

10.3.5. On-study Visits for Part 2: Weeks 25, 26, 28, 32, 36, 40, 44, 48, and 52

In Part 2, all subjects will return to the clinic during 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 who are randomized to continue C5 inhibitor treatment in Part 1 will complete two additional visits at Week 25 (Day 176 ± 1 day) and Week 26 (Day 183 ± 1 day). The Week 25 and Week 26 visits do not need to be completed by subjects randomized to BCX9930 monotherapy in Part 1.

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 (* = only subjects randomized to C5 inhibitor therapy in Part 1)

- 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 26*, 28, 32, 36, 40, 44, 48, and 52
 - QLQ-AA/PNH at Weeks 28, 32, 36, 40, 44, 48, and 52
 - Modified PRO-AA/PNH at Weeks 25*, 26*, 28, 32, 36, 48, and 52
 - TSQM at Weeks 28, 36, and 52
 - EQ-5D-5L at Week 52
 - PGIS-Fatigue, PGIS-Impact of Fatigue, PGIS-Physical Functioning at Week 52
 - PGIC-Fatigue, PGIC-Impact of Fatigue, PGIC-Physical Functioning at Week 52
- 12-lead ECG
- Targeted physical examination
- Body weight at Weeks 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 5](#) and [Table 7](#)):
 - Blood for hematology, clinical chemistry (including haptoglobin), and coagulation testing
 - Blood for iron, total iron binding capacity, transferrin, ferritin, hepcidin, and erythroferrone at Week 52
- Blood collection for PK. A single sample will be collected on each visit unless the subject is participating in the 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 selected substudy visit as described in [Section 11.5.1.1](#) (Week 26 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 selected substudy visit as described in Section 11.5.1.1 (Week 26 or later).
- Blood collection for [REDACTED]
- Urine collection for clinical laboratory evaluations (see Table 5 and Table 7):
 - Urinalysis including microscopy
 - Urine collection for biomarker testing
 - Urine collection for hemosiderin at Week 52
- Urine collection for PK
- Urine pregnancy test for female subjects of childbearing potential (or as required by local or institutional practice) at Weeks 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.
- Study drug 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 toxicity will be performed during the first 12 weeks of study treatment for subjects randomized to BCX9930 in Part 1 and for subjects newly switched to BCX9930 for Part 2 as specified in the schedule of events specified in Table 4 for Part 1 or Table 5 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 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 203.

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/ET visit. Depending on the reason for the visit, any of the assessments described below may be performed, as appropriate.

Following the permanent discontinuation of BCX9930 (or C5 inhibitor therapy), 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 (see Section 12.5.3), 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
- Vital signs (resting blood pressure and pulse rate, and temperature)
- Targeted physical examination
- Blood collection for clinical laboratory evaluations (see Table 4 [Part 1] or Table 5 [Part 2] and Table 7):
 - 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 4](#) [Part 1] or [Table 5](#) [Part 2] and [Table 7](#)):
 - 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 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 BCX9930 or the decision to withdraw from the study (for C5 inhibitor subjects in Part 1).

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 4](#) [Part 1] or [Table 5](#) [Part 2] and [Table 7](#)):
 - 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 PD and clinical laboratory biomarkers
- Blood collection for [REDACTED]
- Urine collection for clinical laboratory evaluations (see [Table 4](#) [Part 1] or [Table 5](#) [Part 2] and [Table 7](#)):
 - 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 required (see Section 12.4).

11. STUDY ASSESSMENTS

11.1. Chronology of Assessments

It is preferred that the PRO questionnaires be administered prior to completing other study procedures, and clinic procedures, such as ECGs, physical examinations, and vital signs measurements, should be completed prior to any blood 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 C5 and other complement inhibitors); 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.

Note: If the minimum period of contraceptive use recommended in the relevant prescribing information after the last dose of eculizumab or ravulizumab, as applicable, is longer than 30 days after the last dose of BCX9930, then the subject should continue to use contraception for that longer period.

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, and bilirubin; 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 of 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 Hb values (or central laboratory values if local laboratory values are not available) and, where 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 B₁₂

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).

