BIOCRYST

PHARMACEUTICALS, INC.

BCX9930

PROTOCOL BCX9930-211

EudraCT NUMBER: 2020-005855-19

An Open-Label, Safety, Tolerability, and Proof-of-Concept Study of Oral BCX9930 Therapy in Subjects with Complement 3 Glomerulopathy, Immunoglobulin A Nephropathy, or Primary Membranous Nephropathy

Version 4.0: 04 August 2022

BioCryst Pharmaceuticals, Inc.
4505 Emperor Blvd., Suite 200
Durham, NC 27703
Phone: (919) 859-1302
Fax: (919) 851-1416

CONFIDENTIAL

SPONSOR SIGNATURE PAGE

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This protocol has been approved by BioCryst Pharmaceuticals, Inc.

Responsible Medical Officer:

DocuSigned by:
[redacted]
Signer Name: [redacted]
Signing Reason: I approve this document
Signing Time: 05-Aug-2022 | 08:49:40 EDT
0894882407F84F54B3F8B5F57AECC354

[redacted] Date

[redacted]
BioCryst Pharmaceuticals, Inc.

Sponsor's Authorized Officer:

DocuSigned by:
[redacted]
Signer Name: [redacted]
Signing Reason: I approve this document
Signing Time: 05-Aug-2022 | 09:47:58 EDT
6F42112F8B93468F87F4A0044917DBE6

[redacted] Date

[redacted]
BioCryst Pharmaceuticals, Inc.

INVESTIGATOR'S AGREEMENT

Protocol No. BCX9930-211

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Version 4.0: 04 August 2022

I have received and read the Investigator's Brochure 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:
[redacted]

Protocol Number: BCX9930-211

Title of Study: An Open-Label, Safety, Tolerability, and Proof-of-Concept Study of Oral BCX9930 Therapy in Subjects with Complement 3 Glomerulopathy, Immunoglobulin A Nephropathy, or Primary Membranous Nephropathy

Study Center(s): This study is planned to be conducted at study centers in countries in Europe, North America, Asia Pacific and other regions.

Lead or Coordinating Investigator:
[redacted]

Central Pathologist:
[redacted]

Phase of Development: 2

The objectives and endpoints in this proof-of-concept (POC) study of orally administered BCX9930 are applicable to the 3 parallel treatment cohorts of subjects with complement 3 glomerulopathy (C3G), immunoglobulin A nephropathy (IgAN), or primary membranous nephropathy (PMN).

Primary Objectives:

- To evaluate the therapeutic potential of BCX9930 as assessed by proteinuria

Secondary Objectives:

- To evaluate the safety and tolerability of BCX9930
- To evaluate the therapeutic potential of BCX9930 as assessed by other measures of clinical benefit
- To evaluate effects on kidney biopsy morphologic findings (C3G cohort only)

Exploratory Objectives:

- [redacted]

[redacted]

state

Primary Endpoint:

- Change in 24-hour urinary protein excretion normalized to urine creatinine as measured by percentage change in urine protein-to-creatinine ratio (uPCR) from baseline

Secondary Endpoints:

- Number and proportion of subjects with a uPCR response defined as:
  - Partial remission, ≥ 50% reduction from baseline
  - Complete remission, ≤ 500 mg/g
  - Normalization, ≤ 200 mg/g
- Change from baseline in 24-hour urinary protein excretion as measured by percentage change in urinary protein from baseline
- Change from baseline in estimated glomerular filtration rate (eGFR)
- Change from baseline in serum albumin
- Number and proportion of subjects with the following parameters:
  - Protein ≥ 3.5 g in a 24-hour urine collection
  - Serum albumin ≤ 2.5 g/dL
- Number and proportion of subjects with a morphologic response in each of the following categories (C3G cohort only at Week 24):
  - Decreased endocapillary hypercellularity, mesangial hypercellularity, active crescents (if present), glomerular leukocyte infiltration, fibrinoid necrosis, membranoproliferative glomerulonephritis pattern
  - Decreased acute tubular injury, interstitial inflammation, interstitial edema
  - Reduction in C3 glomerular staining
  - Reduction in the extent of deposits, clearing of deposits, or no additional active deposits as assessed by electron microscopy (EM)
  - No progression of chronic changes (ie, global, segmental glomerulosclerosis, tubular atrophy/interstitial fibrosis, arteriosclerosis)
- Number and proportion of subjects with a treatment-emergent adverse event(s)(TEAE)

- Number and proportion of subjects who discontinue due to a TEAE
- Number and proportion of subjects who experience a treatment-emergent serious adverse event (TESAE)
- Number and proportion of subjects who experience a Grade 3 or 4 TEAE based on Common Terminology Criteria for Adverse Events (CTCAE)
- Number and proportion of subjects who experience a CTCAE treatment-emergent Grade 3 or 4 laboratory abnormality

Exploratory Endpoints:

[redacted]

Study Design:

This is a Phase 2, open-label, multicenter, POC study to evaluate the safety, tolerability, and therapeutic potential of BCX9930, an oral Factor D inhibitor, administered for up to 52 weeks in adult (≥ 18 years old) subjects with C3G, IgAN, or PMN. After up to a 56-day screening qualification period, approximately 14 eligible subjects will be enrolled into each of three parallel study treatment cohorts and will receive BCX9930 200 mg twice daily (BID) for the first 14 days and 400 mg BID on Day 15 and for the remainder of the treatment period, up to a total duration of 52 weeks. Each cohort may be analyzed separately.

Methodology:

During the study, recruitment into each of the cohorts will be managed independently with a total of approximately 42 subjects enrolled into the study. For the C3G cohort only, up to 7 subjects with at least 6 months of treatment with a stable dosing regimen of mycophenolate mofetil/mycophenolate sodium prior to the Day 1 Visit will be allowed to enroll in the study.

The independent BCX9930 DMC will regularly review cumulative safety data from this study, as well as accumulating, long-term safety data across all BCX9930 studies in all indications.

After providing appropriate written informed consent to participate in the study and confirming that all other study eligibility criteria have been met during screening, subjects will undergo a percutaneous needle biopsy of the kidney per local practice and guidelines. Renal biopsy images and details from the local pathology report will be reviewed by the central pathologist for confirmation of a protocol-defined diagnosis of C3G, IgAN, or PMN. The screening biopsy procedure may be waived with approval of the central pathologist and agreement with the medical monitor for any subject who has undergone a renal biopsy procedure as follows: within 3 months prior to screening for the C3G cohort, or within 6 months prior to screening for the IgAN cohort and PMN cohorts, provided that required materials are adequate for pathology evaluation per protocol procedures.

After the Day 1 Visit, subjects will return to the clinic at Weeks 1, 2, and 4, and then every 4 weeks thereafter through Week 24. Additional safety assessments will be performed at Weeks 3, 5, 6, 7, and 10, either at the investigative site, or at a local laboratory more convenient for the subject or via a home health service. At the Week 24 Visit, the clinical benefit of BCX9930 treatment will be assessed by the investigator. Subjects who are assessed with deriving clinical benefit at the Week 24 Visit will continue study treatment and visits up to Week 52.

An on-treatment, percutaneous needle biopsy of the kidney will be performed at the following visit after completion of all other assessments, or during the time specified below by treatment cohort:

- Week 24 or within 7 days after the visit for subjects with C3G
- Week 36 or within 7 days after the visit for subjects with IgAN (optional)
- Week 48 to within 3 days after the Week 52 Visit for subjects with PMN (optional)

Images of LMs, IFs or IHCs, EMs, and details from the local pathology reports from the on-treatment biopsies will be reviewed by the central pathologist. Protocol-specified, on-treatment biopsies will not be required for subjects who are discontinued from BCX9930 treatment.

Subjects who complete BCX9930 dosing through Week 52 or who discontinue BCX9930 dosing prior to Week 52 will return to the clinic approximately 4 weeks (28 ± 3 days) after the date of their last dose of BCX9930 for the Safety Follow-up (FU) Visit prior to study completion or discontinuation.

An optional serial PK/PD substudy will include subjects who provide consent from each of the 3 cohorts to evaluate the PK and PD of BCX9930 at the Day 1 Visit and/or at a subsequent visit prior to the Week 24 Visit. Serial sampling of urine and blood will be performed over a period of 6 hours. Subjects who do not participate in the Baseline (Day 1) PK/PD sample collection are eligible to participate at a subsequent clinic visit prior to the Week 24 Visit.

All subjects will have a single blood sample drawn for PK analysis at each clinic visit. For subjects participating in the serial PK/PD substudy, a single blood sample will be drawn for PK analysis at visits where serial blood samples are not collected through 6 hours post dose.

All subjects who sign a separate informed consent, will participate in exploratory pharmacogenomics testing at a single visit from Day 1 up to the Week 24 Visit (including the Safety FU Visit, if applicable).

Number of Subjects (Planned):

This study will enroll approximately 14 adult subjects in each of the 3 cohorts: C3G, IgAN and PMN for a total enrollment of approximately 42 subjects.

Inclusion Criteria:

Subjects must meet all of the following inclusion criteria (where applicable) prior to first dose of BCX9930 on Day 1 or specified time below:

1. Willing and able to provide written informed consent.
2. Male or non-pregnant, non-lactating female subjects ≥ 18 years of age.
3. Body weight ≥ 40 kg.
4. Primary diagnosis of C3G, IgAN, or PMN with evidence of disease activity, as confirmed by central pathology review of digital images and pathology reports of renal biopsy samples obtained during screening (or within 3 months prior to screening for subjects with C3G,and within 6 months prior to screening for subjects with IgAN and PMN with approval of the central pathologist and agreement with the medical monitor).
   - All: ≤ 50% global glomerulosclerosis
   - All: ≤ 50% tubulointerstitial fibrosis
5. For subjects with C3G only, documentation of duration of illness of at least 90 days by either a prior biopsy collected ≥ 90 days prior to screening confirming a diagnosis of C3G OR a clinical diagnosis of C3G with at least one documented proteinuria assessment ≥ 90 days prior to initial screening visit.
6. For subjects with C3G only, proteinuria defined as ≥ 1 g of urinary protein per 24 hours at screening that has not shown a ≥ 25% decrease from the most recent documented proteinuria assessment, which was collected ≥ 30 days prior to and ≤ 180 days of initial screening visit.
7. For subjects with IgAN only, proteinuria defined as 1 g to ≤ 4 g of urinary protein per 24 hours at screening that has not shown a ≥ 25% decrease from the most recent documented proteinuria assessment, which was collected ≥ 30 days prior to and ≤ 180 days of initial screening visit.
8. For subjects with PMN only, an anti-phospholipase A2 receptor antibody (aPLA2Rab) immunoglobulin G (IgG) titer of ≥ 150 U/mL and 3.5 g to ≤11 g of urinary protein per

24 hours at screening that has not shown a ≥ 25% decrease from the most recent documented proteinuria assessment, which was collected ≥ 30 days prior to and ≤ 180 days of initial screening visit.

9. An eGFR ≥ 50 mL/min/1.73 m^2 (or ≥ 30 mL/min/1.73 m^2 after DMC recommendation) calculated using the serum creatinine-based Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula.
10. Resting supine vital signs within the following ranges:
    - Systolic blood pressure, 80 to 150 mm Hg, inclusive
    - Diastolic blood pressure ≤ 90 mm Hg
11. Treatment with a stable, maximum recommended or maximum tolerated dose of an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB) for at least 60 days prior to the Day 1 Visit and in the opinion of the investigator the expectation of continuing the same dose and regimen for such treatment during the study.
12. Contraception requirements:

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

    a. Be a woman of nonchildbearing potential, defined as postmenopausal (without menses for ≥ 12 months [without an alternative medical cause] with a follicle-stimulating hormone [FSH] > 40 mIU/mL, or who have had a hysterectomy, bilateral salpingectomy, or bilateral oophorectomy).
    b. Be a woman of childbearing potential (defined as a female following menarche and prior to becoming post-menopausal who has not had a hysterectomy, bilateral salpingectomy, or bilateral oophorectomy) who agrees to use a highly effective contraceptive method while enrolled in the study and for a duration of 30 days after last dose of study drug. The following methods are acceptable:
        - surgical sterilization (ie, bilateral tubal occlusion or vasectomy of the sole male partner and the vasectomized partner has received medical assessment of surgical success)
        - intrauterine device (IUD) or intrauterine system (IUS)
        - Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal)
        - Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable)
    c. Women of childbearing potential who declare themselves sexually abstinent or exclusively having female sexual partners do not need to use highly effective contraception. Abstinence in this study is defined as true abstinence, when it is in line with the subject's preferred and usual lifestyle. If a subject is usually not sexually active but becomes active, she, with her partner, must meet the requirements listed above.

    Male subjects must meet at least one the following requirements:

    d. Subjects with female partners of childbearing potential (defined as without menses ≤ 12 months, or a non-menopausal female who has not had a hysterectomy, bilateral salpingectomy, or bilateral oophorectomy) must agree to utilize a contraceptive method

throughout the study and for at least 90 days after the last dose of study drug. The following methods during the study are acceptable:

- surgical sterilization (ie, vasectomy that has been medically assessed to be successful, or bilateral tubal occlusion of a female partner)
- partner's use of an IUD or IUS
- partner's use of combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal)
- partner's use of progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable)
- use of a condom

13. Documentation of current vaccinations against *Neisseria meningitidis* Types A, C, W, and Y, and *Streptococcus pneumoniae*, or willingness to start vaccination series at least 14 days prior to Day 1.

(Note: Vaccination for *N. meningitidis Type B* and for *Hemophilus influenzae* [Hib] is strongly encouraged, where authorized and available.)

14. In the opinion of the investigator, the subject is likely to comply adequately with all required study procedures and restrictions for the study, including compliance with the BID dosing schedule for BCX9930.

Exclusion Criteria:

Subjects must meet none of the following exclusion criteria (where applicable) prior to first dose of BCX9930 on Day 1 or specified time below:

1. Known congenital deficiency of C1s, C1r, C1q, C2, C4. Known variants in complement Factor H, complement Factor I, C3, and complement Factor B or genomic rearrangements in the complement Factor-H-related proteins are not exclusionary.
2. Receiving hemodialysis or peritoneal dialysis or anticipated to receive dialysis during the duration of this study.
3. History of hematopoietic cell transplant or solid organ transplant or anticipated candidate for transplantation during the study.
4. History of transfusion with blood or blood products, or plasmapheresis or plasma exchange, within 30 days prior to screening.
5. Myocardial infarction or cerebrovascular accident within 30 days prior to screening, or current and uncontrolled clinically significant cardiovascular or cerebrovascular condition, including unstable angina, severe congestive heart failure, unexplained syncope, arrhythmia, and critical aortic stenosis.
6. History of malignancy within 5 years prior to the screening visit, with the exception of adequately treated non-melanoma skin or superficial bladder cancer, curatively treated carcinoma in situ of the cervix, or other curatively treated solid tumor deemed by the investigator and medical monitor to be at low risk for recurrence.

7. Any clinical or pathological evidence of monoclonal gammopathy of unclear or renal significance, lupus or other systemic autoimmune disease, or other conditions (eg, infection-associated disease or associated with another systemic disease, anti-phospholipid antibody syndrome with significant clinical disease, immune complex glomerulonephritis, immunoglobulin A [IgA] vasculitis with nephritis [Henoch-Schönlein purpura] or morphologic features of secondary membranous nephropathy). Presence of C3 or C5 nephritic factors (eg, autoantibodies directed at C3 or C5 convertase), in the absence of known infection or other systemic disease, are not exclusionary for this study.
8. Treatment with azathioprine, canakinumab, cyclophosphamide, cyclosporine, eculizumab, everolimus, hydroxychloroquine, infliximab, sirolimus, ravulizumab, systemic corticosteroids (including budesonide), tacrolimus, or any other systemic immunosuppressive or immunomodulatory therapies (eg, complement inhibitors) within 90 days OR mycophenolate mofetil/mycophenolate sodium treatment within 60 days OR anti-CD20 antibody therapies (eg, rituximab) within 180 days prior to the screening visit.
    a. For subjects with C3G only, ongoing treatment with a stable dosing regimen of mycophenolate mofetil/mycophenolate sodium for at least 6 months prior to Day 1 Visit is allowed.
9. Treatment with renin inhibitors (eg, aliskiren) or sodium-glucose-cotransporter 2 (SGLT2) inhibitors within 60 days prior to Day 1.
10. Current participation in any other investigational drug study or participation in an investigational drug study within 30 days prior to the screening visit, or 5.5 half-lives of the investigational drug, whichever is longer.
11. Any of the following laboratory values at the screening visit: hemoglobin < 8.5 g/dL; total white blood cell (WBC) < 2.5×10^9/L; absolute neutrophil count (ANC) < 1.0×10^9/L; platelet count < 90×10^9/L; alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), or total bilirubin > 1.5 × upper limit of normal (ULN); serum albumin < 1.5 g/dL; or international normalized ratio (INR) > 1.4.
    a. Subjects with Grade 1 elevated bilirubin due to Gilbert's syndrome are allowed to enroll. To document that a subject has Gilbert's syndrome, a diagnosis from the medical record must be provided, or the investigator may make a presumptive diagnosis of Gilbert's syndrome in subjects with unconjugated hyperbilirubinemia on repeated testing (at least 2 samples separated in time) who have ALT, AST, and ALP ≤ 1.5 × ULN, and a normal complete blood count.
12. Any laboratory parameter at screening that, in the judgment of the investigator, is clinically significant and would represent a safety concern.
13. Clinically significant abnormal electrocardiogram (ECG) prior to dosing at the Day 1 Visit.
14. Current use of a prohibited concomitant medication within 7 days prior to Day 1.
15. Active serious bacterial, viral, or fungal infection or any other serious infection, including suspected or confirmed severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2] infection, within 14 days of screening. Dyspnea, vasculitic rash, and persistent fever or other symptoms consistent with multisystem inflammatory syndrome [MIS] are exclusionary in the setting of recent SARS-CoV-2 infection.

16. Positive serology for human immunodeficiency virus (HIV), or active infection with hepatitis B virus (HBV) or hepatitis C virus (HCV).
17. Positive test for drugs of abuse during screening, unless by prescription.
18. Pregnant, planning to become pregnant, or breastfeeding.
19. Known or suspected hypersensitivity to BCX9930 or any of its formulation excipients.
20. History of severe hypersensitivity to any medicinal product, which was associated with swelling, severe rash requiring treatment/hospitalization, or anaphylaxis.
21. Any clinically significant medical or psychiatric condition, including known or suspected substance abuse (including alcohol) that, in the opinion of the investigator or sponsor, would interfere with the subject's ability to participate in the study or increase the risk of participation for that subject.

