BIOCRYST

PHARMACEUTICALS, INC.

GALIDESIVIR (BCX4430)

BCX4430-106/DMID 18-0013

IND NUMBER: 137,833

DMID FUNDING MECHANISM: CONTRACT NO.: HHSN272201300017C

A PHASE 1 DOUBLE-BLIND, PLACEBO-CONTROLLED, DOSE-RANGING STUDY TO EVALUATE THE SAFETY, TOLERABILITY, AND PHARMACOKINETICS OF GALIDESIVIR (BCX4430) ADMINISTERED AS SINGLE DOSES VIA INTRAVENOUS INFUSION IN HEALTHY SUBJECTS

Version 3.0: 11 Jan 2019

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CONFIDENTIAL

SIGNATURE PAGE

Sponsor's Approval

The protocol has been approved by BioCryst Pharmaceuticals, Inc.

Responsible Medical Officer:

15 JAN 2019

William Sheridan, MB BS
Senior Vice President, Chief Medical Officer
BioCryst Pharmaceuticals, Inc.

Date

Sponsor's Authorized Officer:

16 Jan 2019

Elliott Berger, PhD
Senior Vice President, Regulatory Affairs
BioCryst Pharmaceuticals, Inc.

Date

STATEMENT OF COMPLIANCE

The study will be carried out in accordance with Good Clinical Practice (GCP) and as required by the following:

- United States Code of Federal Regulations (CFR) 45 CFR Part 46: Protection of Human Subjects
- Food and Drug Administration (FDA) Regulations, as applicable: 21 CFR Part 50 (Protection of Human Subjects), 21 CFR Part 54 (Financial Disclosure by Clinical Investigators), 21 CFR Part 56 (Institutional Review Boards), 21 CFR Part 11, and 21 CFR Part 312 (Investigational New Drug Application), 21 CFR 812 (Investigational Device Exemptions)
- International Conference on Harmonisation: Good Clinical Practice (ICH E6); 62 Federal Register 25691 (1997); and future revisions
- Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, Report of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research
- National Institutes of Health (NIH) Office of Extramural Research, Research Involving Human Subjects, as applicable
- National Institute of Allergy and Infectious Diseases (NIAID) Clinical Terms of Award, as applicable
- Applicable Federal, State, and Local Regulations and Guidance

INVESTIGATOR'S AGREEMENT

I have received and read the Investigator's Brochure for galidesivir. I have read the BCX4430-106/DMID 18-0013 protocol and agree to conduct the study as outlined and will not make any changes to the protocol without obtaining the Sponsor's approval and IRB approval, except when necessary to protect the safety, rights, or welfare of subjects. I agree to maintain the confidentiality of all information received or developed regarding this protocol. I agree to conduct the study in compliance with GCP and applicable regulatory requirements.

DANIEL DICKERSON MD PHD

Printed Name of Investigator

Signature of Investigator

16 Jan 2019

Date

KEY ROLES

Table 1: Contact Information

Role in Study	Name	Address and Telephone Number
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Central Laboratory	Quest Laboratories	Quest Diagnostics 10101 Renner Blvd Lenexa, KS 66219
Bioanalytical Laboratory	Covance Laboratories	Covance Laboratories 3301 Kinsman Blvd Madison, WI 53704

