BIOCRYST

PHARMACEUTICALS, INC.

BCX9930

Protocol No. BCX9930-201

EUDRACT NUMBER: 2020-000501-93

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

Version 5.0: 01 July 2022

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CONFIDENTIAL

SIGNATURE PAGE

Sponsor's Approval

The protocol has been approved by BioCryst Pharmaceuticals Inc.

Date: Version 5.0: 01 July 2022

Senior Clinical Development Physician:

[redacted] Date

[redacted]

BioCryst Pharmaceuticals, Inc.

Sponsor's Authorized Signatory:

[redacted] Date

[redacted]

[redacted]

BioCryst Pharmaceuticals, Inc.

INVESTIGATOR'S AGREEMENT

Protocol No. BCX9930-201

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

Version 5.0: 01 July 2022

I have received and read the Investigator's Brochure for BCX9930. I have read the BCX9930-201 protocol and agree to conduct the study as outlined. 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 Number:	BCX9930-201
Study Title:	A Phase 2, Open-label Study to Evaluate the Long-term Safety of Oral BCX9930 in Subjects with Paroxysmal Nocturnal Hemoglobinuria (PNH)
EudraCT No.	2020-000501-93
Investigational Product:	BCX9930
Indication Studied:	Paroxysmal nocturnal hemoglobinuria (PNH)
Sponsor:	BioCryst Pharmaceuticals, Inc. 4505 Emperor Boulevard, Suite 200 Durham, NC 27703, USA
Sponsor Medical Monitor:	[redacted]
Coordinating Investigator:	[redacted]
Compliance Statement:	This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and clinical research guidelines established by the Code of Federal Regulations (Title 21, CFR Parts 50, 56, and 312) and 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 5.0: 01 July 2022
Previous Versions:	Version 4.0: 24 June 2021 Version 3.0: 12 November 2020 Version 2.0: 18 August 2020 Version 1.0: 26 May 2020

2. SYNOPSIS

Name of Sponsor/Company:

BioCryst Pharmaceuticals Inc.

Name of Investigational Product:

BCX9930

Name of Active Ingredient:

[redacted]

Title of Study:

A Phase 2, Open-Label Study to Evaluate the Long-term Safety of Oral BCX9930 in Subjects with Paroxysmal Nocturnal Hemoglobinuria (PNH)

Study centers: Centers that have participated in a previous BCX9930 PNH study

Co-ordinating Investigator:

[redacted]

Phase of Development: 2

Primary Objective:

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

Secondary Objectives:

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

Primary Endpoint:

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

Secondary Endpoints:

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

Pharmacodynamic (PD) Endpoint:

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

[redacted]

Study Design:

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

Methodology:

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

Subjects will receive up to 144 weeks of daily BCX9930.

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

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

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

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

PK and PD samples will be collected at each study visit from baseline onwards and at the time of any suspected breakthrough events. PD and complement biomarkers will include PNH RBC and WBC clone size, and plasma Factor Bb and AP activity. Additional exploratory PD and complement biomarkers may be included, if suitable tests are available.

Sample Size Justification:

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

Number of Subjects (planned):

Approximately 200 subjects based upon the anticipated clinical programs for BCX9930.

Inclusion Criteria:

1. Able to provide written informed consent.
2. Male or non-pregnant, non-lactating female subjects.
3. Subjects who have successfully participated in a previous BCX9930 study of PNH and who experienced a clinical benefit, as confirmed by the Investigator. Successful participation is defined as completion of planned duration of dosing with BCX9930 in the prior study, not inclusive of any extension period.
4. Female participants must meet at least 1 of the following contraception requirements:
    a. Be a woman of childbearing potential who agrees to use a highly effective contraceptive method throughout the study and for a duration of 30 days after the last dose of study drug.
    b. Alternatively, true abstinence is acceptable for women of childbearing potential when it is in line with the subject's preferred and usual lifestyle.
    c. Be a woman of nonchildbearing potential.
5. Male participants must meet the following contraception requirements:
    a. Subjects with female partners of childbearing potential must agree to utilize a highly effective contraceptive method.

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

6. In the opinion of the Investigator, the subject is expected to adequately comply with all required study procedures and restrictions for the duration of the study.

Exclusion Criteria:

1. Any clinically significant medical or psychiatric condition that, in the opinion of the Investigator or Sponsor, would interfere with the subject's ability to participate in the study or participation would increase the risk for that subject.
2. Any clinically significant history of angina, known coronary artery disease, myocardial infarction, syncope, clinically significant cardiac arrhythmias, left ventricular hypertrophy, cardiomyopathy, aortic stenosis, or any other cardiovascular abnormality.
3. Chronic systemic corticosteroid use. Note: Topical, inhaled, ocular, or nasal sprays containing corticosteroids are allowed.
4. Investigational drug exposure, other than BCX9930, within 30 days of the baseline visit, or 5.5 half-lives of the investigational drug (whichever is longer).
5. For subjects requiring a screening visit:
    a. Clinically significant abnormal ECG at the screening visit. This includes, but is not limited to, a QT interval corrected using Fridericia's method (QTcF) > 450 msec in males and > 470 msec in females, or ventricular and/or atrial premature contractions that are more frequent than occasional, and/or as couplets or higher in grouping.
    b. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 3 × upper limit of normal (ULN) (Exception: Subjects may be enrolled with ALT or AST > 3 × ULN if explained by hemolysis. In these cases, ALT and AST must be < 5 × ULN.)
    c. Total serum bilirubin > 2 × upper limit of normal (ULN) (Exceptions: Subject may be enrolled with total serum bilirubin > 2 × ULN if the elevated bilirubin is explained by hemolysis or in the case of Gilbert's syndrome. In the case of hemolysis, total serum bilirubin must be < 5 × ULN and in the case of Gilbert's Syndrome, total bilirubin must be < 7 × ULN).
6. Daily use of medications listed in the currently applicable prohibited medications list.
7. Pregnant, planning to become pregnant, or having been pregnant within 90 days of baseline, or lactating.

Investigational Product, Dosage and Mode of Administration:

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

Duration of Treatment:

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

Reference Therapy, Dosage and Mode of Administration:

N/A

Criteria for Evaluation:

Safety:

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

Effectiveness:

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

Patient Reported Outcomes:

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

Pharmacokinetics:

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

Pharmacodynamics and Complement Biomarkers:

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

- Plasma Factor Bb
- PNH RBC and WBC clone size
- AP activity

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

Statistical Methods:

Analysis of Safety

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

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

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

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

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

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

Analysis of Clinical Measurements of PNH

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

Analysis of Effectiveness and Patient Reported Outcomes

Effectiveness and patient-reported outcomes (PROs) will be monitored with disease-specific clinical assessments, laboratory assessments, and questionnaires. Responses for subjects with PNH will be categorized using published draft criteria (Risitano, Marotta, et al. 2019) into complete response, major response, good response, partial response, minor response, and no response, modified for study duration and visit schedule.

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

Analysis of Pharmacokinetic Data

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

Analysis of Pharmacodynamic Data

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

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: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
ACIP	US Centers for Disease Control and Prevention Advisory Committee on Immunization Practices
AE	adverse event
AKI	acute kidney injury
AP	alternative complement pathway
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ARC	absolute reticulocyte count
AST	aspartate aminotransferase
AUC	area under the concentration vs. time curve
AUC_{0-24}	AUC from time 0 through 24 hours
BCRP	breast cancer resistance protein
BID	twice daily
BMI	body mass index
BP	blood pressure
BTH	breakthrough hemolysis
BUN	blood urea nitrogen
C3	complement component 3
C3b	end product of the alternative complement pathway
C3bB	factor B in complex with C3b
C4	complement component 4
C5	complement component 5
CBC	complete blood count
C_{max}	maximum concentration observed
COVID-19	coronavirus disease 2019
CP	classical pathway
CYP	cytochrome P450
DDI	drug-drug interaction
DMID	Division of Microbiology and Infectious Diseases
DMC	Data Monitoring Committee

Abbreviation or Specialist Term	Explanation
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
EOSI	event of special interest
EOSM	events of special monitoring
EVH	extravascular hemolysis
FACIT	Functional Assessment of Chronic Illness Therapy
FDA	US Food and Drug Administration
FIH	first in human
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
βHCG	β human chorionic gonadotropin
IB	Investigator's Brochure
IC_{50}	half-maximal inhibitory concentration
ICF	informed consent form
ICH	International Council on Harmonisation
IEC	Independent Ethics Committee
IMP	investigational medicinal product
INR	international normalized ratio
IRB	Institutional Review Board
KIM-1	kidney injury molecule 1
LDH	lactate dehydrogenase
L-FABP	liver-type fatty acid-binding protein
MAC	membrane attack complex
MedDRA	Medical Dictionary for Regulatory Activities
NGAL	neutrophil gelatinase-associated lipocalin
NRMWG	Nephrology Risk Mitigation Working Group
PD	pharmacodynamic(s)
P-gp	P-glycoprotein
PK	pharmacokinetic(s)
PNH	paroxysmal nocturnal hematuria
PRO	patient-reported outcomes
PT	prothrombin time

Abbreviation or Specialist Term	Explanation
QLQ-AA/PNH	Quality of Life Questionnaire for patients with Aplastic Anemia / Paroxysmal Nocturnal Hemoglobinuria
QT	electrocardiographic interval between the beginning of the Q wave and termination of the T wave, representing the time for both ventricular depolarization and repolarization to occur
QTc	corrected QT interval
QTcF	QT interval corrected for heart rate using Fridericia's formula
RBC	red blood cell
SAE	serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SOC	System Organ Classification
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
TSQM	Treatment Satisfaction Questionnaire for Medication
UACR	urine microalbumin to creatinine ratio
ULN	upper limit of (the) normal (range)
uNGAL	urine neutrophil gelatinase-associated lipocalin
VZV	varicella zoster virus
WBC	white blood cell
WOCBP	Women of child-bearing potential

5. INTRODUCTION

5.1. Background

Complement activation is an innate defense mechanism that, when uncontrolled, leads to inflammation and local tissue damage. The complement system consists of 3 distinct pathways: the classical pathway (CP), lectin pathway, and alternative pathway (AP). Dysregulation of the AP of complement activity by congenital or acquired genetic mutations, neutralizing antibodies to complement regulatory proteins, or stabilizing antibodies to complement complexes predisposes individuals to diverse disorders, including paroxysmal nocturnal hemoglobinuria (PNH), age-related macular degeneration, atypical hemolytic uremic syndrome, and complement 3 (C3) glomerulonephritis (Holers 2008, Brodsky 2014, Zipfel, Skerka, et al. 2015, Ricklin, Reis, et al. 2016).

The AP of complement is constitutively activated at low levels via slow spontaneous hydrolysis of an internal thioester within C3, a key component of the complement cascade, that generates $C3(H_2O)$. This activated $C3(H_2O)$ in solution phase binds factor B to generate the proconvertase $C3(H_2O)B$, which is processed by the serine protease factor D to cleave factor B and generates the AP of complement C3 convertase, $C3(H_2O)Bb$. This C3 convertase then cleaves additional C3 molecules to generate C3a and C3b, the latter of which can covalently attach to available surfaces (Pangburn and Muller-Eberhard 1983). Deposited C3 fragments can then elicit a rapid localized amplification (described as the amplification loop), especially when complement regulation is impaired. Deposited C3b can pair with factor B, which is cleaved by factor D to generate a second form of the alternative pathway of complement C3 convertase, C3bBb. Membrane-bound C3bBb then cleaves additional C3 to generate further C3b deposits, which pair with additional factor B molecules to repeat the cycle. The result of this amplification is C3b opsonization, release of the anaphylatoxins C3a and C5a, and assembly of the terminal complement complex C5b-9 (also known as the membrane attack complex [MAC]) on the target surface resulting in cell lysis (Ricklin, Reis, et al. 2016).

5.2. Indication

Paroxysmal nocturnal hemoglobinuria (PNH) is an acquired disorder characterized by destruction of red blood cells (RBCs) by uncontrolled activity of the complement system. The etiology of PNH is a somatic mutation in hematopoietic stem cells that leads to a deficiency of the complement regulatory proteins CD55 and CD59, resulting in unrestrained complement activity that attacks RBCs leading to episodes of intravascular hemolysis, chronic hemolytic anemia, bone marrow failure, and thrombosis (Parker 2009, Pu and Brodsky 2011, Parker 2012). PNH equally affects men and women but is more common in people of Asian than Caucasian ethnicity (Hill, DeZern, et al. 2017, Jalbert, Chaudhari, et al. 2019). PNH incidence increases with age, with an average age of diagnosis in the early 30s (Socie, Mary, et al. 1996, Schrezenmeier, Muus, et al. 2014).