Investigational Product, Dosage and Mode of Administration:

Subjects who previously received 500 mg BID and remain on study treatment will be dose adjusted to 400 mg BID. For all newly enrolled subjects, subjects will initially receive BCX9930 200 mg BID for the first 14 days of treatment before increasing the dose to 400 mg BID on Day 15 for the remainder of the treatment period. The appropriate quantity of BCX9930 tablets will be taken orally, twice a day, approximately 12 hours apart, without regard to food. Adequate hydration should be maintained to prevent the formation of highly concentrated urine.

Duration of Treatment:

Subjects will receive open-label BCX9930 for up to 52 weeks.

Reference Therapy, Dosage and Mode of Administration:

N/A

Criteria for Evaluation:

Safety: Safety will be evaluated by TEAEs, laboratory analyses (clinical chemistry, hematology, coagulation, urinalysis including microscopy), vital signs, ECGs, and physical examination findings. In addition, potential drug-induced liver injury, potential drug-induced kidney injury, and SARS-CoV-2 infection (asymptomatic and symptomatic) events, including non-serious events, may have enhanced data collection.

Clinical Laboratory and Anatomical Pathology Evaluations of C3G, IgAN, or PMN: Proteinuria as assessed by intended 24-hour urine collection for total daily proteinuria, albuminuria, uPCR, and urine-albumin-to-creatinine ratio (uACR); other kidney biomarkers may be assessed. uPCR, uACR, and other kidney biomarkers may also be assessed by the single void urine collection; serum albumin, serum creatinine, and other analytes for eGFR; percutaneous needle biopsies of the kidney with images of LMs, IFs or IHCs, EMs, and details from the local pathology reports from Screening/Baseline and on-treatment biopsies (optional for subjects with IgAN or PMN) reviewed by the central pathologist to confirm eligibility and to evaluate and describe changes from the baseline pre-treatment digital images. For the PMN cohort only, [redacted] will be measured at Screening, Baseline, and every 4 weeks until Week 52.

Patient-Reported Outcomes: [redacted]

Clinical Laboratory [redacted]

[redacted] circulating in plasma. The capacity of the complement system will be assessed by measuring these analytes and by using ex vivo stimulation assays, such as the AP Wieslab, which activates the alternative pathway (AP) in blood samples using a specific stimulus. Additional exploratory assays may be evaluated. Samples collected may be run in more than one assay to elucidate the PD effects of BCX9930.

Single void urine samples will be analyzed for levels of [redacted]

Single void urine samples will also be analyzed for select chemokines and cytokines (eg, [redacted] normalized to urinary creatinine. Additional exploratory [redacted]

Pharmacokinetics:

Plasma: A single venous blood sample for measurement of plasma BCX9930 concentrations will be collected at each study visit from all subjects receiving BCX9930 (sparse sampling to support population PK and PD modeling). In addition, at selected study centers, with appropriate facilities for the collection and processing of serial plasma samples, an optional PK/PD substudy will be performed to characterize the PK parameters of BCX9930 in these patient populations.

The extent of plasma protein binding may be assessed for selected timepoints.

Urine: Subjects participating in the PK/PD substudy will have single void urine samples collected to evaluate renal excretion of BCX9930 and potentially metabolites, if warranted.

[redacted]

Statistical Methods:

This is a Phase 2, open-label, POC study to estimate the safety, tolerability, and therapeutic potential of BCX9930 administration in subjects with C3G, IgAN, or PMN. As such, no formal power or sample size calculations were performed to determine each cohort size.

Outcome Analyses:

For continuous efficacy variables, descriptive summaries (for the recorded value, change from baseline, and percentage change from baseline) will be presented by study visit and treatment cohort. Point estimates and confidence intervals will be presented for change from baseline and percentage change from baseline by post-baseline study visit and treatment cohort.

For binary efficacy endpoints, summaries will be presented as counts and frequencies by post-baseline study visit and treatment cohort. Confidence intervals will be provided using the Clopper-Pearson Exact method by post-baseline study visit and treatment cohort.

Categorical efficacy data will also be summarized by study visit and treatment cohort.

The following safety outcomes will be summarized in tables and/or figures: TEAEs, clinical laboratory values, morphological response, vital signs, and ECGs. Summaries will be presented by treatment cohort and, where appropriate, by visit or pooled across the three treatment cohorts.

In addition, PK, [redacted]; and QoL measurements.

Interim analyses may be conducted for each study cohort based on ongoing review of individual subject safety and preliminary efficacy data.

Safety Analyses:

Safety endpoints that will be summarized, at a minimum, will include the proportion of subjects 1) with TEAEs; 2) who discontinue BCX9930 due to TEAEs; 3) with TESAEs; 4) with Grade 3 or 4 TEAEs; and 5) with treatment-emergent Grade 3 or 4 laboratory abnormalities.

Pharmacokinetic Analyses (PK/PD Substudy):

Plasma concentrations of BCX9930 and PK parameters will be summarized by dose regimen and study visit. The plasma concentration data for BCX9930 (collected via serial sampling) will be analyzed using non-compartmental techniques to obtain estimates of standard non-compartmental PK parameters.

Pharmacodynamic Analyses:

Descriptive statistics, including change from baseline, will be provided by study visit and dose regimen. Point estimates and 95% confidence intervals will be presented for change from baseline and percent change from baseline by parameter, post-baseline study visit and treatment cohort.

The plans for analysis of other biomarkers may be modified based upon emerging data.

Sample Size Justification:

The proposed sample size of up to approximately 14 subjects per cohort should provide an estimate of uPCR reduction up to 52 weeks to assess the therapeutic potential for BCX9930 in these renal indications and inform sample sizes for future studies of BCX9930.

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4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

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

Table 1: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
ACEi	Angiotensin-converting enzyme inhibitor
ACIP	Advisory Committee on Immunization Practices
ADL	activities of daily living
AE	adverse event
aHUS	atypical hemolytic uremic syndrome
AKI	acute kidney injury
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AP	alternative pathway
[redacted]	[redacted]
ARB	angiotensin receptor blocker
AST	aspartate transferase
BID	twice daily
BMI	body mass index
BQL	below quantification level
C3	complement 3
C3bBb	C3 convertase of the AP
C3G	complement 3 glomerulopathy
CDC	Centers for Disease Control and Prevention
CI	confidence interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CP	classical pathway
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DDD	dense deposit disease
DDI	drug-drug interaction
DMC	Data Monitoring Committee
ECG	electrocardiogram

Abbreviation or Specialist Term	Explanation
eCRF	electronic case report form
EFD	embryo-fetal development
eGFR	estimated glomerular filtration rate
EM	electron microscopy or “electron micrograph” images
EOSM	event of special monitoring
ESRD	end-stage renal disease
[redacted]	[redacted]
FDA	Food and Drug Administration
FU	Follow-up
FIH	first-in-human
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
Hb	hemoglobin
HBV	hepatitis B virus
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
Hib	*Haemophilus influenzae* Type B
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
IB	Investigator’s Brochure
IC_{50}	50% of maximal inhibitory concentration
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	independent ethics committee
IF	immunofluorescence
Ig	immunoglobulin
IgA	immunoglobulin A
IgG	immunoglobulin G
IgAN	immunoglobulin A nephropathy
IHC	immunohistochemistry
IMP	investigation medicinal product or study drug
INR	international normalized ratio

Abbreviation or Specialist Term	Explanation
IRB	institutional review board
IRT	Interactive Response Technology
IST	immunosuppressive therapy
ITT	intent-to-treat
IUD	intrauterine device
IUS	intrauterine system
KDIGO	Kidney Disease Improving Global Outcomes
[redacted]	[redacted]
LC-MS/MS	liquid chromatography- tandem mass spectrometry assay
LDH	lactate dehydrogenase
LP	lectin pathway
MAC	membrane attack complex
[redacted]	[redacted]
MedDRA	Medical Dictionary for Regulatory Activities
NSAID	non-steroidal anti-inflammatory drug
NRMWG	Nephrology Risk Mitigation Working Group
PD	pharmacodynamic(s)
PG	pharmacogenomic(s)
[redacted]	[redacted]
[redacted]	[redacted]
PK	pharmacokinetic(s)
PMN	primary membranous nephropathy
PNH	paroxysmal nocturnal hemoglobinuria
POC	proof-of-concept
PPK	population pharmacokinetic
PRO	patient-reported outcome
QoL	quality of life
QTcF	QT interval corrected using Fridericia's method
RBC	red blood cell
REB	research ethics board
RNA	ribonucleic acid
SAE	serious adverse event

Abbreviation or Specialist Term	Explanation
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
sC5b-9	soluble C5b-9
sCr	serum creatinine
SGLT2	sodium-glucose-cotransporter 2
SOC	system organ class
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
uACR	urine albumin-to-creatinine ratio
[redacted]	[redacted]
uPCR	urine protein-to-creatinine ratio
ULN	upper limit of normal
US	United States
VZV	varicella-zoster virus
WBC	white blood cell
WSI	whole slide image

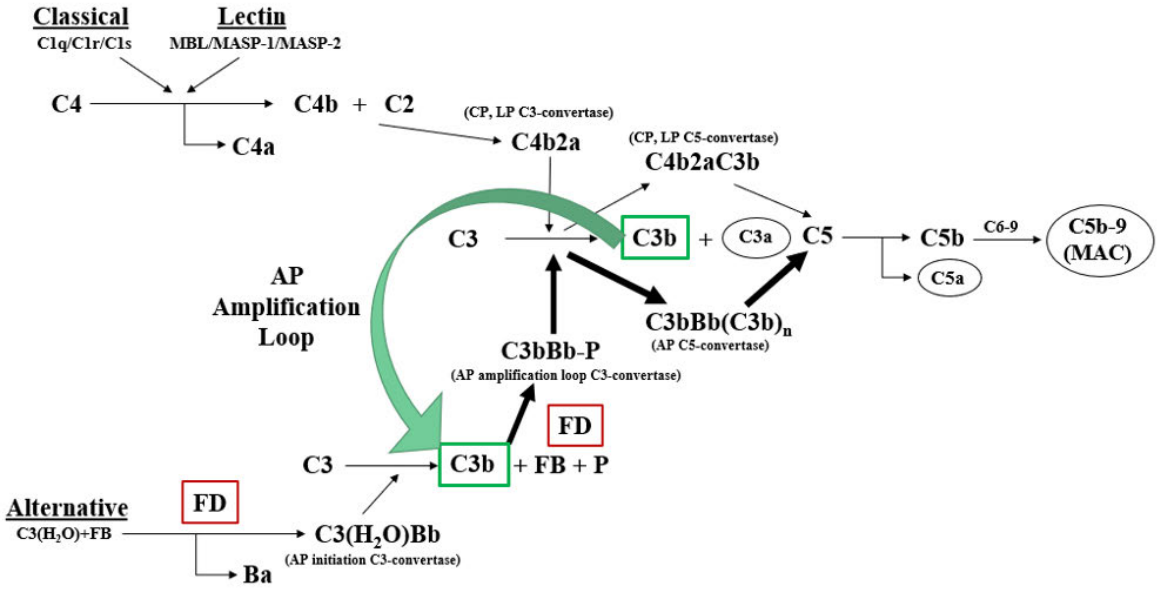
5. INTRODUCTION

5.1. Background

5.1.1. The Complement System

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

Figure 1: Complement Pathways



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

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

The complement system can be activated by each of the 3 complement pathways (ie, the CP, the LP, or the AP) and subsequently amplified by the AP amplification loop. Initial activation of the complement system by any of the 3 pathways results in the production of C3b fragments, which

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

In summary, regardless of whether complement is initially activated via the AP, CP, or LP, activation of the AP amplification loop results in opsonization of cell surfaces by C3b, formation of the complement component 5 (C5) convertase C3bBb(3b)n, cleavage of C5, release of the anaphylatoxins C3a and C5a, and assembly of the terminal MAC on the target surface resulting in cell lysis (Ricklin, Reis et al. 2016).

5.1.2. Factor D in the Complement System

Factor D is the rate-limiting enzyme of the AP (Volanakis and Narayana 1996) and the AP amplification loop and is made constitutively by adipocytes (White, Damm et al. 1992). The only natural substrate for Factor D is complement Factor B bound to C3b (Volanakis and Narayana 1996). Factor D cleaves Factor B only after the latter is bound to C3b or C3(H_2O) at the bond between Factor B amino acid residues 259 and 260, releasing the 30 kD N-terminal Ba fragment and retention of the 60 kD C-terminal Bb fragment that is required for the production of the C3 convertases of the AP [ie, C3bBb and C3(H2O)Bb] (Torreira, Tortajada et al. 2009). In addition, Factor D is essential for the AP amplification loop following generation of C3b by the AP, LP, or CP (Lesavre and Muller-Eberhard 1978, Volanakis and Narayana 1996, Xu, Narayana et al. 2001). Based on in vitro studies using human serum, this AP amplification loop appears to account for up to 80% of the C5a and MAC generated from initial activation of complement by the CP or LP, or other proteolytic enzymes (eg, renin) in the plasma or other body fluids (Thurman and Holers 2006, Ekdahl, Mohlin et al. 2019) (BioCryst internal data on file). As such, Factor D plays a central role in the activation and amplification of the AP, as well as in the amplification of the LP and the CP.

5.2. Indications

5.2.1. Complement 3 Glomerulopathy

Complement 3 glomerulopathy (C3G) is a group of rare kidney diseases in which dysregulation of the complement system results in prominent C3 fragment deposition within the glomerulus (Caravaca-Fontán, Lucientes et al. 2020). C3G is an extremely rare disorder with an estimated incidence between 0.2 to 3 cases per 1 million people in the United States (US) and Europe (Smith, Appel et al. 2019).

The resultant glomerular damage commonly leads to end-stage renal disease (ESRD) and often recurs after renal transplantation (Barbour, Ruseva et al. 2016). C3G is commonly categorized into 2 subsets: 1) dense deposit disease (DDD), which is diagnosed based on linear, hyperosmiophilic electron-dense deposits occupying the middle layer of the glomerular basement membrane; and 2) C3 glomerulonephritis, which refers to those cases of C3G in which dense deposits do not have the characteristics indicative of DDD. Abnormal glomerular accumulation of C3 fragments occurs due to uncontrolled C3b production via the AP of complement (Pickering, D'Agati et al. 2013). In some patients with C3G, acquired or genetic defects in AP regulation can be demonstrated. In others, autoantibodies to complement proteins and complexes that stabilize C3 convertase lead to C3 consumption and deposition of C3 fragments. Current standard of care includes supportive care including blood pressure control, inhibition of the renin-angiotensin system to minimize proteinuria, and the use of corticosteroids plus mycophenolate mofetil. In a recently published retrospective, multicenter, observational cohort study of 97 patients with C3G, mycophenolate mofetil/mycophenolate sodium in combination with corticosteroids was reported to have higher rate of remission (79%) as compared with patients treated with other immunosuppressives (24%) (Caravaca-Fontán, Díaz-Encarnación et al. 2020). Investigational therapy with the C5 inhibitor, eculizumab, has produced mixed results (Bomback, Smith et al. 2012).

5.2.2. Immunoglobulin A Nephropathy

Immunoglobulin A nephropathy (IgAN) is the most common primary glomerular disease worldwide, with an estimated incidence of 2.5 cases per 100,000 individuals per year among adults (McGrogan, Franssen et al. 2011), with geographic, racial, and ethnic variations in prevalence (Barratt and Feehally 2005, Rodrigues, Haas et al. 2017). The prevalence of IgAN may be higher in individuals of Pacific Asian and southern European descent versus those of North American and northern European descent (Barratt and Feehally 2005, Nair and Walker 2006). A diagnosis of IgAN is associated with a reduction in life expectancy by 6 to 10 years (Nair and Walker 2006, Jarrick, Lundberg et al. 2019), and approximately 30% of adult patients with IgAN will develop ESRD (Gutierrez, Carvaca-Fontan et al. 2020). IgAN is an autoimmune disease, caused by abnormal synthesis of IgA1 that is galactose-deficient (Gd-IgA1); Gd-IgA1 and anti-Gd-IgA1 immunoglobulin G (IgG) autoantibodies deposit in the kidney, along with IgG and C3, resulting in mesangial cell proliferation and glomerular inflammation with consequent kidney damage. Although the pathogenesis of kidney injury in IgAN is incompletely understood, associations between IgAN and glomerular and blood markers of complement activation have been established. In addition, C3 is found in glomerular deposits in 80% to 90% of patients with IgAN, implicating involvement of the AP. Currently, there are no complement directed therapies available for the treatment of IgAN. The standard of care for reducing proteinuria is the blockade of the renin-angiotensin-aldosterone system and to control blood pressure. On 17 December 2021, TARPEYO™ (budesonide) was approved by the Food and Drug Administration (FDA) under accelerated approval based on a reduction in proteinuria in adults with primary IgAN at risk for rapid disease progression, generally a urine protein-to-creatinine ratio (uPCR) ≥ 1.5 g/g. It has not been established whether this corticosteroid slows kidney function decline and continued approval may be contingent upon verification and description of clinical benefit in a confirmatory clinical trial.