1. SYNOPSIS

<table>
<tr><td colspan="3">Name of Sponsor/Company:
BioCryst Pharmaceuticals, Inc.</td></tr>
<tr><td colspan="3">Name of Investigational Product:
Galidesivir (BCX4430)</td></tr>
<tr><td colspan="3">Name of Active Ingredient:
(2S, 3S, 4R, 5R)-2-(4-amino-5H-pyrrolo[3,2-d]pyrimidin-7-yl)-5-(hydroxymethyl)pyrrolidine-3,4-diol dihydrochloride</td></tr>
<tr><td>Protocol Number:
BCX4430-106/DMID 18-0013</td><td>Phase: 1</td><td>Country: US</td></tr>
<tr><td colspan="3">Title of Study:
A Phase 1 double-blind, placebo-controlled, dose-ranging study to evaluate the safety, tolerability, and pharmacokinetics of galidesivir (BCX4430) administered as single doses via intravenous infusion in healthy subjects</td></tr>
<tr><td colspan="3">Study center: PRA Lenexa, Kansas</td></tr>
<tr><td colspan="3">Principal Investigator:
Investigators:</td></tr>
<tr><td colspan="2">Studied period (years):
Estimated date first subject enrolled: OCT 2018
Estimated date last subject completed: JAN 2019</td><td>Phase of development: 1</td></tr>
<tr><td colspan="3">Objectives:
Primary:
• To evaluate the safety and tolerability of single ascending doses (SAD) of galidesivir (BCX4430) administered by intravenous (IV) infusion in healthy subjects
Secondary:
• To characterize the plasma pharmacokinetic (PK) profile and urinary elimination of SAD of galidesivir administered by IV infusion in healthy subjects
Endpoints:
Primary:
• Safety and tolerability parameters including adverse events (AEs) and serious adverse events (SAEs), laboratory abnormalities, vital signs, electrocardiograms (ECGs), echocardiograms (ECHOs), cardiac telemetry, and physical examination (PE)
Secondary:
• Plasma and urine PK parameters for galidesivir
• Dose proportionality of galidesivir</td></tr>
<tr><td colspan="3">Methodology:</td></tr>
</table>

This SAD study will evaluate the safety, tolerability, and PK of single doses of galidesivir vs. placebo administered as IV infusions in healthy subjects enrolled in up to four dose cohorts of 8 subjects each. A single dose of study drug will be administered per cohort: 6 subjects will receive galidesivir IV, and 2 subjects will receive matching placebo.

The planned cohorts are as follows:

- Cohort 1, Regimen A: 5 mg/kg galidesivir or placebo, IV infusion × 1 dose
- Cohort 2, Regimen B: 10 mg/kg galidesivir or placebo, IV infusion × 1 dose
- Cohort 3, Regimen C: 15 mg/kg galidesivir or placebo, IV infusion × 1 dose
- Cohort 4, Regimen D: 20 mg/kg galidesivir or placebo, IV infusion × 1 dose

Study drug will be infused IV over 60 minutes at a maximum infusion rate of 8.33 mL/min.

As a safety precaution, on the first day of dosing in all cohorts, only 2 subjects will be dosed (to be referred to as sentinel subjects). The randomization schedule will be constructed such that 1 of the sentinel subjects dosed on the first day will be randomized to receive galidesivir and 1 will be randomized to receive placebo. After review of the safety data from the 24-hour post-dose period for the sentinel subjects, which includes review of any AEs, any abnormalities in the bedside ECGs, safety laboratory assessments and vital signs as described in Section 7.6.1, the remainder of the cohort (5 subjects randomized to galidesivir; 1 randomized to placebo) will be dosed at least 2 days after the sentinel subjects.

Following a 28-day screening period to determine eligibility, subjects in each cohort will be admitted to the Clinical Research Unit (CRU) on Day -1. Study eligibility will be confirmed upon admission to the CRU, and subjects will remain in the CRU overnight prior to dosing on Day 1. Following administration of study drug on Day 1, subjects will remain in the CRU for 96 hours to enable collection of PK samples and safety and tolerability data. Subjects will be discharged from the CRU on Day 5, 96 hours after the start of the infusion. Subjects will return to the CRU for a brief visit (approximately 1 to 2 hours) for PK sample collection on Day 6 (+ 1 day), Day 8 (+ 1 day), and Day 14 (± 1 day). Subjects will return to the CRU for a final follow-up visit on Day 21 (+ 2 days). In the event that there are any unresolved safety findings that are ongoing at Day 21, the subject will be followed at additional study visits until the findings are resolved or stabilized. If it is determined that the median half-life is longer than anticipated following IV infusion, or if after obtaining PK data through 96 hours, the area under the concentration-time curve (AUC) extrapolated to infinity (AUC_{inf}) estimate is > 25% of the AUC from time 0 to the last measurable concentration of drug (AUC_{last}), serial PK sampling may be extended beyond 96 hours in subsequent cohorts, or additional samples may be added in the intervening period between discharge from the CRU and the final follow-up visit at Day 21 (+2 days).