The intra- and extravascular hemolysis 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 red discoloration of the urine due to hemoglobinuria following

intravascular hemolysis. 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).

The main 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). 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).

PNH is associated with significant morbidity and mortality (Harris, Koscick, et al. 1999, Rachidi, Musallam, et al. 2010); prior to the approval of eculizumab and ravulizumab, the median survival after diagnosis of PNH was 10 years (Hillmen, Lewis, et al. 1995). Prior to the approval of eculizumab, the overall survival at 10 years after diagnosis with PNH was estimated to be 65% to 77.6% (Socie, Mary, et al. 1996, Risitano, Notaro, et al. 2009, Ge, Li, et al. 2012). Thrombosis is the leading cause of death in PNH and, while it 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). Visceral thrombosis, cerebrovascular events, and pulmonary embolism predict a poor outcome (Ziakas, Poulou, et al. 2008). Survival of patients with PNH has improved recently, associated with control of intravascular hemolysis and reduced risk of thrombosis following the introduction of eculizumab (Hill, Kelly, et al. 2013, Socie, Schrezenmeier, et al. 2016).

Disease control with complement C5 inhibitors such as eculizumab and ravulizumab is incomplete, with persistent transfusion dependence in approximately 50% of patients, development of extravascular hemolysis because of uncontrolled opsonization of erythrocytes, and concomitant bone marrow dysfunction (Risitano, Notaro, et al. 2009, Hill, DeZern, et al. 2017). The currently approved treatments are administered by repeated intravenous infusions.

As of 9 April 2020, there were 9 products with orphan drug designation for the treatment of PNH in the United States (US) (FDA 2020). These products include Soliris® (eculizumab) and Ultomiris® (ravulizumab), which were the only drugs approved for treatment of PNH in the US. Pegcetacoplan is also approved for the treatment of PNH in the US and for the treatment of adults who are anemic after treatment with a C5 inhibitor for 3 months in Europe (Apellis 2021, Apellis 2022).

Factor D is the rate-limiting enzyme of the AP. Factor D is obligatory for production of the C3 convertase of the AP (C3bBb) as well as amplification of C3 convertase production initiated by the lectin and classical pathways (Lesavre and Muller-Eberhard 1978, Volanakis and Narayana 1996, Xu, Narayana, et al. 2001). Targeting Factor D with a pharmacologic inhibitor is expected to block both the formation of MAC (and hence C5b-9) and formation of C3 fragments and opsonization, and therefore prevent both intravascular and extravascular hemolysis. Factor D inhibitors have a potential clinical advantage over anti-C5 therapy, and an orally bioavailable

small-molecule Factor D inhibitor could potentially abrogate the need for lifelong intravenous infusions of anti-C5 biologics. Therefore, targeting Factor D is a promising therapeutic strategy to inhibit AP activation for the treatment of AP-mediated diseases such as PNH.

BioCryst Pharmaceuticals, Inc. (BioCryst) has developed BCX9930, a novel small-molecule inhibitor of complement Factor D. BCX9930 potently inhibits the esterolytic activity of purified human Factor D against synthetic substrate with a mean 50% of maximal inhibitory concentration (IC_{50}) of 14.3 nM. BCX9930 also inhibits the proteolytic activity of Factor D against its natural substrate C3bB with a mean IC_{50} of 28.1 nM. BCX9930 inhibits AP-mediated hemolysis of rabbit erythrocytes with a mean IC_{50} of 29.5 nM. Using the Ham test with erythrocytes from PNH patients, BCX9930 suppresses complement-mediated hemolysis with a mean IC_{50} of 35.4 nM. Furthermore, BCX9930 completely suppresses C3 fragment deposition on PNH erythrocytes with a mean IC_{50} of 39.3 nM, indicating BCX9930 has the potential to inhibit both intravascular and extravascular hemolysis.

5.3. Nonclinical Findings for BCX9930

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

[redacted]

In rats and dogs, BCX9930 is rapidly absorbed. Increases in exposure of BCX9930 were approximately proportional to increases in dose in both species. [redacted] Additional details can be found in the IB.

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

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

5.4. Clinical Findings for BCX9930

The safety and effectiveness of BCX9930 in PNH was initially evaluated in the Phase 1, three-part, first-in-human (FIH) Study BCX9930-101 (Study 101). In Part 3 of Study 101 a total of 16 subjects with PNH were enrolled. This study, BCX9930-201 (Study 201) is a long-term rollover study for all PNH subjects who previously received BCX9930 in Study 101 Part 3 and derived benefit from BCX9930 treatment. Fifteen subjects from Study 101 Part 3 enrolled into this study. [redacted]

5.4.1. 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 treatment-emergent adverse events (TEAEs). The most common TEAEs related to BCX9930 have been headache and events consistent with a drug rash.

[redacted]

[redacted]

5.4.2. Effectiveness

Administration of BCX9930 at doses of 400 mg or 500 mg BID, both in subjects with PNH who are naïve to C5 inhibitors and in those who are receiving C5 inhibitors and had an inadequate response, has resulted in sustained clinical responses. Moreover, treatment with BCX9930 at doses of 400 or 500 mg BID resulted in improved and sustained clinical responses relative to doses of 50, 100, and 200 mg BID, as measured by hemoglobin in both C5 treatment-naïve subjects and subjects with an inadequate response to C5 inhibition therapy, as well as by decreases in lactate dehydrogenase (LDH) levels in subjects naïve to C5 inhibitors. Additional efficacy information is provided below in Section 5.5.2.

5.5. Rationale for Study

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

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

5.5.1. Rationale for Study Design

This open-label safety study is designed to assess the long-term safety and effectiveness of BCX9930 in subjects who participated in a previous study of BCX9930. BCX9930-201 offers subjects who participated in a BCX9930 study additional or continued access to BCX9930 treatment for 144 weeks, or until drug is available by another mechanism (eg, expanded or market access) or until the Sponsor discontinues development of the product for PNH, whichever comes first.

Eligible subjects may enroll in the current study if the investigator assesses that they may benefit from continued daily administration of BCX9930.

5.5.2. Rationale for Study Drug Dose and Regimen

The dose regimen for this study, prior to this amendment, was [redacted]

[redacted]. The following observations support this dosing regimen:

- [redacted]

[redacted]

[redacted]

[redacted]

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

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

[redacted]

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

[redacted]

5.5.2.2. Summary of PPK and PK/PD Modeling

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

PD endpoints in these models included AP Wieslab in healthy and PNH subjects, LDH in subjects with PNH naïve to C5 inhibitors, and C3 opsonization in PNH subjects with inadequate response to ongoing C5 inhibitor therapy. AP Wieslab was used as a real time marker of overall complement activation. LDH was used as a marker of IVH (terminal complement inhibition) and C3 opsonization was used as a marker of the potential for EVH (proximal complement inhibition) in PNH subjects. Target occupancy of Factor D is not expected to be affected by a terminal complement inhibitor, allowing for models of IVH and EVH to be extrapolated to all subjects with PNH regardless of C5 inhibitor status.

[redacted]

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

[redacted]

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

[redacted]

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).
Notes: PPK simulation assumes perfect adherence and optimal spacing of BID doses (ie, every 12 hours).

Initially, a maximum dose of 500 mg BID was selected for this study 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.

5.5.3. Study Population Rationale

The study population is defined by the prior BCX9930 trial in PNH from which the subjects are eligible for this protocol. Both males and females will be enrolled. As reproductive toxicology studies have been conducted, women of childbearing potential may be enrolled in this trial only if they meet and maintain strict contraceptive and pregnancy test requirements as listed in this protocol.

5.6. Benefit-Risk Analysis

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, electrocardiograms (ECGs), and clinical laboratory testing.

Potential risks associated with complement inhibitors for the treatment of PNH, as well as potential risks associated with BCX9930 based on nonclinical and clinical data to date are described in the IB for BCX9930 and summarized below.

5.6.1. Potential Risks for 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 2020, Alexion Pharmaceuticals 2021).

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.

5.6.2. 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 coronavirus disease 2019 (COVID-19) following infection with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) or to increase the risk of severe illness with COVID-19.

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).

5.6.3. 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 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, Young, et al. 2008, Hillmen, Muus, et al. 2013, Roth, Rottinghaus, et al. 2018). In Study BCX9930-101, 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.

5.6.4. 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.

5.6.5. Potential Risks for Hemolysis After BCX9930 Discontinuation or Interruption in Subjects with PNH

Similar to available complement inhibitors used to treat PNH, discontinuation of BCX9930 may result in increased risk of hemolysis of PNH RBCs (Alexion Pharmaceuticals 2020, Alexion Pharmaceuticals 2021). Accordingly, subjects who discontinue or interrupt BCX9930 may be at risk of hemolysis. Subjects should be instructed to immediately contact the investigative site principal investigator if they miss any BCX9930 doses and experience new or worsening symptoms of hemolysis. In addition, subjects who discontinue permanently BCX9930 will be monitored for potential hemolysis. Assessments to detect hemolysis should be performed according to the schedule in Section 11.3.5.

5.6.6. Potential Risks for 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.

5.6.7. Potential Risks for Renal Effects

[redacted]

Monitoring of renal function will be undertaken in the study using standard measures (eg, sCr, estimated glomerular filtration rate [eGFR], and urinalysis including microscopy and biomarker analysis). Further information can be found in Section 13.6. Any renal events occurring on study should be evaluated as detailed in Section 13.9.5.3.

5.6.8. Overall Benefit-Risk Analysis

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

BCX9930 is expected to provide greater efficacy than the currently available C5 inhibitors by not only preventing IVH, but also by preventing C3 mediated extravascular hemolysis (EVH), thereby reducing symptom burden, reducing hemolysis, including EVH and breakthrough hemolysis (BTH), improving patient function, changing the administration route from IV to oral, and improving health-related quality of life. Study subject selection criteria, dose selection, and study monitoring assessments have been included to optimize benefit and to minimize the risk of toxicities to study participants. Regular monitoring of safety parameters, including AEs, clinical laboratory abnormalities, vital signs measurements, ECGs, and physical examination findings, will ensure that the benefit-risk profile supports continued dosing. In addition, an independent, program-wide data monitoring committee (DMC) will continue to provide oversight of the ongoing exposure of subjects to BCX9930 in this and other clinical studies. The overall benefit-risk balance is therefore considered to be acceptable.

6. TRIAL OBJECTIVES AND PURPOSE

6.1. Primary Objective

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

6.2. Secondary Objectives

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

6.3. Primary Endpoint

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

6.4. Secondary Endpoints

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

6.5. Pharmacodynamic (PD) Endpoint

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

[redacted]

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

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

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

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

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

The screening and baseline visit requirements are depicted in Table 3.

Table 3: Study BCX9930-201: Screening and Baseline Visit Requirements

Visit Required	Interrupted Study Drug ≥ 31 Days	Interrupted Study Drug 1 to 30 Days	No Interruption of Study Drug
Screening visit	Yes	No	No
Baseline visit	Yes	Yes	No [a]

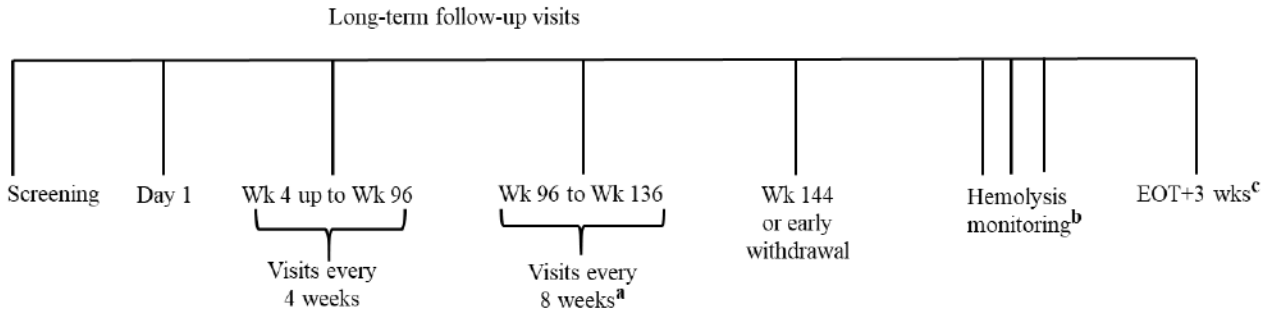
[a] No baseline visit required if the subject rolls from the previous study without dose interruption; the final on-treatment visit from the previous BCX9930 study will serve as the baseline visit for the current study, although additional assessments may be required.