5.2.3. Primary Membranous Nephropathy

Primary membranous nephropathy (PMN) is the most common cause of idiopathic nephrotic syndrome in non-diabetic white adults with an estimated incidence of 1.2 to 2 cases per 100,000 persons in the US, with a mean age at diagnosis between 50 and 60 years and a 2:1 male predominance (Couser 2017). PMN is a kidney-specific, autoimmune glomerular disease; approximately 70% of adult patients with PMN have IgG4 antibodies to podocyte M-type phospholipase receptor (PLA2R) that are present in the circulation and also deposited in glomeruli. Patients typically present with nephrotic syndrome (proteinuria, edema, hypoalbuminemia, and hyperlipidemia) or nephrotic-range or sub-nephrotic proteinuria, and renal biopsy shows a pathognomonic pattern of glomerular injury with "spikes" of deposits projecting from the outer surface of the glomerular basement membrane. About 10% to 20% of patients with PMN progress to ESRD, and recurrence of disease occurs in approximately 40% of renal allograft recipients. Podocyte injury in PMN patients appears to be mediated primarily by the MAC. A role for the AP and LP of complement in PMN is also suggested by the facts that C3, C4d, and C5b-9 (but not C1q, a key component of the classical pathway of complement) are prominent in glomerular deposits; complement activation products are elevated in the serum; and levels of serum and urine soluble C5b-9 (sC5b-9) seem to parallel disease activity. There are no FDA-approved therapies for the treatment of PMN. Alkylating agents represent the only therapy with evidence of being effective at reducing the risk of ESRD or death, although other immunosuppressive therapies (ISTs), including calcineurin inhibitors or rituximab, have been shown to reduce proteinuria in patients with PMN (Floege, Barbour et al. 2019). The treatment of PMN typically begins with supportive care alone, including blood pressure control, inhibition of the renin-angiotensin system to minimize proteinuria and enhance the chance of a spontaneous remission, statin therapy for hyperlipidemia, salt restriction and diuretics to control edema, and a low-protein diet. ISTs are often reserved for use in patients with proteinuria that is resistant to supportive care alone after 6 months.

5.3. BCX9930

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

[redacted]

Targeting Factor D, the rate-limiting enzyme of the AP and C3 amplification loop, may represent a promising therapeutic strategy for the treatment of renal diseases associated with the dysregulation of complement such as C3G, IgAN, and PMN.

[redacted]

[redacted]

5.3.1. Nonclinical Findings for BCX9930

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

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

Following an oral dose of ^{14}C-BCX9930 in humans, [redacted]

[redacted] thus, no intervention to prevent phototoxicity is indicated in clinical trials.

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

5.3.2. Clinical Findings for BCX9930

The multipart first-in-human (FIH) study (BCX9930-101; Study 101) of single ascending dose and multiple ascending dose oral treatment with BCX9930 in healthy subjects and ascending doses in PNH subjects has completed enrollment and the final CSR is in progress. Subjects with PNH judged as benefiting from treatment on Day 28 could continue to receive BCX9930 longer term, either in Study 101 and/or roll-over study (BCX9930-201, Study 201). Two pivotal Phase 2 studies in subjects with PNH, Studies BCX9930-202 and BCX9930-203, are ongoing.

In Study 101 Part 3/Study 201, administration of BCX9930 50 to 500 mg has been generally well tolerated for up to 746 days (approximately 107 weeks) in subjects with PNH. There have been no discontinuations due to drug-related treatment-emergent adverse events (TEAEs). The most common TEAEs related to BCX9930 have been headache and a drug-related rash. [redacted]

Other Clinical Studies

Five additional Phase 1 clinical studies in adult subjects have completed dosing or reported as of 24 January 2022. Dosing has completed for a drug-drug interaction (DDI) study (Study BCX9930-102), a renal impairment study (Study BCX9930-104), and an analysis of safety and PK study in healthy Japanese subjects (Study BCX9930-105). Clinical study reports have been completed for an absorption, metabolism, and excretion study (Study BCX9930-103) and a relative bioavailability study of BCX9930 tablet and capsule formulations (Study BCX9930-106).

Additional information on the clinical data for BCX9930 is available in the current version of the IB.

5.4. Rationale for Study

5.4.1. Rationale for Study Design and Study Population

BCX9930 is a small-molecule inhibitor of human Factor D that is being developed as a chronic, oral treatment for PNH and other diseases associated with the dysregulation of the AP. As overactivity of the AP and/or AP amplification loop is the common pathogenesis underlying C3G, IgAN, PMN, and PNH, inhibiting Factor D with BCX9930 provides a unified pharmacological approach for the treatment of these complement-mediated disorders. In addition, ex vivo complement activation assays using samples from healthy subjects dosed orally with BCX9930 in Study BCX9930-101 show that BCX9930 can also reduce activity of the LP and CP via inhibition of the C3 amplification loop, which is driven by Factor D. Thus, treatment with BCX9930 has the potential to address the unmet medical needs of patients with C3G, IgAN, and PMN, in addition to other diseases associated with the dysregulation of complement, including PNH.

BCX9930-211 (Study 211) is an open-label, multicenter, exploratory, proof-of-concept (POC) study to evaluate the safety, tolerability, and preliminary efficacy of treatment with an oral Factor D inhibitor, BCX9930, administered for up to 52 weeks in adult (≥ 18 years old) subjects with C3G, IgAN, or PMN. This study will enroll approximately 14 subjects into each of the 3 parallel study treatment cohorts of C3G, IgAN, and PMN to evaluate BCX9930 activity, preliminary clinical outcomes, and safety in all 3 renal diseases to inform future development of BCX9930. Subjects will be qualified for inclusion on the basis of pathologic confirmation of specific diagnosis, active disease, and complement deposition in recent biopsy samples. As the diseases under study are rare and necessitate the enrollment of subjects across multiple sites and countries, a central laboratory and a central pathologist will be used to standardize laboratory and pathology data for consistent evaluation of eligibility, safety, and efficacy across study sites.

Due to the limited sample sizes across 3 rare renal diseases, an open-label design is being used to increase the number of subjects who receive BCX9930 in each cohort to measure changes from baseline to inform designs of future studies. As there are limited treatment options available to patients with C3G, IgAN, or PMN, subjects who are assessed by investigators as deriving clinical benefit at Week 24 will be allowed to continue in the study through up to 52 weeks. The up to 52-week study duration will allow the capture of longer-term safety and clinical outcome data to inform future, pivotal study designs across all 3 diseases including the assessment of primary efficacy measures after 24 weeks of BCX9930 treatment for IgAN and PMN. For the C3G treatment cohort, a duration of at least 24 weeks is anticipated to provide adequate time to measure changes from baseline in clinically relevant laboratory parameters (eg, proteinuria), and in morphological findings in kidney biopsies such as C3 deposits and cellular infiltration and other markers of inflammation.

Factor D, the target of BCX9930, is cleared renally, and the concentration of Factor D in blood increases with declining renal function due to decreased clearance, most notably below a creatinine clearance of ≤ 30 mL/min/1.73 m^2. Factor D blood concentration levels were reported to be > 20-fold that of normal in patients with ESRD who are receiving hemodialysis (Volanakis, Barnum et al. 1985, Pascual, Steiger et al. 1988). To limit the variation of Factor D blood concentrations in this study, only subjects with an estimated glomerular filtration rate (eGFR) of ≥ 30 mL/min/1.73 m^2 will be included. This eGFR cutoff is further supported by Factor D

concentration data recently generated in Study BCX9930-104. These data (discussed further in the IB) suggest that Factor D is not meaningfully elevated in subjects with eGFR $\geq$ 30 mL/min/1.73 m^2 compared to those with normal renal function, consistent with the literature.

Within each of the disease specific cohorts, this study will evaluate several sub-populations for preliminary efficacy and safety. Initial enrollment in all cohorts will be limited to subjects with an eGFR $\geq$ 50 mL/min/1.73 m^2, and after protocol-specified criteria are met, enrollment may be expanded to subjects with an eGFR $\geq$ 30 mL/min/1.73 m^2. Thus, enrolled subjects are expected to exhibit a broad range of renal dysfunction.

In this study, a single-dose regimen of BCX9930 will be evaluated as monotherapy in subjects with C3G, IgAN, and PMN. In addition, BCX9930 will be evaluated as an add-on therapy to a stable dose of mycophenolate mofetil or mycophenolate sodium in up to 7 subjects with C3G whose disease is not adequately controlled. In summary, Study 211 is designed to enroll a minimum number of subjects with each of the rare glomerular diseases under study, while capturing safety and preliminary efficacy data to inform future, pivotal study designs.

5.4.2. Dose Rationale

The dose regimen selected for this study is [redacted] based on efficacy and safety considerations. The following considerations support this dosing regimen:

- [redacted]

The underlying disease mechanism in PNH, dysregulation of the AP and AP amplification loop, is similar to that in C3G, PMN, and IgAN, and Factor D is not mutated or dysregulated in any of these diseases. Therefore, barring disease specific differences (eg, nephrotic proteinuria, elevated Factor D levels due to renal impairment, and need for local complement suppression in the kidney), PK/PD relationships and safety data in healthy subjects and in subjects with PNH, as well as effectiveness data in subjects with PNH, are generally applicable to the dose selection for a clinical study of patients with C3G, IgAN, and PMN.

5.4.2.1. Summary of Hematologic Response in Subjects with PNH with BCX9930 at 400 and 500 mg BID – Studies 101 and 201

Available clinical efficacy data support the potential for lowering the target dose of BCX9930 from 500 to 400 mg BID in the ongoing clinical studies in subjects with PNH. As dosing of

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

[redacted]

cut.

5.4.2.2. Summary of PPK and PK/PD Modeling

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

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

allowing for models of IVH and EVH to be extrapolated to all subjects with PNH regardless of C5 inhibitor status.

[redacted]

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

[redacted]

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

[redacted]

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

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

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

5.5. Benefit-Risk Analysis

Subjects may derive a benefit in improving surrogate clinical markers of disease progression (eg, reducing proteinuria) and controlling the symptoms of their disease with BCX9930. Study subject selection criteria, dose selection, assessment of clinical benefit at Week 24, and study monitoring assessments have been designed to maximize the potential benefit-risk ratio of BCX9930 in subjects with C3G, IgAN, and PMN.

Regular monitoring of safety parameters, including AEs, laboratory assessments, vital signs, ECGs, and physical examination findings, will be mandated to ensure that the benefit-risk profile supports continued dosing.

The DMC will regularly review the cumulative safety data from this study, as well as the accumulating, long-term safety data across all BCX9930 studies in all indications per Section 13.7. Subject data may be reviewed by a Nephrology Risk Mitigation Working Group (NRMWG) for additional recommendations, including dose reduction, interruption of dosing, and permanent discontinuation.

It is anticipated that BCX9930 will continue to be made available in each country until such time as BCX9930 either receives commercial approval or until BioCryst discontinues development of the product, whichever comes first.

Potential risks associated with complement inhibitors for the treatment of C3G, IgAN, and PMN as well as potential risks associated with BCX9930 based on nonclinical and clinical data to date are described in the IB for BCX9930 and are summarized below.

5.5.1. Potential Risks of Bacterial Infections

The most significant risk associated with complement inhibitor therapies, including the approved therapies eculizumab or ravulizumab, is the risk of life-threatening or fatal meningococcal infections (Figueroa and Densen 1991, Hillmen, Young et al. 2006). This risk is well known and included as a warning in relevant labels for both Soliris® (eculizumab) and Ultomiris® (ravulizumab) (Alexion Pharmaceuticals 2020, Alexion Pharmaceuticals 2021).

As BCX9930 blocks the AP of complement, subjects may have increased susceptibility to bacterial infections, especially infections with encapsulated organisms, such as *Neisseria meningitidis, Streptococcus pneumoniae*, and *Haemophilus influenzae*, but also with unencapsulated strains of *Neisseria meningitidis* and other bacteria such as *Neisseria gonorrhoeae* (Ram, Lewis et al. 2010). Study subjects receiving BCX9930 will be monitored closely for signs and symptoms of infection, and infection risk will be mitigated by requiring subjects to have up-to-date vaccinations against appropriate bacterial strains. If required on an individual basis, prophylactic antibiotic administration will be allowed.

5.5.2. Potential Risk of SARS-CoV-2 Infection and Vaccination

Complement inhibitors do not inhibit cellular or humoral immunity. Therefore, BCX9930 is not expected to increase the risk of contracting coronavirus disease (COVID-19) following infection with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) or to increase the risk of severe illness with COVID-19.

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

Vaccination against SARS-CoV-2, the causal agent for COVID-19 infection, is allowed, if authorized and available in country or area, and based on investigator's judgment.

The sponsor's current risk assessment, relative to COVID-19 vaccination in clinical trials with BCX9930, is that authorized or available COVID-19 vaccinations are unlikely to have any potential interaction or added safety risk, if given in combination with ongoing investigational product BCX9930. While there is a known or expected higher risk of certain bacterial infections in patients treated with complement inhibition (including with BCX9930 treatment), or in patients with certain hereditary complement deficiencies, there is no clear known increased or compounded risk with vaccinations (such as currently authorized COVID-19 vaccinations) in the setting of complement inhibition. Also, currently there is no theoretical concern or data to

suggest that complement inhibition with ongoing BCX9930 treatment would impact potential efficacy of vaccinations against SARS-CoV-2.

5.5.3. Potential Risks of Adverse Events with BCX9930

5.5.3.1. Potential Risks for Headache

In Study 101, early-onset headache was the most common TEAE in subjects with PNH treated with BCX9930, likely consistent with restoration of nitric oxide homeostasis due to improved control of intravascular hemolysis with BCX9930. This is likely to be a PNH-specific event and is usually mild and transient.

5.5.3.2. Potential Risks for Drug Rash

A benign maculopapular rash with consistent onset and clinical course has been observed with multiple-day dosing of BCX9930 in both healthy volunteers and subjects with PNH. Clinical experience to date indicates that this rash occurs early in treatment, persists for approximately 5 to 8 days, and resolves while continuing dosing of BCX9930.

5.5.3.3. Potential Risks for Hepatic Effects

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

5.5.3.4. Potential Risks for Renal Effects

[redacted]

Monitoring of renal function will be undertaken in the study using standard measures (eg, sCr, eGFR, and urinalysis including microscopy, and safety biomarker analysis) Further information can be found in Section 12.11.5. [redacted], the frequency of laboratory assessments has been increased to monitor for any changes in renal function. Any kidney-related events occurring on study should be evaluated as detailed in Section 13.5.2.

5.5.4. Risks of Potential Adverse Events with Trial-Mandated Procedures

Outpatient percutaneous needle biopsies of the kidney will be conducted during the study in accordance with the schedule of assessments and local practice and guidelines. The risk of complications, such as major bleeding, is low (< 1%) for outpatients with proteinuric kidney disease and preserved kidney function with normal hematologic parameters (Koirala and Jefferson 2020).

To reduce the risk of complications from the biopsy procedure and to minimize the total number of study-related biopsy procedures conducted during screening, study subject selection criteria exclude patients with a higher risk of complications, and the screening biopsy will be performed only after all other study eligibility criteria are met for each subject. In addition, the screening biopsy may be waived with the approval of the central pathologist and agreement of the medical monitor for any subject with a recent biopsy as specified in section 7.1.

5.5.5. Overall Benefit-Risk Analysis

The development of BCX9930 may be of benefit to patients with complement-mediated diseases, including those with C3G, IgAN, or PMN, that are clinically important and associated with chronic morbidity and that are potentially life-threatening.

Treatment-emergent increases in [redacted] dose level. Based on the sponsor's preliminary investigations, reducing the BCX9930 dose to 400 mg BID and introducing a step-up regimen (ie, starting dosing at 200 mg BID for 2 weeks before escalating to 400 mg BID) is anticipated to mitigate the risk of renal injury while maintaining the potential for demonstrating clinical benefit in the subjects with C3G, IgAN, or PMN. Study subject eligibility criteria, dose selection, staggered enrollment of subjects with an eGFR of $\geq$ 30 mL/min/1.73 m^2, as well as more frequent study monitoring assessments have been included to optimize benefit and to minimize the risk of toxicities to study participants. Regular monitoring of safety parameters, including AEs, clinical laboratory abnormalities, vital signs measurements, ECGs, and physical examination findings, will ensure that the benefit-risk profile supports continued dosing. In addition, an independent, program-wide DMC, whose membership includes a nephrologist, will regularly review the cumulative safety data from this study, as well as the accumulating, long-term safety data across all BCX9930 studies in all indications. The overall benefit-risk balance is, therefore, considered to be acceptable for this study.

6. STUDY OBJECTIVES AND PURPOSE

6.1. Objectives

The objectives in this POC study of orally administered BCX9930 are applicable to the 3 parallel treatment cohorts of subjects with C3G, IgAN, or PMN.

6.1.1. Primary Objective

The primary objective of this study is:

- To evaluate the therapeutic potential of BCX9930 as assessed by proteinuria

6.1.2. Secondary Objectives

The secondary objectives of this study are:

- To evaluate the safety and tolerability of BCX9930
- To evaluate the therapeutic potential of BCX9930 as assessed by other measures of clinical benefit
- To evaluate effects of BCX9930 on kidney biopsy morphologic findings (C3G cohort only)

6.1.3. Exploratory Objectives

The exploratory objectives of this study are:

[redacted]

6.2. Endpoints

The endpoints in this POC study of orally administered BCX9930 are applicable to the 3 parallel treatment cohorts of subjects with C3G, IgAN, or PMN.

6.2.1. Primary Endpoints

The primary endpoint of this study is:

- Change in 24-hour urinary protein excretion normalized to urine creatinine as measured by percentage change in uPCR from baseline

6.2.2. Secondary Endpoints

The secondary endpoints of this study are:

- Number and proportion of subjects with a uPCR response defined as:
  - Partial remission, ≥ 50% reduction from baseline
  - Complete remission, ≤ 500 mg/g
  - Normalization, ≤ 200 mg/g
- Change from baseline in 24-hour urinary protein excretion as measured by percentage change in urinary protein from baseline
- Change from baseline in eGFR
- Change from baseline in serum albumin
- Number and proportion of subjects with the following parameters:
  - Protein ≥ 3.5 g in a 24-hour urine collection
  - Serum albumin ≤ 2.5 g/dL
- Number and proportion of subjects with a morphologic response in each of the following categories (C3G cohort only at Week 24):
  - Decreased endocapillary hypercellularity, mesangial hypercellularity, active crescents (if present), glomerular leukocyte infiltration, fibrinoid necrosis, membranoproliferative glomerulonephritis pattern
  - Decreased acute tubular injury, interstitial inflammation, interstitial edema
  - Reduction in C3 glomerular staining
  - Reduction in the extent of deposits, clearing of deposits, or no additional active deposits as assessed by electron microscopy (EM)
  - No progression of chronic changes (ie, global, segmental glomerulosclerosis, tubular atrophy/interstitial fibrosis, arteriosclerosis)
- Number and proportion of subjects with a TEAE
- Number and proportion of subjects who discontinue due to a TEAE
- Number and proportion of subjects who experience a treatment-emergent serious adverse event (TESAE)
- Number and proportion of subjects who experience a Grade 3 or 4 TEAE based on Common Terminology Criteria for Adverse Events (CTCAE)
- Number and proportion of subjects who experience a CTCAE treatment-emergent Grade 3 or 4 laboratory abnormality

6.2.3. Exploratory Endpoints

The exploratory endpoints of this study are:

[redacted]

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

This is a Phase 2, open-label, multicenter, POC study to evaluate the safety, tolerability, and therapeutic potential of BCX9930, an oral Factor D inhibitor, administered for up to 52 weeks in adult (≥ 18 years old) subjects with either C3G, IgAN, or PMN. After up to a 56-day screening

qualification period, approximately 14 eligible subjects will be enrolled into each of 3 parallel study treatment cohorts and will receive BCX9930 200 mg BID for the first 14 days and will increase to BCX9930 400 mg BID on Day 15 for the remainder of the treatment period.

