BIOCRYST

PHARMACEUTICALS, INC.

BCX9930

PROTOCOL No. BCX9930-205

EudraCT No. 2021-006776-17

An Open-label Study to Evaluate the Long-term Safety of BCX9930 Monotherapy in Subjects with Paroxysmal Nocturnal Hemoglobinuria Who Previously Received BCX9930 in a BioCryst-sponsored Study

Version 4.0: 27 July 2023

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CONFIDENTIAL

SPONSOR SIGNATURE PAGE

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Sponsor's Approval

The protocol has been approved by BioCryst Pharmaceuticals, Inc.

Senior Clinical Development Physician:

Please see the last page for electronic signature

PPD Date

PPD

BioCryst Pharmaceuticals, Inc.

Sponsor's Authorized Signatory:

Please see the last page for electronic signature

PPD Date

PPD

BioCryst Pharmaceuticals, Inc.

INVESTIGATOR AGREEMENT

Protocol No. BCX9930-205

An Open-label Study to Evaluate the Long-term Safety of BCX9930 Monotherapy in Subjects with Paroxysmal Nocturnal Hemoglobinuria Who Previously Received BCX9930 in a BioCryst-sponsored Study

Version 4.0: 27 July 2023

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

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

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

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

2. SYNOPSIS

Name of Sponsor/Company:
BioCryst Pharmaceuticals, Inc.

Name of Investigational Product:
BCX9930

Name of Active Ingredient:
2-(2-((7-(2-(aminomethyl)-3-fluoropyridin-4-yl)benzofuran-5-yl)methoxy)phenyl)acetic acid

Title of Study:
An Open-label Study to Evaluate the Long-term Safety of BCX9930 Monotherapy in Subjects with Paroxysmal Nocturnal Hemoglobinuria Who Previously Received BCX9930 in a BioCryst-sponsored Study

BioCryst Protocol No.: BCX9930-205

Regulatory Agency Identifier Number(s):
EudraCT No. 2021-006776-17
EU CT Number: 2023-507315-35
UTN Number: U1111-1295-6848

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

Lead or Coordinating Investigator:
PPD
PPD

Phase of development: 2b

Objectives

- To provide continued access to BCX9930 for subjects with paroxysmal nocturnal hemoglobinuria (PNH) who have benefited from treatment with BCX9930 in another BioCryst-sponsored study and who, in the opinion of the investigator, would benefit from continued treatment with BCX9930, and who do not have access to other effective treatment options
- To monitor the safety of BCX9930 in subjects continuing to receive BCX9930 for the treatment of PNH

Endpoints

- Subject incidence of graded treatment-emergent adverse events (TEAEs), laboratory abnormalities, changes to vital signs, and physical examination findings

Study Design:
This study is designed to provide continued access to treatment with BCX9930 for subjects currently receiving treatment with BCX9930 in another BioCryst-sponsored clinical study for PNH (ie, Studies BCX9930-201, -202, and -203, hereafter referred to as the "prior study") who, in the opinion of the

investigator, have both benefited from treatment with BCX9930 and would benefit from continued treatment with BCX9930, who wish to continue treatment, and who do not have access to other effective treatment options.

Methodology:

Subjects who meet all of the inclusion and none of the exclusion criteria can be enrolled into Study 205. The last on-treatment visit completed for the prior study will also serve as the baseline visit for Study 205. If subjects have completed at least 24 weeks of BCX9930 treatment in the prior study, study visits will occur every 8 weeks to Week 48, then every 12 weeks until Week 96. Subjects who have not completed 24 weeks of treatment with BCX9930 prior to enrolling in Study 205 must return to the clinic every 4 weeks until they have completed 24 weeks of cumulative treatment with BCX9930. Subjects who discontinue treatment with BCX9930 for any reason (complete study visits or discontinue early), will be asked to complete an end-of-study or early termination visit, as applicable, approximately 3 weeks (± 3 days) after the last dose of BCX9930.

Number of Subjects (Planned):

Up to 30 subjects are planned.

Diagnosis and Main Criteria for Inclusion:

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

1. Able to provide written informed consent.
2. Non-pregnant, non-lactating female subjects.
3. Subjects with PNH who are participating in another BCX9930 clinical study, have completed at least 12 weeks treatment with BCX9930, and, in the opinion of the investigator, have benefited from treatment with BCX9930 and would benefit from continued treatment with BCX9930, wish to continue treatment, and do not have access to other effective treatment options.
4. For female subjects:
    a. Must be of nonchildbearing potential, or
    b. If a woman of childbearing potential, must agree to use one of the following methods of highly effective contraception throughout the study and for a duration of 30 days after the last dose of study drug. Highly effective contraceptive methods are restricted to the following:
        - Implantable progestogen-only hormonal contraception associated with inhibition of ovulation:
            - *For South Africa only*: Progestogen-only hormonal contraception injection, with active monitoring of compliance, is allowed as a contraceptive method.
        - An intrauterine device
        - An intrauterine hormone-releasing system
        - A bilateral tubal occlusion
        - A vasectomized or sterile partner

Abstinence as a contraceptive method will not be an option regardless of lifestyle or sexual activity.

5. Male subjects with a female partner of childbearing potential, unless vasectomized, must use condoms (with spermicide, where available) throughout the study and for a duration of 90 days after the last dose of study drug. Subjects with a pregnant female partner must use condoms to avoid potential exposure of the partner and fetus in utero through semen. Abstinence as a contraceptive method will not be an option regardless of lifestyle or sexual activity.
6. In the opinion of the investigator, the subject is expected to adequately comply with all required study procedures and restrictions for the study.

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

1. Any clinically significant medical or psychiatric condition including alcohol or drug dependency that, in the opinion of the investigator or sponsor, would interfere with the subject's ability to participate in the study or increase the risk of participation for that subject.
2. An ongoing adverse event (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 or benefit-risk assessment is no longer in favor of the subject's continued treatment.
3. Daily use of medications listed in the currently applicable prohibited medications list.
4. Known or suspected hypersensitivity to BCX9930 or any of its formulation excipients. (Note: prior drug rash is not exclusionary.)

Investigational Product, Dosage, and Mode of Administration:

Based on safety and efficacy data from previous studies, all subjects enrolled into this study will receive BCX9930 400 mg twice a day, with or without food.

Duration of Treatment:

Each subject will be eligible to receive study drug (BCX9930) under this protocol for up to 96 weeks as long as the investigator believes it is in the subject's best interest to continue treatment, or until the subject has access to other therapy for PNH, whichever comes first. Treatment with BCX9930 will be discontinued for subjects who are deriving no meaningful clinical benefit, or who experience an unacceptable drug-related AE or are otherwise intolerant of study drug.

Reference Therapy, Dosage and Mode of Administration:

Not applicable.

Criteria for Evaluation:

Safety: Safety will be evaluated by TEAEs, laboratory analyses (clinical chemistry, hematology, coagulation, urinalysis including microscopy), vital signs, and physical examination findings.

Statistical Methods:

Data will be listed and summarized using descriptive statistics.

3. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

TABLE OF CONTENTS

LIST OF TABLES

4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

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

Table 1: List of Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
ACIP	Advisory Committee on Immunization Practices
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase (also SGPT)
AP	alternative complement pathway
ARC	absolute reticulocyte count
AST	aspartate transferase (also SGOT)
BCRP	breast cancer resistance protein
BID	twice a day
BMI	body mass index
C3	complement component 3
COVID-19	coronavirus disease 2019
CP	classical complement pathway
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DDI	drug-drug interaction
DMC	data monitoring committee
eCRF	electronic case report form
EFD	embryo-fetal development
eGFR	estimated glomerular filtration rate
EOS	end of study
EOSM	events of special monitoring
ET	early termination
EU	European Union
EVH	extravascular hemolysis
FDA	US Food and Drug Administration
FIH	first in human
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
Hb	hemoglobin

Abbreviation or Specialist Term	Explanation
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
IB	Investigator's Brochure
IC_{50}	50% of maximal inhibitory concentration
ICF	informed consent form
ICH	International Council for Harmonisation
IMP	investigational medicinal product
INR	international normalized ratio
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	intravenous
IVH	intravascular hemolysis
LDH	lactate dehydrogenase
LP	lectin complement pathway
MAC	membrane attack complex
MAD	multiple ascending dose
MAVE	major adverse vascular event
MedDRA	Medical Dictionary for Regulatory Activities
N, n	number of subjects or events (uppercase is total population; lowercase is subgroup population)
NCI	US National Cancer Institute
NRMWG	Nephrology Risk Mitigation Working Group
PD	pharmacodynamic(s)
P-gp	P-glycoprotein
PK	pharmacokinetic(s)
PNH	paroxysmal nocturnal hemoglobinuria
RBC	red blood cell
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
sCr	serum creatinine
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event

Abbreviation or Specialist Term	Explanation
TID	three times a day
uACR	urine microalbumin to creatinine ratio
ULN	upper limit of normal (reference range)
US	United States
WBC	white blood cell

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 linked pathways: the classical pathway (CP), lectin pathway (LP), and alternative pathway (AP). Dysregulation of AP activity by germ line or somatic genetic mutations of complement regulatory proteins or enzymes, neutralizing antibodies to complement regulatory proteins, or stabilizing antibodies to complement enzyme complexes predisposes individuals to diverse disorders, including paroxysmal nocturnal hemoglobinuria (PNH), age-related macular degeneration, atypical hemolytic uremic syndrome, and complement 3 glomerulopathy (Holers 2008; Brodsky 2014; Zipfel et al. 2015; Ricklin et al. 2016).

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

PNH is an acquired, rare, serious, and potentially life-threatening disorder characterized by destruction of red blood cells (RBCs) resulting from uncontrolled activity of complement. PNH is caused by a somatic mutation in the phosphatidylinositol glycan anchor biosynthesis class A (PIG-A) gene in hematopoietic stem cells that leads to a deficiency of the membrane-displayed complement regulatory proteins CD55 and CD59 that normally protect RBCs from effective opsonization and lysis by the complement system. These deficiencies result in unrestrained complement activity that attacks RBCs, leading to episodes of intravascular hemolysis (IVH), extravascular hemolysis (EVH), chronic hemolytic anemia, bone marrow failure (BMF), and thrombosis (Parker 2009; Pu and Brodsky 2011), and EVH in patients treated with C5 inhibitors. PNH affects men and women equally and is more common in people of Asian rather than Caucasian ethnicity (Hill et al. 2017; Jalbert et al. 2019). The onset of PNH can occur at any age. The median (interquartile range) age of patients with PNH at diagnosis reported in a large series was 44 years (30 to 60 years) (Curran et al. 2012; Ge et al. 2015; Mercuri et al. 2017; Narita et al. 2017; Cannizzo et al. 2019; Griesser et al. 2020).

PNH is associated with significant morbidity and mortality (Harris et al. 1999; Rachidi et al. 2010). Median survival in the era prior to use of C5 inhibitors was reported in one study as 10 years (Hillmen et al. 1995); a retrospective analysis found that approximately 20% of patients

with only supportive care died within 6 years of diagnosis (Loschi et al. 2016). Thrombosis was the leading cause of death in PNH patients, accounting for up to 67% of (Loschi et al. 2016). While thrombosis is relatively rare as a presenting symptom, it has historically occurred in up to 40% of patients during the course of disease (Pu and Brodsky 2011); a history of major adverse vascular events (MAVEs), including thromboembolism, was reported in 19% of patients with PNH in a large series (Schrezenmeier et al. 2020). Visceral thrombosis, cerebrovascular events, and pulmonary embolism predict a poor outcome (Ziakas et al. 2008).

BioCryst Pharmaceuticals, Inc. ("BioCryst") was developing BCX9930, a potent and selective, orally bioavailable, small-molecule inhibitor of complement Factor D, as a potential treatment for PNH and other complement-mediated diseases. Targeting Factor D with a pharmacologic inhibitor prevents both IVH and EVH in patients with PNH by blocking the formation of MAC and inhibiting the formation of C3 fragments. This represents a promising therapeutic strategy for the treatment of AP-mediated diseases such as PNH. The results of clinical studies and nonclinical pharmacology, pharmacokinetics (PK), and toxicology studies of BCX9930 can be found in the Investigator's Brochure (IB).

5.2. Rationale for Study

On 15 December 2022, BioCryst announced that, based on new competitive data recently presented at the 2022 American Society of Hematology Annual Meeting, the company no longer believed that BCX9930 would be commercially competitive, and would, therefore, be discontinuing the development of BCX9930 (BioCryst Press Release 2022). Enrollment into the pivotal studies (Study 202 and Study 203) was halted permanently. Subjects already enrolled in the pivotal studies who were benefiting from treatment with BCX9930 were allowed to continue treatment. In addition, subjects in Study 202 randomized to continue C5 inhibitor therapy were offered the option to begin treatment with BCX9930. In Study 203, the treatment assignments of subjects was unblinded with subjects randomized to placebo given the option to transition to treatment with open-label BCX9930. Treatment with BCX9930 may be continued in the pivotal studies (and in ongoing rollover Study 201) until the subjects can be transitioned into this study, allowing those studies to be closed.

As the development program is not being discontinued for safety reasons or a lack of efficacy, and the preliminary data available from the ongoing clinical studies in PNH do not change the current safety or efficacy profile for BCX9930, BioCryst remains committed to providing BCX9930 to those subjects participating in the ongoing studies who are currently receiving benefit from BCX9930 and wish to continue treatment. This study will be used to meet that commitment by allowing for continued access to treatment with BCX9930 for any subject with PNH currently receiving treatment with BCX9930 in a BioCryst-sponsored study who do not have access to other effective treatment options. As the development of BCX9930 is now terminated, treatment will be provided for a maximum of 96 weeks under this version of the protocol, as long as the investigator believes it is in the subject's best interest to continue treatment, or until the subject has access to alternative therapy for PNH, whichever comes first.

5.2.1. Rationale for Study Population and Design

Subjects who are enrolled in a prior BCX9930 study for PNH (ie, Studies 201, 202, or 203), have completed at least 12 weeks of treatment with BCX9930 in the prior study, and, in the opinion of

the investigator, have both benefited from that treatment and would continue to benefit from treatment, and who do not have access to other effective treatment options will be eligible for this study. Most participants in Studies 201 and 203 do not have access to approved therapies for PNH. Participants in Study 202 had access to one or both of the approved C5 inhibitors, but had an inadequate response to those therapies. Requiring subjects to complete a minimum of 12 weeks of treatment in the prior study will allow adequate time to confirm tolerability to the recommended 400 mg twice a day (BID) BCX9930 dose regimen, including completing any enhanced safety monitoring needed to monitor for potential renal toxicity, before entering into this study. The study features (eg, endpoints, withdrawal criteria, assessments, etc.) were selected to align closely with previous PNH studies of BCX9930 and will allow for the continued monitoring of subject safety and the ongoing assessment of risks and benefits in subjects previously exposed to BCX9930 continuing treatment in this study.