Safety and tolerability will be evaluated through assessments of AEs, laboratory analyses (clinical chemistry, hematology, coagulation, urinalysis, creatine kinase-MB [CK-MB], troponin), vital signs, ECGs, ECHOs, cardiac telemetry, and PE examination findings at the time points indicated in the schedule of assessments. PK parameters will be analyzed from the plasma and urine samples collected at the time points indicated in the schedule of assessments.

Dose Escalation Decision Process: Enrollment of subjects in each sequential higher dose level cohort will occur only after completion of a clinical safety review of laboratory, AE, vital sign, ECG (12-lead and telemetry), and PE data for all subjects up through 96 hours post-dose and plasma PK data through 24 hours post-dose, by the Sponsor medical monitor, clinical pharmacologist, and principal investigator (PI) at a dose escalation review meeting. Safety data summaries will be prepared by the PI; PK analyses will be performed by the clinical pharmacologist; and the dose escalation safety review summary and decision will be documented by the PI and clinical

pharmacologist. Based upon safety review and evaluation of the data for each subject, adjustments in the dose escalation scheme for the next cohort may be made, including omission of higher dose cohorts in the event that the safety and PK parameters have been adequately characterized with lower dose cohorts. Where considered appropriate to meet the study objectives, adjustments in the protocol-specified dose escalation for subsequent cohorts are permissible (i.e., an intermediate dose between the previous tolerable dose and the scheduled next higher dose). Dose escalation will be stopped if any one of the stopping criteria are met. The highest dose stated in the protocol will not be exceeded without a protocol amendment.

Criteria for stopping dose escalation for review of the PK and safety data:

- One or more subjects with a treatment-emergent QT interval corrected by Fridericia's formula (QTcF) > 480 ms (Grade 2 per the DMID scale) as determined from bedside ECGs (with repeat ECG). If this occurs, the SMC may consult with an independent cardiologist as needed. If it is deemed acceptable to restart the study following review of the data and discussion with an independent cardiologist, if needed, dosing may resume.
- One or more subjects experiences an increase in BP that requires acute treatment, or has a confirmed systolic BP > 160 mmHg, or a confirmed diastolic BP > 100 mmHg (Grade 3 per DMID scale). Confirmed BP changes require at least 2 measurements at least 2 hours apart, each measured after at least 5 minutes of supine rest.
- Anaphylactic reaction occurs in 1 subject.
- One or more subjects experience a similar Grade 3 treatment-emergent laboratory abnormality or AE that is suspected to be drug-related as determined by the investigator.
- One subject experiences an SAE.
- A cohort's median AUC from time 0 to 24 hours (AUC_{24}) is ≥ 52,500 ng.h/mL, equivalent to the NOAEL exposure in cynomolgus monkeys.

Sample Size Justification:

No formal power or sample size calculations were used to determine cohort sizes. Cohort sizes were based upon experience in other SAD Phase 1 studies. A sample size of 6 subjects receiving active drug per cohort should provide adequate characterization of PK and safety assessments within this setting.

Number of subjects (planned):

32 subjects, with 8 subjects enrolled per cohort (6 receiving galidesivir and 2 receiving placebo)

Criteria for inclusion:

1. Able to provide written, informed consent.
2. Males or non-pregnant, non-lactating females age 18–55 years.
3. Body mass index of 19.0 to 32.0 kg/m^2, inclusive
4. Weight ≥ 50 kg (110 lb.) and ≤ 100 kg (220 lb.)
5. Male and female subjects must agree to the contraception requirements and must meet the inclusion criteria regarding contraception as outlined in the protocol.
6. Has normal vital signs at screening visit at rest, after 10 minutes in a supine position:
   - Oral temperature < 38°C; no recent hot or cold beverages

- Resting heart rate is between 60–100 beats per minute (bpm). If a subject is a young healthy volunteer without cardiac disease or symptomatology, heart rate 45–59 bpm will be allowed.
- BP: systolic ≥ 90 mmHg and ≤ 140 mmHg, diastolic ≥ 40 mmHg and ≤ 90 mmHg
- Respiratory rate < 20 respirations per minute

7. Suitable veins for cannulation/multiple venipunctures as assessed by the investigator or designee at screening.
8. In the opinion of the investigator, the subject is able and willing to adequately comply with all required study procedures and restrictions for the duration of the study.