To investigate the iron status in the study participants, all subjects will have blood samples drawn for assessment of iron, total iron binding capacity, transferrin, ferritin, hepcidin, and erythroferrone at baseline, Week 24, Week 52, and the EOS/ET visit; urine collected at these visits will be analyzed for hemosiderin. Iron, ferritin, total iron binding capacity, vitamin B₁₂, 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, PGIS-Physical Functioning
- PGIC-Fatigue, PGIC-Impact of Fatigue, 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 Scale

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, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52 for all subjects, and at Week 26 for subjects randomized to continue C5 inhibitor therapy.

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, 28, 32, 36, 40, 44, 48, and 52 for all subjects.

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 World Health Organization (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, 24, 28, 32, 36, 48, and 52 for all subjects and at Weeks 25 and 26 for subjects randomized to continue C5 inhibitor therapy.

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, 24, 28, 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 5 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 5 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 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 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 24 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 24, all 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 study. At Week 52, subjects who switched from the C5 inhibitor to BCX9930 will be asked to rate the change since stopping their C5 inhibitor and starting BCX9930. All other subjects will be asked how their fatigue, the impact of their fatigue, and interference of their PNH symptoms with physical functioning have changed, thinking back over the past 6 months. 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 24 and 52.

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

For subjects randomized to BCX9930, single venous blood samples for measurement of plasma BCX9930 concentrations (“sparse sampling” to support PPK and PK/PD modeling) will be collected 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. For subjects randomized to continue C5 inhibitor therapy, PK samples will not be collected until after they have been switched to BCX9930 in Part 2 (ie, beginning at the Week 25 visit for subjects not participating in the PK/PD substudy).

Sparse PK blood samples may be drawn at any time without regard to 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 BCX9930 doses during these visits or take a dose in the clinic, unless the visit falls during the subject’s normal dose time or the subject is participating in the 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.

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 for subjects randomized to BCX9930 or during the Week 24 visit for subjects randomized to continue C5 inhibitor therapy in Part 1 of the study. The second sample collection will assess the PK of BCX9930 at steady state, with samples collected during the Week 2 or any later visit for subjects randomized to BCX9930 or during the Week 26 or any later visit for subjects randomized to continue C5 inhibitor therapy in Part 1 of the study.

For subjects randomized to BCX9930:

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

For subjects randomized to continue C5 inhibitor therapy:

- At the Week 24 visit, 4 PK blood samples will be collected at 0.5 (\pm 0.25), 1.5 (\pm 0.5), 3.5 (\pm 0.5), and 6 (\pm 1) hours after administration of the first dose of BCX9930.
- At the Week 26 or later visit, 5 PK blood samples will be collected; the first sample will be collected prior to BCX9930 dosing (\leq 15 minutes), with subsequent samples collected at 0.5 (\pm 0.25), 1.5 (\pm 0.5), 3.5 (\pm 0.5), and 6 (\pm 1) hours post-dose.

For the second sample collections (ie, on or after Week 2/Week 26 or later visit), 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), with the remaining samples collected after dosing in the clinic. The pre-dose blood sample should be collected immediately (\leq 15 minutes) prior to dosing.

On both occasions, the actual date and time of each blood sample collection and the actual date and time of observed BCX9930 dose will be recorded in the eCRF. In addition, for the steady-state collection at the Week 2/Week 26 or later visit, 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 taken 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.

For subjects randomized to BCX9930:

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

For subjects randomized to continue C5 inhibitor therapy:

- At the Week 24 visit, the first sample will be collected prior to BCX9930 dosing (≤ 2 hours), with subsequent samples collected at 0.5 (± 0.25), 1.5 (± 0.5), 3.5 (± 0.5), and 6 (± 1) hours post-dose.
- At the Week 26 or later visit, the first sample will be collected prior to BCX9930 dosing (≤ 15 minutes), with subsequent samples collected at 0.5 (± 0.25), 1.5 (± 0.5), 3.5 (± 0.5), and 6 (± 1) hours post-dose.

As applicable, PD blood samples will be collected at the same time as the corresponding PK blood sample (ie, excluding the pre-dose sample on Day 1 or Week 24). 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/Week 24 serial PK/PD sample collection can still participate in the later steady-state PK/PD collection.

Plasma PK parameters of BCX9930 metabolites may also be assessed using these samples.

A tabular summary of the PK and PD sampling is provided in [Table 6](#).