During the study, recruitment into each of the cohorts will be managed independently with a total of approximately 42 subjects enrolled into the study. For the C3G cohort only, up to 7 subjects with at least 6 months of treatment with a stable dosing regimen of mycophenolate mofetil or mycophenolate sodium prior to the Day 1 Visit will be allowed to enroll in the study per Section 8.2. Sites will be notified when enrollment is complete for subjects with C3G receiving mycophenolate mofetil/mycophenolate sodium.

After providing written informed consent to participate in the study and confirming that all other study eligibility criteria have been met during screening, subjects will undergo a percutaneous needle biopsy of the kidney per local practice and guidelines. Renal biopsy images and details from the local pathology report will be reviewed by the central pathologist for confirmation of a protocol-defined diagnosis of C3G, IgAN, or PMN. The screening biopsy procedure may be waived with approval of the central pathologist and agreement with the medical monitor for any subject who has undergone a renal biopsy procedure as follows: within 3 months prior to screening for the C3G cohort, within 6 months prior to screening for the IgAN or PMN cohorts, provided that required materials are adequate for pathology evaluation per protocol procedures.

After the Day 1 Visit, subjects will be required to return to the clinic at Weeks 1, 2, and 4, and then every 4 weeks thereafter through Week 24. Additional safety assessments will be performed at Weeks 3, 5, 6, 7, and 10, either at the investigative site, or at a local laboratory more convenient for the subject or via a home health service (where permitted and available). At the Week 24 Visit, the clinical benefit of BCX9930 treatment will be assessed by the investigator. Subjects who are assessed as deriving clinical benefit will continue treatment up to Week 52. described in Table 2 and Table 3.

An on-treatment, percutaneous needle biopsy of the kidney will be performed at the following visit after completion of all other assessments, or during the time specified below by treatment cohort:

- Week 24 or within 7 days after the visit for subjects with C3G
- Week 36 or within 7 days after the visit for subjects with IgAN (optional)
- Week 48 to within 3 days after the Week 52 Visit for subjects with PMN (optional)

The on-treatment biopsy is optional for subjects with IgAN or PMN. For subjects with PMN, if the biopsy is scheduled after the Week 52 Visit, then dosing with BCX9930 will continue until the day of the biopsy procedure. WSIs of LMs, digital IFs or IHCs, digital EMs, and details from the local pathology reports from the on-treatment biopsies will be reviewed by the central pathologist. Protocol-specified, on-treatment biopsies will not be required for subjects who are discontinued from BCX9930 treatment.

Subjects who complete BCX9930 dosing through Week 52 and who are discontinued from BCX9930 dosing prior to Week 52 will return to the clinic approximately 4 weeks (28 ± 3 days) after the date of their last dose of BCX9930 for the Safety Follow-up (FU) Visit prior to study completion/discontinuation.

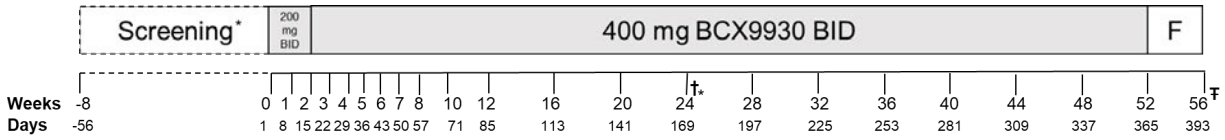
A study schema is shown in Figure 3.

An optional serial PK/PD substudy will include subjects who provide consent from each of the 3 cohorts to evaluate the PK and PD of BCX9930 at the Day 1 Visit and/or at a subsequent visit prior to the Week 24 Visit. Serial sampling of urine and blood will be performed over a period of 6 hours. Subjects who do not participate in the Baseline (Day 1) PK/PD sample collection are eligible to participate at a subsequent clinic visit prior to the Week 24 Visit.

All subjects will have a single blood sample drawn for PK analysis at each clinic visit ("sparse sampling" to support PPK and PK/PD modeling). For subjects participating in the serial PK/PD substudy, a single blood sample will be drawn for PK and PD analysis at visits where serial blood samples are not collected through 6 hours post dose.

All subjects who sign a separate informed consent (optional) will participate in exploratory pharmacogenomics testing at a single visit from Day 1 up to the Week 24 Visit (including the safety FU Visit, if applicable).

Figure 3: Study Schema



• **= Kidney Biopsies:** A screening biopsy may be waived with approval of central pathologist and agreement with the medical monitor for any subject who has undergone a renal biopsy procedure as follows: within 3 months prior to screening for the C3G cohort, within 6 months prior to screening for the IgAN or PMN cohorts.
Subjects with C3G will undergo a percutaneous needle biopsy of the kidney at the Week 24 Visit or within 7 days after the visit.

† = Clinical Benefit Assessment
Ŧ = Safety Follow-up Visit: 28 ± 3 days after last dose of BCX9930 for all subjects
F = Safety Follow-Up
Note: Subjects will return to the clinic at Weeks 1, 2, and 4, and then every 4 weeks thereafter through Week 52. Additional safety assessments will be performed at Weeks 3, 5, 6, 7, and 10, either at the investigative site or at a laboratory local to the subject or via a home health service.
Additional visits may occur during the study and are not represented (eg, additional screening visits, unscheduled visits, or visits for biopsy procedures)

7.2. Number of Subjects

This study will enroll approximately 14 adult subjects in each of the C3G, IgAN and PMN cohorts for a total enrollment of approximately 42 subjects.

7.3. Treatment Assignment

All eligible subjects will receive BCX9930 200 mg BID for the first 14 days and will increase to BCX9930 400 mg BID on Day 15 for the remainder of the treatment period; doses should be taken approximately 12 hours apart. The first dose of BCX9930 will be administered at the Day 1 Visit after completion of all baseline procedures and under supervision of clinic staff.

7.4. Individual and Study Termination Criteria

7.4.1. Study Drug Treatment Discontinuation Criteria

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

- Pregnancy in a female subject.

- Emergence of an AE, including a laboratory abnormality, or other unacceptable toxicity that, in the judgment of the investigator, compromises the ability of the subject to continue study-specific procedures or it is considered not to be in the subject's best interest to continue due to an altered benefit-risk profile.
- Intercurrent illness or the emergence of a new medical condition that would, in the judgment of the investigator, affect assessments of clinical status to a significant degree.
- Treatment-emergent alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 3 × ULN combined with either laboratory abnormalities indicative of significant hepatic toxicity (ie, meeting Hy's law, total bilirubin > 2 × ULN OR with an INR > 1.5) or with symptomatology of acute hepatitis (ie, severe fatigue, nausea, vomiting, right upper quadrant pain and tenderness, fever, rash, and/or eosinophilia [> 5%]) and assessed by the investigator as probably, or definitely related to BCX9930 treatment.
- Treatment-emergent increase in sCr ≥ 3 × ULN (confirmed by repeat testing) without any other potential cause of renal dysfunction
- In the investigator's opinion it is in the best interest of the subject to discontinue from further dosing.
- Invasive meningococcal infection or any serious invasive bacterial infection that occurs after BCX9930 is initiated.
- Subject request to discontinue for any reason.
- Subject noncompliance (eg, protocol deviation), as assessed by the sponsor or investigator, to be detrimental to study or subject benefit-risk profile.
- Discontinuation at the request of the sponsor, relevant competent authority, or the governing institutional review board (IRB), research ethics board (REB), or independent ethics committee (IEC) (collectively referred to as "ethics committee").

Whenever possible, the investigator will consult with the sponsor medical monitor (or designee) before discontinuing study treatment. The reason for discontinuation of study treatment will be recorded in the source documents and electronic case report form (eCRF). Subjects who are discontinued from BCX9930 dosing prior to Week 52 will return to the clinical site approximately 4 weeks (28 ± 3 days) after the date of their last dose for a safety FU Visit prior to discontinuation from the study.

7.4.2. Subject Withdrawal Criteria

Participation in the study is strictly voluntary. Subjects have the right to withdraw from study drug or from the study at any time and for any reason. A subject's participation may be terminated for any of the reasons delineated in Section 7.4.1. 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 7.4.1 and Section 13.4. Vigorous attempts will be made for follow-up of all subjects who miss a study visit. 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.

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

7.4.3. Criteria for Study Termination

The following study stopping criteria will be used to stop the study (permanent termination or suspension of enrollment/treatment) or the participation of a particular investigational site:

- Emergence of unacceptable risk, toxicity, or negative change in the benefit-risk assessment
- In the event that 3 subjects are determined by the NRMWG to have confirmed elevations of sCr ≥ 3 × ULN considered related to BCX9930
- Request of the relevant competent authority or ethics committee
- Non-compliance with the study protocol, including inaccurate or incomplete recordkeeping, that jeopardizes the scientific integrity of the study or subject safety

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

7.4.4. End of Study Definition

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

8. SELECTION AND WITHDRAWAL OF SUBJECTS

8.1. Subject Inclusion Criteria

Subjects must meet all of the following inclusion criteria (where applicable) prior to first dose of BCX9930 on Day 1 or specified time below:

1. Willing and able to provide written informed consent (or, for subjects who have not reached the age of maturity, willing and able to provide written assent with written informed consent additionally provided by the subject's parent[s] or legal guardian).
2. Male or non-pregnant, non-lactating female subjects ≥ 18 years of age.
3. Body weight ≥ 40 kg.

4. Primary diagnosis of C3G, IgAN, or PMN with evidence of disease activity, as confirmed by central pathology review of digital images and pathology reports of renal biopsy samples obtained during screening as described in Section 12.4.2.1 (or within 3 months prior to screening for subjects with C3G and 6 months prior to screening for subjects with IgAN and PMN with approval of the central pathologist and agreement with the medical monitor).
   - All: ≤ 50% global glomerulosclerosis
   - All: ≤ 50% tubulointerstitial fibrosis
5. For subjects with C3G only, documentation of duration of illness of at least 90 days by either a prior biopsy collected ≥ 90 days prior to screening confirming a diagnosis of C3G OR a clinical diagnosis of C3G with at least one documented proteinuria assessment ≥ 90 days prior to initial screening visit.
6. For subjects with C3G only, proteinuria defined as ≥ 1 g of urinary protein per 24 hours at screening that has not shown a ≥ 25% decrease from the most recent documented proteinuria assessment, which was collected at least 30 days prior to and within 180 days of initial screening visit.
7. For subjects with IgAN only, proteinuria defined as 1 g to ≤ 4 g of urinary protein per 24 hours at screening that has not shown a ≥ 25% decrease from the most recent documented proteinuria assessment, which was collected at least 30 days prior to and within 180 days of initial screening visit.
8. For subjects with PMN only, an [redacted] of ≥ 150 U/mL and 3.5 g to ≤ 11 g of urinary protein per 24 hours at screening that has not shown a ≥ 25% decrease from the most recent documented proteinuria assessment, which was collected ≥ 30 days prior to and ≤ 180 days of initial screening visit.
9. An eGFR ≥ 50 mL/min/1.73 m^2 (or ≥ 30 mL/min/1.73 m^2 after DMC recommendation) calculated using the serum creatinine-based Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula.
10. Resting supine vital signs within the following ranges:
    - Systolic blood pressure, 80 to 150 mm Hg, inclusive
    - Diastolic blood pressure ≤ 90 mm Hg
11. Treatment with a stable, maximum recommended or maximum tolerated dose of an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB) for at least 60 days prior to the Day 1 Visit and in the opinion of the investigator the expectation of continuing the same dose and regimen for such treatment during the study.
12. Contraception requirements:

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

    a. Be a woman of nonchildbearing potential, defined as postmenopausal (without menses for ≥ 12 months [without an alternative medical cause] with a follicle-

stimulating hormone [FSH] > 40 mIU/mL, or who have had a hysterectomy, bilateral salpingectomy, or bilateral oophorectomy).

b. Be a woman of childbearing potential (defined as a female following menarche and prior to becoming post-menopausal who has not had a hysterectomy, bilateral salpingectomy, or bilateral oophorectomy) who agrees to use a highly effective contraceptive method while enrolled in the study and for a duration of 30 days after last dose of study drug. The following methods are acceptable:

   – surgical sterilization (ie, bilateral tubal occlusion or vasectomy of the sole male partner and the vasectomized partner has received medical assessment of surgical success)

   – intrauterine device (IUD) or intrauterine system (IUS)

   – Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal)

   – Progestogen only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable)

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

Male subjects must meet at least one the following requirements:

d. Subjects with female partners of childbearing potential (defined as without menses ≤ 12 months, or a non-menopausal female who has not had a hysterectomy, bilateral salpingectomy, or bilateral oophorectomy) must agree to utilize a contraceptive method throughout the study and for at least 90 days after the last dose of study drug. The following methods during the study are acceptable:

   – surgical sterilization (ie, vasectomy that has been medically assessed to be successful, or bilateral tubal occlusion of a female partner)

   – partner's use of an IUD or IUS

   – partner's use of combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal)

   – partner's use of progestogen only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable)

   – use of a condom

13. Documentation of current vaccinations against *N. meningitidis* Types A, C, W, and Y, and *S. pneumoniae* vaccine, or must be vaccinated or willingness to start vaccination series for any of the missing protocol required vaccines at least 14 days prior to Day 1 per Section 12.2.1.

(Note: Vaccination for *N. meningitidis* Type B and for *H. influenzae* Type B (Hib) is strongly encouraged where authorized and available.)

14. In the opinion of the investigator, the subject is likely to comply adequately with all required study procedures and restrictions for the study, including compliance with the BID dosing schedule for BCX9930.

8.2. Subject Exclusion Criteria

Subjects must meet none of the following exclusion criteria (where applicable) prior to first dose of BCX9930 on Day 1 or specified time below:

1. Known congenital deficiency of C1s, C1r, C1q, C2, C4. Known variants in complement Factor H, complement Factor I, C3, and complement Factor B or genomic rearrangements in the complement Factor-H-related proteins are not exclusionary
2. Receiving hemodialysis or peritoneal dialysis or anticipated to receive dialysis during the duration of this study.
3. History of hematopoietic cell transplant or solid organ transplant or anticipated candidate for transplantation during the study.
4. History of transfusion with blood or blood products, or plasmapheresis or plasma exchange, within 30 days prior to screening.
5. Myocardial infarction or cerebrovascular accident within 30 days prior to screening, or current and uncontrolled clinically significant cardiovascular or cerebrovascular condition, including unstable angina, severe congestive heart failure, unexplained syncope, arrhythmia, and critical aortic stenosis.
6. History of malignancy within 5 years prior to the screening visit, with the exception of adequately treated non-melanoma skin or superficial bladder cancer, curatively treated carcinoma in situ of the cervix, or other curatively treated solid tumor deemed by the investigator and medical monitor to be at low risk for recurrence.
7. Any clinical or pathological evidence of monoclonal gammopathy of unclear or renal significance, lupus or other systemic autoimmune disease, or other conditions (eg, infection-associated disease or associated with another systemic disease, anti-phospholipid antibody syndrome with significant clinical disease, immune complex glomerulonephritis, immunoglobulin A [IgA] vasculitis with nephritis [Henoch-Schönlein purpura] or morphologic features of secondary membranous nephropathy). Presence of C3 or C5 nephritic factors (eg, autoantibodies directed at C3 or C5 convertase), in the absence of known infection or other systemic disease, are not exclusionary for this study.
8. Treatment with azathioprine, canakinumab, cyclophosphamide, cyclosporine, eculizumab, everolimus, hydroxychloroquine, infliximab, sirolimus, ravulizumab, systemic corticosteroids (including budesonide), tacrolimus, or any other systemic immunosuppressive or immunomodulatory therapies (eg, complement inhibitors) within 90 days OR mycophenolate mofetil/mycophenolate sodium treatment within 60 days OR anti-CD20 antibody therapies (eg, rituximab) within 180 days prior to the screening visit.

a. For subjects with C3G only, ongoing treatment with a stable dose of mycophenolate mofetil/mycophenolate sodium for at least 6 months prior to the Day 1 Visit is allowed

9. Treatment with renin inhibitors (eg, aliskiren) or sodium-glucose-cotransporter 2 (SGLT2) inhibitors within 60 days prior to Day 1.
10. Current participation in any other investigational drug study or participation in an investigational drug study within 30 days prior to the screening visit, or 5.5 half-lives of the investigational drug, whichever is longer.
11. Any of the following laboratory values at the screening visit: hemoglobin < 8.5 g/dL; total white blood cell (WBC) < 2.5×10^9/L; absolute neutrophil count (ANC) < 1.0×10^9/L; platelet count < 90×10^9/L; ALT, AST, alkaline phosphatase (ALP), or total bilirubin > 1.5 × ULN; serum albumin < 1.5 g/dL; or INR > 1.4.

    a. Subjects with Grade 1 elevated bilirubin due to Gilbert's syndrome are allowed to enroll. To document that a subject has Gilbert's syndrome, a diagnosis from the medical record must be provided, or the investigator may make a presumptive diagnosis of Gilbert's syndrome in subjects with unconjugated hyperbilirubinemia on repeated testing (at least 2 samples separated in time) who have ALT, AST, and ALP ≤ 1.5 × ULN, and a normal complete blood count.

12. Any laboratory parameter at screening that, in the judgment of the investigator, is clinically significant and would represent a safety concern.

    Note: Enrollment of a subject with laboratory value(s) outside of the reference range may be permissible if the abnormality is documented by the investigator to not be of clinical significance, or is disease related, and does not pose a safety concern.