Criteria for exclusion:

1. Any clinically significant medical conditions or medical history 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*.

   *Note: Significant medical history would include, but not be limited to, kidney disease with creatinine clearance < 90 mL/min/1.73m^2, known active liver disease (including steatosis), ischemic heart disease, cardiac conduction disorder, chronic intestinal disease, hypertension (including treated), arrhythmia requiring treatment, diabetes requiring insulin, neuropathy, myopathy, and malignancy (not including squamous cell skin cancer, basal cell skin cancer, or cervical low-grade squamous intraepithelial lesions).

2. Any clinically significant psychiatric condition or history of psychiatric condition that, in the opinion of the Investigator or Sponsor, would interfere with the subject's ability to participate in the study or increase the risk of participation for that subject.
3. Abnormal ECG at the screening visit*.

   *Note: Abnormalities include but are not limited to, a QT_cF > 450 ms in men or >460 ms in women, a PR > 220 ms, or ventricular and/or atrial premature contractions that are more frequent than occasional, and/or as couplets or higher in grouping, second or third degree heart block, or long QT syndrome.

4. Clinically significant abnormalities found on the screening echocardiogram*.

   *Note: abnormalities include but are not limited to: ejection fraction < 55% or structural abnormalities such as valvular and septal defects. Incident mitral valve prolapse with none-to-trace regurgitation is not an exclusion.

5. Known family history of sudden death or long QT syndrome, or family or personal history of QT prolongation or poison/drug-induced arrhythmia that required medical intervention.
6. History of or current implanted defibrillator or pacemaker.
7. Any inclusion laboratory test performed at screening with an abnormal result that is DMID Grade 1 or greater. The inclusion tests are defined to be: alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, creatinine, urine protein, hemoglobin, serum potassium, and white blood cell count.
8. Any other screening laboratory test (other than the above stated inclusion tests) with an abnormal result that is DMID Grade 2 or higher.
9. Current participation in any other investigational drug study or participation in an investigational drug study within 30 days of the Screening visit, or 5.5 half-lives of the

investigational drug. Eligible subjects should not have more than 100 mL of blood withdrawn in an investigational study in the 30 days prior to participation in this study.

10. Subject use of prescription, over-the-counter medications, or herbal supplements*, is prohibited during the study.

    *Note: an exception is the use of any contraceptive medication allowed under this protocol and 2 g/day of acetaminophen, for a period of 7 days prior to and during the study. Over-the-counter medication including herbal products not otherwise excluded per Section 9.12 must be stopped 7 days prior to the study.

11. History of alcohol or drug abuse in the year prior to the screening visit, or current evidence of drug dependence*.

    *Note: A positive result for any drug listed in Table 8 on the urine drug screen is exclusionary.

12. Self-reported alcohol intake > 3 drinks/day or a positive alcohol test at screening.
13. A positive cotinine test
14. Positive serology for human immunodeficiency virus or active infection with hepatitis B virus or hepatitis C virus.
15. Pregnant, lactating, or has plans to become pregnant during the study or within 30 days of dosing.
16. Donation or loss of > 400 mL of blood in the 3 months prior to screening.
17. History of serious adverse reaction to or known serious hypersensitivity to any drug.
18. Presence or history of severe allergic reaction with generalized urticaria, angioedema, or anaphylaxis requiring treatment, as judged by the Investigator.
19. Employment by the study site, or an immediate family relationship to either study site employees or Sponsor employee.
20. Male subjects with pregnant female partners.

Investigational product, dosage and mode of administration:

Galidesivir for IV infusion: galidesivir is dissolved in Sterile Water for Injection United States Pharmacopeia (USP) with a pH adjusted to 3.0. For the 60-minute IV infusion the drug product will be further diluted in Lactated Ringer's (LR) solution (USP) to achieve a solution with pH of approximately 4.0 to 5.0.