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 during Part 1 for subjects randomized to BCX9930 and from all subjects in Part 2.

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

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

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. Deposition of

complement byproducts onto cell membranes (such as C3-opsonized RBCs) will be measured using flow cytometry to assess potential drug-induced changes in opsonization of PNH RBCs. 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, so more than one collection tube type will be needed.

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. Subjects randomized to continue C5 inhibitor therapy in Part 1 should have their Week 24 PD sample collected prior to administration of the first dose of BCX9930.

The 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 [ie, Type II plus Type III], PNH WBC, and the ratio of total PNH RBC to PNH WBC) will be assessed at each visit, along with C3 deposition (ie, C3 RBC opsonization) as a marker of the potential for EVH. [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 6](#).

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

Table 6: Summary of Pharmacokinetic and Pharmacodynamic Blood Sampling

PK or PD Sampling	Screening	Day 1	Study Week																	Hemolysis Assessment/ Monitoring
			Wk1	Wk2	Wk4	Wk8	Wk12	Wk16	Wk20	Wk24	Wk25	Wk26	Wk28	Wk32	Wk36	Wk40	Wk44	Wk48	Wk52	
Randomized to BCX9930																				
PK ^a	-	-	X	X	X	X	X	X	X	X	NA	NA	X	X	X	X	X	X	X	X
PD ^b	X	X	X	X	X	X	X	X	X	X	NA	NA	X	X	X	X	X	X	X	X
Optional PK/PD Substudy ^c																				
PK	-	4 ^d	-	< ----- 5 ^e ----- >																-
PD	-	5 ^f	-	< ----- 5 ^e ----- >																-
Randomized to Continue C5 inhibitor																				
PK ^g		-	-	-	-	-	-	-	-	-	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 ^h																				
PK	-	-	-	-	-	-	-	-	-	4 ^d	-	< ----- 5 ^e ----- >								-
PD	-	-	-	-	-	-	-	-	-	5 ^f	-	< ----- 5 ^e ----- >								-

Abbreviations: C5 = complement component 5; 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 if and when symptoms occur.

^c The first sample collection will be performed on Day 1 and the second sample collection during the Week 2 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 BCX9930.

^e Five blood samples will be collected, where possible; the first sample will be collected prior to BCX9930 dosing (≤ 15 minutes), with subsequent samples collected at 0.5 (± 0.25), 1.5 (± 0.5), 3.5 (± 0.5), and 6 (± 1) hours post-dose. As applicable, PD blood samples will be collected at the same time as the corresponding PK blood samples.

^f Five blood samples will be collected, where possible; the first sample will be collected prior to BCX9930 dosing (≤ 2 hours), with subsequent samples collected at 0.5 (± 0.25), 1.5 (± 0.5), 3.5 (± 0.5), and 6 (± 1) hours post-dose. As applicable, PD blood samples will be collected at the same time as the corresponding PK blood samples.

^g Single venous blood samples for measurement of plasma BCX9930 concentrations will be collected at each scheduled study visit, beginning at the Week 25 visit, 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).

^h The first sample collection will be performed during the Week 24 visit and the second sample collection during the Week 26 or any later visit.

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 4](#) for Part 1 and [Table 5](#) 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 presented in [Table 4](#) for Part 1 and [Table 5](#) 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 4](#) for Part 1 and [Table 5](#) 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 4](#) for Part 1 and [Table 5](#) 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 24 visit for subjects randomized to C5 inhibitor before they are switched to BCX9930 in Part 2.

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, or where applicable, Week 24 for subjects randomized to C5 inhibitor therapy) 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 4](#) for Part 1 and [Table 5](#) for Part 2. Individual laboratory tests are specified in [Table 7](#).

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 7: 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	
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	Iron, Folate, and Vitamin B₁₂
	Erythroferrone Ferritin Folate Hepcidin Hemosiderin (urine) Iron Total iron binding capacity Transferrin Vitamin B ₁₂
	Other Testing
	C3 opsonized RBCs

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

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

^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.

^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.

^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. Additional biomarkers may be recommended by the Nephrology Risk Mitigation Working Group.

^l Urine will be aliquoted, frozen, and sent to the central laboratory for possible future analysis of urine biomarkers.