5.2.2. Rationale for Dose Selection

Based on safety and efficacy data from previous studies, all subjects enrolled into Study 205 will receive BCX9930 at a dose of 400 mg BID, which is the dose regimen that was being evaluated in the pivotal studies prior to the decision to discontinue further development of the drug.

5.3. Benefit-Risk Assessment

Subjects participating in this study will have already been administered BCX9930 in a previous study; thus, the benefit-risk profile of initial treatment with BCX9930 will previously have been assessed by the investigator in each subject eligible for Study 205. The benefit-risk profile of long-term treatment with BCX9930 will be evaluated throughout the duration of this study. Treatment with BCX9930 will be discontinued for subjects who are deriving no meaningful clinical benefit, or who experience an unacceptable drug-related adverse event (AE) or are otherwise intolerant of study drug.

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 detail in the IB for BCX9930.

A significant risk associated with complement inhibitor therapies is the risk of life-threatening or fatal meningococcal infections (Figueroa and Densen 1991; Hillmen et al. 2006). 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 *Neisseria gonorrhoeae* (Ram 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.

Like other complement inhibitor therapies, discontinuation or interruption of BCX9930 may result in increased risk of hemolysis of PNH RBCs (Soliris-USPI 2020; Empaveli-USPI 2021; Ultomiris-USPI 2022). Subjects should be instructed to immediately contact the investigative site if they miss any BCX9930 doses and experience new or worsening symptoms of hemolysis. A suggested dose tapering schedule is provided in Section 9.4.2 for subjects who discontinue study

drug permanently. All subjects who discontinue BCX9930 permanently will be monitored for potential hemolysis as described in Section 12.5.3. Treatment can lead to increase in the PNH RBC clone size (deCastro et al. 2020), which may be associated with potential risks of hemolysis. Risk and susceptibility to hemolysis due to expanded RBC clone size could occur with other triggers or stressors that activate complements, such as infection, even with ongoing BCX9930 treatment. Ongoing laboratory and clinical monitoring for potential hemolysis, as well as RBC clone size, will occur during the study.

Common AEs (10% or higher risk) noted from this treatment experience with BCX9930 include headache, skin rash, and infections.

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Although no embryo-fetal development (EFD) risks have been identified in nonclinical studies in rats or rabbits, an EFD study in mice demonstrated cranio-facial (cleft palate, nasopharynx, palatine bones) abnormalities, skull (exoccipital), limb (polydactyly, syndactyly, bent long bones), and other skeletal malformations in a dose-dependent manner. The maternal exposure to BCX13559 (a major circulating metabolite of BCX9930) in this study was less than the observed exposure in humans indicating a margin of safety < 1. No congenital malformations have been reported with BCX9930 use during the first trimester of 3 pregnancies that have occurred in clinical studies. However, the non-clinical data in mice indicates a potential risk of teratogenicity in fetuses whose mothers are exposed to BCX9930. Therefore, female subjects will be required to use highly effective contraception methods which have a low user dependency, where available. As the risk for partner pregnancies is unknown, the contraception precautions are extended to men enrolled in BCX9930 studies as well.

Targeting Factor D is a promising therapeutic strategy to inhibit AP activation for the treatment of AP-mediated diseases such as PNH. BCX9930 is expected to provide greater efficacy than the currently available C5 inhibitors by not only preventing IVH, but also by preventing C3-mediated EVH, thereby reducing symptom burden, reducing hemolysis, and improving health-related quality of life. Regular monitoring of safety parameters, including AEs, clinical laboratory abnormalities, vital sign measurements, and physical examination findings, will ensure that the benefit-risk profile supports continued dosing in subjects until an alternative therapy option becomes available to study participants. In addition, an independent, program-wide data monitoring committee (DMC) will provide oversight of the ongoing safety of subjects to BCX9930. Therefore, the overall benefit-risk balance is considered to be acceptable.

6. STUDY OBJECTIVES

6.1. Objectives

The objectives of this study are:

- To provide continued access to BCX9930 for subjects with PNH who have benefited from treatment with BCX9930 in another BioCryst-sponsored study and who, in the opinion of the investigator, would benefit from continued treatment with BCX9930, and who do not have access to other effective treatment options
- To monitor the safety of BCX9930 in subjects continuing to receive BCX9930 for the treatment of PNH

6.2. Endpoints

The endpoints of this study are:

- Subject incidence of graded TEAEs, laboratory abnormalities, changes to vital signs, and physical examination findings

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

This study is designed to provide continued access to BCX9930 for subjects currently receiving treatment with BCX9930 in another BioCryst-sponsored clinical study for PNH (ie, Studies 201, 202, or 203, hereafter referred to as the "prior study") who, in the opinion of the investigator, have both benefited from treatment with BCX9930 and would benefit from continued treatment with BCX9930, who wish to continue treatment, and who do not have access to other effective treatment options.

Subjects will be eligible to receive study drug (BCX9930) under this version of the protocol for up to 96 weeks for as long as the investigator believes it is in the subject's best interest to continue treatment, or until the subject has access to another therapy for PNH, whichever comes first. Treatment with BCX9930 will be discontinued for subjects who are deriving no meaningful clinical benefit, or who experience an unacceptable drug-related AE or are otherwise intolerant of study drug.

An independent BCX9930 program-wide DMC will provide oversight of the safety of subjects receiving BCX9930 in this study.

7.2. Number of Subjects

The number of subjects will depend on the number of potentially eligible subjects still participating in prior studies, estimated to be up to 30 subjects.

7.3. Treatment Dosing

Subjects will take 400 mg BCX9930 orally BID, approximately 12 hours apart. BCX9930 may be taken with or without food.

7.4. Individual and Study Termination Criteria

7.4.1. Subject Withdrawal from Study Treatment

A subject will be permanently discontinued from BCX9930 for any of the following reasons:

- Subject request to discontinue for any reason.
- Emergence of an AE, including a laboratory abnormality, or other unacceptable toxicity that, in the judgment of the investigator, compromises the ability of the subject to continue study-specific procedures or it is considered not to be in the subject's best interest to continue due to an altered benefit-risk profile.
- Intercurrent illness or the emergence of a new medical condition that would, in the judgment of the investigator, affect assessments of clinical status to a significant degree.
- Treatment-emergent ALT (serum glutamic-pyruvic transaminase [SGPT]) > 3 × ULN (confirmed by repeat testing, ie, from different samples collected on different days, irrespective of source laboratory) 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 CCI [redacted] for a recommendation regarding the subject's continued participation in the study.)

- 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.
- In the opinion of the investigator or sponsor, the subject is no longer receiving meaningful clinical benefit from continued treatment with BCX9930, or the subject qualifies for treatment with an available alternative therapy for PNH.
- Subject pregnancy
- 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".

The reason for discontinuation of study treatment will be recorded in the source documents and electronic case report form (eCRF).

Subject who discontinue treatment with BCX9930 will not be allowed to re-enroll in the study or restart treatment with BCX9930 at a later date following a change in circumstances (eg, after a pregnant subject delivers her baby or a subject discontinues alternative therapy for PNH, including after completion of or discontinuation from a clinical study of another investigational agent for PNH).

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

7.4.2. Criteria for Study Termination

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

- Request of the relevant competent authority or ethics committee
- Emergence of unacceptable risk, toxicity, or negative change in the benefit-risk assessment, including (but not limited to):
  - If any 3 subjects have elevated CCI [redacted]
- Non-compliance with the study protocol, including inaccurate or incomplete recordkeeping, which jeopardizes the scientific integrity of the study or subject safety

BioCryst reserves the right to discontinue the study (eg, if alternative therapy for PNH becomes available) but intends only to exercise this right for valid scientific, medical, or administrative reasons. If BioCryst does discontinue the study, the investigator must contact all participating subjects immediately after notification of study termination.