Duration of treatment:

Single dose administration of galidesivir via a 60-minute infusion.

For each cohort, a subject's participation is anticipated to be approximately 7 weeks, including screening and the follow-up period.

Reference therapy, dosage and mode of administration:

Matched placebo for IV infusion to match active treatment. The placebo will be LR solution (USP).

Criteria for evaluation:

Safety: AEs, laboratory analyses (clinical chemistry, hematology, coagulation, urinalysis, CK-MB, troponin), vital signs, ECGs, ECHOs, cardiac telemetry, and physical examinations.

PK: Venous blood samples will be collected via an indwelling cannula or by venipuncture at regular intervals throughout the study. The plasma concentration data for galidesivir will be analyzed using non-compartmental techniques to obtain estimates of standard non-compartmental PK parameters, including: maximum concentration (C_{max}), last measurable concentration of drug (C_{last}), time to maximum concentration (T_{max}), AUC_{last}, AUC_{inf}, clearance (CL), volume of distribution (V_z), percentage of AUC extrapolated between AUC_{last} and AUC_{inf} (AUC_{extrap}), λ_z, and half-life ($t_{1/2}$), and other parameters, where appropriate.

Plasma Sampling:

Samples will be collected pre-dose, 30 min (halfway through the infusion), 1 h (end of the infusion), 1.25 h, 1.5 h, 2 h, 3 h, 4 h, 6 h, 8 h, 10 h, 12 h,16 h, 24 h, 36 h, 48 h, 60 h, 72 h, and 96 h following the start of the infusion. All sampling times are in relation to the start of the infusion.

After discharge from the CRU, subjects will return to the CRU for a brief visit (approximately 1-2 hours) for PK sample collection on Day 6 (+ 1 day), Day 8 (+ 1 day) and Day 14 (± 1 day). A PK sample will also be collected at the Day 21 (+ 2 days) follow-up visit or early termination visit (if applicable).

Urine Sampling:

Predose, 0–12 h, 12–24 h, 24–48 h, 48–72 h, 72–96 h.

Statistical methods:

Safety:

AEs will be mapped to a Medical Dictionary for Regulatory Activities (MedDRA) preferred term (PT) and system organ classification (SOC). Any event reported on the subject's study record that occurs on or after the initiation of study drug is defined as treatment emergent. Additionally, it is assumed that an AE that is reported to have started on Day 1 of a given treatment period without an associated onset time may have occurred after the initiation of study drug. Hence, AEs occurring on Day 1 with no associated onset time will be assumed to be treatment emergent. The occurrence of treatment-emergent AEs will be summarized by cohort and treatment assignment using MedDRA PT, SOC, and severity. Separate summaries of treatment-emergent SAEs and AEs considered to be related to study drug will be generated. All AEs will be listed for individual subjects showing both verbatim and preferred terms.

Descriptive summaries of vital signs, ECG parameters (12-lead and telemetry), ECHOs, and clinical laboratory results will be presented separately for each cohort by study visit and treatment assignment. Laboratory abnormalities will be graded according to the modified DMID criteria (2014) in APPENDIX A.

Physical examination results will be presented in listings.

Concomitant medications will be coded using the World Health Organization Dictionary. These data will be summarized by cohort and treatment assignment.

Pharmacokinetics:

Concentrations of galidesivir will be determined by validated plasma and urine assays and will be summarized by treatment and displayed in figures. Plasma PK parameters for each subject will be estimated over the sampling interval using noncompartmental analysis (Phoenix WinNonlin Version 7.0 or higher, Certara) and summarized by treatment group using descriptive statistics. The amount and percentage of galidesivir excreted in the urine will be assessed at all doses.

Dose proportionality will be evaluated over all doses and will be based upon AUC_{inf}, AUC from time 0 to time "t" (AUC_t), and C_{max} using both the power model and the analysis of variance method.