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 4](#) for Part 1 and [Table 5](#) 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 C5 inhibitor therapy, 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 condition(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 14.4).

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 12.5.4). 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]

[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. The SAE eCRF is an additional form to the AE eCRF that provides important details on the SAE. 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]
[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.

12.5. 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 $> 3 \times \text{ULN}$ 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 $> 3 \times \text{ULN}$ 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 $> 8 \times \text{ULN}$
- ALT or AST $> 5 \times \text{ULN}$ for more than 2 weeks
- ALT or AST $> 3 \times \text{ULN}$ and (total bilirubin $> 2 \times \text{ULN}$ [unless there is evidence that the increase in bilirubin is due to hemolysis or Gilbert’s syndrome] or INR $> 1.5 \times \text{ULN}$ in the absence of warfarin therapy)

- ALT or AST $> 3 \times$ 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 7.4.1, 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 $> \text{ULN}$ or $\geq 0.3 \text{ mg/dL}$ ($\geq 26.5 \text{ } \mu\text{mol/L}$) 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 $\leq 1.5 \times \text{ULN}$	<ul style="list-style-type: none"> • Assessment frequency as per the schedule specified in Table 4 (Part 1) or Table 5 (Part 2) (ie, every 1 to 4 weeks, as applicable) until sCr is $\leq \text{ULN}$ • Consider evaluation by nephrologist
sCr > $1.5 \times \text{ULN}$ but $< 3 \times \text{ULN}$	<ul style="list-style-type: none"> • Assessment frequency weekly until sCr is $\leq \text{ULN}$ • Evaluation by nephrologist
sCr $\geq 3 \times \text{ULN}$	<ul style="list-style-type: none"> • BCX9930 should be discontinued, with taper (see Section 9.4.4), 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 $\geq 3 \times \text{ULN}$, 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 $\geq 3 \times \text{ULN}$ 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

12.5.3.1. 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 BCX9930 (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 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 10.3.6 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, treatment should be provided according to the judgement of the investigator.

Treatment with 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 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 after BCX9930 for missed doses, treatment interruption, and permanent discontinuation of BCX9930 for subjects who experience signs or symptoms of hemolysis are in Section 10.3.6.

12.5.3.2. C5 Inhibitor Therapy

Subjects who permanently discontinue C5 inhibitor therapy, other than to begin treatment with BCX9930, should be monitored for hemolysis as described per the relevant prescribing information, product monograph, or summary of product characteristics, with standard-of-care supportive treatment provided, as needed.

The sponsor medical monitor should be notified in the event of hemolysis symptoms, treatment interruption, and permanent discontinuation of C5 inhibitor therapy. 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 after C5 inhibitor therapy for missed doses, treatment interruption, and permanent discontinuation of C5 inhibitor therapy for subjects who experience signs or symptoms of hemolysis are in Section 10.3.6. 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.

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, hemoglobinuria, new signs and/or symptoms suggestive of thrombosis, or

new or worsening erectile dysfunction, upon first awareness and regardless of treatment assignment. 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 BCX9930, 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 subjects seen in person for evaluation of possible acute symptomatic hemolysis, the assessments outlined in Section 10.3.6 should be performed, as appropriate.

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

- ≥ 1 new or worsening acute sign or symptom of IVH (fatigue, hemoglobinuria, abdominal pain, dyspnea, MAVE [including thrombosis], dysphagia, erectile dysfunction, or acute kidney injury [AKI; defined as an eGFR decrease of $\geq 50\%$ 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 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 BCX9930 for those assigned to BCX9930 in Part 1, and 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 CFB in Hb [mean of values at Weeks 12, 16, 20, and 24] between BCX9930 and C5 inhibitor therapy.

The primary null and alternative hypotheses are:

- H_0 : $Hb_B = Hb_C$; BCX9930 does not have a differential effect on the mean of values at Weeks 12, 16, 20, and 24 CFB in Hb (g/dL) as compared to C5 inhibitor therapy
- H_A : $Hb_B \neq Hb_C$; BCX9930 does have a differential effect on the mean of values at Weeks 12, 16, 20, and 24 CFB in Hb (g/dL) as compared to C5 inhibitor therapy

where Hb_B is the mean of values at Weeks 12, 16, 20, and 24 CFB in Hb for BCX9930 and Hb_C is the mean of values at Weeks 12, 16, 20, and 24 CFB for C5 inhibitor therapy.