A subject may be enrolled once all eligibility criteria and study requirements are met. On-treatment study visits will occur on Day 1, then every 4 weeks up to Week 96 and then every 8 weeks until Week 144. Subjects with sCr elevations will be required to complete additional assessments at the investigational site, at a laboratory local to the subject, or via a home health service (where permitted and available) as indicated in Section 11.3.4.1 and Section 13.9.5.3. An independent DMC will continue to review the safety data from this study in concert with the accumulating safety information generated across the BCX9930 clinical development program. The DMC convened and reviewed safety data once the first 4 subjects enrolled completed 12 weeks of dosing. Subsequent DMC meetings were and will be convened as detailed in the DMC Charter.

Up to approximately 200 subjects may be enrolled into the study. Subjects will be eligible to receive BCX9930 for up to 144 weeks, or until drug is available by another mechanism (eg, expanded or market access) or until the Sponsor discontinues development of the product for PNH; whichever comes first.

A study schema is shown in Figure 2.

Figure 2: Study Schema



Abbreviations: EOT = end of treatment; Wk = week.

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

[b] Following discontinuation of study drug, either following completion of the treatment period or on premature discontinuation, subjects will return to the clinic for a minimum of 3 consecutive days to monitor for the onset of hemolysis.

[c] Subjects will return to the clinic 3 weeks (21 ± 3 days) after the date of their last dose of BCX9930 for their end of study assessments.

Safety and tolerability will be evaluated through assessments of TEAEs, laboratory analyses (clinical chemistry, hematology, coagulation, and urinalysis), vital signs, ECGs, and physical examinations at the study visits indicated in the schedule of assessments (see Table 4).

Disease-specific assessments will be performed at study visits as indicated in the schedule of assessments (see Table 4).

7.2. Number of Subjects

Up to approximately 200 subjects are planned to be enrolled in the study based upon the anticipated clinical programs for BCX9930.

7.3. Treatment Dosing

The protocol-specified dose prior to this amendment was 500 mg BCX9930 BID. Under this amendment, subjects will take 400 mg BCX9930 BID orally .

7.4. Individual and Study Stopping Rules

7.4.1. Subject Discontinuation from Study Drug

A subject will be permanently withdrawn from study drug 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 > 3 × upper limit of normal (ULN) (confirmed by repeat testing) combined with either:
  - laboratory abnormalities indicative of significant hepatic toxicity (ie, meeting Hy's law, total bilirubin > 2 × ULN or with a new increase in INR > 1.5 in the absence of warfarin therapy)

  OR

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

  AND

  - assessed as probably or definitely related to BCX9930

AND

– without clinical and/or laboratory evidence of hemolysis or any other potential alternative etiology.

- Treatment-emergent increase in sCr ≥ 3 × ULN (confirmed by repeat testing) without clinical and/or laboratory evidence of hemolysis or any other potential cause of renal dysfunction.
- Invasive meningococcal infection or invasive encapsulated bacterial infection. Discontinuation of BCX9930 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 study drug for any reason will be monitored for hemolysis (see Section 11.3.5 and Section 11.3.6).

7.4.2. Study Stopping Rules

The following study stopping rules will be used to terminate either the whole study or terminate a particular site:

- Request of a competent authority or the supervising IEC
- Emergence of unacceptable risk, toxicity, or negative change in the benefit-risk assessment
- Recommendation of the DMC
- Inaccurate or incomplete record keeping
- Non-compliance with the study protocol that jeopardizes the scientific integrity of study assessments or subject safety

BioCryst reserves the right to discontinue the trial prior to inclusion of the intended number of subjects but intends only to exercise this right for valid scientific or administrative reasons. After such a decision, the Investigator must contact all participating subjects immediately after notification. As directed by BioCryst, all study materials must be collected and all eCRFs completed to the greatest extent possible.

If the trial is halted due to safety concerns or based on a DMC decision, re-start of the trial will occur 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 inclusion criteria to be eligible for participation in this study:

1. Able to provide written informed consent.
2. Male or non-pregnant, non-lactating female subjects.
3. Subjects who have successfully participated in a previous BCX9930 study of PNH and who experienced a clinical benefit, as confirmed by the Investigator. Successful participation is defined as completion of planned duration of dosing with BCX9930 in the prior study, not inclusive of any extension period.
4. Female participants must meet at least 1 of the following contraception requirements (for details see Section 11.4.1):
    a. Be a woman of childbearing potential who agrees to use a highly effective contraceptive method throughout the study and for a duration of 30 days after the last dose of study drug.
    b. Alternatively, true abstinence is acceptable for women of childbearing potential when it is in line with the subject's preferred and usual lifestyle.
    c. Be a woman of nonchildbearing potential.
5. Male participants must meet the following contraception requirements (for details see Sections 11.4.1 and 11.4.2):
    a. Subjects with female partners of childbearing potential must agree to utilize a highly effective contraceptive method.
    b. Alternatively, true abstinence is acceptable when it is in line with the subject's preferred and usual lifestyle.
6. In the opinion of the Investigator, the subject is expected to adequately comply with all required study procedures and restrictions for the duration of the study.

8.2. Subject Exclusion Criteria

Subjects must meet none of the following exclusion criteria to be eligible for participation in the study:

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

2. Any clinically significant history of angina, known coronary artery disease, myocardial infarction, syncope, clinically significant cardiac arrhythmias, left ventricular hypertrophy, cardiomyopathy, aortic stenosis, or any other cardiovascular abnormality.
3. Chronic systemic corticosteroid use. Note: Topical, inhaled, ocular, or nasal sprays containing corticosteroids are allowed.
4. Investigational drug exposure, other than BCX9930, within 30 days of the baseline visit, or 5.5 half-lives of the investigational drug (whichever is longer).
5. For subjects requiring a screening visit:
    a. Clinically significant abnormal ECG at the screening visit. This includes, but is not limited to, a QTcF > 450 msec in males and > 470 msec in females, or ventricular and/or atrial premature contractions that are more frequent than occasional, and/or as couplets or higher in grouping.
    b. ALT or AST > 3× ULN (Exception: Subjects may be enrolled with ALT or AST > 3 × ULN if explained by hemolysis. In these cases, ALT and AST must be < 5 × ULN).
    c. Total serum bilirubin > 2 × ULN (Exceptions: Subject may be enrolled with total serum bilirubin > 2 × ULN if the elevated bilirubin is explained by hemolysis or in the case of Gilbert's syndrome. In the case of hemolysis, total serum bilirubin must be < 5 × ULN and in the case of Gilbert's Syndrome, total bilirubin must be < 7 × ULN).
6. Daily use of medications listed in the currently applicable prohibited medications list (See Section 9.2).
7. Pregnant, planning to become pregnant, or having been pregnant within 90 days of baseline, or lactating.

8.3. Subject Withdrawal Criteria

Participation in the study is strictly voluntary. Subjects have the right to withdraw from study drug or from the study at any time and for any reason. A subject's participation may be terminated for any of the reasons delineated in Section 7.4. Whenever possible, the Investigator will consult with the Sponsor Medical Monitor before halting a subject's participation in the study.

In all cases, the reason for withdrawal from study drug must be recorded in the subject's medical records (source documents). If the reason is not known, the subject must be followed 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 7.4.1 and Section 13.9.3. Vigorous attempts will be made for follow-up of all subjects who miss a study visit. In general, although study drug may be stopped, subjects will be strongly encouraged to continue to complete the scheduled study visits for hemolysis monitoring (see Section 11.3.5). If the subject is withdrawn from the study prior to scheduled study completion, an early termination visit to complete all end-of-study evaluations will be required. If a subject's participation in this study is terminated, the responsible Investigator/clinical staff member will document termination in the source documents.

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.

9. TREATMENT OF SUBJECTS

Throughout treatment with BCX9930, subjects should maintain adequate hydration to prevent the formation of highly concentrated urine.

9.1. Concomitant Medications

During the course of the study, 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. Subjects may take their normal medications, with the exception of any changes to nephrotoxic medications and prohibited medications detailed below (Section 9.2).

Vaccination against *N. meningitidis* types A, C, W, Y, and B, *S. pneumoniae, H. influenzae* type B (Hib) and varicella zoster virus (VZV) will be allowed up to at least 14 days prior to Day 1.

As part of their treatment for PNH, subjects should be assessed by the investigator for infection risk as described in Section 11.3.2. Prophylactic antibiotic and/or antiviral medications may be considered if clinically indicated (eg, valacyclovir/acyclovir if subject is seropositive for VZV or tenofovir/lamivudine if at risk for reactivation of HBV).

Subjects may be encouraged to begin tapering or to discontinue medications that suppress the immune system if clinically indicated.

Based upon the mechanism of action of proximal AP inhibition targeting Factor D and demonstration that BCX9930 monotherapy is sufficient to control hemolysis in PNH in C5 inhibitor-naïve subjects (see Section 5.4), subjects who commence the study with a background treatment of eculizumab or ravulizumab should be considered for a discontinuation of these medications. The treating Investigator should discontinue the C5 inhibitor once the subject is on an optimized dose of BCX9930. It is expected that all subjects will discontinue background C5 inhibitor therapy as there should be no pharmacological benefit to terminal AP inhibition with effective proximal AP inhibition via BCX9930, unless there is a medical reason not to do so. In this case, discontinuation from the study should be considered if the medical reason is nonresponse to BCX9930 therapy.

Details of all prior (within 30 days of Screening) and concomitant medication use, including all medications administered for the treatment of AEs, will be recorded in the source documentation/case report form (eCRF).

9.2. Prohibited Medications

All subjects in the study should refrain from daily use of taking prohibited medications throughout their study participation. A list of prohibited medications will be provided to sites. If

during the course of this study, additional information about the interaction of BCX9930 with prohibited medications becomes available from Phase 1 drug interaction studies, the list will be updated.

Throughout the course of the study, Investigators should inquire about newly initiated daily medications; the Investigator should compare these medications to the prohibited medication list.

Similarly, subjects should be made aware that there may be restricted medication in this study and should inform their treating physicians of the possibility of potential interactions.

Subjects and investigators should work with treating physicians to ensure that newly initiated daily medications are not included in the prohibited medication list. If the initiation of such a medication is unavoidable (ie, medically necessary and without an acceptable alternative), the Medical Monitor should be contacted to discuss the continued eligibility of the subject.

Prohibited medications currently include (see also Section 8.2):

[redacted]

9.3. Treatment Compliance

For subjects who have had a dose interruption since the previous BCX9930 study, the first dose on Day 1 will be given in the clinic. All other doses and all doses for subjects continuing from the prior study without interruption, will be taken at home during the dosing period following the instructions provided by the study site staff. BCX9930 may be taken with or without food.

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). 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. Investigators should remind participants who regularly miss doses of BCX9930 about the importance of treatment compliance.

In-Clinic Dosing:

Investigational product administered in the clinic will be given directly by the investigator, or qualified staff member, under medical supervision to confirm compliance. The date and time of the administered dose in the clinic will be recorded in the subject's source documents and eCRF.

At-Home Dosing:

Subjects will be provided instructions for taking daily doses of investigational product at home, including frequency and time of administration. Subjects will be instructed to maintain approximately the same dosing interval between study drug doses each day.

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.

Subjects will be instructed to bring all drug kits (both unused and used bottles) with them for each study visit. Accountability and adherence will be reviewed at each clinic visit. 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.

9.3.1. 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.

9.4. Randomization and Blinding

This is an open-label, non-randomized study. All subjects enrolled in the study will receive BCX9930 orally for up to 144 weeks, until drug is available by another mechanism (eg, expanded or market access) or until the Sponsor discontinues development of the product for PNH, whichever comes first.

9.5. Vaccination Requirements, and Vaccinations during Study, and Prophylactic Antibiotic Coverage

Unless local guidelines are more stringent, the 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).

Investigators will 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.

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.

10. STUDY DRUG MATERIALS AND MANAGEMENT

10.1. Study Drug

BCX9930 is a small molecule inhibitor of Factor D. The IMP will be supplied by BioCryst as 100, 200, and/or 250 mg tablets to allow for dose adjustments if needed for the safety management of the subject.

The active ingredient for this study is BCX9930, supplied by BioCryst. BCX9930 is a white or off-white powder.

The IMP will be administered by the oral route.

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

10.2. Study Drug Packaging and Labeling

The study drug will be packaged in the appropriate size bottle. Each bottle will be labeled with the information required per local law and may include: Sponsor name, study protocol number, description of the contents, a statement regarding the investigational (clinical trial) use of the study drug and expiry date.