13. Clinically significant abnormal ECG prior to dosing at the Day 1 Visit.
14. Current use of a prohibited concomitant medication within 7 days prior to Day 1 as detailed in Section 9.2.
15. Active serious bacterial, viral, or fungal infection or any other serious infection, including suspected or confirmed severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2] infection, within 14 days of screening. Dyspnea, vasculitic rash, and persistent fever or other symptoms consistent with multisystem inflammatory syndrome [MIS] are exclusionary in the setting of recent SARS-CoV-2 infection.
16. Positive serology for human immunodeficiency virus (HIV), or active infection with hepatitis B virus (HBV) or hepatitis C virus (HCV).
17. Positive test for drugs of abuse during screening, unless by prescription where legal.
18. Pregnant, planning to become pregnant, or breastfeeding.
19. Known or suspected hypersensitivity to BCX9930 or any of its formulation excipients as detailed in Section 10.1.
20. History of severe hypersensitivity to any medicinal product, which was associated with swelling, severe rash requiring treatment/hospitalization, or anaphylaxis.

21. Any clinically significant medical or psychiatric condition, including known or suspected substance abuse (including alcohol) 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.

9. TREATMENT OF SUBJECTS

9.1. Prior/Concomitant Medications

All medications will be documented beginning 30 days prior to the screening visit. All concomitant medication use, beginning with the screening visit and including all medications administered for the treatment of AEs, will be recorded.

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

With the exception of any changes to nephrotoxic medications and prohibited and restricted medications detailed in Section 9.2, subjects should continue their normal medications. Dosing of medications that increase infection risk (eg, mycophenolate mofetil/mycophenolate sodium) should remain stable until at least the Week 52 visit unless taper or discontinuation needs to be done for safety reasons.

If any dose adjustments to the protocol-required stable, maximum tolerated dose of either an ACEi or ARB are needed for the treatment of a subject during the study or if it is discovered that the subject's ACEi or ARB dose has been changed, then the investigator (or qualified designee) should notify the medical monitor.

Prophylactic use of antibacterial and antiviral medications 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 9.2).

Please refer to inclusion criterion 13 and Section 12.2.1 for vaccination requirements and recommendations.

9.2. Prohibited and Restricted Medications

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

All subjects in the study should refrain from taking the following prohibited medications from the screening visit through the safety FU visit:

- Any systemic immunosuppressive or immunomodulatory medications (eg, azathioprine, canakinumab, cyclophosphamide, cyclosporine, eculizumab,

everolimus, hydroxychloroquine, infliximab, sirolimus, ravulizumab, systemic corticosteroids, tacrolimus, anti-CD20 antibody therapies [eg, rituximab], or complement inhibitors other than study drug)

- Renin inhibitors (eg, aliskiren)
- SGLT2 inhibitors

  Note: Up to 7 adults with C3G with at least 6 months of stable dosing with mycophenolate mofetil or mycophenolate sodium prior to the Day 1 Visit will be allowed to continue dosing throughout the study as described in Section 9.1.

[redacted]

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

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

During the study, the CYP enzymes and drug transporters of clinical concern may be modified based on drug interaction studies. Medications that potentially affect the metabolic pathways or transport of BCX9930 may also be added, pending availability of additional data.

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

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

If any of these prohibited medications are determined to be needed for the treatment of a subject during the study or if it is discovered that the subject is already receiving a prohibited medication during study participation, then the investigator (or qualified designee) should contact the medical monitor. Investigators should contact the sponsor medical monitor for specific questions regarding prohibited and restricted medications as needed.

9.3. Treatment Compliance

The first dose of BCX9930 on Day 1 will occur in the clinic under supervision. All subsequent doses can be taken at home; subjects do not need to withhold any doses on clinic days or take a dose at the clinic, unless the clinic visit falls during the subject's normal time of dosing, or the subject is participating in the optional PK/PD substudy on a given visit. For subjects who are participating in the PK/PD substudy and are scheduled to have serial PK/PD collections on a clinic day, the morning dose of BCX9930 will need to be withheld until the scheduled visit. Subjects will be provided instructions for taking daily doses of study drug, including frequency and time of administration. Subjects will be instructed to maintain approximately the same approximate 12-hour dosing interval between study drug doses each day (eg, 8:00 AM and 8:00 PM).

It is anticipated that subject compliance with the BID dosing schedule for BCX9930 is important for the benefit of subjects and for success of this study. Investigators should remind participants who regularly miss doses about the importance of treatment compliance. Drug compliance will be recorded in the eCRF.

9.3.1. Missed Doses:

If the subject forgets to take the study drug at the correct time, the dose may be taken as late as 6 hours after the scheduled dose time. If more than 6 hours has passed, subjects should skip the missed dose entirely and take the next dose at the scheduled time. 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.

9.4. Randomization and Blinding

This is an open-label, non-randomized study. No study treatments will be blinded or masked.

10. STUDY DRUG MATERIALS AND MANAGEMENT

10.1. BCX9930

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

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

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

Additional details of the chemical and physical characteristics of BCX9930 may be found in the IB for BCX9930 and investigational medication product (IMP) manual. Please note both IMP and study drug refer to BCX9930 in this protocol.

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

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

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

10.3. Administration

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

For newly enrolled subjects, BCX9930 will be initiated at a dose of 200 mg BID for the first 14 days and will be increased to 400 mg BID on Day 15 for the remainder of the up to 52-week treatment period. Subjects will be instructed to take the BCX9930 tablets orally twice daily at approximately the same times each day (ie, at intervals of approximately 12 hours), either with or without food. Adequate hydration should be maintained to support kidney function and prevent the formation of highly concentrated urine.

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

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

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

Subjects will be instructed to bring all bottles of study drug (both unused and used bottles) with them to all study visits at the investigative site (including any unscheduled visits, when possible). Drug accountability and treatment adherence will be reviewed at these visits.

10.3.1. 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. Any treatment interruption or dose reduction will be recorded in the eCRF and source documents, including the reason for the interruption or reduction. Resumption of study drug administration is also permissible upon resolution of the event, as assessed by the investigator, with a plan for monitoring of the subject for recurrence of the AE, as appropriate. Any treatment resumption will be recorded in the eCRF and source documents. See Section 10.3.2 for potential dose reduction options.

10.3.2. Dose Tapering

In the event of permanent discontinuation of BCX9930, the dose of BCX9930 may be tapered using the following schedule as a guideline:

[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.

10.4. Study Drug Accountability

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

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

At the end of the study, all study drug not administered and any returned study drug (including empty bottles) will be returned to the sponsor or destroyed onsite as instructed by the sponsor

following IMP accountability by the study monitor, abiding by appropriate standard operating procedure(s) at the participating institution.

11. STUDY CONDUCT

11.1. Overview

A subject's participation in this study is expected to be up to 64 weeks (including the screening, dosing, and follow-up periods) with a minimum of 18 planned in-clinic visits and 5 additional safety assessment visits at the investigative site or at a local laboratory more convenient for the subject or via a home health service (where permitted and available).

After confirming that all other study eligibility criteria have been met during a screening period of up to 56 days, subjects will undergo a percutaneous needle biopsy of the kidney per local practice and guidelines. The screening biopsy will also serve as the baseline, pretreatment biopsy for the C3G cohort and for the subjects who choose to have an on-treatment biopsy in the IgAN and PMN cohorts. Biopsy eligibility criteria and baseline assessments will be reviewed by the central pathologist by review of digital images and details from the local pathology report. In addition, unstained EM grids may be shipped from sites to the central pathologist for additional baseline EM assessments and reporting. The screening biopsy procedure may be waived after review by the medical monitor and central pathologist for any subject who has undergone a renal biopsy procedure as follows: within 3 months prior to screening for the C3G cohort, within 6 months prior to screening for the IgAN or PMN cohorts, provided that required materials are adequate for pathology evaluation per protocol procedures.

Each eligible subject who consents to participate in the study will receive up to 52 weeks of BCX9930. All subjects will be required to attend at least 9 in-clinic study visits through 24 weeks: Day 1 (Baseline), Week 1 (Day 8), Week 2 (Day 15), Week 4 (Day 29), Week 8 (Day 57), Week 12 (Day 85), Week 16 (Day 113), Week 20 (Day 141), and Week 24 (Day 169) and 5 additional safety assessments visits at Weeks 3 (Day 22), Week 5 (Day 36), Week 6 (Day 43), Week 7 (Day 50), and Week 10 (day 71), either at the investigative site, at a local laboratory more convenient for the subject or via a home health service (where permitted and available). At the Week 24 Visit, the clinical benefit of BCX9930 treatment will be assessed by the investigator. Subjects who are assessed as deriving clinical benefit will continue treatment up to Week 52 and be required to attend at least 7 additional in-clinic visits: Week 28 (Day 197), Week 32 (Day 225), Week 36 (Day 253), Week 40 (Day 281), Week 44 (Day 309), Week 48 (Day 337), and Week 52 (Day 365). All subjects will return to the clinic approximately 4 weeks (28 ± 3 days) after the date of their last dose of BCX9930 for the safety FU Visit.

An on-treatment, percutaneous needle biopsy of the kidney will be performed for subjects with C3G at a specified visit after completion of all other assessments, or during the specified times as described in Section 12.4.2. The on-treatment biopsy is optional for the IgAN and PMN cohorts. All subjects who undergo kidney biopsy should remain on study drug at least until the day of biopsy. Digital images and details from the local pathology reports from the on-treatment biopsies will be reviewed by the central pathologist to evaluate and describe changes from the baseline, pre-treatment digital images.

An optional serial PK/PD substudy will include subjects who provide consent from each of the 3 cohorts to evaluate the PK and PD of BCX9930 at the Day 1 Visit and/or at a subsequent visit prior to the Week 24 Visit. Serial sampling of urine and blood will be performed over a period of 6 hours. Subjects who do not participate in the Baseline (Day 1) PK/PD sample collection are eligible to participate at a subsequent clinic visit prior to the Week 24 Visit.

All subjects who sign a separate informed consent will participate in exploratory pharmacogenomics testing at a single visit from Day 1 up to the Week 24 Visit (including the safety FU Visit, if applicable).

11.2. Schedule of Assessments

The schedule of assessments for this study is presented in Table 2 (Screening through Week 24) and Table 3 (Week 28 through Week 52). The schedule of assessments for the PK/PD substudy is presented in Table 4.

Table 3: Schedule of Assessments (Screening - Week 24)

Assessment/Procedure	Screening [a]	Baseline	Dosing Phase (Study Week)													Safety FU Visit [d]
	(Up to Day - 56)	Day 1 [b]	1 (± 1 d)	2 (± 1 d)	3 [c] (± 1 d)	4 (± 1 d)	5 [c] (± 3 d)	6 [c] (± 3 d)	7 [c] (± 3 d)	8 (± 3 d)	10 [c] (± 3 d)	12 (± 3 d)	16 (± 3 d)	20 (± 3 d)	24 (± 3 d)	28 ± 3 days after last dose
Written informed consent [e]	X															
Review eligibility criteria	X	X														
Demographics	X															
Medical & medication history	X															
Disease Specific Medical History Form [f]	X															
Height, body weight, and BMI [g]	X	X				X				X		X	X	X	X	X
Physical examination [h]	X	X	X	X		X				X		X	X	X	X	X
12-lead ECG [i]	X	X	X	X		X				X		X	X	X	X	X
Vital signs [j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology and coagulation	X	X	X	X		X				X		X	X	X	X	X
Chemistry	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis including microscopy [k]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Intended 24-hour urine collection [l]	X	X	X	X		X				X		X	X	X	X	X
eGFR [m]	X	X	X	X		X				X		X	X	X	X	X
Percutaneous renal biopsy [n,o]	X														X [q]	
Urine for biomarker testing [p]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Drugs of abuse screen	X															
Pregnancy test [q]	X	X	X	X		X				X		X	X	X	X	X
FSH [r]	X															

Assessment/Procedure	Screening [a]	Baseline	Dosing Phase (Study Week)												Safety FU Visit [d]
	(Up to Day - 56)	Day 1 [b]	1 (± 1 d)	2 (± 1 d)	3 [e] (± 1 d)	4 (± 1 d)	5 [e] (± 3 d)	6 [e] (± 3 d)	7 [e] (± 3 d)	8 (± 3 d)	10 [e] (± 3 d)	12 (± 3 d)	16 (± 3 d)	20 (± 3 d)	24 (± 3 d)	28 ± 3 days after last dose
HBV, HCV, HIV, VZV serology [s]	X															
PRO questionnaires [t]		X								X		X	X	X	X	X [d]
[redacted] [u]		X													X (C3G only)	X [d]
PK blood sample collection [v,w]			X	X	X	X	X	X	X	X	X	X	X	X	X	
PD blood sample collection [x]	X	X	X	X		X				X		X	X	X	X	X
PK urine sample collection [y,z]			X	X	X	X	X	X	X	X	X	X	X	X	X	
Interactive Response Technology (IRT)	X	X				X				X		X	X	X	X	
BCX9930 dispensing		X				X				X		X	X	X	X	
BCX9930 accountability			X	X		X				X		X	X	X	X	X
BCX9930 dosing			←	—	—	—	—	—	—	—	—	—	—	—	→	
Record AEs [aa]	←	—	—	—	—	—	—	—	—	—	—	—	—	—	→	X
Prior/concomitant medications [bb]	←	—	—	—	—	—	—	—	—	—	—	—	—	—	→	X
Assessment of the clinical benefit of BCX9930 [cc]															X	
Optional entry/exit interview by phone [dd]	X															X
Pharmacogenomics sample [ee]			←	—	—	—	—	—	—	—	—	—	—	—	—	→

Abbreviations: AE = adverse event; AP = alternative pathway; BMI = body mass index; C3G = complement 3 glomerulopathy; d = day(s); ECG = electrocardiogram; eCRF = electronic case report form; eGFR = estimated glomerular filtration rate; EM = electron microscopy; FU = follow-up; FSH = follicle-stimulating hormone; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; IgAN = immunoglobulin A nephropathy; IRT = Interactive Response Technology; LC-MS/MS = liquid chromatography-assisted tandem mass spectrometry; [redacted]; PD = pharmacodynamic(s); [redacted] questionnaire; PK = pharmacokinetic(s); PMN = primary membranous nephropathy; PRO = patient-reported outcome; SAE = serious adverse event; uACR = urine albumin-to-creatinine ratio; uPCR = urine protein-to-creatinine ratio; VZV = varicella-zoster virus

[a] All screening procedures do not need to be completed on the same day and the screening period can be extended up to 28 additional days with approval by the medical monitor on a case-by-case basis.

[b] All baseline/Day 1 study procedures should be evaluated or obtained prior to first dose of BCX9930.

[c] Additional safety assessments visits at Weeks 3, 5, 6, 7, and 10 can be conducted either at the investigative site, or at a local laboratory more convenient for the subject or via a home health service (where permitted and available); Results from local laboratory testing must be provided to the investigative site.

[d] All subjects including who discontinues the study prior to Week 52 will be asked to complete the safety FU Visit approximately 4 weeks (28 ± 3 days) after their last dose of BCX9930. Assessments indicated "X^{d}" will be completed for subjects who discontinue prior to the Week 52 Visit only.

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

[f] Disease specific medical history form which will include baseline C3G, IgAN, or PMN clinical characteristics and disease.

[g] Height and weight will be measured, and BMI calculated at screening only; at all other indicated visits, only weight will be measured and used with the height measurement from screening for subsequent BMI calculations.

[h] Screening and Day 1 pre-dose physical examinations will be full physical examinations. All post-Day 1 physical examinations will be abbreviated (ie, symptom driven) examinations, targeted to new signs and symptoms.

[i] Bedside 12-lead ECGs will be conducted in triplicate at the baseline (Day 1) visit; all other ECGs may be single assessments. Subjects should rest quietly for 5 minutes in a supine position prior to the ECGs being performed. Any blood draws scheduled at the same time should occur after obtaining the ECG.

[j] Vital signs (to include blood pressure, pulse rate, and temperature) after ECGs will be performed at investigative site visits only (ie, excluding non-investigative site visits) and the subject has rested in a supine position.

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

[l] Subjects will receive instructions and a collection container for the intended 24-hour urine sample collection. During screening, subjects will be provided the urine collection containers at the screening visit and will return the collection container with the 24-hour urine specimen to the clinic as specified in a separate document for screening and, if applicable, at the Day 1 Visit. At all other clinic visits, subjects will be provided collection containers at the previous visit and will return the collection container with the 24-hour urine specimen as specified in a separate document within 3 days of the next scheduled visit. An aliquot from these collections may be reserved for analysis of the concentration and urinary excretion of BCX9930 and metabolites.

[m] Calculated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula.

[n] Digital images of screening renal biopsy samples and local pathology report will be reviewed by the central pathologist to confirm biopsy criteria prior to scheduling Day 1 Visit. If a subject underwent renal biopsy procedure within 3 months of initiating screening with C3G, or within 6 months of initiating screening with IgAN or PMN, and digital images, and a pathology report are available that meet study requirements, then the screening biopsy requirement may be waived by the medical monitor and central pathologist on a case-by-case basis. An EM grid may be provided to the central pathologist for review if available.

[o] For subjects with C3G only, the biopsy may be performed within 7 days after completion of the Week 24 Visit but may not be performed prior to the Week 24 Visit. Protocol-specified, on-treatment biopsies will not be required for subjects with C3G who are discontinued from BCX9930 treatment prior to or at the Week 24 Visit.

[p] Single void urine sample will be analyzed for uPCR, uACR, [redacted] Single void urine samples from Day 1 (pre-dose) and Week 24 may be processed for LC-MS/MS to evaluate changes from baseline. Additional exploratory assays may be evaluated.

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

[r] FSH will be measured at screening to confirm postmenopausal state in women who report no menses for ≥ 12 months and ≤ 2 years. FSH measurement is not needed at screening to confirm postmenopausal state in women who report no menses for > 2 years.

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

[t] [redacted]) and [redacted]) questionnaires will be administered in the clinic.

[u] [redacted] will be administered in the clinic. Only the [redacted] will be administered at the Day 1 Visit for all 3 treatment cohorts. At the Week 24 Visit, the [redacted] will be administered to subjects with C3G only.

[v] A single venous blood sample for measurement of plasma concentration of BCX9930 and metabolites will be collected at each study visit, beginning at the Week 1 Visit (except if subject is participating in the PK/PD substudy procedures, in which case PK/PD substudy procedures will apply at the specified visits per Table 4). The time of sample collection, food status, and the time of the last 2 doses will be recorded for all PK samples.