Key secondary hypotheses comparing BCX9930 to C5 inhibitor therapy are as follows:

- Proportion of subjects who are transfusion-free from Week 4 to Week 24
 - H_0 : $TA_B = TA_C$; BCX9930 does not have a differential effect on the proportion of subjects who are transfusion-free from Week 4 to Week 24
 - H_A : $TA_B \neq TA_C$; BCX9930 does have a differential effect on the proportion of subjects who are transfusion-free from Week 4 to Week 24

where TA_B is the proportion of subjects who are transfusion-free from Week 4 to Week 24 for BCX9930 and TA_C is the proportion of subjects who are transfusion-free from Week 4 to Week 24 for C5 inhibitor therapy.

- Number of units of pRBCs transfused from Week 4 to Week 24
 - H_0 : $pRBC_B = pRBC_C$; BCX9930 does not have a differential effect on the number of units of pRBCs transfused from Week 4 to Week 24
 - H_A : $pRBC_B \neq pRBC_C$; BCX9930 does have a differential effect on the number of units of pRBCs transfused from Week 4 to Week 24

where $pRBC_B$ is the number of units of pRBCs transfused from Week 4 to Week 24 for BCX9930 and $pRBC_C$ is the number of units of pRBCs transfused from Week 4 to Week 24 for C5 inhibitor therapy.

- Change from baseline in FACIT-Fatigue scale score [mean of values at Weeks 12, 16, 20, and 24]
 - H_0 : $FACIT_B = FACIT_C$; BCX9930 does not have a differential effect on the mean of values at Weeks 12, 16, 20, and 24 CFB in FACIT-Fatigue

- H_A : $FACIT_B \neq FACIT_C$; BCX9930 does have a differential effect on the mean of values at Weeks 12, 16, 20, and 24 CFB in FACIT-Fatigue

where $FACIT_B$ is the mean CFB at Week 12, 16, 20, and 24 in FACIT-Fatigue for BCX9930 and $FACIT_C$ is the mean of values at Weeks 12, 16, 20, and 24 CFB for C5 inhibitor therapy.

Inferential testing for the primary endpoint of interest (CFB in Hb) 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

Four endpoints are being tested: the primary endpoint and 3 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 24]
2. Number of units of pRBCs transfused [from Week 4 to Week 24]
3. CFB in FACIT-Fatigue scale score [mean of values at Weeks 12, 16, 20, and 24]

13.2. Sample Size Considerations

Assuming a Type 1 error rate of 0.05, 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 66 subjects (44 subjects in the BCX9930 200/400 mg BID arm, 22 subjects in the control arm) will have 90% power to detect a treatment difference of 2.0 g/dL in Hb from baseline for subjects randomized to BCX9930 compared to subjects randomized to continue C5 inhibitor therapy, based on a two-sample t-test. To account for potential dropouts, approximately 81 subjects (ie, approximately 54 subjects in the BCX9930 200/400 mg BID arm and approximately 27 subjects in the control arm) will be enrolled.

13.3. Sample Size Re-estimation

No sample size re-estimation is planned.

13.4. Stratification

Randomization of subjects will be stratified by C5 inhibitor (ravulizumab vs. eculizumab) and 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 C5 inhibitor or BCX9930. This population will be used for all analyses of accountability, demographics, and safety. Subjects will be analyzed according to the treatment received.

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 24 weeks of 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 one 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.

Baseline measures for Hb and FACIT-Fatigue scale scores will be summarized using descriptive statistics.

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 [mean of values at Weeks 12, 16, 20, and 24].

The primary efficacy analysis will be produced using the ITT population. The estimand will be based on observed data from subjects who are on study drug. Observed data will be included up to the time of discontinuation of study treatment, if applicable. CFB Hb values (in Weeks 12, 16, 20, and 24) that occur within 14 days after the subject 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 value if one is available within the 14-day period prior to the visit and if 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 is ≤ 0 . Central laboratory values will be used. If a central laboratory value is missing but a local laboratory is available, the local laboratory value will be used in place of the censored laboratory value. Statistical testing will be two-sided.