10.3. Study Drug Storage

Study drug will be stored between 15°C and 25°C (room temperature).

10.4. Study Drug Preparation

No study drug preparation is required. Tablets will be taken from the provided bottles.

10.5. Administration

Subjects will take BCX9930 orally, either with or without food. Subjects will be treated for up to 144 weeks. Subjects should be encouraged to maintain an every-12-hour regimen and reminded of the importance of adherence to the dose schedule.

Subjects will take 400 mg BCX9930 BID. Throughout treatment with BCX9930, subjects should maintain adequate hydration to prevent the formation of highly concentrated urine.

10.5.1. Treatment Interruption and 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 13.9.5.4. Dose reduction should be done in consultation with the sponsor medical monitor (or designee). 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 10.5.2 for potential dose tapering options.

10.5.2. Dose Tapering

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

The decision to taper the dose and duration of any taper will 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.

10.6. Study Drug Accountability

The Investigator must maintain accurate records on a drug accountability form 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 supplies (eg, lot numbers) and disposition of supplies must be provided, signed by the Investigator or designee, and collected by the study monitor.

10.7. Study Drug Handling and Disposal

All medication not administered and used packaging materials 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 at the participating institution.

11. STUDY CONDUCT

11.1. Overview

This is an open-label, non-randomized study to evaluate the long-term safety and effectiveness of daily oral BCX9930.

Subjects will be eligible to receive study drug (BCX9930) for up to 144 weeks, until drug is available by another mechanism (eg, expanded or market access) or until the Sponsor discontinues development of the product for PNH (See Section 7.4), whichever comes first. Study drug will be discontinued for subjects who are deriving no clinical benefit, are intolerant of study drug, or experience an unacceptable drug-related TEAE as defined in more detail in Section 7.4. The Study will be discontinued if ongoing regulatory or Institutional Review Board/Ethics Committee (IRB/EC) approval is withdrawn, or in the event that technical or logistical factors prevent the ongoing conduct of the study. Subjects who discontinue study drug will have a minimum of 3 days hemolysis testing and then return to the clinic for an end-of-study visit 3 weeks after the last dose of study drug.

11.2. Schedule of Assessments

The schedule of assessments for this study is presented in Table 4 and procedures are described below. Where possible, it is preferred that procedures are performed in the following sequence during each clinic visit:

1. Questionnaires
2. 12-lead ECG
3. Blood pressure (BP), temperature, and pulse rate
4. Blood sampling; the preferred order for blood sampling is:

a. Hematology
b. Coagulation
c. Clinical chemistry and other laboratory assessments
d. PK blood sample

Table 4: Study Design and Schedule of Assessments

Assessment	***Screening Period*** [a]	***Baseline Visit*** [b]	***Treatment Period (Visit Schedule)***		***Unscheduled Visit Following BTH (within 48 hrs or next working day)***	***Discontinuation of Study Drug***	***End of Study Assessment***
	Screening Visit (Up to Day -28)	**(Day 1)**	**Week 4 and Every 4 wks up to Wk 96** [c] **(± 3 days)**	**Week 96 and Every 8 wks Until Wk 144** [d] **(± 6 days)**		**Hemolysis Monitoring for at least 3 Consecutive Days** [e]	**3 Weeks (± 3 Days) After Last Dose of Study Drug**
Informed consent [f]	X	X					
Inclusion-exclusion criteria	X	X					
Medical and medication history [g]	X	X					
Weight/height/BMI [h]	X	X	X	X			X
Physical examination [i]	X	X	X	X	X	X	X
ECG [j]	X	X	X	X			X
Pregnancy test (women) [k]	X	X	X	X			X
FSH test (women) [l]	X	X					
Vital signs	X	X	X	X	X	X	X
Clinical chemistry [m]/ hematology/coagulation/ urinalysis with microscopy [n]/iron, folate, vitamin B_{12} status labs [o]	X	X	X	X	X[p]	X[p]	X
Urine for biomarkers [q]			X	X	X	X	X

Assessment	***Screening Period*** [a]	***Baseline Visit*** [b]	***Treatment Period (Visit Schedule)***		***Unscheduled Visit Following BTH (within 48 hrs or next working day)***	***Discontinuation of Study Drug***	***End of Study Assessment***
	Screening Visit (Up to Day -28)	**(Day 1)**	**Week 4 and Every 4 wks up to Wk 96** [c] **(± 3 days)**	**Week 96 and Every 8 wks Until Wk 144** [d] **(± 6 days)**		**Hemolysis Monitoring for at least 3 Consecutive Days** [e]	**3 Weeks (± 3 Days) After Last Dose of Study Drug**
PNH symptoms assessment	X	X	X	X	X	X	X
Assessment of blood transfusions	X	X	X	X			X
Assess AEs, concomitant medications	X	X	X	X	X	X	X
PNH RBC and WBC clone size	X	X	X	X			
FACIT fatigue scale		X	X[r]	X			
QLQ-AA/PNH		X	X[s]	X			
TSQM		X	X[t]	X			
PK blood sample		X	X	X	X	X[u]	
PK urine collection [v]			X	X	X	X	
PD blood sample		X	X	X	X	X[u]	X
Study drug dosing [w]		←	———	→	X[x]		
Study drug accountability/ dispensing		X	X	X			X

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

[s] Every 6 months through Week 96 only (ie, Weeks 24, 48, 72, and 96 only).

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

11.3. Study Visits

Written informed consent must be obtained from each subject before initiation of any screening (or baseline, if no screening visit) assessments or procedures. Each subject will receive a copy of the signed and dated study-specific informed consent form (ICF). Subjects who have signed an ICF who are interested in participating in the study will then undergo assessments at a screening visit to determine eligibility (as applicable). Signing of the ICF may occur prior to the first on-study visit, which is defined as the visit where site-conducted procedures are first performed. For subjects who directly roll over from a previous study without interruption of dosing, the written informed consent will be obtained at the final on-study visit of the prior study.

11.3.1. Screening and Baseline Visit Requirements

If subjects have interrupted treatment for ≥ 31 days since last treatment in the prior BCX9930 study, they will need to be screened for participation in this study. Each subject will be determined as eligible for the study based upon screening evaluations.

A baseline visit is necessary for subjects who have had an interruption of treatment of 1 to 30 days. Those who roll over directly from the prior study without interruption must ensure all baseline assessments listed in Section 11.3.3 below are completed at the final on-treatment visit in the prior study.

11.3.2. Screening Visit

The Investigator (or designee) will conduct the following assessments at the screening visit, including:

- Signing of ICF
- Review of inclusion and exclusion criteria
- Medical and medication history including confirmation of adequate vaccination
- Complete physical examination
- 12-lead ECG
- Height/weight/body mass index (BMI) estimation
- Vital signs (BP, temperature, and pulse rate)
- Serum pregnancy test for female subjects of child-bearing potential
- Blood collection for follicle-stimulating hormone (FSH) for any woman post-menopausal ≤ 2 years (this may be omitted if menopausal status was demonstrated with elevated FSH in the prior study)
- Blood collection for clinical chemistry, hematology, coagulation
- Blood collection for PNH clone (RBC and WBC)
- Urine collection for urinalysis

- Recording of AEs and concomitant medications
- Disease-specific assessments
  - Assessment of PNH symptoms (fatigue, dyspnea, chest pain/discomfort, difficulty swallowing (esophageal pain), abdominal pain, headache, erectile dysfunction, hemoglobinuria, jaundice)
  - Review of blood transfusion history

In the case of time limitations for conduct of the screening visit, a site is permitted to perform screening assessments over more than one screening visit.

As part of general good medical practice, investigators should include vaccination history status as part of the medical history, assess risk of exposure, and arrange for any appropriate vaccinations to be administered based on local recommendations as well as individual subject considerations.

Rescreening of ineligible subjects, where there is a reasonable expectation that the subject will become eligible, will be approved or denied on a case-by-case basis by the Sponsor Medical Monitor. Retesting of specific assessments without entirely rescreening a subject may be permitted.

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

11.3.3. Baseline Visit (Day 1)

For all subjects, Informed Consent and Inclusion/ Exclusion criteria will be reviewed to ensure continued subject eligibility.

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

- Signing of ICF (if no screening visit)
- Review of inclusion and exclusion criteria and prohibited medications
- Review of medical and medication history
- Administration of questionnaires:
  - FACIT fatigue scale
  - QLQ-AA/PNH
  - TSQM
- Subject weight
- Complete physical examination
- Vital signs (BP, temperature, and pulse rate)
- 12-lead ECG
- Blood collection for clinical chemistry, hematology, and coagulation

- Blood sample for PNH clone (RBC and WBC)
- Urine pregnancy test for female subjects of child-bearing potential. A negative urine pregnancy result must be recorded in order for the subject to receive study drug.
- Urine collection for urinalysis with microscopy
- PK blood sample
- PD blood sample
- Review of concomitant medications and AEs
- Disease-specific assessments
  - Assessment of PNH symptoms (fatigue, dyspnea, chest pain/discomfort, difficulty swallowing (esophageal pain), abdominal pain, headache, erectile dysfunction, hemoglobinuria, jaundice)
  - Review of blood transfusions
- Study drug dispensing

Where possible, the questionnaires should be completed by the subject prior to other assessments (except signing of the ICF) to prevent influencing subject perceptions.

11.3.4. On-study Visits (Week 4 and every 4 weeks up to Week 96; Week 96 and every 8 weeks to Week 144)

Subjects will return to the clinic during Week 4 (Study Day 29 ± 3 days) and every 4 weeks up to Week 96 (Study Day 673, ± 3 days). Visits should be every 4 weeks until a subject has completed a total of 96 weeks on treatment with BCX9930 (ie, weeks in this study plus weeks in the previous study). Starting at Week 96 (Study Day 673, ± 3 days), subjects will return to the clinic every 8 weeks to Week 144 (Study Day 1009, ± 6 days).

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

The following assessments will be performed:

- Administration of questionnaires. Where possible, the questionnaires should be completed by the subject prior to other assessments:
  - FACIT fatigue scale at each visit through Week 96 only
  - TSQM questionnaire at Weeks 12, 24, 48, 72, and 96 only
  - QLQ-AA/PNH at Weeks 24, 48, 72, and 96 only
- Targeted physical examination
- Subject weight
- Vital Signs (BP, temperature, and pulse rate)

- 12-lead ECG every 12 weeks up to Week 96 (ie, Weeks 12, 24, 36, 48, 60, 72, 84, and 96) and every 24 weeks thereafter (ie, Weeks 120 and 144)
- Blood collection for clinical chemistry, hematology, coagulation, and iron, folate, B_{12} status labs (iron, folate, vitamin B_{12} status labs at Weeks 48, 96, and 144 only)
- Blood sample for PNH clone (RBC and WBC)
- PK plasma sample
- PK urine collection
- PD blood sample
- Urine collection for urinalysis with microscopy and urine pregnancy test for female subjects of child-bearing potential
- Urine collection for biomarker testing
- Review of concomitant medications and AEs
- Disease-specific assessments
  - Assessment of PNH symptoms (fatigue, dyspnea, chest pain/discomfort, difficulty swallowing (esophageal pain), abdominal pain, headache, erectile dysfunction, hemoglobinuria, jaundice)
  - Review of blood transfusions
- Study drug accountability and study drug dispensing (where necessary)

11.3.4.1. Safety Assessments for Renal Events

Subjects with sCr elevations as described in Section 13.9.5.3 will be required to complete additional assessments to monitor for potential renal toxicity at the investigational site, at a remote laboratory more convenient for the subject, or via a home health service. The minimum procedures to be completed at each assessment will depend on whether the subject is assessed at the investigative 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

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)

11.3.5. Hemolysis Monitoring Visits

Following discontinuation of study drug, either following completion of the treatment period or on premature discontinuation, subjects will return to the clinic for a minimum of 3 consecutive days to monitor for the onset of hemolysis. The following assessments will be performed:

- Targeted physical examination
- Vital signs (BP, temperature, and pulse rate)
- Blood collection for clinical chemistry and hematology
- Review of PNH symptoms
- Review of concomitant medications and AEs
- A single blood sample for PK and PD assessments will be collected 48 hours after treatment discontinuation

Following the 3 days of monitoring, if required, subjects may continue to be assessed every 2 days thereafter until the subject has stabilized to a new hemoglobin baseline (See Section 13.7).