[w] At study centers with appropriate facilities for the collection and processing of serial plasma samples, an optional PK/PD substudy will be performed per Table 4.

[x] Ex vivo AP Wieslab, and ex vivo AP-activated [redacted] Additional exploratory assays may be evaluated. PD samples should be collected as close as possible to the same time as PK samples, where applicable.

[y] For subjects not enrolled in the optional PK/PD substudy, a single urine void for analysis of urine concentration of BCX9930 and metabolites will be collected at each investigative site visit from Week 1. PK samples and PD samples should be collected from the same single urine void, where applicable.

[z] For subjects enrolled in the optional PK/PD substudy, urine will be collected per Table 4.

[aa] AEs will be assessed and recorded from the time of signing of the informed consent through the appropriate follow-up period.

[bb] All medications during the study will be captured and concomitant medications will be captured on the prior/concomitant eCRF pages(s) during the study.

[cc] The clinical benefit of BCX9930 treatment will be assessed by the investigator to determine continued BCX9930 dosing up to Week 52.

[dd] An optional semi-structured entry interview will be completed by phone during the screening period and an exit interview after either the safety FU Visit or Week 52 Visit (per Table 3) to capture patient experience and symptoms for subjects who agree to participate as captured in each subject's informed consent.

[ee] All subjects who sign a separate informed consent will participate in exploratory pharmacogenomics testing at a single visit from Day 1 up to the Week 24 Visit (including the safety FU Visit, if applicable).

Table 4: Schedule of Assessments (Week 28-Week 52)

Assessment/Procedure	Dosing Phase (Study Week)							Safety FU Visit [a]
	28 (± 3 d)	32 (± 3 d)	36 (± 3 d)	40 (± 3 d)	44 (± 3 d)	48 (± 3 d)	52 (± 3 d)	28 ± 3 days after last dose
Height, body weight, and BMI [b]	X	X	X	X	X	X	X	X
Physical examination [c]	X	X	X	X	X	X	X	X
12-lead ECG [d]	X	X	X	X	X	X	X	X
Vital signs [e]	X	X	X	X	X	X	X	X
Hematology and coagulation	X	X	X	X	X	X	X	X
Chemistry	X	X	X	X	X	X	X	X
Urinalysis including microscopy [f]	X	X	X	X	X	X	X	X
Intended 24-hour urine collection [g]	X	X	X	X	X	X	X	X
eGFR [h]	X	X	X	X	X	X	X	X
Percutaneous renal biopsy [i,j]			X			X	X	
Urine for biomarker testing [k]	X	X	X	X	X	X	X	X
Pregnancy test [l]	X	X	X	X	X	X	X	X
PRO questionnaires [m]			X				X	X [a]
[redacted]			X (IgAN only)				X (PMN only)	X [a]
PK blood sample collection [o]	X	X	X	X	X	X	X	
PD blood sample collection [p]	X	X	X	X	X	X	X	X
PK urine sample collection [q]	X	X	X	X	X	X	X	

Assessment/Procedure	Dosing Phase (Study Week)							Safety FU Visit [a]
	28 (± 3 d)	32 (± 3 d)	36 (± 3 d)	40 (± 3 d)	44 (± 3 d)	48 (± 3 d)	52 (± 3 d)	28 ± 3 days after last dose
Interactive Response Technology (IRT)	X	X	X	X	X	X		
BCX9930 dispensing	X	X	X	X	X	X	X	
BCX9930 accountability	X	X	X	X	X	X	X	X
BCX9930 dosing	←	—	—	—	—	—	→	
Record AEs [r]	←	—	—	—	—	—	→	X
Prior/concomitant medications [s]	←	—	—	—	—	—	→	X
Optional entry/exit interview by phone [t]							X	X

Abbreviations: AE = adverse event; AP = alternative pathway; BMI = body mass index; C3G = complement 3 glomerulopathy; d = day(s); ECG = electrocardiogram; eCRF = electronic case report form; eGFR = estimated glomerular filtration rate; EM = electron microscopy; FU = follow-up; IgAN = immunoglobulin A nephropathy; IRT = Interactive Response Technology; LC-MS/MS = liquid chromatography-assisted tandem mass spectrometry; [redacted]; PD = pharmacodynamic(s); [redacted] PK = pharmacokinetic(s); PMN = primary membranous nephropathy; PRO = patient-reported outcome; SAE = serious adverse event; uACR = urine albumin-to-creatinine ratio; uPCR- = urine protein-to-creatinine ratio

[a] All subjects will be asked to complete the safety FU Visit approximately 4 weeks (28 ± 3 days) after their last dose of BCX9930. Assessments indicated "X[a]" will be completed for subjects who discontinue the study prior to the Week 52 Visit only.

[b] Height and weight will be measured, and BMI calculated at screening only; at all other indicated visits, only weight will be measured and used with the height measurement from screening for subsequent BMI calculations.

[c] All post-Day 1 physical examinations will be abbreviated (ie, symptom driven) examinations, targeted to new signs and symptoms.

[d] Subjects should rest quietly for 5 minutes in a supine position prior to the single assessment ECGs being performed. Any blood draws scheduled at the same time should occur after obtaining the ECG.

[e] Vital signs to include blood pressure, pulse rate, and temperature after ECGs will be performed at investigative site visits only (ie, excluding remote visits) and the subject has rested in a supine position.

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

[g] Subjects will receive instructions and a collection container for the intended 24-hour urine sample collection. Subjects will be provided collection containers at the previous visit and will return the collection container with the 24-hour urine specimen as specified in a separate document within 3 days of the next scheduled visit. An aliquot from these collections may be reserved for analysis of the concentration and urinary excretion of BCX9930 and metabolites.

[h] Calculated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula.

[i] IgAN Cohort: The Week 36 on-treatment biopsy is optional. For patients who agree to have on-treatment biopsy, the biopsy will be performed after completion of all other assessments at the visit or within 7 days after completion of the Week 36 Visit but may not be performed prior to the Week 36 Visit.

[j] PMN Cohort: the Week 48-52 on-treatment biopsy is optional. For patients who agree to have on-treatment biopsy, the biopsy will be performed at the Week 48 up to within 3 days after the Week 52 Visit. If the biopsy is scheduled during the Week 48 or Week 52 Visit, the procedure will be after completion of all other assessment at the visit. If the biopsy procedure is performed after the Week 52 Visit, the subject will continue dosing until the day of the biopsy procedure and study drug (BCX9930) return and accountability will occur on the date of the procedure.

[k] Single void urine sample will be analyzed for uPCR, uACR, [redacted] Single void urine samples from Day 1 (pre-dose) and Week 36 or Week 52 may be processed for LC-MS/MS to evaluate changes from baseline. Additional exploratory assays may be evaluated.

[l] Administer a urine pregnancy test (for women of childbearing potential only).

[m] [redacted] questionnaires will be administered in the clinic.

[n] [redacted] will be administered in the clinic. Only the [redacted] will be administered at the Day 1 Visit for all 3 treatment cohorts. After the Day-1 Visit, the [redacted] will be administered once at the following specified visits by treatment cohort: Week 36 for IgAN only and Week 52 for PMN only (or at the safety FU visit, if not previously administered as described).

[o] A single venous blood sample for measurement of plasma concentration of BCX9930 and metabolites will be collected at each study visit. The time of sample collection, food status, and the time of the last 2 doses will be recorded for all PK samples.

[p] Ex vivo AP Wieslab, and ex vivo AP-activated [redacted]. Additional exploratory assays may be evaluated. PD samples should be collected as close as possible to the same time as PK samples, where applicable.

[q] Spot urine samples will be collected for analysis of the concentration of BCX9930 and metabolites at each investigative site visit until Week 52. PK samples and PD samples should be collected from the same single urine void, where applicable..

[r] AEs will be assessed and recorded from the time of signing of the informed consent through the appropriate follow-up period.

[s] All medications during the study will be captured and concomitant medications will be captured on the prior/concomitant eCRF pages(s) during the study.

[t] An optional semi-structured entry interview will be completed by phone during the screening period and an exit interview after either the safety FU Visit or Week 52 Visit to capture patient experience and symptoms for subjects who agree to participate as captured in each subject's informed consent.

Table 5: Timing of Blood Sample and Urine Collection for PK/PD Substudy at Baseline (Day 1 Visit) and a Visit prior to Week 24

Collection		Required Post Dose			
	Pre-dose	[redacted]	[redacted]	[redacted]	[redacted]
PK Blood Sample [a]	X [b]	X	X	X	X
PD Blood Sample [c]	X		X	X	X
Urine Collection [d]	X	←	—	—	→

Abbreviations: PD = pharmacodynamics; PK = pharmacokinetics

Note: Subjects who do not participate at the Day 1 serial collection through 6 hours post dose are eligible to participate at another clinic visit prior to the Week 24 Visit.

[a] The actual date and time of each blood sample collection, the observed BCX9930 dose time, and whether the subject had eaten recently prior to dosing will be recorded in the eCRF. For the second (steady-state) PK/PD substudy visit, the date and time of the last 2 doses taken prior to the pre-dose blood collection, and whether these were taken with or without food, will also be recorded in the eCRF.

[b] A pre-dose PK sample is not required at the Day 1 Visit but is required at the second (steady-state) PK/PD substudy visit. At this visit, the PK sample should be collected immediately prior to dosing and as close as possible to 12 hours following the previous dose.

[c] PD samples should be taken at the same time as the associated PK samples, where applicable

[d] A single void urine sample will be collected pre-dose and up to two single void urine samples can be collected after dosing. If fewer than 2 voids are collected during the post-dose period, then subjects will be asked to provide a single void urine sample at the 6-hour post-dose timepoint.

11.3. Study Visits

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

11.3.1. Screening

Subjects with C3G, IgAN, or PMN who may require additional treatment to an ACEi or ARB may be screened for this study.

Written consent must be obtained from the subject as required by national or local law and institutional practice, prior to conducting any study-related assessments/procedures. Signing of the informed consent form (ICF) may occur prior to the first on-study visit, which is defined as the visit where site-conducted screening procedures are first performed.

A 56-day window is provided to qualify subjects for the study. All screening procedures do not need to be completed on the same day, but all screening procedures must be completed, and the results reviewed and approved by the investigator (or designee) prior to dosing a subject. The screening period can be extended up to 28 additional days with approval by the medical monitor (or designee) on a case-by-case basis.

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

- Signing of the ICF
- Review of inclusion and exclusion criteria
- Demographic information
- Medical and medication history including confirmation of adequate vaccination and either providing protocol required vaccinations or scheduling with local health care provider to vaccinate prior to Baseline (Day 1); see Section 12.2.1.
- Disease Specific Medical History Form
- 12-lead ECG
- Vital signs (blood pressure, temperature, and pulse rate)
- Complete physical examination
- Height/weight/body mass index (BMI) calculation
- Serum pregnancy test for female subjects of childbearing potential
- Blood collection for FSH for any woman post-menopausal for ≥ 12 months and ≤ 2 years (FSH measurement is not needed at screening to confirm postmenopausal state in women who report no menses for > 2 years)
- Blood collection for clinical chemistry, hematology, coagulation, and PD biomarkers
- Blood collection for HBV, HCV, HIV, and VZV serology
- Single void collection for urinalysis including microscopy and drugs of abuse screen

- Recording of prior medications within 30 days prior to first dose and current medications
- Provide collection containers with instructions for collection and return of an intended 24-hour urine sample to the clinic during screening and, if applicable, at the Day 1 Visit
- Register the subject in Interactive Response Technology (IRT)
- After confirmation that all other study eligibility criteria are met (including intended 24-hour uPCR criterion), a percutaneous needle biopsy of the kidney per local practice and guidelines will be required, unless a kidney biopsy with digital images and a pathology report are available within 3 months of the screening visit with C3G or 6 months of the screening visit with IgAN or PMN that meets all protocol requirements and is confirmed by the medical monitor and central pathologist

  Note: The central pathologist will determine eligibility by confirmation of the primary diagnosis of either C3G, IgAN, or PMN and active disease prior to the Day 1 Visit and first dose of BCX9930

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

11.3.2. Rescreening/Retesting

Rescreening of ineligible subjects, where there is a reasonable expectation that the subject will become eligible, is permitted. If a subject is unable to be qualified in the 56-day window, eg, due to a dose change of an ACEi/ARB or acute illness or retesting of screening labs or delays related to screening biopsy, the screening window may be extended up to 28 additional days with the approval of the sponsor medical monitor (or designee). Retesting of specific assessments without entirely rescreening a subject may be permitted with the approval of the sponsor medical monitor (or designee).

11.3.3. Baseline Visit (Day 1)

For subjects participating in the PK/PD substudy, please refer to Table 2 and Table 4 for procedures and timings.

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

- Administration of questionnaires:
  - [redacted]
  - [redacted]
  - [redacted]
- Review of inclusion and exclusion criteria and prohibited medications
- Review of medical and medication history
- Review of Disease Specific Medical History Form
- Weight and BMI

- 12-lead ECG (triplicate ECGs)
- Vital signs (blood pressure, temperature, and pulse rate)
- Complete physical examination
- Single void urine collection for urinalysis including microscopy and biomarkers
- A urine pregnancy test for female subjects of childbearing potential. A negative urine pregnancy result must be recorded in order for the subject to receive study drug.
- Blood collection for clinical chemistry, hematology, coagulation, and PD biomarkers
- Review concomitant medications and AEs
- Provide collection container with instructions and return of an intended 24-hour urine sample
- Study drug dispensing (via IRT)

Where possible, the questionnaires should be completed by the subject prior to other assessments to prevent influencing subject perceptions.

11.3.4. On-study Visits (Weeks 1, 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52)

Subjects will return to the clinic during Week 1 (Day 8 ± 1 day),Week 2 (Day 15 ± 1 day), Week 4 (Day 29 ± 1 day), Week 8 (Day 57 ± 3 days), Week 12 (Day 85 ± 3 days), Week 16 (Day 113 ± 3 days), Week 20 (Day 141 ± 3 days), Week 24 (Day 169 ± 3 days) Week 28 (Day 197 ± 3 days), Week 32 (Day 225 ± 3 days), Week 36 (Day 253 ± 3 days), Week 40 (Day 281 ± 3 days), Week 44 (Day 309 ± 3 days), Week 48 (Day 337 ± 3 days), and Week 52 (Day 365 ± 3 days).

At the Week 24 Visit, the clinical benefit of BCX9930 treatment will be assessed by the investigator. Subjects who are assessed as deriving clinical benefit will continue treatment up to Week 52. Subjects who continue BCX9930 treatment will complete study visits and assessments through the Week 52 Visit.

Subjects do not need to withhold any doses on clinic days or take a dose in the clinic, unless the clinic visit falls during the subject's normal time of dosing or PK/PD substudy procedures are also being conducted. PK/PD substudy visits for participating subjects should be scheduled such that the subject's normal dosing time occurs during the clinical visit, if possible. On these days, subjects should be instructed not to take their dose of BCX9930 until they are in clinic and the pre-dose PK and PD samples have been collected.

For subjects participating in the PK/PD substudy, please refer to Table 4 for procedures and timings.

The following assessments will be performed:

- Administration of questionnaires. Where possible, the questionnaire should be completed by the subject prior to other assessments:

  - [redacted] at Weeks 8, 12, 16, 20, 24, 36, and 52 only (or at the safety FU, if applicable)
  - [redacted] at Weeks 8, 12, 16, 20, 24, 36, and 52 only (or at the safety FU, if applicable)
  - [redacted] at Week 24 Visit for C3G only, Week 36 Visit for IgAN only, and Week 52 for PMN only (or at the safety FU, if not previously administered as described)
  - [redacted] at Week 24 Visit for C3G only, Week 36 Visit for IgAN only, and Week 52 for PMN only (or at the safety FU, if not previously administered as described)
- 12-lead ECG
- Vital signs (blood pressure, temperature, and pulse rate)
- Targeted physical examination (ie, symptom-driven, targeted to new signs and symptoms)
- Weight and BMI (not performed at the Week 1 and Week 2 Visits)
- Single void urine collection for urinalysis including microscopy, PK and biomarkers
- A urine pregnancy test for female subjects of childbearing potential
- Blood collection for clinical chemistry, hematology, coagulation, and PD biomarkers
- Blood collection for sparse PK plasma sample and documentation of time of sample collection, food status and the time of the last two doses of study drug taken
- Review/capture of concomitant medications and AEs
- Assessment of the clinical benefit of BCX9930 (at the Week 24 Visit only)
- Provide collection container with instructions and return of an intended 24-hour urine sample
- Study drug dispensing (via IRT) and accountability, as per Table 2 and Table 3

A percutaneous needle biopsy of the kidney per local practice and guidelines will be performed at Week 24 for subjects with C3G. An optional percutaneous needle biopsy of the kidney can be performed at Week 36 for subjects with IgAN or at Week 48-52 for subjects with PMN if a subject consents for the optional procedure. The biopsy should be scheduled during the specified visit after completion of all other assessments or within the timeframe after the visit as specified in Section 12.4.2, but may not be performed prior the specified visit. For subjects with PMN, if the biopsy procedure is performed after the Week 52 Visit, the subject will continue dosing until the day of the biopsy procedure and study drug return and accountability will occur on the date of the biopsy procedure.

All subjects who sign a separate informed consent will participate in exploratory pharmacogenomics testing at a single visit from Day 1 up to the Week 24 Visit (including the Safety FU Visit, if applicable).

11.3.5. Additional Assessments for Renal and Hepatic Safety Monitoring

Additional assessments to monitor for potential renal and hepatic toxicity will be performed at Week 3 (Day 22 ± 1 day), Week 5 (Day 36 ± 3 day), Week 6 (Day 43 ± 3 day), Week 7 (Day 50 ± 3 day), and Week 10 (Day 71 ± 3 day). The assessments may be performed at the investigative site, at a local laboratory more convenient for the subject, or via a home health service (where permitted and available) and will be continued until sufficient data are available to allow for reduction or elimination of the additional assessments.

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

For subjects assessed at the investigative site:

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

The above assessments will also be performed for subjects identified with potential renal or hepatic events who are required to return to the investigative site (Section 13.5).

For subjects assessed at non-investigative sites:

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

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

11.3.6. Safety follow-up Visit

All subjects will return to the clinic approximately 4 weeks (28 ± 3 days) after the date of their last dose of BCX9930 for safety assessments.