CFB in Hb will be summarized by treatment and visit (including mean in Weeks 12, 16, 20, and 24).

The difference between treatment groups in CFB Hb [mean of values at Weeks 12, 16, 20, and 24] 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.

The primary efficacy analysis will be conducted using Part 1 data and the primary efficacy endpoints will be summarized and listed by Part 1 treatment group.

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.

Hb and CFB Hb will be listed for each subject and visit.

The potential impact of missing data on the primary efficacy outcome will be explored. 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.
- 2) Analyses based on data from subjects who are in the PP population.
- 3) An analysis in which missing data are imputed using the method of Jump-to-Reference (J2R) ([Carpenter, Roger, et al. 2013](#)), an analysis in which data missing not at random are imputed to be similar to data observed on the reference treatment (treatment with C5 inhibitors) and data missing at random are imputed to be similar to that of the randomized treatment group for the subject.
- 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 on sensitivity analyses and missing data imputations 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.

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 C5 inhibitor therapy for Part 1 will be analyzed as follows:

1. Proportion of subjects who are transfusion-free [from Week 4 to Week 24]

2. Number of units of pRBCs transfused [from Week 4 to Week 24]
3. CFB in FACIT-Fatigue scale score [mean of values at Weeks 12, 16, 20, and 24]

The proportion of subjects who are transfusion-free from Week 4 to Week 24 will be summarized by treatment. Subjects who either (1) discontinue treatment prior to Week 24, or (2) do not receive a transfusion during the Week 4 to Week 24 time period despite recording a Hb value ≤ 9 g/dL with symptoms assessed by the investigator as 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 C5 inhibitor. As a supportive analysis, a logistic regression model will be conducted with a fixed effect for treatment and indicator variables for the randomization factors. In addition, a sensitivity analysis using CMH will be conducted in which subjects who discontinue treatment prior to Week 24 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 24 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 24. In 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 24 as the dependent variable, the treatment and indicator variables for the randomization factors 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 24 will be reported for each treatment group. A rate ratio (with 95% CI) comparing BCX9930 to C5 inhibitor treatment will be obtained as well as a percent reduction in rate (with 95% CI) for BCX9930 as compared to C5 inhibitor treatment.

The actual and change from baseline in FACIT-Fatigue scale score will be summarized by treatment group and visit. The difference between treatment groups in CFB FACIT-Fatigue score [mean of values at Weeks 12, 16, 20, and 24] will be analyzed using an ANCOVA model. The model will include CFB FACIT-Fatigue score [mean of values at Weeks 12, 16, 20, and 24] as the dependent variable with treatment, indicator variables for the randomization factors, and baseline FACIT-Fatigue score as independent variables. 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. An additional supportive analysis of CFB FACIT-Fatigue scores will be conducted using a MMRM model 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. Cumulative density function (CDF) and probability density function (PDF) plots of CFB FACIT-Fatigue (mean of Weeks 12, 16, 20, and 24) will be produced. Further sensitivity analyses for FACIT-Fatigue scale score to address missing data will be detailed in the SAP (eg, J2R and tipping point).

Nominal p-values will be provided for the following other secondary and exploratory endpoints:

- Percent CFB in LDH [mean of values at Weeks 12, 16, 20, and 24]
- Percent reduction in the rate of pRBC units transfused [from Week 4 to Week 24 vs. prestudy transfusion rate]
- Proportion of subjects with Hb \geq 12 g/dL [at Week 24]
- 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 24]
- CFB in C3-opsonized RBCs [mean of values at Weeks 12, 16, 20, and 24]
- CFB in total PNH RBC clone size [mean of values at Weeks 12, 16, 20, and 24]
- CFB in ratio of total PNH RBC clone size to PNH WBC clone size (ie, ratio of percent PNH RBCs / percent PNH WBCs) [mean of values at Weeks 12, 16, 20, and 24]
- CFB in absolute reticulocyte count (ARC) [mean of values at Weeks 12, 16, 20, and 24]
- Proportion of subjects with ARC in the normal range [at Week 24]
- CFB in haptoglobin [mean of values at Weeks 12, 16, 20, and 24]
- Proportion of subjects with haptoglobin \geq LLN [at Week 24]
- CFB in total bilirubin [mean of values at Weeks 12, 16, 20, and 24]
- [REDACTED]
- [REDACTED]