11.3.6. Unscheduled Visit for Breakthrough Hemolysis

If subjects attend an unscheduled visit to assess BTH (See Section 13.9.5.5), the following parameters should be assessed:

- Targeted physical examination
- Vital signs (BP, temperature, and pulse rate)
- Review of PNH symptoms
- Review of concomitant medications and AEs
- Blood collection for hematology and clinical chemistry
- PK plasma sample

- Urine collection for biomarker testing
- PK urine collection
- PD blood sample

11.3.7. End of Study Visit

Subjects who permanently discontinue treatment will return to the clinic for the hemolysis monitoring visits detailed in Section 11.3.5. Subsequently they will return to the clinic 3 weeks (21 ± 3 days) after the date of their last dose of BCX9930 for their end-of-study assessments.

The following assessments will be performed at the end of study visit:

- Subject weight
- Targeted physical examination
- Vital signs (BP, temperature, and pulse rate)
- 12-lead ECG
- Blood collection for clinical chemistry, hematology, coagulation
- Urine collection for urinalysis with microscopy, urine pregnancy test for female subjects of childbearing potential
- Urine collection for biomarker testing
- Disease-specific assessments:
  - Assessment of PNH symptoms (fatigue, dyspnea, chest pain/discomfort, difficulty swallowing (esophageal pain), abdominal pain, headache, erectile dysfunction, hemoglobinuria, jaundice)
  - Review of blood transfusions
- PD blood sample
- Review of concomitant medications and AEs
- Study drug accountability (for early withdrawal visit only)

If an AE is ongoing at the end-of-study visit, additional clinic visit(s) or telephone contact(s) may be warranted (see Section 13.9.3).

11.4. Contraception Requirements

11.4.1. Female Subjects and Female Partners of Male Subjects

A woman of childbearing potential (WOCBP) is defined as a nonmenopausal female who has not had a hysterectomy, bilateral salpingectomy or bilateral oophorectomy.

WOCBP must agree to use a highly effective contraceptive method throughout the study and for a duration of 30 days after the last dose of study drug. The following methods are acceptable:

- Surgical sterilization (ie, hysterectomy, bilateral salpingectomy or bilateral oophorectomy)
- Vasectomy of the sole male partner, and the vasectomized partner has received medical assessment of surgical success
- Placement of an intrauterine device or intrauterine system
- Hormonal contraception associated with inhibition of ovulation (implantable, injectable, patch or oral contraceptives)

True abstinence is acceptable 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.

A woman of nonchildbearing potential is defined as postmenopausal (without menses for ≥ 12 months [without an alternative medical cause] with follicle-stimulating hormone (FSH) > 40 mIU/mL, or who have had a hysterectomy, bilateral salpingectomy or bilateral oophorectomy.

Female participants must abstain from egg donation for a period of up to 90 days after last dose of study drug.

11.4.2. Male Subjects

Highly effective contraceptive methods for male subjects are:

- Surgical sterilization (ie, vasectomy that has been confirmed to be successful), or hysterectomy, bilateral salpingectomy or bilateral oophorectomy of a female partner
- Partner's use of an intrauterine device or intrauterine system
- Partner's use of hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable, or patch)

True abstinence is acceptable when it is in line with the subject's preferred and usual lifestyle. If a subject is usually not sexually active but becomes active, he, with his female partner, must meet the requirements listed above.

Male subjects must abstain from sperm donation for a period of 90 days after last dose of study drug and if the subject has a female partner, he must agree to use a barrier method of contraception for at least 90 days after last dose of study drug.

12. ASSESSMENT OF EFFICACY

12.1. Clinical Response Assessment

The following clinical parameters will be assessed at baseline and each study visit:

- Red or black (cola) colored urine
- Dyspnea

- Difficulty swallowing (esophageal pain)
- Abdominal pain
- Erectile dysfunction
- Fatigue
- Headache
- Jaundice
- Chest pain/discomfort

12.2. Blood Transfusions Review

At screening, the number of blood transfusions since the end of the prior trial will be recorded. During the trial, all blood transfusions will be documented, including the number of units and the blood product administered.

12.3. Pharmacokinetic Blood Sample Collection

A single blood sample for PK analyses (ie, "sparse sampling" to support population PK and PK/PD modeling) will be drawn from all subjects at baseline and every study visit to the investigative site thereafter, at any BTH visit to the investigative site, and 48 hours after treatment discontinuation at the hemolysis monitoring visit.

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 visits to facilitate PK sampling at different times relative to the previous dose. It is preferred that the cumulative sparse PK data for each subject will contain samples drawn within each of the following intervals (all relative to the previous dose for BID dosing): 0.5 to 2 hours, 2 to 5 hours, and 10 to 12 hours post dose.

Subjects do not need to withhold any study drug/BCX9930 doses on clinic days or take a dose in the clinic, unless the clinic visit falls during the subject's normal time of dosing.

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.

Instructions for collection, processing, storage, and shipment of PK samples will be provided to the clinical site in the Laboratory Manual.

12.4. Pharmacodynamic Blood Sample Collection

Venous blood samples will be withdrawn via an indwelling cannula or by venipuncture at Baseline and each subsequent visit during the treatment period. Where feasible, and as applicable, blood samples for PD analyses should be collected at the same time as sparse PK samples. Additional details of sample tubes and processing will be contained in the Laboratory Manual.

Blood samples will be collected for plasma Factor Bb, PNH clone size (RBC and granulocyte), AP activity as assessed via AP Wieslab, and additional exploratory assays at baseline and subsequent visits. An aliquot of serum and plasma will be retained for potential exploratory PD assays to elucidate the PD properties of BCX9930.

For those subjects who discontinue study drug therapy, a sample of blood for PD analysis (which may include Factor Bb, PNH clone size (RBC and granulocyte), AP activity and exploratory assays) will be collected 48 hours after the last dose of BCX9930. This may be split into multiple samples, if needed.

For subjects being evaluated for BTH, a single blood sample for PD analysis (which may include Factor Bb, PNH clone size (RBC and granulocyte), AP activity, and exploratory assays) will be collected.

12.5. Urine Collection for Measurement of Parent-Metabolite Concentration

Spot urine samples will be collected for analysis of the concentration of BCX9930 and metabolites.

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.

12.6. Patient Reported Outcomes

The following questionnaires will be completed by study subjects through Week 96 only:

The QLQ-AA/PNH will be completed at Baseline and at the Week 24, 48, 72, and 96 visits only.

The TSQM questionnaire will be completed at Baseline and at the Week 12, 24, 48, 72, and 96 visits only.

The FACIT fatigue scale will be completed at Baseline and subsequent treatment visits through Week 96 only.

Each questionnaire will be translated into the local language as required. For all subject-completed forms, clinic staff should ensure the subject reads the instructions and completes the questionnaire in full. The Investigator or clinic staff is 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.

13. ASSESSMENT OF SAFETY

13.1. Demographic/Medical History

Demographic information, including year of birth, sex, race and ethnicity, and medical and medication history will be captured for each subject participating in the study at the Screening visit, or Baseline visit if Screening visit is omitted. Medical history, medication review, and review of inclusion and exclusion criteria and prohibited medications will also be rechecked as outlined in Section 11.

13.2. Vital Signs

Vital signs comprised of temperature, BP, and pulse rate will be taken per the schedule of assessments specified in Table 4.

Vital sign measurements should be obtained after resting at least 5 minutes in a quiet room at a comfortable temperature, with the subject's arm unconstrained by clothing or other material. BP 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 BP or ECG machine.

13.3. Weight, Height, and Body Mass Index

Height and weight should be determined as outlined in Table 4 and Section 11. Both height and weight are measured at screening. For all subsequent visits, only weight is measured.

For determination of height and weight, subjects should be dressed, without shoes. BMI should be calculated using the following formula:

$$\text{BMI} = \text{weight (kg)}/\text{height (m)}^2$$

13.4. Physical Examination

Subjects will undergo a physical examination at per the schedule of assessments specified in Table 4. A full physical examination should be conducted at Screening (if applicable) and baseline. All subsequent physical examinations may be targeted (ie, symptom-driven). Genitourinary and breast examinations may be omitted when not required by normal site practice. Subjects receiving immunosuppressive therapy should be monitored for signs and symptoms of infection.

13.5. Electrocardiogram

A standard bedside 12-lead ECG machine or telemetry system that calculates HR and measures the PR, QRS, QT, RR, and corrected QT (QTcF) intervals will be utilized. Twelve-lead ECGs

will be measured after the subject has been in the supine position for a minimum of 10 minutes as detailed in Table 4 and Section 11. All ECGs will be single assessments.

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 an additional 10-minute rest in a supine position in the event of a change from baseline in QTcF > 60 msec or a QTcF interval > 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 ECGs may be requested by the Sponsor.

13.6. Laboratory Assessments

Blood and urine samples will be obtained per the schedule of assessments in Table 4. A list of the laboratory parameters measured is presented in Table 5.

Samples will be collected into appropriate tubes, as specified by the clinical laboratory. All laboratory samples, with the exception of hemolysis testing at study drug discontinuation, will be analyzed by a central laboratory. Local laboratories may be used in place of the central laboratory at the investigator's discretion for logistical reasons (eg, such as delays in transport due to COVID-19), they may also be utilized for analysis of samples collected for assessment of possible AEs. Urine microscopy for samples collected at the investigative site will be performed at the site's local laboratory, where appropriate on-site testing capability exists (see Section 13.6.1). The additional renal and hepatic safety assessments may be performed at the investigative 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 laboratory must be provided to the investigational site. Reference ranges for each local laboratory will be provided to the Sponsor and included in data listings. 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 in the opinion of the Investigator should be recorded as an AE and handled as described in Section 13.9.

Table 5: Clinical Laboratory Evaluations

Chemistry	**Coagulation**
• Albumin • Alkaline phosphatase (ALP) • Alanine aminotransferase (ALT) • Aspartate aminotransferase (AST) • Bilirubin (total and direct) • Blood glucose • Blood urea nitrogen (BUN) • Calcium • Sodium • Potassium • Chloride • Creatine kinase • Creatinine (sCr) and estimated glomerular filtration rate (eGFR) • Lactate dehydrogenase (LDH) • Total serum protein • Uric acid • Amylase • Lipase (reflex test if amylase elevated) • Cholesterol (total, high- and low-density lipoprotein) • Magnesium • Triglycerides	• Prothrombin time (PT) and international normalized ratio (INR) • Activated partial thromboplastin time (aPTT) • Thrombin time • D-dimer • Prothrombin fragment 1+2
	Pregnancy Test
	Serum (screening) and urine (other scheduled visits) βHCG for women of childbearing potential only
	Hematology
	• Hemoglobin • Hematocrit • Erythrocytes (RBC) • Mean corpuscular hemoglobin (MCH) • Mean corpuscular hemoglobin concentration (MCHC) • Mean corpuscular volume (MCV) • White blood cell count, with differential (lymphocytes, monocytes, neutrophils, eosinophils, and basophils) • Absolute reticulocyte count • Platelets • PNH RBC clone • PNH WBC clone
Urinalysis with microscopy	**Additional Tests**
• Specific gravity • Blood • Bilirubin • Glucose • Leukocytes • Ketones • Nitrites • pH • Protein • Urobilinogen • Microalbumin to creatinine ratio	• FSH for women with no menses for ≥ 12 months • C3 and C4 (at baseline) • Haptoglobin • C-reactive protein • Cystatin C (in blood)
Hemolysis monitoring at discontinuation of study drug or following BTH	**Iron, Folate, and Vitamin B_{12}**
• Lactate dehydrogenase (LDH) • Serum creatinine • Blood urea nitrogen (BUN) • RBC • Hemoglobin • Complete blood count • PK and PD blood samples	• Ferritin • Folate • Hepcidin • Iron • Total iron binding capacity • Transferrin • Vitamin B_{12}

Urine Biomarkers
• β-2-microglobulin • Cystatin C (in urine) • Kidney injury molecule 1 (KIM-1) • Liver-type fatty acid-binding protein (L-FABP) • Urine albumin to creatinine ratio (uACR) • Urine neutrophil gelatinase-associated lipocalin (uNGAL) • Urine aliquots for storage (urine will be aliquoted, frozen and sent to the central laboratory for possible future analysis of urine biomarkers)

13.6.1. 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 investigative 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 laboratory does not have on-site testing capability, the sample may be sent to the designated central laboratory.

Urine will be collected at all investigative site visits for analysis of uACR, β-2-microglobulin, cystatin C, uNGAL, KIM-1, and 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.

13.6.2. Menopause and Pregnancy Screen

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

For women of childbearing potential, a serum pregnancy test will be administered at screening. Urine pregnancy tests will be assessed at all subsequent visits. A serum pregnancy test should immediately be drawn and sent for analysis for any positive urine pregnancy test.

Urine pregnancy test kits will be provided by the central laboratory but will be resulted locally.