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3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

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

Table 2: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANOVA	Analysis of variance
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC_{24}	area under the concentration-time curve from time 0 to 24 hours
AUC_{inf}	area under the concentration-time curve extrapolated to infinity
AUC_t	area under the concentration-time curve from time 0 to time "t"
AUC_{tau}	area under the concentration-time curve from time 0 to the end of the dosing interval
BCX4430	galidesivir
BCX6870	triphosphate active drug anabolite of galidesivir
BMI	body mass index
BP	blood pressure
BQL	below the quantitation limit
CI	confidence interval
CK	creatine kinase
CK-MB	creatine kinase-MB fraction
C_{max}	maximum concentration
CRF	case report form
CRU	clinical research unit
CSR	clinical study report
CV	coefficient of variation
DEC	Dose Escalation Committee
DMID	Division of Microbiology and Infectious Diseases

Abbreviation or Specialist Term	Explanation
DSUR	development safety update report
EBOV	Ebola virus
ECG	electrocardiogram
ECHO	Echocardiogram
ECRF	electronic case report form
EF	ejection fraction
EVD	Ebola virus disease
FDA	US Food and Drug Administration
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GD	gestational day
GLP	Good Laboratory Practice
GLS	geometric least squares
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IM	intramuscular
IMP	investigational medicinal product
IMPD	investigational medicinal product dossier
IND	Investigational New Drug
IP	intraperitoneal
IRB	Institutional Review Board
ISM	Independent Safety Monitor
IV	intravenous
LR	Lactated Ringer's
MAD	multiple ascending dose
MARV	Marburg virus
MedDRA	Medical Dictionary for Regulatory Activities
MTD	maximum-tolerated dose

Abbreviation or Specialist Term	Explanation
MVD	Marburg virus disease
MVP	mitral valve prolapse
NGAL	neutrophil gelatinase-associated lipocalin
NHP	non-human primate
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
NOAEL	no observed adverse effect level
NZW	New Zealand White
pc	post-coitum
PE	physical examination
PI	principal investigator
PK	pharmacokinetic
QD	once daily
QTcF	QT interval corrected using Fridericia's method
RNA	ribonucleic acid
RSI	Reference Safety Information
SAD	single ascending dose
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard
SMC	Safety Monitoring Committee
SOC	system organ class
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
T_{max}	time to C_{max}
UACR	urine albumin to creatinine ratio
USP	United States Pharmacopeia

4. INTRODUCTION

4.1. Background

Marburg virus (MARV) belongs to the *Filoviradae* family of viruses. Diseases caused by filoviruses are among the most lethal of primate pathogens (Changula, Kajihara et al. 2014). MARV is the causative agent of Marburg Virus disease (MVD), which was first discovered in 1967 with a simultaneous outbreak in Marburg and Frankfurt, Germany and Belgrade, Serbia that was tied to use of nonhuman primates that were imported from Uganda. The natural host for the virus is thought to be fruit bats, with transmission to humans occurring from fruit bats, and then subsequent human-to-human transmission. Since that initial outbreak, outbreaks of MVD infections in humans have been sporadic and unpredictable, similar to outbreaks of other filovirus diseases. Mortality from MVD is high; case-fatality rates range from 23% to 88% (Kuhn, Dodd et al. 2011, CDC 2014, WHO 2017).

No specific treatments are currently available for filovirus diseases. In recent filovirus outbreaks, such as the Sudan Ebola virus disease (EVD) outbreak in 2014, both vaccines and direct antivirals have been investigated in clinical studies (Cross, Mire et al. 2018). After the outbreak, vaccines have been a focus for prevention of EVD, with several vaccines in development. Both medical countermeasures and vaccines that are effective against multiple filoviruses, are of interest for MVD.

Galidesivir (also referred to as BCX4430 in study titles, study reports and supporting documents) is an adenosine analog that inhibits viral ribonucleic acid (RNA)-dependent RNA polymerase activity, and is being developed by BioCryst Pharmaceuticals Inc. (BioCryst, the Sponsor of this study) as a direct-acting antiviral drug (Julander, Bantia et al. 2012, Warren, Wells et al. 2014). The drug is currently being developed as an intravenous (IV) formulation as a post-exposure prophylaxis and for the treatment of confirmed or suspected MVD.