Percent CFB in LDH, CFB in C3-opsonized RBCs, CFB in total PNH RBC clone size, CFB in ratio of total PNH RBC clone size to PNH WBC clone size, CFB in ARC, CFB in haptoglobin, CFB in total bilirubin, [REDACTED] will be summarized by visit. Analysis of the endpoints represented as the mean of Weeks 12, 16, 20, and 24 will be conducted using ANCOVA with effects for treatment, randomization stratum, and baseline value. Missing data will not be imputed. For this analysis, CFB total PNH RBC, and CFB ratio of total PNH RBC clone size to PNH WBC clone size, CFB in ARC, and CFB in haptoglobin values will be censored if the subject had a transfusion within 14 days prior to the visit in which the measurement was taken (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 24 will be calculated and compared to the rate of pRBC units transfused prestudy 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 $\geq 50\%/70\%/90\%$ reduction in rate will be reported.

Proportions of subjects with Hb ≥ 12 g/dL [at Week 24], proportion of subjects with Hb stabilization [from Week 4 to Week 24], proportion of subjects with ARC in the normal range [at

Week 24], and proportion of subjects with haptoglobin \geq LLN [at Week 24] will be summarized and analyzed using the CMH method. For proportion of subjects with Hb \geq 12 g/dL at Week 24, proportion of subjects with ARC in the normal range at Week 24, and proportion of subjects with haptoglobin \geq LLN at Week 24, subjects will be considered as failing to meet these endpoints if they had a transfusion within the 14 days prior to Week 24.

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 24]
- CFB in QLQ-AA/PNH Physical Functioning and other domain scores [at Week 24]
- 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 [at Week 24]
- CFB in individual PNH symptom items on the modified PRO-AA/PNH [at Week 24]
- CFB in EQ-5D-5L utility and VAS scores [at Week 24]
- TSQM scale score [at Week 24]
- 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 24]
- 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 24]

The proportion of subjects achieving a within-subject meaningful change for the FACIT-Fatigue scale at Week 24 and the proportion of subjects with improvement on individual PNH symptom items as assessed using the modified PRO-AA/PNH at Week 24 will be analyzed using the CMH 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 for fatigue, impact of fatigue, and physical functioning scores will be summarized by visit for both actual and CFB values and the Week 24 CFB result will be analyzed using ANCOVA with effects for treatment, randomization stratum, and baseline value. Note that for TSQM, a similar analysis will be conducted but with the actual Week 24 value rather than CFB Week 24 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 24.

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 24 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 C5 inhibitor therapy 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, LDH, ARC, haptoglobin, C3-opsonized RBCs, total PNH RBC clone size, ratio of total PNH RBC clone size to PNH WBC clone size, [REDACTED] and [REDACTED]. The mean and standard deviation of CFB values from Weeks 28 to 52 for subjects randomized to BCX9930 in Part 1 and from Weeks 36 to 52 for subjects randomized to continue C5 inhibitor therapy will be provided.

The proportion of subjects with Hb ≥ 12 g/dL at Week 52, with Hb stabilization during the relevant Part 2 period, with ARC in the normal range at Week 52, with haptoglobin \geq LLN at Week 52, 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 prestudy transfusion rate. Summary statistics will be provided along with a summary of the number of subjects with a $\geq 50\%/70\%/90\%$ reduction in rate of pRBC units transfused.

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 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. Descriptive summaries will be provided 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 ≤ 450 , > 450 to ≤ 480 , > 480 to ≤ 500 , and > 500 msec; or CFB of ≤ 30 , > 30 to ≤ 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 $\geq 50\%$ or \geq 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 [$\text{Hb} < 10 \text{ g/dL}$], MAVE [including thrombosis], dysphagia, or erectile dysfunction) in the presence of $\text{LDH} \geq 2 \times \text{ULN}$ after prior reduction of LDH to $\leq 1.5 \times \text{ULN}$ on treatment. 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 4](#) to [Table 6](#). Plasma PK sampling will include both sparse (all subjects) and serial (subjects participating in the PK/PD substudy only) collection. Urine sampling will include spot collections only.

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 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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