If the study is halted due to safety concerns, the study will not be re-started.

8. SELECTION AND WITHDRAWAL OF SUBJECTS

8.1. Subject Inclusion Criteria

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

1. Able to provide written informed consent.
2. Non-pregnant, non-lactating female subjects.
3. Subjects with PNH who are participating in another BCX9930 clinical study, have completed at least 12 weeks treatment with BCX9930, and, in the opinion of the investigator, have benefited from treatment with BCX9930 and would benefit from continued treatment with BCX9930, wish to continue treatment, and do not have access to other effective treatment options.
4. For female subjects:
   a. Must be of nonchildbearing potential, or
   b. If a woman of childbearing potential, must agree to use one of the following methods of highly effective contraception throughout the study and for a duration of 30 days after the last dose of study drug. Highly effective contraceptive methods are restricted to the following:
      - Implantable progestogen-only hormonal contraception associated with inhibition of ovulation
        - *For South Africa only*: Progestogen-only hormonal contraception injection, with active monitoring of compliance, is allowed as a contraceptive method.
      - An intrauterine device (IUD)
      - An intrauterine hormone-releasing system (IUS)
      - A bilateral tubal occlusion
      - A vasectomized or sterile partner

      Abstinence as a contraceptive method will not be an option regardless of lifestyle or sexual activity.
5. Male subjects with a female partner of childbearing potential, unless vasectomized, must use condoms (with spermicide, where available) throughout the study and for a duration of 90 days after the last dose of study drug. Subjects with a pregnant female partner must use condoms to avoid potential exposure of the partner and fetus in utero through semen. Abstinence as a contraceptive method will not be an option regardless of lifestyle or sexual activity.

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.

   Additional details are provided in Section 11.2.1.

8.2. Subject Exclusion Criteria

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

1. Any clinically significant medical or psychiatric condition including alcohol or drug dependency that, in the opinion of the investigator or sponsor, would interfere with the subject's ability to participate in the study or increase the risk of participation for that subject.
2. An ongoing 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 or benefit-risk assessment is no longer in favor of the subject's continued treatment.
3. Daily use of medications listed in the currently applicable prohibited medications list.
4. Known or suspected hypersensitivity to BCX9930 or any of its formulation excipients. (Note: prior drug rash is not exclusionary.)

8.3. Subject Withdrawal

Participation in the study is strictly voluntary; a subject may withdraw consent to contribute additional study information at any point. Subjects have the right to withdraw from the study at any time and for any reason. In addition, a subject's participation may be terminated for any of the reasons described in Section 7.4.1. Whenever possible, the investigator will consult with the sponsor medical monitor before halting a subject's participation in the study.

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

Unless consent is withdrawn, subjects who discontinue study treatment will be monitored for potential hemolysis and may be required to return to the clinic for an additional visit(s) to assess for acute symptomatic hemolysis, if and when symptoms occur. A dose tapering schedule should be considered (Section 9.4.2). An early termination (ET) visit will be completed approximately 3 weeks after the date of last dose of BCX9930 (see Table 2).

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

8.4. End of Study Definition

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

9. TREATMENT OF SUBJECTS

9.1. Description of Study Drug and Study Drug Product

BCX9930 is a small-molecule inhibitor of Factor D and will be supplied by BioCryst as 100-mg tablets for oral administration. The active ingredient is BCX9930 drug substance.

BCX9930 tablets contain the active ingredient blended with the excipients CCI [redacted]
CCI [redacted]
CCI [redacted]
CCI [redacted]

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

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

BCX9930 tablets will be packaged in an appropriate size bottle. Each bottle will be labeled with the information required per local law, which may include sponsor name, study protocol number, description of the contents, a statement regarding the investigational (clinical study) use of the study drug, and expiry date.

The bottles of BCX9930 tablets should be stored at 15°C to 25°C (59ºF to 77ºF).

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

9.3. Randomization and Blinding of Study Treatment

This is an open-label, non-randomized study. Study treatment will not be blinded or masked.

9.4. Study Drug Administration

BCX9930 will be supplied as 100-mg tablets. Subjects will take four BCX9930 100-mg tablets orally BID, approximately 12 hours apart. BCX9930 may be taken with or without food. Subjects should be counseled to maintain adequate hydration throughout the treatment period to prevent the formation of highly concentrated urine.

9.4.1. Treatment Interruption or Dose Reduction

Treatment interruption or dose reduction as a result of investigator management of AEs potentially related to study drug is permissible with appropriate monitoring for potential

hemolysis as described in Section 12.5.3. Any treatment interruption or dose reduction will be recorded in the eCRF and source documents, including the reason for the interruption or reduction. Resumption of study drug administration (up to the recommended 400 mg BID dose regimen) 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. Dose adjustment to a dose regimen > 400 mg BID is not permitted.

See Section 9.4.2 for potential dose reduction options.

9.4.2. Dose Tapering

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

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

9.5. Treatment Compliance

All doses can be taken at home; subjects do not need to withhold any doses on clinic days or take a dose at the clinic, unless the clinic visit falls during the subject's normal time of dosing. Subjects will be provided instructions for taking the twice-daily doses of BCX9930 at home, including frequency and time of administration. Where possible, the BCX9930 doses should be taken at the same times each day as close as possible to 12 hours apart (eg, 8:00 AM and 8:00 PM).

Subject compliance with the BID dosing schedule for BCX9930 is critical for optimizing suppression of the AP and minimizing the risk of hemolysis. Missing more than 2 consecutive doses of BCX9930 increases the risk of subjects experiencing a hemolytic episode. Therefore, participants must be re-educated about and understand the importance of compliance with the dosing schedule, be reminded about the risks associated with breakthrough hemolysis, and the need to promptly report new or worsening signs and symptoms of potential hemolysis to staff, especially when associated with missed doses. Once enrolled in this study, each participant will need to be responsible for taking BCX9930 twice a day, at approximately the same times and as close as possible to 12 hours apart. BioCryst will provide materials that can be used to

communicate the importance of compliance. Subjects will be required to bring the bottles of BCX9930 to clinic visits, including any unscheduled visit to assess for potential hemolysis, when possible. Investigators should remind participants who regularly miss doses of BCX9930 about the importance of treatment compliance.

9.6. Missed Doses and Special Considerations for Dosing

If BCX9930 needs to be withheld (eg, to assess a potentially drug-related TEAE), the investigator should consider the potential for hemolysis as described in Section 12.5.3.

9.6.1. Missed Doses

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

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

9.6.2. Special Considerations for Dosing, Including Inability to Take 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 within 5 minutes after taking a dose of BCX9930 or intact tablets or pieces of the tablets are seen in the vomitus (vomit contents), the subject may be re-dosed (ie, take new tablets).

Please refer also to the IMP manual for specific instructions.

9.7. Study Drug Accountability

Accountability of BCX9930 dispensed and returned (as applicable) will be performed at Day 1 and at each subsequent study visit (including at unscheduled visits, when possible). Returned study drug bottles should be retained and reviewed during monitoring visits by the study monitor.

The investigator or designee (eg, pharmacist) must maintain accurate records of the disposition of all study drugs received from the sponsor, directly administered to the subject (if applicable)

or dispensed to the subject. At the end of the study, information describing study drug accountability must be maintained at the site.

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

9.8. Prior and Concomitant Medications

All concomitant medication use, beginning with the baseline visit, will be recorded in the source documentation and eCRF.