Starting at Week 100, women of childbearing potential will start performing urine pregnancy tests at home every 4 weeks (i.e., in between clinic visits). The results will be recorded by the site. If the urine pregnancy test is positive, the subject should contact the site immediately.

13.7. Monitoring for Hemolysis at Discontinuation of BCX9930

By inhibiting the alternative pathway of complement, the factor D inhibitor BCX9930 may improve hemoglobin levels by reducing the hemolysis of PNH RBCs. Thus, following discontinuation of BCX9930 treatment, subjects may be at risk of serious hemolysis.

Based on available data regarding the PK and PD of BCX9930, serious hemolysis, if it occurs, would be expected to present within days after discontinuation of therapy, therefore when subjects stop study drug therapy, either at the scheduled end of treatment or on premature discontinuation, they must be monitored for hemolysis, as described below. Samples may be analyzed at a local laboratory.

Hemolysis will be monitored by daily laboratory assessment of LDH, hemoglobin, complete blood count (CBC), and serum chemistry (serum creatinine, blood urea nitrogen [BUN]), along with vital signs and a targeted physical examination, for at least 3 consecutive days after discontinuing BCX9930. Sample(s) for PD biomarker analysis and PK will be collected 48 hours after the last dose of BCX9930.

Following the 3 days of monitoring, additional laboratory monitoring may be necessary, based upon the safety assessment of the Investigator and the Sponsor Medical Monitor.

13.8. Assessment of Breakthrough Hemolysis Episodes

It is possible that subjects may experience episodes of BTH while on study drug. Symptoms of BTH may include fatigue, hemoglobinuria, abdominal pain, dysphagia, shortness of breath, or thrombosis. Subjects who experience such symptoms should contact their study Investigator upon first awareness and should be assessed for BTH within 48 hours of this contact, or on the first working day following this contact.

Assessment of episodes of BTH will include LDH, hemoglobin, CBC, and serum chemistry (serum creatinine, BUN), along with vital signs and a targeted physical examination. In addition, sample(s) for PD and PK will be collected.

Local laboratory tests may be used for parts of hemolysis monitoring, as necessary.

13.9. Adverse Events

AEs will be assessed and recorded from the time of signing of the informed consent through the appropriate follow-up period. Full details on recording and reporting AEs are provided in Sections 13.9.3 and 13.9.4.

13.9.1. Definition of Adverse Events

13.9.1.1. 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.

AEs include the following:

- AEs not previously observed in the subject that emerge during the protocol-specified AE reporting period (see Section 13.9.3).
- Findings from protocol-mandated interventions. This can include laboratory assessments performed in the clinical study. AEs should only be reported 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.
- In addition, in this study the disease-related events of BTH and thromboembolic events will be reported as AEs, even if deemed related to the disease under investigation.

An adverse reaction is defined in ICH Harmonised Tripartite Guideline E2A 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.

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

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

13.9.1.2. Serious Adverse Event

An SAE is an AE/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 a SAE 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, abortion (spontaneous or induced), fetal demise, and still birth along with congenital abnormalities in the newborn, should be reported as separate SAEs (see Section 13.9.4.3).

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 13.9.5.6) Details of signs or symptoms, clinical management, and outcome should be reported, if available. Overdose without associated signs or symptoms should not be recorded as AEs but should be recorded as protocol deviations.

13.9.1.3. Events of Special Interest

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

At each visit, subjects will be assessed for EOSIs that may have occurred since the last visit. All EOSI are considered AEs and should be reported on the AE eCRF. For each EOSI reported, sites will be prompted to complete an EOSI Targeted Assessment. (In case an EOSI meets criteria to be reported as an SAE, please follow procedures as described in Section 13.9.3).

13.9.1.4. 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 hemolysis, SARS-CoV-2 infections (asymptomatic and symptomatic), [redacted]

13.9.1.5. Definition of Severity

All AEs will be assessed (graded) for severity by the Investigator and classified using the DMID criteria for grading AEs (November 2007, see Appendix 1). Any AEs not covered by the DMID criteria will be assessed and classified into 1 of the 4 clearly defined categories as follows:

Mild:	(Grade 1): Transient or mild symptoms; no limitation in activity; no intervention required. The AE does not interfere with the participant's normal functioning level. It may be an annoyance.
Moderate:	(Grade 2): Symptom results in mild to moderate limitation in activity; no or minimal intervention required. The AE produces some impairment of functioning, but it is not hazardous to health. It is uncomfortable or an embarrassment.
Severe:	(Grade 3): Symptom results in significant limitation in activity; medical intervention may be required. The AE produces significant impairment of functioning or incapacitation.
Life-threatening:	(Grade 4): Extreme limitation in activity, significant assistance required; significant medical intervention/therapy required to prevent death, hospitalization or hospice care probable.

13.9.1.6. Relationship to Study Drug

An Investigator who is qualified in medicine must make the determination of relationship to the investigational product 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 investigational product 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 AE/SAE and the investigational product is determined to be "possible," "probable," or "definite," the event will be considered to be related to the investigational product for the purposes of expedited regulatory reporting.

13.9.2. Recording Adverse Events

AEs spontaneously reported by the subject and/or in response to an open question from the study personnel or revealed by observation will be recorded during the study at the investigational site. Only clinically significant changes from baseline in protocol-mandated assessments such as vital signs, laboratory values, and ECGs should be reported as AEs. Information about AEs and SAEs will be collected from the signing of consent form until the end of the study. The AE term should be reported in standard medical terminology and as a diagnosis (not symptoms) when possible. For each AE, the Investigator will evaluate and report the onset (date and time), resolution (date and time), severity, causality, action taken with study drug, seriousness, and outcome,

Severity will be assessed by the Investigator using the DMID scale.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity, defined in Section 13.9.1.5, whereas seriousness is defined by the criteria under Section 13.9.1.2 An AE of severe intensity may or may not be considered serious.

Should a pregnancy occur, it must be reported and recorded on BioCryst's pregnancy form. Pregnancy is not regarded as an AE unless there is a suspicion that an investigational product may have interfered with the effectiveness of a contraceptive medication.

The outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth, or congenital abnormality) must be followed up and documented, even if the subject was discontinued from the study.

All reports of congenital abnormalities/birth defects are SAEs. Spontaneous miscarriages, elective abortions, and still-births should also be reported and handled as SAEs.

13.9.3. 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 informed consent. All AEs and SAEs are to be reported on the AE eCRF.

AEs should be documented on 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 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 13.9.1.5 for AE grading). For all Grade 3 and 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 submission of an SAE report form via email and entering the event onto the AE eCRF. The SAE report form is a detailed, written report 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.

13.9.4. Reporting

13.9.4.1. Serious Adverse Events and Suspected Unexpected Serious Adverse Reactions

All SAEs regardless of relationship to study drug must be reported within 24 hours to the Sponsor. Email or phone call to the Sponsor Medical Monitor should be followed by submission of the SAE report form (completed with as much information as available) via email and entry of the event on the eCRFs. The SAE report forms should be sent to the following email address:

[redacted]
Email: safety@biocryst.com

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.

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 their 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 IEC/IRBs 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 IEC/IRBs, 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.

13.9.4.2. Reporting Events of Special Interest

All EOSIs are considered AEs and should be reported on the AE eCRF. For each EOSI reported, sites will be prompted to complete an EOSI Assessment Form. The EOSI Assessment Form will collect targeted information such as specific physical exam findings and relevant investigative studies and procedures.

13.9.4.3. Pregnancy

Any female subject who becomes pregnant during the course of the study should have study drug/IMP 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 Confirmation 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 13.9.3 and Section 13.9.4. Any complications reported in a subject's pregnant partner should be reported on the Pregnancy Confirmation 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.

13.9.4.4. Serious Breaches

It is the responsibility of the Sponsor to notify the competent authority of any serious breach of Good Clinical Practice (GCP), which 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.

13.9.5. Toxicity Management

The Investigator (or qualified designee) will grade clinically significant events and laboratory abnormalities (if considered AEs) according to that detailed in Section 13.9.1.5. Grade 3 and 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.

13.9.5.1. Severe Infections

Special evaluation of all study drug-related severe infections is required as per Section 13.9.1.3 and reporting per Section 13.9.4.2. Subjects should be instructed regarding the risk of infections and contact the Investigator immediately on becoming aware of any new or worsening symptoms. Management of infections should be based on best medical practice and address the subject's presentation.

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

All treatment-emergent ALT elevations > 3 × ULN should be confirmed, preferably within 72 hours, with repeat assessment of ALT, AST, total bilirubin, ALP, prothrombin time/INR, and complete blood count with differential. These may be repeated at a local laboratory as long as the

results are reported to the investigator when available and the investigative site contacts the subject to ascertain any symptoms.

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

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

- ALT or AST > 8 × ULN
- ALT or AST > 5 × ULN for more than 2 weeks
- ALT or AST > 3 × ULN and (total bilirubin > 2 × ULN [unless there is evidence that the increase in bilirubin is due to hemolysis or Gilbert's syndrome] or INR > 1.5 × ULN in the absence of warfarin therapy)

ALT or AST > 3 × ULN with the appearance of fatigue (over baseline fatigue), nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%)

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

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

If Hy's Law criterion is met and is assessed as probably or definitely related per treatment discontinuation criterion in Section 7.4.1, 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.

13.9.5.3. Renal Events: Monitoring, Evaluation, and Discontinuation Criteria

There are multiple potential reasons that sCr can increase in those with PNH, including hemolysis. For subjects who have a confirmed treatment-emergent increase in sCr, evaluations to investigate potential etiology should be chosen considering baseline renal function, history of

prior renal events including those due to PNH, other comorbidities, concomitant medications, and other relevant factors. In addition:

- For all subjects, ensure adequate hydration, stop or substitute potentially nephrotoxic medications, and evaluate for tuberculosis if sterile pyuria is present if potential exposure
- For treatment-emergent increases in sCr > ULN 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 the 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

Table 6 provides additional guidance based on sCr levels.

Table 6: Actions Based on Serum Creatinine Levels

sCr > ULN but ≤ 1.5 × ULN	• Assessment frequency based on the magnitude of the sCr rise until sCr ≤ ULN (ie, every 2 to 4 weeks). • Consider evaluation by nephrologist
sCr > 1.5 × ULN but < 3 × ULN	• Assessment frequency weekly until sCr ≤ ULN • Evaluation by nephrologist
sCr ≥ 3 × ULN	• BCX9930 should be discontinued, with taper (see Section 10.5.2), after confirmation • If hemolysis or any other potentially reversible cause is suspected, contact sponsor medical monitor

Abbreviations: sCr = serum creatinine; ULN = upper limit of normal.

13.9.5.4. Hemolysis After Discontinuation of BCX9930

Subjects should be instructed regarding the risk of hemolysis that may occur after the discontinuation or interruption of BCX9930. Subjects will come to the clinic for hemolysis monitoring for at least 3 days following BCX9930 discontinuation or interruption and should contact the Investigator if they experience any worsening of their PNH symptoms, such as fatigue, hemoglobinuria, abdominal pain, dysphagia, shortness of breath, or thrombosis, after the discontinuation or interruption of BCX9930. Monitoring parameters for hemolysis after study drug discontinuation or interruption are listed in Section 13.7.

If hemolysis occurs after discontinuation of BCX9930, treatment considerations may include blood transfusion (packed RBCs), exchange transfusion, anticoagulation, or local standard of care, as determined by the Investigator.

13.9.5.5. Breakthrough Hemolysis

Subjects should be instructed regarding the risk of BTH. Subjects should contact the Investigator immediately after becoming aware of any worsening of their PNH symptoms, such as fatigue, hemoglobinuria, abdominal pain, dysphagia, shortness of breath, or thrombosis while continuing dosing of BCX9930. Study assessments for BTH are described in Section 13.8.

BTH, if it occurs, should be treated according to local standard of care, as determined by the Investigator. Subjects should continue dosing with BCX9930 unless instructed to discontinue by the Investigator.

Management of thrombotic events should be according to local standard of care.

13.9.5.6. Overdose

To date, there is no experience with overdose of BCX9930. In the event that study personnel become aware of an overdose of study drug/IMP 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.

13.10. Data Monitoring Committee

An independent DMCwill be assembled for this study. The DMC convened and reviewed safety data once the first 4 subjects enrolled completed 12 weeks of dosing. Subsequent meetings were convened as detailed in the DMC Charter.

The DMC may meet at any time should a safety issue arise that requires DMC input or a partial or full data review. A separate DMC charter maintained in the trial master file describes membership, roles, timing of DMC review, and responsibilities of the DMC members.