4.2. Nonclinical Findings

The results of nonclinical pharmacology, pharmacokinetics (PK), and toxicology studies of galidesivir are described briefly below; details can be found in the Investigator's Brochure (IB). Nonclinical in vivo safety pharmacology and PK studies and in vitro safety pharmacology studies detailed in the IB support clinical studies with galidesivir as a parenterally administered antiviral drug.

4.2.1. Nonclinical Pharmacology

Galidesivir is a novel adenosine nucleoside analog, which inhibits viral RNA polymerase activity indirectly through non-obligate RNA chain termination. This mechanism involves anabolism of galidesivir to BCX4430 triphosphate (BCX6870). Galidesivir has broad-spectrum antiviral activity against bunyaviruses, arenaviruses, paramyxoviruses, picornaviruses, coronaviruses, and flaviviruses (Warren, Wells et al. 2014). In MARV-infected HeLa cells, galidesivir reduced production of intracellular MARV RNA, and reduced production of infectious virus (inhibitory concentration 90% value of 5.4 µM). Galidesivir decreased expression of MARV glycoprotein on the cell surface in virus-infected cells (effective concentration 50% values of 4.4, 6.7, and 5.0 µM for MARV Musoke, Ci67, and Angola variants, respectively) (Warren, Wells et al. 2014).

Galidesivir has been administered parenterally (intramuscular [IM], IV, or intraperitoneal [IP]) in multiple experiments conducted in nonclinical filovirus disease models. Reproducible evidence of efficacy was observed in the established mouse model that utilizes an Ebola Zaire Mayinga variant, adapted for pathogenicity in mice by serial passage (Bray, Davis et al. 1999, Warfield, Bradfute et al. 2009), with clear dose-related effects and statistically significant protection when dosing is delayed up to 96 hours post-infection. Similarly, galidesivir administration in nonclinical species infected with either mouse-adapted MARV (in mice), guinea pig-adapted MARV (in guinea pig), or wild-type MARV (in non-human primates [NHPs]) has shown reproducible evidence of efficacy. Statistically significant protection from mortality in experimental MVD models was observed when dosing was begun up to 48 hours post-infection in the NHP (Warren, Wells et al. 2014) and guinea pigs, and up to 96 hours post-infection in mice. Experiments in hamsters infected with the Jimenez variant of rodent-adapted yellow fever virus provide additional nonclinical evidence of efficacy of IP administered galidesivir in hemorrhagic fevers (Julander, Bantia et al. 2014).

4.2.2. Nonclinical Pharmacokinetics

The PK of galidesivir administered by IV bolus, IM injection, or oral gavage have been evaluated in several studies in mice, rats, guinea pigs, and non-human primates (NHP). A summary of the PK of galidesivir across species following IV bolus, IM injection, and oral administration can be found in the IB.

In summary, when galidesivir is administered by IV bolus and IM injection routes, PK profiles are very similar and exposures (maximum concentration [C_{max}] and area under the concentration-time curve [AUC]) are indistinguishable. After IV infusion over 30 min, C_{max} is lower compared to after IV bolus or IM injection. The PK profile in plasma in all species examined is characterized by a rapid distribution phase followed by a slow terminal clearance phase; the volume of distribution is high, indicating extensive tissue uptake. Exposure is approximately linearly proportional to dose. ^{14}C-Galidesivir is rapidly distributed, with a tissue distribution profile in the rat that is not different for IV bolus and IM injection. The highest concentrations of administered radioactivity were seen in the liver. Mean dose-adjusted exposure to BCX6870 in liver was approximately 30- to 200-fold higher than that of parent drug in plasma. Metabolism of galidesivir is insignificant with no metabolites over 2% of dose. Galidesivir is excreted in the urine in the rat and monkey.

4.2.3. Nonclinical Toxicology

The nonclinical safety and toxicological evaluation of galidesivir has been conducted in vitro and in vivo in both a rodent species (rat) and NHP species (Cynolomolgus macaque) to support administration of IV infusions (and IM injections) to humans. Full details of these studies can be found in the IB.