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 while taking BCX9930. With the exception of any changes to nephrotoxic medications and prohibited and restricted medications detailed below (Section 9.8.1), subjects should continue their normal medications.

Prophylactic use of antibacterial and antiviral medications, other than those expressly prohibited on the prohibited and restricted medication list, may be considered if clinically indicated and after discussion with the sponsor medical monitor (or designee), with consideration of the list of prohibited and restricted medications separate from this protocol (see Section 9.8.1).

Please refer to Section 9.9 for vaccination requirements.

9.8.1. Prohibited and Restricted Medications

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

All subjects should observe the prohibitions and restrictions on concomitant use described in Section 8.2 and in the following text.

Use of the following medications is currently excluded while subjects are receiving treatment with BCX9930, as is the planned initiation of treatment with such medications during the study:

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI

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CCI

The sponsor will provide a list separate from the protocol of prohibited and restricted medications for which there may be a drug interaction with BCX9930 based upon regulatory labeling for individual medications, regulatory guidance, peer-reviewed literature, and regularly updated drug interaction reference databases (eg, University of Washington School of Pharmacy Drug Interaction Database, Pharmapendium). The sponsor may modify this list of prohibited medications based upon available PK and safety data on concomitant medications, ongoing clinical findings, and continued review of labeling, regulatory guidance, literature, and reference databases. A memorandum of any such changes to this list will be provided to all clinical sites.

Subjects should inform all treating physicians of their participation in this study and the possibility of potential interactions with BCX9930.

Throughout the course of the study, investigators should inquire about newly initiated, daily, chronic-use medications; the investigator should compare these medications to the prohibited medication list. Please contact the sponsor medical monitor for specific questions regarding prohibited and restricted medications if needed.

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

Subjects participating in this study will have been required to meet the vaccine requirements for entry into the prior study. In this study, booster vaccinations will be maintained according to either the US Centers for Disease Control and Prevention Advisory Committee on Immunization Practices (ACIP) recommendations for meningococcal vaccination and ACIP guidance for altered immunocompetence (including complement inhibition therapy) or to local guidelines, whichever are more stringent (Mbaeyi et al. 2020; Kroger et al. 2021).

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. Site personnel should contact the sponsor medical monitor or designee for any questions.

If a live vaccine needs to be given during the study, the site should contact the sponsor medical monitor or designee for the most up-to-date information.

Prophylactic antibiotic therapy may be administered at the discretion of the investigator. If administered, local treatment guidelines for patients receiving treatment with complement inhibitors should be followed. Before administration of antibiotics, the investigator must check the prohibited medication list.

10. STUDY CONDUCT

10.1. Overview

Subjects who meet all of the inclusion and none of the exclusion criteria can be enrolled into Study 205. Prospective subjects should have completed at least 12 weeks treatment with BCX9930 in the prior study. The last on-treatment visit completed for the prior study will also serve as the baseline visit for Study 205. Therefore, procedures at the last on-treatment visit in the prior study and any specific assessments for Study 205 that may be needed will be conducted at this visit. (Note: With the expected overlap in study procedures, it is anticipated that few, if any, specific procedures for Study 205 will need to be completed. Please contact the sponsor medical monitor [or designee] if this is unclear). If subjects have completed at least 24 weeks of BCX9930 treatment in the prior study, study visits will occur every 8 weeks to Week 48, then every 12 weeks until Week 96. Subjects who have not completed 24 weeks of treatment with BCX9930 prior to entering this study must return to the clinic every 4 weeks until they have completed 24 weeks of cumulative treatment with BCX9930. More frequent monitoring may be required for subjects with any ongoing safety concern, including CCI [redacted]

Additional visits may be required for subjects who experience hemolysis on study or who require unscheduled visits for additional or repeat evaluations. Additional visits will be required in the case of CCI [redacted] for additional detail).

Subjects who discontinue dosing with BCX9930 for any reason (complete study visits or discontinue early), will be asked to complete an EOS or ET visit, as applicable, approximately 3 weeks (± 3 days) after last dose of BCX9930.

10.2. Schedule of Assessments

The schedule of study assessments/procedures for this study is presented in Table 2.

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

Table 2: Study BCX9930-205: Schedule of Study Assessments/Procedures

Assessment/Procedure	Baseline Day 1[a]	Treatment Period (Weeks 8, 16, 24, 32, 40, 48, 60, 72, 84, and 96[b])	EOS/ET[c]
Written informed consent	X		
Review eligibility criteria	X		
Medical & medication history[d]	X		
HBV, HCV, HIV viral load testing[e]	←	⟷	→
Height, body weight & BMI	X		
Symptom-directed physical examination[f]	X	X	X
Vital signs[g]	X	X	X
Clinical chemistry[h]/hematology[i]/coagulation/ urinalysis including microscopy[j]	X	X	X
Pregnancy test[k]	X	X	X
FSH test[l]	X	X	X
Study drug administration[m]	←	⟷	→
Study drug accountability	X	X	X
Record AEs, concomitant medications & transfusions	X	X	X

Abbreviations: AE = adverse event; BID = twice daily; BMI = body mass index; EOS = end of study; ET = early termination; FSH = follicle-stimulating hormone; HBV = hepatitis B virus; HBC = hepatitis C virus; HIV = human immunodeficiency virus; ICF = informed consent form; PNH = paroxysmal nocturnal hemoglobinuria; RBC = red blood cell; WBC = white blood cell.

[a] The last on-treatment visit completed for the prior study will also serve as the baseline visit for Study 205. Therefore, procedures at the last on-treatment visit in the prior study and any specific assessments for Study 205 will be conducted at this visit. If there will be a lapse between the end of the prior study and rollover into Study 205 such that the baseline visit for Study 205 is not conducted coincident with the last on-treatment visit in the prior study, the site must contact the sponsor medical monitor (or designee) to determine whether the subject will be eligible to participate in Study 205. If eligible and subsequently enrolled into Study 205, the subjects must complete the Study 205 baseline visit. The sponsor medical monitor (or designee) will recommend which procedures need to be performed at that visit.

[b] Visits may be performed within a window of ± 6 days. Subjects who have not completed 24 weeks of treatment with BCX9930 prior to entering this study must return to the clinic every 4 weeks until they have completed 24 weeks of cumulative treatment. Subjects with CCI will be required to complete additional assessments CCI at the investigational site, or at a remote laboratory more convenient for the subject as indicated in Section 10.3.1 and Section 12.5.2. Additional visits may be required for subjects who experience hemolysis on study or following the permanent discontinuation of BCX9930, or who require unscheduled visits for additional or repeat evaluations. Subjects do not need to withhold any BCX9930 doses on clinic days or take a dose in the clinic, unless the clinic visit falls during the subject's normal time of dosing.

[c] Subjects who discontinue dosing with BCX9930 for any reason (complete study visits or discontinue early), will be asked to complete an EOS or ET visit, as applicable, approximately 3 weeks (± 3 days) after last dose of BCX9930.

[d] Medical and medication history will be obtained from the prior study.

[e] For those who entered the prior study with positive serology for HIV or active infection with HBV or HCV, the appropriate testing for viral load should be repeated approximately yearly from the date of first viral load assessment. If positive, contact the medical monitor to discuss the best option for the subject.

[f] Symptom-directed physical examinations will be performed at all regularly scheduled visits.

[g] To include blood pressure, pulse rate, and temperature. Prior to obtaining blood pressure and pulse rate, subjects should rest quietly for a brief period.

[h] Cholesterol and triglycerides will be measured every 6 months (ie, Weeks 24, 48, 72, and 96).

[i] PNH RBC and WBC clone size included.

[j] Urine microscopy will be performed at the central laboratory as reflex testing in the event of an abnormal urinalysis.