The following assessments will be performed:

- Administration of questionnaires. Where possible, the questionnaire should be completed by the subject prior to other assessments (for early discontinued subjects only):
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
- 12-lead ECG
- Vital signs (blood pressure, temperature, and pulse rate)
- Targeted physical examination (ie, symptom driven, targeted to new signs and symptoms)
- Weight and BMI
- Single void urine collection for urinalysis including microscopy, and biomarkers
- Blood collection for clinical chemistry, hematology, coagulation, and PD biomarkers
- A urine pregnancy test for female subjects of childbearing potential
- Review and capture of concomitant medications and AEs
- Collection of intended 24-hour urine sample with the number of days between last dose and collection documented
- Study drug accountability

12. STUDY ASSESSMENTS

12.1. Chronology of Assessments

The following chronology of events should be adhered to during the scheduled visits, as applicable:

- Subject questionnaires: obtain prior to other study procedures
- ECGs: obtain prior to vital signs and urine specimen collection
- Vital signs: obtain prior to urine specimen collection
- Urine collection: obtain prior to blood collection

- Blood collection

It is preferred that the patient-reported outcomes (PRO) questionnaires be administered prior to completing other study procedures, and clinic procedures, such as ECGs, physical examinations, and vital signs measurements, should be completed prior to any blood collection.

12.2. Demographic/Medical History

Demographic information and medical and medication history will be captured for each subject participating in the study at the Screening Visit. Medical history, medication review, and review of inclusion and exclusion criteria, potentially nephrotoxic medications, and prohibited medications will also be updated and rechecked at baseline (Day 1) as outlined in Section 11.3.3.

A Disease Specific Medical History Form including baseline C3G, IgAN, or PMN clinical characteristics and disease burden including prior genetic screening for complement-related mutations, nephritic factors, or other disease characteristics, clinical labs (eg, serum creatinine), and copies of pathology reports with WSIs (if available) will be captured during screening. Medication history will include details of C3G, IgAN, or PMN treatments administered (including plasma exchange therapy and other investigational product).

12.2.1. Vaccination Requirements

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

For those who have not received all of the required vaccines (including boosters) or vaccine series, administration of any needed vaccines should start no later than 14 days prior to Day 1. If the recommended vaccination coverage requires more than a single dose, then the additional dose(s) may be administered after Day 1 to complete the recommended vaccination coverage. If a vaccine is not available, the sponsor medical monitor (or designee) should be contacted to discuss potential options in order to satisfy eligibility requirements prior to completing the Day 1 visit. Appropriate antibiotics for prophylaxis may be given during the study in accordance with local standard of care and any relevant vaccination guidance (see Section 9.1).

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

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

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

Investigators should review each subject's vaccination status at periodic intervals to ensure that any needed booster vaccinations are administered at the optimal timing during the study. Please contact the sponsor medical monitor or designee for any questions.

If a patient receives a SARS-CoV-2 vaccination, this should be captured as a prior or concomitant medication entry. Vaccinations that require more than one inoculation should have a separate prior or concomitant medication entry for each injection.

If patient experiences any AEs related to SARS-CoV-2 vaccination, or any AE in temporal relation to the vaccination, these should be entered on the adverse events page.

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

12.3. Immunity Assessment

In Study 101, a subject with PNH and multiple risk factors, including occupation, concomitant corticosteroids, and additional immunosuppression, developed disseminated varicella infection as an unrelated SAE. Antibodies to VZV will be tested in all subjects at screening. If an exposure to VZV occurs during the study, this will help the investigator assess the risk for developing primary varicella for non-immune subjects if an exposure occurs. 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.

12.4. Efficacy/Effectiveness Assessments

12.4.1. Intended 24-hour Urine Collection

An intended 24-hour urine collection will be required prior to each clinic visit except for the initial Screening Visit. All subjects will receive a container and patient instructions for the collection and return of an intended 24-hour urine sample that will be initiated out of the clinic. After completion of the intended 24-hour collection, the sample will be returned to the clinic. A phone call to remind subjects to complete the intended 24-hour collection will be conducted within a week prior to the scheduled visit. Urine samples are intended to be collected over a 24-hour period and intended 24-hour samples will be accepted even if there are reports of missing a single void collection.

An aliquot from 24-hour urine collections may be reserved for analysis of the urine concentration of BCX9930 and metabolites.

12.4.2. Percutaneous Needle Biopsy of the Kidney

After confirmation that all other study eligibility criteria are met during screening per local practice and guidelines:

- Subjects will undergo a percutaneous needle biopsy of the kidney during screening

Note: The screening biopsy procedure may be waived with approval of the central pathologist and agreement with the medical monitor for any subject who has undergone a renal biopsy procedure within 3 months prior to initiating screening with C3G, and within 6 months prior to initiating screening with IgAN or PMN, provided that required materials are adequate for pathology evaluation per protocol procedures

An on-treatment, percutaneous needle biopsy of the kidney will be performed at the following visit after completion of all other assessments, or during the specified times below by treatment cohort:

- Week 24 or within 7 days after the visit for subjects with C3G
- Week 36 or within 7 days after the visit for subjects with IgAN (optional)
- Week 48 to within 3 days after the Week 52 Visit for subjects with PMN (optional)

The on-treatment biopsy is required for subjects with C3G but is optional for subjects with IgAN or PMN. For subjects with PMN, if the biopsy is scheduled after the Week 52 Visit, then dosing with BCX9930 will continue until the day of the procedure. Protocol-specified, on-treatment biopsies will not be required for subjects who are discontinued from BCX9930 treatment.

12.4.2.1. Central Pathologist

A pathology manual of procedures will be provided to sites with study-specific methods regarding specimen processing, scanning, capture of morphologic/morphometric features, computer assessment, and data collection. Each investigator should review the pathology manual of procedures with an experienced, on-site renal pathologist.

Renal biopsy samples will be processed locally according to the pathology manual. Images (WSIs of the light microscopy, digital IFs or IHCs, and digital EMs), and details from the local pathology report will be reviewed by the central pathologist for confirmation of a protocol defined diagnosis of C3G, IgAN, or PMN based on the following inclusion criteria:

- **C3G:** a sole or dominant glomerular IF or IHC staining for C3 of at least two orders of magnitude greater intensity than for any other immunoreactant (D'Agati and Bomback 2012).

  Evidence of disease activity as follows:

  – C3GN with at least 25% of glomeruli with at least segmental mesangial and segmental endocapillary hypercellularity.

  – DDD with at least 2 of the following 3:

  - at least 25% of glomeruli with segmental mesangial hypercellularity

  - at least 25% of glomeruli with segmental endocapillary hypercellularity

  - at least one active crescent

  A minimum of 4 patent glomeruli between the light microscopy and EM thick section WSIs is required. At least one patent glomerulus is required for IF or IHC digital images.

- **IgAN:** IF or IHC staining for IgA and C3, with dominant IgA compared to other Igs/immunocomplexes. Disease activity required with M1 and E1 and/or C1, including active crescents and/or necrosis as per Oxford IgA scoring (Haas, Verhave et al. 2017, Trimarchi, Barratt et al. 2017). A minimum of 8 patent glomeruli between the light microscopy and EM thick section WSIs is required. At least one patent glomerulus is required for IF or IHC digital images.
- **PMN:** IF or IHC capillary wall granular staining for IgG and C3 with at least 50% of the deposits being active Ehrenreich and Churg stage I and/or II by EM; stage III deposits are allowed (Ehrenreich and Churg 1968). Active crescents ≤ 10% are allowed. A minimum of 6 patent glomeruli between the light microscopy and EM thick section WSIs is required. At least one patent glomerulus is required for IF or IHC digital images.
- **All:** Images for LM, IF or IHC, and EM are of sufficient quality to allow for interpretation and diagnosis
- **All:** ≤ 50% global glomerulosclerosis
- **All:** ≤ 50% tubulointerstitial fibrosis
- **C3G and IgAN:** ≤ 50% active crescents

The WSIs of LMs, digital IFs or IHCs, digital EMs, and report findings for study eligibility will also serve as the pre-treatment baseline for change from baseline comparisons to the on-treatment biopsies by the central pathologist. In addition, unstained EM grids will be shipped from sites to the central pathologist for additional baseline EM assessments and reporting if a biopsy is performed during the screening period. For a biopsy performed prior to the screening, unstained EM grids may be shipped to the central pathologist if available.

If other biopsies not specified per protocol are performed during the study, the available images (WSIs of the light microscopy, digital IFs or IHCs, and digital EMs) and details from the local pathology report will be reviewed by the central pathologist, if available.

12.4.3. [redacted]

For the PMN cohort only, [redacted] will be measured at Screening, Baseline, and every 4 weeks until Week 52.

12.5. Patient-reported Outcomes

The following PRO instruments will be used during this study:

- [redacted])
- [redacted]
- [redacted]
- [redacted]

Each questionnaire will be translated into the local language, as required. For all subject-completed forms, clinic staff should ensure the subject reads the instructions and

completes the questionnaire in full. The investigator or clinic staff is not permitted to provide any assistance, interpretation, or clarification of information or questions contained in the questionnaires. The questionnaires should be completed by the subject prior to other assessments for that visit to prevent assessments from influencing subject perceptions (see Section 12.1).

[redacted]

12.5.4. Optional Entry and Exit Phone Interviews

An optional phone entry and exit interview by a third-party vendor will be completed during the screening period and after either the safety FU visit or Week 52 Visit in a subset of subjects. The intent of the interviews is to capture patient experience and symptoms. Subjects will sign a separate informed consent which details further information on the interviews. A separate communication will be provided to sites. Subjects may participate in one or both of the entry and exit interviews.

12.6. Blood Pharmacokinetic and Pharmacodynamic Assessments at Scheduled Visits

Blood samples for plasma PK concentrations ("sparse sampling" to support PPK and PK/PD modeling) will be collected from all subjects receiving study drug at each study visit to the investigative site, beginning at Week 1, and at any visits to the investigative site to perform additional safety assessments. PK samples will not be collected at the baseline (Day 1) visit unless subjects participate in the optional PK/PD substudy.

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

Subjects do not need to withhold any BCX9930 doses during these visits or take a dose in the clinic, unless the visit falls during the subject's normal dose time or the subject is participating in the PK/PD substudy on that day (see Section 12.9.1).

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

Plasma samples for determination of BCX9930 will be analyzed using validated liquid chromatography - tandem mass spectrometry (LC-MS/MS) assays. BCX9930 metabolites may also be analyzed using these samples. Instructions for collection, processing, storage, and shipment of PK samples will be provided in a separate laboratory manual.

Blood samples for the analysis of ex vivo PD and [redacted]s will be collected in all subjects at each study visit, including Baseline/Day 1, as outlined in Table 2 and Table 3. Where feasible, and as applicable, blood samples for PD analyses should be collected at the same time as sparse PK samples. The plasma PD and [redacted] for assessment may include, but are not limited to:

- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

12.7. Urine Collection for Measurement of BCX9930 and Metabolite Concentrations

Spot urine samples will be collected for analysis of the concentration of BCX9930 and metabolites. Additionally, an aliquot of 24-hour urine collections may be reserved for concentration analysis, as described in (Section 12.4.1).

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

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

12.8. Urine Pharmacodynamic and Biomarker Assessments

Single void urine samples will be analyzed for levels of constitutive complement biomarkers, including but not limited to [redacted] he single void PD urine samples may be aliquoted from the same urine collection as used for the PK urine samples (Section 12.7).

In addition to the above biomarkers, an aliquot of urine will be stored for potential future analysis.

12.8.1. Urine Biomarkers of Kidney Injury

Single void urine samples will be analyzed for biomarkers of kidney injury, including but not limited to [redacted] Schrezenmeier, Barasch et al. 2017). These urine biomarkers will be assessed, in addition to serum creatinine, to identify potential associations or correlations of urine biomarker changes and timing to other assessments of kidney health to define subclinical kidney injury events or kidney improvement.

12.9. Pharmacokinetic and Pharmacodynamic Substudy

Blood and single void urine samples will be collected from subjects participating in the PK/PD substudy, as outlined in Table 4.

[redacted]

[redacted]

12.9.2. Urine Assessment of BCX9930 and Metabolite Concentrations in PK/PD Substudy

Subjects who participate in the PK/PD substudy will have single void urine samples collected pre-dose and up to two more single void urine samples collected post dose. If fewer than 2 voids have been collected during the post-dose period, then subjects will be asked to provide a single void urine sample at the [redacted] post-dose timepoint.

For each single void sample in the PK/PD substudy, the full volume of urine should be collected and recorded.

The urine concentration data for BCX9930 will be summarized and putative BCX9930 metabolites may also be assessed.

12.9.3. Urine Pharmacodynamic Assessments in PK/PD Substudy

An aliquot of each single void urine sample collected for urine PK (Section 12.9.2) will be reserved for analysis of ex vivo PD and [redacted].

The urine PD and complement biomarkers may include, but are not limited to:

- [redacted]

[redacted]

12.11. Safety Assessments

12.11.1. Vital Signs

Vital signs comprising temperature, blood pressure, and pulse rate will be recorded at the visits according to the schedule of assessments (Table 2 and Table 3).

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

12.11.2. Weight, Height, and Body Mass Index

For determination of height and body weight, subjects should be clothed with shoes removed. Body mass index (BMI) should be calculated using the following formula:

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

Height will be recorded at the screening visit. Weight will be recorded at the visits according to the schedule of assessments (Table 2 and Table 3).

12.11.3. Physical Examination

Subjects will undergo a physical examination according to the schedule of assessments. (Table 2 and Table 3).

A full physical examination should be conducted at the Screening Visit and at the Baseline Visit (Day 1). All subsequent physical examinations may be targeted (ie, symptom driven) to include, at a minimum, evaluation of any new signs or symptoms or infection risk (eg, vaccination status). Genitourinary and breast examinations may be omitted when not required by normal site practice.

12.11.4. Electrocardiogram

Electrocardiograms will be obtained per the schedule of assessments as specified in Table 2 and Table 3.

A standard bedside 12-lead ECG machine system that calculates heart rate and measures the PR, QRS, QT, RR, and corrected QT (QTcF) intervals will be used. Twelve-lead ECGs will be measured after the subject has been in the supine position for a minimum of 5 minutes according to Section 11 and the schedule of assessments. All ECGs will be single assessments, with the exception of the Day 1 Visit ECG, which will be recorded in triplicate.

Qualified site personnel should review the ECGs and automated findings in real time for gross abnormalities and interval measurements of concern (absolute readings and change from baseline). An ECG should be repeated after at least an additional 10-minute rest in a supine position in the event of a change from baseline in QTcF > 60 msec or a QTcF interval > 500 msec.

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

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

Blood and urine samples will be obtained per the schedule of assessments as specified in Table 2 and Table 3. Individual laboratory tests are provided in Table 5.

In general, laboratory samples collected at visits to the investigative site should be collected using kit supplies provided by the 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 investigative site or at a local laboratory more convenient for the subject or via a home health service. The results from laboratory testing performed at a local 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 laboratories should be reviewed as received by the investigator. Evidence of this review should be provided in the source records and may include printing of the laboratory reports with a signature attesting to a review. For out-of-range findings, the interpretation of clinically significant or not clinically significant should be denoted in the source records. Clinically significant laboratory findings in the opinion of the investigator should be recorded as AEs and handled as described in the protocol (Section 13).

Table 6: Clinical Laboratory Evaluations

Chemistry	**Coagulation**
• Albumin • Alkaline phosphatase (ALP) • Alanine aminotransferase (ALT) • Aspartate aminotransferase (AST) • Bilirubin (total and direct) • Blood glucose • Blood urea nitrogen (BUN) • Bicarbonate • Calcium • Sodium • Potassium • Chloride • Creatine kinase • Serum creatinine (SCr) and calculated estimated glomerular filtration rate (eGFR) • Serum cystatin C (Scys) • Lactate dehydrogenase (LDH) • Total serum protein • Uric acid • Amylase • C-reactive protein • Lipase (reflex test if amylase elevated) • Cholesterol, total • Cholesterol, high-density lipoprotein (HDL) • Cholesterol, low-density lipoprotein (LDL) • Triglycerides	• Prothrombin time (PT) and international normalized ratio (INR) • Activated partial thromboplastin time (aPTT) • Thrombin time
	Pregnancy Test
	• Serum (screening) and urine (other scheduled visits) beta human chorionic gonadotropin (β-hCG) for women of childbearing potential only • Follicle-stimulating hormone (FSH) for women with no menses for ≥ 12 months and ≤ 2 years
	Hematology
	• Hemoglobin • Hematocrit • Erythrocyte count • Mean corpuscular hemoglobin (MCH) • Mean corpuscular hemoglobin concentration (MCHC) • Mean corpuscular volume (MCV) • White blood cell count, with differential (lymphocytes, monocytes, neutrophils, eosinophils, and basophils) • Platelet count
Urinalysis	
• Specific gravity • Blood • Bilirubin • Glucose • Leukocytes • Ketones • Nitrites • pH • Protein	**Other** • Hepatitis B virus (HBV) surface antigen (HbsAg) • Hepatitis B Core antibody (positive test will reflex to HBV deoxyribonucleic acid [DNA] viral load assay)

• Urobilinogen • Creatinine • Albumin • Cystatin C • [redacted] • α1-microglobulin • β2-microglobulin • [redacted] • Protein to creatinine ratio • Albumin to creatinine ratio • [redacted] • α1-microglobulin to creatinine ratio • β2-microglobulin to creatinine ratio • [redacted] • Microscopic evaluation (where capabilities exist) • [redacted]	• Hepatitis C virus (HCV) antibody (HCVAb) ○ If HCVAb positive, reflex to HCV ribonucleic acid (RNA) testing • Human immunodeficiency virus (HIV) antibody • Varicella-zoster immunoglobulin G (IgG) titer • Plasma pharmacokinetics (PK) • Serum pharmacodynamics (PD) • Urine PK (PK/PD substudy only) • Urine PD • [redacted]
Urine drug screen • Amphetamines • Methamphetamine • Ecstasy • Barbiturates • Benzodiazepines • Opiates	

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

Investigators should emphasize to staff and subjects the importance of collecting fresh, high-quality urine specimens (clean-catch, mid-void, etc.) and ensuring appropriate handling and prompt analysis of the samples for urinalysis. Urine microscopy will be performed on all urine samples collected for urinalysis at investigative site visits. Because of the potential for extended transit times to the central laboratory, where possible, the urine microscopy should be performed using the site's local laboratory (where appropriate on-site testing capability exists) in lieu of the designated central laboratory. Urine microscopy should also be performed at any remote laboratory where appropriate on-site testing capability exists. If the local or remote laboratory does not have on-site testing capability, the sample may be sent to the designated central laboratory.