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 will be outlined in a separate charter.

14. STATISTICS

14.1. Sample Size Considerations

No sample size calculations were conducted for this open-label, long-term safety study. Approximately 200 subjects may be enrolled in this study, to allow continued access to BCX9930 following a subject's participation in a prior BCX9930 study.

14.2. Stratification

Not applicable.

14.3. 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.

14.3.1. Analysis Populations

The analysis populations are defined below.

14.3.1.1. Safety Population

The safety population will include all subjects who received at least 1 tablet of study drug. This population will be used for all analyses of accountability, demographics, BCX9930 drug concentrations, and safety.

14.3.1.2. Intent to Treat Population

The intent to treat (ITT) population will include all subjects who receive at least 1 tablet of study drug and have post baseline assessment of PNH symptoms and/or laboratory data. The ITT population will be the population for effectiveness analyses.

14.3.2. 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 study visit.

For subjects directly rolling over from another BCX9930 study without treatment interruption, the change from baseline analyses will use the baseline value as reported in the prior study.

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).

14.3.3. Missing Data

For subjects who prematurely discontinue the study, all available data will be included for the key safety and effectiveness analyses.

14.3.4. Subject Demographic and Disposition Data

Demographic data and baseline characteristics including age, gender, race or ethnicity, height, weight, BMI, and PNH history will be summarized. Time from last BCX9930 dose to baseline will be summarized and listed as applicable.

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

14.3.5. Analysis of Safety Variables

Safety endpoints that will be summarized, at a minimum, include the proportion of subjects 1) with TEAEs; 2) who discontinue BCX9930 due to TEAEs; 3) with treatment-emergent SAEs; 4) with treatment-emergent Grade 3 or 4 AEs; and 5) with treatment-emergent Grade 3 or 4 laboratory abnormalities. In addition, the proportion of subjects who received a reduced dose due to tolerability issues at the full dose will be summarized.

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

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, treatment-emergent SAEs, AEs considered 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.

Descriptive summaries for vital signs, weight, bedside ECG parameters, and clinical laboratory results will be presented. Laboratory abnormalities will be graded according to the DMID Adult Toxicity Table (Publish Date: Draft, November 2007; Appendix 1).

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

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

Clinically significant abnormal morphological ECG findings will be summarized.

The change from baseline in QTcF will be determined by routine ECGs. At each time point ECGs are analyzed, an individual subject's change from baseline will be calculated as:

Δ_{ik}= (QTcF for subject at time point k – Baseline QTcF)

For subjects who are directly rolling over from a previous study, the pretreatment ECG value obtained at the final on-treatment visit in the previous study will serve as the baseline ECG value.

For routine ECGs, the number and proportion of subjects with QTcF $\leq$ 450, > 450 to $\leq$ 480, > 480 to $\leq$ 500, and > 500 msec; or changes of $\leq$ 30, > 30 to $\leq$ 60, or > 60 msec will be summarized.

Physical examination findings will be listed.

Concomitant medications and those discontinued during the study will be coded using the World Health Organization drug dictionary and summarized. Subjects with medications changes prior to baseline may also be summarized.

14.3.6. Analysis of Clinical Measurements of PNH

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

Breakthrough hemolysis is defined as ≥ 1 new or worsening symptom/sign of intravascular hemolysis (fatigue, hemoglobinuria, abdominal pain, dyspnea, anemia [hemoglobin < 10 g/dL], major adverse vascular event [including thrombosis], dysphagia, or erectile dysfunction) in the presence of lactate dehydrogenase (LDH) ≥ 2 times the upper limit of normal (ULN). Frequency of BTH and time to first BTH will be summarized by treatment group.

14.3.7. Analysis of Effectiveness Variables for PNH

The following effectiveness endpoints will be summarized and listed:

- Durability of response
- Categorization of response according to the criteria in Section 14.3.7.1
- PROs: QLQ-AA/PNH, FACIT fatigue scale, TSQM scores
- Clinical measurements of PNH (LDH, hemoglobin, haptoglobin, reticulocytes, transfusion requirements)
- Subjects with dose escalation
- Discontinuations due to lack of efficacy
- Disease severity

Details of these analyses will be provided in the SAP.

14.3.7.1. Hematological Response Categories

Hematological response will be assessed every 6 months according to the criteria proposed by Risitano and colleagues (Risitano, Marotta, et al. 2019). Hemoglobin and RBC transfusions will be primarily used to assess response. Additionally, LDH and absolute reticulocyte count (ARC) will be used to distinguish between complete and major response (Table 7):

Table 7: Hematological Response Categories

Response Category	RBC Transfusions	Hemoglobin (g/dL) [a]	LDH × ULN [a]	ARC (/µL)[a]
Complete response	None	≥ 12	≤ 1.5	≤ 150,000
Major response	None	≥ 12	> 1.5	Or > 150,000

Response Category	RBC Transfusions	Hemoglobin (g/dL) [a]	LDH × ULN [a]	ARC (/µL)[a]
Good Response	None	≥ 10 and < 12		
Partial response	≤ 2 every 6 months	≥ 8 and < 10		
Minor response	≤ 2 every 6 months	< 8		
	3 to 6 every 6 months, or reduction of ≥ 50%[b]	< 10		
No response	> 6 every 6 months	< 10		

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

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

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

14.3.8. Interim and Final Analyses

Interim analyses may be performed during the course of the study as needed to support regulatory filings and safety updates. The final analysis will be performed when the last subject has completed the final study visit, the data are cleaned, and the database has been authorized for analysis.

14.3.9. Pharmacokinetic Analyses

Sparse plasma and spot urine samples for determination of BCX9930 concentrations are planned to be collected at each study visit to the investigative site and 48 hours after evidence of BTH. Plasma and urine concentrations of BCX9930 will be summarized by dose regimen and study visit. Metabolites of BCX9930 may also be analysed if deemed important.

PK data will be incorporated into models of PPK and PK/PD as appropriate. These analyses will include data pooled across multiple studies and will be reported separately from the clinical study report.

14.3.10. Pharmacodynamic Analyses

Descriptive statistics, including change from baseline, will be provided by study visit and dose regimen. Exposure-response analyses of the relationships between efficacy endpoints and BCX9930 plasma concentrations may be explored using model-based techniques as applicable. Model-based analyses will incorporate data from multiple studies and will be summarized separately from the clinical study report.

15. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

15.1. Study Monitoring

Before an investigational site can enter a subject into the study, a representative of BioCryst will visit 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 representatives. This will be documented in a Clinical Study Agreement between BioCryst and the investigator.

During the study, a monitor from BioCryst or representative will have regular contacts with the investigational site, 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 case report forms, and that investigational product accountability checks are being performed
- Perform source data verification. This includes a comparison of the data in the case report forms 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.
- Confirm AEs and SAEs have been properly documented on eCRFs and confirm any SAEs have been forwarded to BioCryst.

The monitor will be available between visits if the investigator(s) or other staff needs information or advice.

15.2. Audits and Inspections

Authorized representatives of BioCryst, a regulatory authority, an IEC or an IRB 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, GCP guidelines of the ICH, and any applicable regulatory requirements. The investigator should contact BioCryst immediately if contacted by a regulatory agency about an inspection.

16. QUALITY CONTROL AND QUALITY ASSURANCE

To ensure compliance with Good Clinical Practices and all applicable regulatory requirements, BioCryst may conduct a quality assurance audit. Please see Section 15.2 for more details regarding the audit process.

17. REGULATORY AND ETHICAL CONSIDERATIONS

17.1. Ethics Review

Before initiation of the study at the investigational site, the protocol, ICF, subject information sheet (if applicable), written information provided to subjects and any other relevant study documentation will be submitted to the appropriate IRB/IEC. Written approval of the study must be obtained before the investigational medicinal product is released to the Investigator and the study site may be opened for enrollment. Any necessary extensions or renewals of IRB/IEC approval must be obtained for changes to the study such as modification of the protocol, ICF, written information provided to subjects, and/or other procedures. After the protocol has been submitted, any amendment must be agreed by the Investigator after discussion with the Sponsor and will be formally documented. All substantial amendments will be submitted for an opinion as required by current regulations.

Written reports of clinical study status will be submitted to the IRB/IEC in accordance with the applicable regulations. The IRB/IEC will be promptly provided any new information that may adversely affect the safety of the subjects or the conduct of the study. The study will be considered to be completed once the last subject completes the last study visit (follow-up visit after the last study dose). A final study notification will also be forwarded to the IRB/IEC and competent authority after the study is completed or in the event of premature termination of the study in accordance with the applicable regulations.

Copies of all contacts with the IRB/IEC should be maintained in the study file. Copies of clinical study status reports (including termination) should be provided to BioCryst.

17.2. Ethical Conduct of the Study

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

17.3. Written Informed Consent

The Investigator(s) at each center will ensure that the subject is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Subjects must also be notified that they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

The subject's signed and dated informed consent must be obtained before conducting any study procedures.

The Investigator(s) must maintain the original, signed ICF. A copy of the signed ICF must be given to the subject.

17.4. Insurance

Insurance coverage shall be provided in accordance with the regulations of each individual country for all subjects enrolled in the trial from the time of the subject's inclusion into the trial (ie, from the time informed consent is given). Appropriate insurance coverage is provided by the Sponsor, in line with legal requirements and ICH-GCP guidance and in accordance with the (local) regulations of each individual country.

17.5. Payment to Subjects

Reasonable compensation to study subjects and reimbursement of travel expenses (where applicable) will be provided as approved by the IRB/IEC responsible for the study at the Investigator's site.

17.6. Treatment After a Subject's Study Completion or Withdrawal

Following completion of the planned study treatment, or following early withdrawal, subjects will be offered the standard care offered by their study center.

18. DATA HANDLING AND RECORD KEEPING

18.1. Inspection of Records

BioCryst 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.

18.2. Retention of Records

The Principal Investigator must maintain all documentation relating to the study for a period of 2 years after the last marketing application approval, or if not approved 2 years following the discontinuance of the test article for investigation. If it becomes necessary for BioCryst or the Regulatory Authority to review any documentation relating to the study, the Investigator must permit access to such records.

18.3. 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 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.

19. 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 trial results.

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21. APPENDICES

APPENDIX 1: DMID ADULT TOXICITY TABLE (DRAFT: NOVEMBER 2007)

Copies of the DMID Toxicity Table will be available to medical staff throughout the project.

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ABBREVIATIONS: Abbreviations utilized in the Table:

ULN = Upper Limit of Normal	LLN = Lower Limit of Normal
R_x = Therapy	Req = Required
Mod = Moderate	IV = Intravenous
ADL = Activities of Daily Living	Dec = Decreased

ESTIMATING SEVERITY GRADE

For abnormalities NOT found elsewhere in the Toxicity Tables use the scale below to estimate grade of severity:

GRADE 1	**Mild**	Transient or mild discomfort (< 48 hours); no medical intervention/therapy required
GRADE 2	**Moderate**	Mild to moderate limitation in activity - some assistance may be needed; no or minimal medical intervention/therapy required
GRADE 3	**Severe**	Marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalizations possible
GRADE 4	**Life-threatening**	Extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable

SERIOUS OR LIFE-THREATENING AEs

ANY clinical event deemed by the clinician to be serious or life-threatening should be considered a grade 4 event. Clinical events considered to be serious or life-threatening include, but are not limited to: seizures, coma, tetany, diabetic ketoacidosis, disseminated intravascular coagulation, diffuse petechiae, paralysis, acute psychosis, severe depression.

COMMENTS REGARDING THE USE OF THESE TABLES

- Standardized and commonly used toxicity tables (Division of AIDS, NCI's Common Toxicity Criteria (CTC), and World Health Organization (WHO)) have been adapted for use by the Division of Microbiology and Infectious Diseases (DMID) and modified to better meet the needs of participants in DMID trials.
- For parameters not included in the following Toxicity Tables, sites should refer to the "Guide For Estimating Severity Grade" located above.
- Criteria are generally grouped by body system.
- Some protocols may have additional protocol specific grading criteria, which will supercede the use of these tables for specified criteria.