[k] For women of childbearing potential, a urine pregnancy test will be assessed at baseline, at onsite visits during the treatment period, and at the EOS/ET visit. Women of childbearing potential will be provided with urine pregnancy test kits for home testing once a month.
[l] FSH may be assessed at any visit if menopausal status changes to confirm menopausal status. The subject must have a negative urine pregnancy test as per protocol until menopausal status is confirmed.
[m] BCX9930 will be administered orally at a total dose of 400 mg BID without regard to food.

10.3. Study Visits

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

Written informed consent must be obtained from each subject before initiation of any assessments or procedures conducted specifically for Study 205. Where practical to do so, informed consent should be obtained a minimum of 4 weeks prior to the end of the prior study to allow the sponsor adequate time to provide new study drug and other supplies to the site.

The current study will consist of the following visits:

- Baseline Visit (Day 1)
- On-study Visits
  - Occurring in clinic every 8 weeks at Week 8 (Day 57 ± 6 days), Week 16 (Day 113 ± 6 days), Week 24 (Day 169 ± 6 days), Week 32 (Day 225 ± 6 days), Week 40 (Day 281 ± 6 days), until Week 48 (Day 337 ± 6 days), then every 12 weeks at Week 60 (Day 421 ± 6 days), Week 72 (Day 505 ± 6 days), Week 84 (Day 589 ± 6 days), until Week 96 (Day 673 ± 6 days). Subjects who have not completed 24 weeks of treatment with BCX9930 prior to enrolling in this study must return to the clinic every 4 weeks until they have completed 24 weeks of cumulative treatment.
- Unscheduled Visit
  - Subjects should be instructed to immediately contact the investigator if they have new or worsening symptoms of hemolysis. Following the permanent discontinuation of BCX9930, subjects may be required to complete an additional visit(s) to assess for acute symptomatic hemolysis if and when symptoms occur (see Section 12.5.3).

    CCI [redacted]
    CCI [redacted]
    CCI [redacted]
- EOS/ET Visit
  - Subjects who discontinue dosing with BCX9930 for any reason (complete study visits or discontinue early), will be asked to complete an EOS or ET visit, as applicable, approximately 3 weeks (± 3 days) after last dose of BCX9930.

For the assessments to be performed at each visit, see Table 2.

10.3.1. Additional Assessments for Renal and Hepatic Safety Monitoring

CCI [redacted]
CCI [redacted]
CCI [redacted] 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
- Urine collection for clinical laboratory evaluations:
  - Urinalysis including microscopy
  - Urine albumin to creatinine ratio (uACR)

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)
  - uACR

11. STUDY ASSESSMENTS

11.1. Chronology of Assessments

Clinic procedures, such as physical examinations, and vital signs measurements, should be completed prior to any blood collection.

11.2. Demographic Information, Medical and Medication History

Demographic information and medical and medication history will be obtained from the prior study. Medication review and review of inclusion and exclusion criteria and prohibited and restricted medications will also be updated and rechecked at baseline (Day 1). For subjects completing a Study 205-specific baseline visit, demographic information and medical and medication history will be rechecked at baseline (Day 1) and updated.

A PNH history will have been taken in the prior study to document PNH clinical characteristics and disease burden.

11.2.1. Contraception Requirements

The following represents the minimum contraception that should be used by study participants and their partners. Additional contraceptive requirements (eg, requiring the

female partners of male subjects to additionally use highly effective contraception) may be required by local site practice and/or the governing ethics committee. All participants must follow all country, regional, and local contraceptive guidelines. It is anticipated that that not all contraceptive methods may be available in all countries/regions, so the list should be modified accordingly.

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

Female subjects must continue to meet at least one of the following requirements:

1. Be a woman of nonchildbearing potential, either postmenopausal (defined as without menses for ≥ 12 months without an alternative medical cause with a follicle-stimulating hormone [FSH] > 40 mIU/mL) or had a hysterectomy, bilateral salpingectomy, or bilateral oophorectomy
2. Be a woman of childbearing potential (defined as a female following menarche and prior to becoming postmenopausal who has not had a hysterectomy, bilateral salpingectomy, or bilateral oophorectomy) who agrees to use an acceptable highly effective contraceptive method while enrolled in the study and for a duration of 30 days after last dose of study drug.

   Acceptable highly effective contraceptive methods are restricted to the following methods with low user dependency:

   - surgical sterilization (ie, bilateral tubal occlusion or vasectomy of the sole male partner and the vasectomized partner has received medical assessment of surgical success)
   - IUD or IUS
   - implantable progestogen-only hormonal contraception associated with inhibition of ovulation

   Exception for South Africa only: Progestogen-only hormonal contraception injection, with active monitoring of compliance, is allowed as a contraceptive method.

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

Male subjects with a female partner of childbearing potential, unless vasectomized, must use condoms (with spermicide, where available) for the purposes of contraception throughout the study and for a duration of 90 days after the last dose of study drug. It is not known if BCX9930 or BCX13559, the major metabolite of BCX9930, are present in human semen. Therefore, subjects with a pregnant female partner must use condoms to avoid potential exposure of the partner and fetus in utero through semen.

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

Abstinence as a contraceptive method will not be an option for subjects regardless of lifestyle or sexual activity.

Per European Clinical Trials Facilitation and Coordination Group guidance, contraception and pregnancy testing requirements must remain in place through the end of relevant systemic exposure (CTFG 2020). Based on data generated in healthy subjects in Study 101, the geometric mean half-life of BCX9930 was ≤ 17.35 hours (suggesting that 5 half-lives are elapsed within approximately 3.6 days). Further, the human mass balance study (Study 102) identified BCX13559 (an acyl glucuronide) as the only major metabolite of BCX9930. Clearance of BCX13559 was determined to be formation-rate limited. Study 102 also showed all subjects achieved > 90% recovery of the administered radioactive dose within 12 days (single dose). Together, these findings suggest that the end of relevant systemic exposure for BCX9930 and BCX13559 occurs well before the ET or EOS visit performed approximately 3 weeks after the last dose of BCX9930.

Methods of contraception, as applicable, for both male and female participants should be documented in the source documentation. Investigators will also review each subject's continued use of contraception at periodic intervals to ensure compliance with the protocol contraception requirements, including reminding subjects about the need to renew their contraception.

11.3. Virology Assessments

Antibodies to varicella-zoster virus were tested at the screening visit in the prior study. For this study, any subject who has an exposure to someone with primary varicella (chickenpox) or herpes-zoster (shingles), or who has recently received a live varicella vaccine, should contact the investigator, and administration of varicella zoster immune globulin or other medications should be considered where available.

For those who entered the prior study with positive serology for HIV or active infection with HBV or HCV, the appropriate testing for viral load should be repeated approximately yearly from the date of first viral load assessment. If positive, contact the medical monitor to discuss the best option for the subject.

11.4. Effectiveness Assessments

As currently amended, the protocol no longer requires specific effectiveness assessments to be performed. The clinical benefit of treatment with BCX9930 will be assessed for each individual subject based on the medical judgement of the investigator and the standard-of-care practices for the treatment and management of PNH disease at his or her institution. Common laboratory measurements of PNH will continue to be assessed and reported in the safety testing (eg, Hb, LDH, absolute reticulocyte count, AST, bilirubin, etc.) performed by the designated clinical safety laboratory. Any other laboratory testing should be performed and monitored per appropriate medical judgement. This information will be used to assess the ongoing benefit-risk of continued treatment with BCX9930.

11.5. Safety Assessments

All assessments will be performed as indicated in the schedule of assessments (Table 2).