12.11.5.2. Calculations for estimating Glomerular Filtration Rate

eGFR will be calculated by the CKD-EPI equation (Levey and Stevens 2010) (SCr method), in units of mL/min/1.73 m^2, presented below:

$$eGFR\ (mL/min/1.73\ m^2) = 141 \times [\min(SCr/\kappa,1)]^{\alpha} \times [\max(SCr/\kappa,1)]^{-1.209} \times (0.993)^{Age\ in\ years} \times (1.018\ if\ female) \times (1.159\ if\ African\ Ethnic\ Heritage)$$

Where:

- $\kappa = 0.7$ for females and 0.9 for males
- $\alpha = -0.329$ for females and -0.411 for males
- min (SCr/κ,1) indicates the minimum of SCr/κ or 1
- max (SCr/κ,1) indicates the maximum of SCr/κ or 1

Additional equations and analytes, such as cystatin C, may be used to calculate eGFR for purposes of sensitivity analyses.

12.11.6. Menopause and Pregnancy Testing

Follicle-stimulating hormone (FSH) will be measured at screening in women declaring themselves postmenopausal for ≥ 12 months and ≤2 years to confirm nonchildbearing status. FSH measurement is not needed at screening to confirm postmenopausal state in women who report no menses for > 2 years.

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

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

13. ADVERSE EVENTS

AEs will be assessed and recorded from the time of signing of the informed consent through the appropriate follow-up period.

13.1. Definitions

13.1.1. 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 13.4).
- 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 preexisting condition has changed by including applicable descriptors (eg, “more frequent headaches”).

Symptoms or abnormalities related to the underlying disease (C3G, IgAN, and PMN), such as worsening of kidney laboratory parameters, are considered disease progression and are not to be recorded as AEs unless the event is an SAE or related to treatment with BCX9930 or related to some other cause (eg, concomitant treatment/procedure).

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.” Serious Adverse Events (SAEs) are described in Section 13.1.3.

Hospitalization scenarios do not require reporting as a 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 preexisting 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 preexisting 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.

13.1.2. Adverse Reaction

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.

13.1.3. Serious Adverse Event

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

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

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

In addition, the sponsor considers any abortions (elective or spontaneous), fetal demise, and still birth to be SAEs for reporting purposes (see Section 13.4.2).

Some hospitalization scenarios, as outlined in Section 13.1.1, 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 13.5.2). Details of signs or symptoms, clinical management, and outcome should be reported, if available. Overdose without associated signs or symptoms should not be recorded as AEs but should be recorded as protocol deviations.

13.1.4. Events of Special Monitoring

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

EOSM for this study are:

- potential drug-induced liver injury

- [redacted]
- SARS-CoV-2 infection (asymptomatic and symptomatic)

EOSMs may include the collection of additional data in the eCRF.

13.2. Definition of Severity

All AEs will be assessed (graded) for severity by the investigator and classified using the National Cancer Institute CTCAE Grades 1 through 5 (Version 5.0, published 27 November 2017). Any AEs not covered by the CTCAE criteria will be assessed and classified into 1 of the 5 clearly defined categories as follows:

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 activities of daily living (ADL).*
Severe:	(Grade 3): Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL. **
Life-threatening:	(Grade 4): Life-threatening consequences; urgent intervention indicated.
Death	(Grade 5): Death related to AE. ***

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
**Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.
*** Grade 5 (Death) is not appropriate for some AEs and therefore is not an option.

In addition, the investigators will provide a qualitative assessment of AE intensity (mild, moderate, or severe).

It is important to distinguish between serious AEs (SAEs) and AE grading, such as severe AEs. Severity is a measure of intensity, as defined above, whereas seriousness is defined by the criteria under Section 13.1.3. An AE of severe intensity may or may not be considered serious.

13.3. Relationship to Study Drug

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

suspecting a possible cause-and-effect relationship between the investigational product and the occurrence of the AE, then the AE should be considered "related."

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

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

The sponsor may upgrade causality if deemed appropriate.

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

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

AEs should be entered in 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 2 events do not need to be followed if the event is deemed unlikely to be related or not related to study drug/IMP (see Section 13.2 for AE grading). For all Grade 3 and 4 events or events deemed possibly, probably, or definitely related to use of study drug/IMP, the event should be followed until the AE is resolved or the subject is in a clinically stable condition with 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 onto the AE and SAE eCRFs. 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, 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.

13.4.1. Serious Adverse Events and Suspected Unexpected Serious Adverse Reactions

All SAEs must be reported immediately and no later than 24 hours of investigator awareness to the sponsor medical monitor via the AE and SAE eCRFs. Investigators should adhere to their country or region requirements for the reporting timeframe, which may not allow any delay. 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 recipients. As soon as the eCRF system is functioning, that particular SAE must be entered into the SAE eCRF. All follow-up information on the SAE should be reported via the SAE eCRF. The eCRF system automatically sends SAE notifications to the following email address:

Email: safety@biocryst.com

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

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

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

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

inform the investigator. Although acute kidney injury is considered an expected event (see Section 6.11 of the IB), the event will be reported in an expedited manner.

13.4.2. Pregnancy

Any female subject who becomes pregnant during the course of the study should have study drug/IMP discontinued immediately and must be followed through the end of the pregnancy. While pregnancy is not considered an AE, all cases of fetal drug exposure via the parent as a study participant (including partners of study participants) are to be reported immediately to BioCryst or its designee. Consent from study partners who become pregnant will be obtained prior to reporting any details of the pregnancy. Information related to the pregnancy must be given on a "Pregnancy 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 13.1.3. 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.

13.5. Adverse Event Management

The investigator (or qualified designee) will grade clinically significant events and laboratory abnormalities (if considered AEs) as detailed in Section 13.2. Grade 3 and 4 clinically significant laboratory abnormalities should be confirmed by repeat testing and before any contemplated study drug discontinuation, unless such a delay is not consistent with good medical practice.

13.5.1. 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 potential drug-induced liver injury (pDILI) meeting this ALT elevation must be assessed to determine whether study drug must be withheld or discontinued per Sections 7.4.1. 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, 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 Gilbert's syndrome) or INR > 1.5 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, 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.

If Hy's Law criterion is met and assessed as probably or definitely related to study drug by the investigator, then study drug must be discontinued per treatment discontinuation criterion in Section 7.4.1. The investigator should contact the sponsor medical monitor for a discussion regarding the event and assessment. If medically indicated, the investigator can discontinue the subject immediately and follow up with the sponsor within 24 hours.

13.5.2. [redacted]

[redacted]

13.5.3. SARS-CoV-2 and COVID-19

As complement inhibitors do not inhibit cellular or humoral immunity, BCX9930 is not expected to increase the risk of contracting COVID-19 following infection with SARS CoV-2 or to increase the risk of severe illness with COVID-19. However, all study activity will be conducted in accordance with relevant local, regional, and national guidance around COVID-19. In order to minimize the risk of COVID-19 transmission, additional procedures or assessments (which may include but are not limited to symptom assessment, temperature, viral RNA testing, and antibody testing) may be implemented at the discretion of the investigator beyond those required for this protocol.

13.6. Overdose

To date, there is no experience with overdose of BCX9930. Healthy subjects received BCX9930 at a dose of 2000 mg administered as single doses and as multiple once-daily doses for 3 days in Study 101 with no clinically significant safety concerns. In the event that study personnel become aware of an overdose of BCX9930 that is associated with an AE, both the overdose and the resultant event should be reported as AEs. Overdose without any symptoms (ie, AEs) does not need to be reported as an AE but would be captured as a protocol deviation. 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 13.1.3.

13.7. Data Monitoring Committees

An independent, program-wide DMC, which will include a nephrologist and other members with relevant expertise, will regularly review the cumulative safety data from this study, as well as the accumulating, long-term safety data across all BCX9930 studies.

Prior to opening enrollment to subjects with an eGFR $\geq$ 30 mL/min/1.73 m^2, a minimum of at least 4 subjects with an eGFR $\geq$ 50 mL/min/1.73 m^2 must have completed at least 4 weeks of BCX9930 dosing. After the minimum number of subjects and duration of dosing are met, the DMC may recommend expanding enrollment to include subjects with an eGFR

≥ 30 mL/min/1.73 m^2 based on an acceptable renal safety profile of BCX9930. Enrollment under existing inclusion for subjects with an eGFR ≥ 50 mL/min/1.73 m^2 will not be paused during this DMC review.

In the event that a new clinically significant safety signal emerges, a meeting of the DMC may be convened by the sponsor to evaluate risk to subjects and recommend appropriate actions. Based on the data presented, a decision will be made as to whether to halt the study, to continue dosing, or to continue dosing with provisions introduced into the protocol via substantial amendment.

The specific responsibilities and composition of the DMC are outlined in a separate DMC charter.

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

14. STATISTICS

14.1. Hypotheses

This is a POC study to estimate the therapeutic potential of BCX9930 administered in subjects with C3G, IgAN, or PMN. Post-baseline measurements will be assessed against their applicable baseline measurements.

14.2. Sample Size Considerations

No formal power or sample size calculations are planned to determine the sample size for each cohort. The proposed sample size of approximately 14 subjects per cohort should provide an estimate of uPCR reduction up to 52 weeks to estimate the safety and therapeutic potential for BCX9930 in these renal indications and inform sample sizes for future studies of BCX9930.

Several recent Phase 2 studies that evaluated investigational products with similar or identical mechanisms of action as BCX9930 enrolled 5 to 7 subjects with C3G per study and reported reductions in proteinuria after treatment durations ranging from 2 to 48 weeks (unpublished data).

No sample size re-estimations are planned.

14.3. Stratification

No stratifications are planned.

14.4. Statistical Methods

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

safety and preliminary efficacy data for each treatment cohort, if conducted, will be provided in the SAP.

14.4.1. Analysis Populations

The analysis populations are defined below.

14.4.1.1. Full Analysis Set Population

The Full Analysis Set (FAS) population is defined as all subjects who receive at least one dose of study drug. The FAS population will be used as the primary population for demographics, baseline characteristics, safety, and efficacy analyses.

14.4.1.2. Pharmacokinetic Population

The PK population will include all FAS population subjects for whom PK concentration data are available.

14.4.1.3. Pharmacokinetic Substudy Population

The PK substudy population will include all FAS population subjects for whom serial PK concentration data are available and PK parameters can be estimated.

14.4.1.4. Pharmacodynamic Population

The PD population will include all FAS population subjects for whom at least 1 pre-dose and at least 1 post-dose PD/biomarker measurement can be obtained. This population will be used for all PD/biomarker analyses.

14.4.2. General Considerations for Data Analysis

In general, descriptive summaries will include n, mean, standard deviation, median, minimum, and maximum for continuous variables and n and percentage for categorical variables. Summaries will be presented by treatment cohort and, where appropriate, by visit or pooled across the treatment cohorts.

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

14.4.3. Subject Demographic and Disposition Data

Demographic data and baseline characteristics including age, sex, race or ethnicity, height, weight, and BMI will be summarized by treatment cohort and overall.

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

14.4.4. Analysis of Efficacy Variables

The efficacy analyses will be based on the FAS population. Efficacy data will be summarized by treatment cohort and study visit.

For continuous variables, descriptive summaries (for the recorded value, change from baseline, and percentage change from baseline) will be presented by study visit and treatment cohort. For specific parameters of interest, point estimates for the changes and percent changes from baseline will be summarized along with their 80% CIs, 95% CIs and p-values using the one-sample t-test.

For binary endpoints (eg, uPCR response), summaries will be presented as counts and frequencies by post-baseline visit and treatment cohort. Corresponding confidence intervals (80% and 95%) will be provided for specific parameters of interest using the Clopper-Pearson Exact method.

Categorical data will be summarized by study visit and treatment cohort using counts and percentages or descriptively (depending on the number of categories and whether the categories are nominal or ordered). Details will be provided in the SAP.

Plots of individual efficacy assessments over time with an overlay of the group mean will be provided by treatment cohort. Results will be presented by parameter, with all time points reported.

14.4.5. Analysis of Safety Variables

The safety analyses will be analyzed by treatment cohort and overall.

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

Adverse events will be mapped to a Medical Dictionary for Regulatory Activities (MedDRA) preferred term and system organ class (SOC). The occurrence of treatment-emergent AEs will be summarized using MedDRA preferred terms, SOCs, and severity. Separate summaries of TEAEs, TESAEs, AEs considered to be related to study drug, and AEs leading to study drug interruption will be generated. All AEs will be listed for individual subjects showing both verbatim and preferred terms.

Descriptive summaries (actual and change from baseline) of vital signs, weight, bedside ECG parameters, and clinical laboratory results will be presented. Laboratory and ECG abnormalities will be graded according to CTCAE (Version 5.0, 27 November 2017).

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

Clinically significant abnormal morphological ECG findings will be summarized.

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

$$\Delta_{ik} = (\text{QTcF for subject at time point k} - \text{baseline QTcF})$$

Where QTcF measurements will be the average of triplicate ECGs at baseline, and single values at each time point.

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

Physical examination findings will be listed.

Concomitant medications will be coded using the World Health Organization drug dictionary and summarized.

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

No formal tests of hypothesis are planned for safety data.

14.4.6. Patient-reported Outcomes

Patient-reported outcomes ([redacted] will be summarized descriptively (actual and change from baseline, as applicable) by study visit and treatment cohort.

14.4.7. Pharmacokinetic Analyses

Sparse plasma and spot urine samples will be collected for analysis of BCX9930 and metabolite concentrations as described in Table 2 and Table 3.

Sparse plasma and urine PK data will be listed.

Subjects enrolled in the PK/PD substudy will have plasma and urine samples collected as described in Table 4. Plasma concentration data will be summarized by visit (first dose vs. steady state) and nominal timepoint. Urine concentration data will be summarized by visit and void (first or second void within the sample collection period).

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

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

14.4.8. Pharmacodynamic and Biomarker Analyses

Descriptive summaries (actual, change from baseline, and percentage change from baseline) will be presented by parameter, time point, and treatment cohort (and overall) for each PD parameter. Point estimates and 95% CIs will be presented for change from baseline and percentage change from baseline by parameter, post-baseline study visit, and treatment cohort.

Plots of individual and mean PD assessments and biomarkers over time will be provided by treatment cohort.

PD data may be analyzed in combination with data from other studies as appropriate (which may include model-based analyses of population PK and/or PK/PD). These analyses will be reported separately from the CSR.

15. STUDY ADMINISTRATION

15.1. Study Monitoring

Before an investigational site can enter a patient into the study, a representative of BioCryst will assess the investigational study site to:

- Determine the adequacy of the facilities
- Discuss with the investigator(s) and other personnel their responsibilities with regard to protocol adherence, and the responsibilities of BioCryst or its representatives. 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 monitors will review source documents to confirm that the data recorded on eCRFs are accurate. The investigator and institution will allow BioCryst representatives, monitors, or its designees direct access to source documents to perform this verification.

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

During the study, a monitor from BioCryst or representative will have regular contacts with the investigational site personnel, for the following:

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

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

15.2. Audits and Inspections

Authorized representatives of BioCryst, US FDA and other regulatory authorities, and/or ethics committees 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 will permit study-related audits mandated by the sponsor, after reasonable notice, and inspection by domestic or foreign regulatory authorities. 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.

15.3. Ethics Committee

Ethics approval for the investigation must be obtained prior to commencing the study. 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.

15.4. 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.

16. QUALITY CONTROL AND QUALITY ASSURANCE

During study conduct, BioCryst or its designee will conduct periodic monitoring visits to ensure that the protocol and GCP are being followed as described in Section 15.1.

To ensure compliance with GCP and all applicable regulatory requirements, BioCryst or its designee may conduct a quality assurance audit. Please see Section 15.2 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.

17. ETHICS

17.1. Ethics Review

The final study protocol, including the final version of the ICF, must be approved or given a favorable opinion in writing by an ethic committee, as appropriate. For the purposes of this protocol, “ethics committee” describes the applicable governing IRB, REB, or IEC. 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 all 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.

17.2. 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.

17.3. 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, as per local practice.

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.

18. DATA HANDLING AND RECORDKEEPING

18.1. Inspection of Records

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

18.2. Retention of Records

The 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 until at least 2 years after the last approval of a marketing application in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirement(s) or be an agreement with BioCryst.

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.

18.3. Confidentiality of Information and Data

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

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

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

19. PUBLICATION POLICY

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

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APPENDIX 1. STUDY INFORMATION

Protocol Number:	BCX9930-211
Study Title:	An Open-Label, Safety, Tolerability, and Proof-of-Concept Study of Oral BCX9930 Therapy in Subjects with Complement 3 Glomerulopathy, Immunoglobulin A Nephropathy, or Primary Membranous Nephropathy
EudraCT No.	2020-005855-19
Investigational Product:	BCX9930
Indications Studied:	Complement 3 Glomerulopathy (C3G), Immunoglobulin A Nephropathy (IgAN), Primary Membranous Nephropathy (PMN)
Sponsor:	BioCryst Pharmaceuticals, Inc. 4505 Emperor Boulevard, Suite 200 Durham, NC 27703, USA
Sponsor Medical Monitor:	[redacted] Phone: [redacted] ([redacted] for contact information for SAE reporting.)
Sponsor Clinical Study Manager:	[redacted]
Lead or Coordinating Investigator:	[redacted] University of Iowa Stead Family Children's Hospital, Iowa City, USA
Central Pathologist:	[redacted]
Compliance Statement:	This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and clinical research guidelines established by the Code of Federal Regulations (Title 21, CFR Parts 50, 56, and 312) and International Council for Harmonisation Guidelines. Essential study documents are currently archived in accordance with applicable regulations.
Final Protocol Date:	Version 4.0: 04 August 2022
Previous Version(s):	Version 3.0: 27 January 2022
	Version 2.1: 13 August 2021 (UK only)
	Version 2.0: 23 June 2021
	Version 1.0: 16 April 2021