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HEMATOLOGY				
	Grade 1	Grade 2	Grade 3	Grade 4
Hemoglobin	9.5 - 10.5 gm/dL	8.0 - 9.4gm/dL	6.5 - 7.9 gm/dL	< 6.5 gm/dL
Absolute Neutrophil Count	1000-1500/mm^3	750-999/mm^3	500-749/mm^3	<500/mm^3
Platelets	75,000-99,999/mm^3	50,000-74,999/mm^3	20,000-49,999/mm^3	<20,000/mm^3
WBCs	11,000-13,000/mm^3	13,000-15,000 /mm^3	15,000-30,000/mm^3	>30,000 or <1,000 /mm^3
% Polymorphonuclear Leucocytes + Band Cells	> 80%	90 – 95%	>95%	---
Abnormal Fibrinogen	Low: 100-200 mg/dL High: 400-600 mg/dL	Low: <100 mg/dL High: >600 mg/dL	Low: < 50 mg/dL ---	Fibrinogen associated with gross bleeding or with disseminated coagulation
Fibrin Split Product	20-40 mcg/ml	41-50 mcg/ml	51-60 mcg/ml	> 60 mcg/ml
Prothrombin Time (PT)	1.01 - 1.25 x ULN	1.26-1.5 x ULN	1.51 -3.0 x ULN	>3 x ULN
Activated Partial Thromboplastin (APPT)	1.01 -1.66 x ULN	1.67 - 2.33 x ULN	2.34 - 3 x ULN	> 3 x ULN
Methemoglobin	5.0 - 9.9 %	10.0 - 14.9 %	15.0 - 19.9%	> 20.0 %

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CHEMISTRIES				
	Grade 1	Grade 2	Grade 3	Grade 4
Hyponatremia	130-135 mEq/L	123-129 mEq/L	116-122 mEq/L	< 116 mEq/L or abnormal sodium *with* mental status changes or seizures
Hypernatremia	146-150 mEq/L	151-157 mEq/L	158-165 mEq/L	> 165 mEq/L or abnormal sodium *with* mental status changes or seizures
Hypokalemia	3.0 - 3.4 mEq/L	2.5 - 2.9 mEq/L	2.0 - 2.4 mEq/L or intensive replacement therapy or hospitalization required	< 2.0 mEq/L or abnormal potassium *with* paresis, ileus or life-threatening arrhythmia
Hyperkalemia	5.6 - 6.0 mEq/L	6.1 - 6.5 mEq/L	6.6 - 7.0 mEq/l	> 7.0 mEq/L or abnormal potassium *with* life-threatening arrhythmia
Hypoglycemia	55-64 mg/dL	40-54 mg/dL	30-39 mg/dL	<30 mg/dL or abnormal glucose *with* mental status changes or coma
Hyperglycemia (nonfasting and no prior diabetes)	116 - 160 mg/dL	161- 250 mg/dL	251 - 500 mg/dL	> 500 mg/dL or abnormal glucose *with* ketoacidosis or seizures
Hypocalcemia (corrected for albumin)	8.4 - 7.8 mg/dL	7.7 - 7.0 mg/dL	6.9 - 6.1 mg/dL	< 6.1 mg/dL or abnormal calcium *with* life threatening arrhythmia or tetany

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CHEMISTRIES (continued)

	Grade 1	Grade 2	Grade 3	Grade 4
Hypercalcemia (correct for albumin)	10.6 - 11.5 mg/dL	11.6 - 12.5 mg/dL	12.6 - 13.5 mg/dL	> 13.5 mg/dL or abnormal calcium *with* life threatening arrhythmia
Hypomagnesemia	1.4 - 1.2 mEq/L	1.1 - 0.9 mEq/L	0.8 - 0.6 mEq/L	< 0.6 mEq/L or abnormal magnesium *with* life-threatening arrhythmia
Hypophosphatemia	2.0 - 2.4 mg/dL	1.5 -1.9 mg/dL or replacement Rx required	1.0 -1.4 mg/dL intensive therapy or hospitalization required	< 1.0 mg/dL or abnormal phosphate *with* life-threatening arrhythmia
Hyperbilirubinemia (when accompanied by any increase in other liver function test)	1.1 - <1.25 x ULN	1.25 - <1.5 x ULN	1.5 – 1.75 x ULN	> 1.75 x ULN
Hyperbilirubinemia (when other liver function are in the normal range)	1.1 - <1.5 x ULN	1.5 - <2.0 x ULN	2.0 – 3.0 x ULN	> 3.0 x ULN
BUN	1.25 - 2.5 x ULN	2.6 - 5 x ULN	5.1 - 10 x ULN	> 10 x ULN
Hyperuricemia (uric acid)	7.5 – 10.0 mg/dL	10.1 – 12.0 mg/dL	12.1 – 15.0 mg/dL	>15.0 mg/dL
Creatinine	1.1 - 1.5 x ULN	1.6 - 3.0 x ULN	3.1 - 6 x ULN	> 6 x ULN or dialysis required

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ENZYMES				
	Grade 1	Grade 2	Grade 3	Grade 4
AST (SGOT)	1.1 - <2.0 x ULN	2.0 – <3.0 x ULN	3.0 – 8.0 x ULN	> 8 x ULN
ALT (SGPT)	1.1 - <2.0 x ULN	2.0 – <3.0 x ULN	3.0 – 8.0 x ULN	> 8 x ULN
GGT	1.1 - <2.0 x ULN	2.0 – <3.0 x ULN	3.0 – 8.0 x ULN	> 8 x ULN
Alkaline Phosphatase	1.1 - <2.0 x ULN	2.0 – <3.0 x ULN	3.0 – 8.0 x ULN	> 8 x ULN
Amylase	1.1 - 1.5 x ULN	1.6 - 2.0 x ULN	2.1 - 5.0 x ULN	> 5.1 x ULN
Lipase	1.1 - 1.5 x ULN	1.6 - 2.0 x ULN	2.1 - 5.0 x ULN	> 5.1 x ULN

URINALYSIS				
	Grade 1	Grade 2	Grade 3	Grade 4
Proteinuria	1+ or 200 mg - 1 gm loss/day	2-3+ or 1- 2 gm loss/day	4+ or 2-3.5 gm loss/day	nephrotic syndrome or > 3.5 gm loss/day
Hematuria	microscopic only <10 rbc/hpf	gross, no clots >10 rbc/hpf	gross, with or without clots, OR red blood cell casts	obstructive or required transfusion

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CARDIOVASCULAR				
	Grade 1	Grade 2	Grade 3	Grade 4
Cardiac Rhythm		asymptomatic, transient signs, no Rx required	recurrent/persistent; symptomatic Rx required	unstable dysrythmia; hospitalization and treatment required
Hypertension	transient increase > 20 mm/Hg; no treatment	recurrent, chronic increase > 20mm/Hg. /treatment required	acute treatment required; outpatient treatment or hospitalization possible	end organ damage or hospitalization required
Hypotension	transient orthostatic hypotension with heart rate increased by <20 beat/min or decreased by <10 mm Hg systolic BP, No treatment required	symptoms due to orthostatic hypotension or BP decreased by <20 mm Hg systolic; correctable with oral fluid treatment	requires IV fluids; no hospitalization required	mean arterial pressure <60mm/ Hg or end organ damage or shock; requires hospitalization and vasopressor treatment
Pericarditis	minimal effusion	mild/moderate asymptomatic effusion, no treatment	symptomatic effusion; pain; EKG changes	tamponade; pericardiocentesis or surgery required
Hemorrhage, Blood Loss	microscopic/occult	mild, no transfusion	gross blood loss; 1-2 units transfused	massive blood loss; > 3 units transfused

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RESPIRATORY				
	Grade 1	Grade 2	Grade 3	Grade 4
Cough	transient- no treatment	persistent cough; treatment responsive	Paroxysmal cough; uncontrolled with treatment	----------
Bronchospasm, Acute	transient; no treatment; 70% - 80% FEV_1 of peak flow	requires treatment; normalizes with bronchodilator; FEV_1 50% - 70% (of peak flow)	no normalization with bronchodilator; FEV_1 25% - 50% of peak flow; or retractions present	cyanosis: FEV_1 < 25% of peak flow or intubation necessary
Dyspnea	dyspnea on exertion	dyspnea with normal activity	dyspnea at rest	dyspnea requiring Oxygen therapy

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GASTROINTESTINAL				
	Grade 1	Grade 2	Grade 3	Grade 4
Nausea	mild or transient; maintains reasonable intake	moderate discomfort; intake decreased significantly; some activity limited	no significant intake; requires IV fluids	hospitalization required;
Vomiting	1 episode in 24 hours	2-5 episodes in 24 hours	>6 episodes in 24 hours or needing IV fluids	physiologic consequences requiring hospitalization or requiring parenteral nutrition
Constipation	requiring stool softener or dietary modification	requiring laxatives	obstipation requiring manual evacuation or enema	obstruction or toxic megacolon
Diarrhea	mild or transient; 3-4 loose stools/day or mild diarrhea last < 1 week	moderate or persistent; 5-7 loose stools/day or diarrhea lasting >1 week	>7 loose stools/day or bloody diarrhea; or orthostatic hypotension or electrolyte imbalance or >2L IV fluids required	hypotensive shock or physiologic consequences requiring hospitalization
Oral Discomfort/Dysphagia	mild discomfort; no difficulty swallowing	some limits on eating/drinking	eating/talking very limited; unable to swallow solid foods	unable to drink fluids; requires IV fluids

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NEUROLOGICAL				
	Grade 1	Grade 2	Grade 3	Grade 4
Neuro-Cerebellar	slight incoordination dysdiadochokinesis	intention tremor, dysmetria, slurred speech; nystagmus	locomotor ataxia	incapacitated
Psychiatric	mild anxiety or depression	moderate anxiety or depression; therapy required; change in normal routine	severe mood changes requiring therapy; or suicidal ideation; or aggressive ideation	acute psychosis requiring hospitalization; or suicidal gesture/attempt or hallucinations
Muscle Strength	subjective weakness no objective symptoms/ signs	mild objective signs/symptoms no decrease in function	objective weakness function limited	paralysis
Paresthesia (burning, tingling, etc.)	mild discomfort; no treatment required	moderate discomfort; non-narcotic analgesia required	severe discomfort; or narcotic analgesia required with symptomatic improvement	incapacitating; or not responsive to narcotic analgesia
Neuro-sensory	mild impairment in sensation (decreased sensation, e.g., vibratory, pinprick, hot/cold in great toes) in focal area or symmetrical distribution; or change in taste, smell, vision and/or hearing	moderate impairment (mod decreased sensation, e.g., vibratory, pinprick, hot/cold to ankles) and/or joint position or mild impairment that is not symmetrical	severe impairment (decreased or loss of sensation to knees or wrists) or loss of sensation of at least mod degree in multiple different body areas (i.e., upper and lower extremities)	sensory loss involves limbs and trunk; paralysis; or seizures

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MUSCULOSKELATEL				
	Grade 1	Grade 2	Grade 3	Grade 4
Arthralgia (joint pain)	mild pain not interfering with function	moderate pain, analgesics and/or pain interfering with function but not with activities of daily living	severe pain; pain and/or analgesics interfering with activities of daily living	disabling pain
Arthritis	mild pain with inflammation, erythema or joint swelling – but not interfering with function	moderate pain with inflammation, erythema or joint swelling – interfering with function, but not with activities of daily living	severe pain with inflammation, erythema or joint swelling –and interfering with activities of daily living	permanent and/or disabling joint distruction
Myalgia	myalgia with no limitation of activity	muscle tenderness (at other than injection site) or with moderate impairment of activity	severe muscle tenderness with marked impairment of activity	frank myonecrosis

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SKIN

	Grade 1	Grade 2	Grade 3	Grade 4
Mucocutaneous	erythema; pruritus	diffuse, maculo papular rash, dry desquamation	vesiculation or moist desquamation or ulceration	exfoliative dermatitis, mucous membrane involvement or erythema, multiforme or suspected Stevens-Johnson or necrosis requiring surgery
Induration	< 15mm	15-30 mm	>30mm	
Erythema	< 15mm	15-30 mm	>30mm	
Edema	< 15mm	15-30 mm	>30mm	
Rash at Injection Site	< 15mm	15-30 mm	>30mm	
Pruritus	slight itching at injection site	moderate itching at injection extremity	itching over entire body	

SYSTEMIC

	Grade 1	Grade 2	Grade 3	Grade 4
Allergic Reaction	pruritus without rash	localized urticaria	generalized urticaria; angioedema	anaphylaxis
Headache	mild, no treatment required	transient, moderate; treatment required	severe; responds to initial narcotic therapy	intractable; requires repeated narcotic therapy
Fever: oral	37.7 - 38.5 C or 100.0 - 101.5 F	38.6 - 39.5 C or 101.6 - 102.9 F	39.6 - 40.5 C or 103 - 105 F	> 40 C or > 105 F
Fatigue	normal activity reduced < 48 hours	normal activity decreased 25-50% > 48 hours	normal activity decreased > 50% can't work	unable to care for self