11.5.1. Vital Signs

Measurements of vital signs will include blood pressure, pulse rate, and temperature and should be obtained after the subject has rested for at least 5 minutes in a quiet room at a comfortable temperature, with the subject's arm unconstrained by clothing or other material. Blood pressure measurements will be obtained with the appropriate cuff size, with the

subject's arm supported at the level of the heart, while the subject is resting in a semi-supine position.

11.5.2. Body Weight, Height, and Body Mass Index

Body weight, height, and body mass index (BMI) will be recorded at the last on-treatment visit in the prior study/baseline. For determination of height and body weight, subjects should be clothed with shoes removed.

11.5.3. Physical Examination

A targeted (ie, symptom driven) physical examination will be performed at all regularly scheduled assessments to assess for any changes from the previous examination, including, at a minimum, evaluation of new or worsening signs or symptoms.

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

The following text assumes the use of a central laboratory to support the clinical laboratory testing for safety monitoring, including testing for laboratory measurements of the effectiveness of PNH treatment. However, at investigational sites where it is no longer considered necessary and/or practical to use a central laboratory for the safety oversight of clinical study subjects, local laboratory services may be used. Data will continue to be reported and available to the sponsor to meet ongoing safety review commitments.

Blood and urine samples will be collected during the study. Individual laboratory tests are specified in Table 3. In general, all laboratory samples collected at visits to the investigational site should be collected using kits provided by the designated central laboratory. However, at the investigator's discretion, local laboratories may be used in place of the central laboratory (eg, for logistical reasons such as delays in transport due to COVID-19) or for analysis of samples collected for assessment of possible AEs (eg, when emergent safety concerns require expedited turnaround times for safety laboratory assessments). The additional renal and hepatic safety assessments may be performed at the investigational site or remotely at a location more convenient for the subject. The results from laboratory testing performed at a local or remote laboratory must be provided to the investigational site. The use of a local or remote laboratory in this manner, and any differences in analyte panels with the central laboratory, based on the availability of testing at the local or remote laboratory, will not be considered protocol deviations for the purposes of this protocol. Reference ranges for each local or remote laboratory used will be provided to the sponsor and included in data listings.

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

Table 3: Clinical Laboratory Evaluations

Serum Chemistry	**Urinalysis with Microscopy**[a]
Albumin Alanine aminotransferase (ALT) (SGPT) Alkaline phosphatase (ALP) Amylase[b] Aspartate aminotransferase (AST) (SGOT) Bilirubin (total and direct) Blood urea nitrogen (BUN) Calcium Chloride Cholesterol (total, high- and low-density lipoprotein) Creatine (phospho)kinase (C[P]K) Creatinine (sCr) Glucose Haptoglobin Lactate dehydrogenase (LDH) Magnesium Potassium Sodium Protein (total) Triglycerides Uric acid	Albumin Bilirubin Blood Creatinine Glucose Ketones Leukocytes Nitrites pH Protein Specific gravity Urine albumin to creatinine ratio (uACR) Urobilinogen
Hematology	**Pregnancy/Menopause**
Hemoglobin (Hb) Hematocrit (Hct) Mean corpuscular hemoglobin (MCH) Mean corpuscular hemoglobin concentration (MCHC) Mean corpuscular volume (MCV) Platelet count (PLT) Red blood cell (erythrocyte) count (RBC) Reticulocyte count White blood cell count (WBC) with differential	Follicle-stimulating hormone (FSH) Urine pregnancy test[c]
	Coagulation/Fibrinolysis
	Activated partial thromboplastin time (aPTT) Prothrombin time (PT) International normalized ratio (INR) Thrombin time
	Other Testing
	Estimated glomerular filtration rate(eGFR)[d] PNH RBC clone size (total) PNH WBC clone size Varicella-zoster virus (VZV) immunoglobulin G (IgG) titer (where appropriate) Hepatitis B virus (HBV), hepatitis C virus (HCV), human immunodeficiency virus (HIV) viral load (where appropriate)

Abbreviations: DNA = deoxyribonucleic acid; PNH = paroxysmal nocturnal hemoglobinuria; RNA = ribonucleic acid; SGOT = serum glutamic-oxaloacetic transaminase; SGPT = serum glutamic-pyruvic transaminase.

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

[a] Reflex to microscopy if dipstick is abnormal. For local laboratory testing, urinalysis analytes may be different.

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

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

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

11.5.4.1. Urine Collections for Urinalysis and Urine Microscopy

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 processing of the samples for urinalysis. Urine microscopy will be performed at the central laboratory as a reflex test if the urinalysis testing is abnormal. For subjects with CCI sites are encouraged to perform urine microscopy using their local laboratory, where appropriate on-site testing capabilities are available, to assess for crystals and/or casts (see also Section 12.5.2).

11.5.5. Menopause and Pregnancy Testing

FSH may be assessed at any visit if menopausal status changes to confirm menopausal status. The subject must have a negative urine pregnancy test as per protocol until menopausal status is confirmed.

For women of childbearing potential, a urine pregnancy test will be assessed at baseline, at monthly intervals during the treatment period, and at the EOS/ET visit, or as required per normal site practice. A serum pregnancy test should immediately be drawn and sent for analysis for any positive urine pregnancy test. Where required, pregnancy testing may be performed using the local laboratory, and using serum testing in lieu of the urine pregnancy tests.

Women of childbearing potential will be provided with urine pregnancy test kits for home testing once a month.

12. ADVERSE EVENTS

12.1. Definition of Adverse Events

12.1.1. Adverse Event

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

This includes the following:

- AEs not previously observed in the subject that emerge during the protocol-specified AE reporting period (see Section 12.4.1).
- Findings from protocol-mandated interventions. This can include laboratory assessments performed in the course of the clinical study. AEs should be reported only if the abnormalities are changes from baseline and are clinically significant as described above.
- Pre-existing medical conditions (other than the condition being studied) judged by the investigator to have worsened in severity or frequency or changed in character during

the protocol-specified AE reporting period. When recording such events on an AE/SAE eCRF page, it is important to convey the concept that the pre-existing condition has changed by including applicable descriptors (eg, "more frequent headaches").

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

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

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

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

AEs are designated as "nonserious" or "serious".

12.1.2. Serious Adverse Event

A serious adverse event (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 SAEs when, based upon appropriate medical judgment, they may jeopardize the subject's health or may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such events

may include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias, or convulsions that do not result in subject hospitalization.

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

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

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

12.1.3. Events of Special Monitoring

Events of special monitoring (EOSM) are AEs or safety topics for which special monitoring, additional data collection activities, and/or enhanced signal detection activities within BioCryst are considered appropriate for this population and study. Identified EOSMs can be of particular concern based on findings from the IMP clinical program to date, potential and/or known risks generally associated with the underlying disease, or comorbidities and risk factors prevalent in the study population.

EOSM for this study include CCI [redacted]
CCI [redacted]
CCI [redacted]

12.2. Definition of Severity

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

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

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

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

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

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

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

12.3. Relationship to Study Drug

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

Not Related:	The event can be readily explained by other factors such as the subject's underlying medical condition, concomitant therapy, or accident, and no temporal relationship exists between the study drug/IMP and the event.
Unlikely Related:	The event does not follow a reasonable temporal sequence from drug administration and is readily explained by the subject's clinical state or by other modes of therapy administered to the subject.
Possibly Related:	There is some temporal relationship between the event and the administration of the study drug/IMP and the event is unlikely to be explained by the subject's medical condition, other therapies, or accident.
Probably Related:	The event follows a reasonable temporal sequence from study drug/IMP administration, abates upon discontinuation of the study drug/IMP, and cannot be reasonably explained by the known characteristics of the subject's clinical state.
Definitely Related:	The event follows a reasonable temporal sequence from study drug/IMP administration, follows a known or suspected response pattern to the study drug/IMP, is confirmed by improvement upon stopping the study drug/IMP (dechallenge), and reappears upon repeated exposure (rechallenge, if rechallenge is medically appropriate).

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

The sponsor may upgrade causality if deemed appropriate.

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

Reports of all AEs and SAEs, regardless of investigator attribution, are to be collected from the time of enrollment through to the last study visit (ie, through the post-treatment follow-up

visit). If AEs/SAEs occur after the subject has signed the informed consent form (ICF) for Study 205 but while the subject is still enrolled in the prior study, the AEs/SAEs will be collected according to the procedures specified in the prior study protocol. All AEs and SAEs are to be reported on the AE eCRF.

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

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

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

12.4.1. Serious Adverse Events and Suspected Unexpected Serious Adverse Reactions

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

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

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

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

BioCryst shall ensure that all relevant information about SUSARs that are fatal or life-threatening is recorded and reported as soon as possible to all competent authorities, and to the applicable ethics committee in any case no later than 7 calendar days after knowledge by BioCryst of such a case, and that relevant follow-up information is subsequently communicated within an additional 8 days. All other SUSARs shall be reported to the competent authorities concerned and to the ethics committees, as applicable, according to local regulations, as soon as possible but in no case later than 15 calendar days of first knowledge by BioCryst. BioCryst or designee shall also inform the investigator. CCI [redacted]
CCI [redacted]
CCI [redacted]

12.4.2. Pregnancy

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

12.5. Adverse Event Management

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

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

All treatment-emergent ALT elevations > 3 × 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.

12.5.2. 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, the following recommendations are made:

CCI

[redacted]

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

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

Monitoring for hemolysis should be performed based on the medical judgement of the investigator. However, when subjects permanently discontinue BCX9930 at any time during the study, the following recommendations are made:

- If the subject is asymptomatic, it is recommended that contact with the subject be maintained on a daily basis for a minimum of 7 days. Contact may be conducted by telephone, email, or other means, including in person, if preferred. When any sign or symptom of hemolysis occurs, the subject should be promptly evaluated. Additional monitoring following the first contact after permanent discontinuation should be guided by the medical judgement of the investigator.

- For subjects who are already symptomatic when treatment is discontinued, whether the subject should be assessed in person or can be followed with daily contact will be based on the investigator's medical judgement taking into account the severity of the reported signs or symptoms and/or any reported worsening of the signs or symptoms. When possible, subjects should return to the investigative center; however, when this is not possible, arrangements may be made for the subject to be assessed by his or her local hematologist and a local laboratory used for clinical laboratory testing. When hemolysis occurs after the permanent discontinuation of BCX9930, treatment should be provided according to the judgement of the investigator.
- Subjects should be asked to contact the investigator if they experience any new or worsening signs or symptoms of hemolysis. Subjects should be evaluated per the investigator's medical judgement. A review of dosing compliance to ensure that the subject is taking the drug should be performed, regardless of the method used to evaluate the subject (ie, in-person or remote assessment). It should also be determined whether the subject has had any recent complement-activating conditions (eg, infection, trauma, or surgery) that may have contributed to the hemolytic event.
- Treatment with BCX9930 should not be interrupted or withheld unless there is an absolute contraindication for continued dosing. Suggestions for anti-emetic therapy for subject with active nausea and vomiting when tablet contents are vomited are given in Section 9.6.2.

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

12.6. Overdose

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

12.7. Data Monitoring Committees

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

CCI [redacted]
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CCI [redacted]

13. STATISTICS

13.1. Sample Size Considerations

No sample size calculations were conducted for this open-label, long-term safety study. Up to 30 subjects may be enrolled in this study, to allow continued access to BCX9930 following a subject's participation in another BCX9930 study.

13.2. Stratification

Not applicable.

13.3. 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.

13.3.1. Analysis Populations

The analysis populations for the study are defined below.

13.3.1.1. Safety Population

The safety population is defined as all subjects who receive at least 1 dose of study drug. This population will be used for all analyses of accountability, demographics, and safety.

13.3.2. General Considerations for Data Analysis

In general, descriptive summaries will include the sample size (n), mean, standard deviation (SD) and/or standard error (SE), median, minimum, and maximum for continuous variables and n and percentage for categorical variables. Data will be summarized by prior study and overall. Summaries will be presented by study visit where appropriate (eg, laboratory data) until subjects complete or withdraw from the study. No missing value imputation will be done. No statistical testing is anticipated as there are no a priori hypotheses stated for this 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), using version 9.4 or higher.

13.3.3. Subject Demographic and Disposition Data

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

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

13.3.4. Analysis of Safety Variables

Safety endpoints will be summarized and will include, at a minimum, the proportion of subjects 1) with TEAEs; 2) who discontinue due to a TEAE; 3) with treatment-emergent SAE; 4) with a Grade 3 or 4 TEAE; and 5) with Grade 3 or 4 laboratory abnormalities.

AEs will be mapped to a Medical Dictionary for Regulatory Activities (MedDRA, Version 24.0) 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.

For all analyses of change from baseline, the baseline is the baseline value for the current study.

Descriptive statistics for vital signs, weight, and clinical laboratory results will be presented by study visit. Laboratory abnormalities will be graded according to CTCAE scales (Version 5.0, 27 November 2017). The number and percentage of subjects experiencing treatment-emergent graded laboratory toxicities will be summarized. Laboratory toxicity shifts from baseline to the worst post-baseline value as well as to 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 US FDA's Premarketing Clinical Evaluation on Drug-Induced Liver Injury Guidance for Industry (FDA 2009).

14. STUDY ADMINISTRATION

14.1. Study Monitoring

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

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

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

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

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

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

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

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

14.2. Audits and Inspections

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

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

14.3. Ethics Committee

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

14.4. Serious Breaches of GCP

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

15. QUALITY CONTROL AND QUALITY ASSURANCE

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

To ensure compliance with GCP and all applicable regulatory requirements, BioCryst or its designee may conduct a quality assurance audit. Please see Section 14.2 for more details

regarding the audit process. The investigator agrees to allow the auditors to inspect the drug storage area, study drug stocks, drug accountability records, subject charts and study source documents, and other records relative to study conduct.

16. ETHICS

16.1. Ethics Review

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

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

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

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

16.2. Ethical Conduct of the Study

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

16.3. Written Informed Consent

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

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

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

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

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

17. DATA HANDLING AND RECORDKEEPING

17.1. Inspection of Records

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

17.2. Retention of Records

The investigator will maintain adequate records for the study, including the identity of all participating subjects (sufficient information to link records, eCRFs, and medical/hospital records), all original signed ICFs, all original signed assents (if applicable), all eCRFs, drug dispensing and disposition records, safety reports, information regarding participants who discontinued, and other pertinent data.

All essential documents should be retained by the investigator according to local regulations or as specified in the Clinical Study Agreement, whichever is longer. It is the responsibility of BioCryst to inform the investigator/institution as to when these documents no longer need to be retained. It is the investigator's responsibility to notify BioCryst if they relocate or retire so that document storage can be addressed. The investigator must obtain BioCryst's written permission before disposing of any records and must notify BioCryst before transferring any records to another facility.

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

17.3. Confidentiality of Information and Data

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

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

waiver/authorization in writing from the appropriate individual. HIPAA authorizations are required for US sites only.

18. PUBLICATION POLICY

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

19. LIST OF REFERENCES

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