In vitro studies with galidesivir showed that galidesivir has a low concern for genotoxicity, is not toxic to mitochondrial function, did not inhibit human DNA polymerases, and has limited toxicity, compared with other antiviral compounds, on the proliferation of myeloid, erythroid and megakaryocyte progenitors, suggesting a low potential for bone marrow toxicity.

Secondary and safety pharmacology studies suggest that galidesivir has a low potential to lead to unwanted cellular toxicities or effects in key mammalian functions, such as respiratory, central

nervous system (CNS), or electrocardiology. Increases in blood pressure (BP) and heart rate were observed at IM doses greater than 10 mg/kg in nonclinical studies in conscious monkeys. In vitro, galidesivir is compatible with human blood and does not cause hemolysis at 15 mg/mL, the highest concentration tested. Animal safety studies performed to support the IV infusion route of administration have used galidesivir formulated in Lactated Ringer's (LR).

Toxicity studies of galidesivir in the cynomolgus monkey and rat used the IV infusion (30 minutes) and IM administration routes. The systemic toxicologic profile for each route is similar. The primary target organs of toxicity in the rat were the kidney and liver, with toxicities also observed in the spleen, testes, thymus, heart, hematopoietic system, and IM injection sites. Target organs of toxicity in the monkey were kidney, liver, lymphoid system, and IM injection sites. Toxicities in both species were dose related. Microscopic changes in liver and kidney were correlated to monitorable changes in relevant clinical chemistry analytes, and reversible.

4.3. Clinical Findings

One study is complete in human subjects with data available (BCX4430-101). A brief description of the study, as well as a general summary of the safety and PK is described below; details can be found in the BCX4430-101 Clinical Study Report (CSR) and the IB.

4.3.1. Study BCX4430-101

4.3.1.1. BCX4430-101: Study Design

Study BCX4430-101 was a 3-part, Phase 1, dose-ranging study of galidesivir administered by IM injection. In all parts of the study, safety and tolerability were evaluated through assessments of treatment-emergent adverse events (TEAEs), laboratory analyses (clinical chemistry, hematology, and urinalysis), vital signs, electrocardiograms (ECG; 12 lead and telemetry), echocardiograms (ECHOs), injection site assessments, and physical examinations (Pes). Subjects used a visual analog scale (VAS; 0–100 mm) to measure injection site pain following IM injection(s). In addition, study personnel performed clinical assessments at injection sites for erythema, pain, swelling, and tenderness.

For the evaluation of galidesivir plasma PK parameters, blood samples were collected at multiple time points during the study. Dose proportionality was evaluated (power model and analysis of variance [ANOVA]) following single (Part 1) and multiple (Part 3) ascending galidesivir doses. The effect of lidocaine on the PK of galidesivir was evaluated (geometric least squares [GLS] mean ratios and 90% confidence intervals [CI]) in Part 2. Additionally, dose accumulation was evaluated (ANOVA) in Part 3.

In Part 1, 6 ascending dose levels (0.3, 0.75, 1.8, 4.0, 7.0, and 10.0 mg/kg) were administered to separate cohorts of subjects in a double-blind, placebo-controlled fashion. Eight subjects received a single dose of study drug per cohort (6 subjects received galidesivir; 2 subjects received matching placebo). Subject dosing was staggered as a safety precaution.

In parallel with Part 1 Cohort 6, 14 subjects in Part 2 completed a 2-period crossover evaluation of the effect of lidocaine on IM injections of galidesivir. Subjects received 4.0 mg/kg galidesivir with and without 20 mg lidocaine administered IM. A summary of this part of the study, which is not relevant to IV infusion administration, can be found in the IB.

In Part 3, three ascending dose levels (2.5, 5.0, and 10.0 mg/kg) were administered to separate cohorts of subjects in a double-blind, placebo-controlled, sequential manner. Ten subjects received a 7-day course of study drug per dose cohort (8 subjects received galidesivir and 2 subjects received placebo). Lidocaine was administered with all IM injections in Part 3.

4.3.1.2. Study BCX4430-101: Pharmacokinetic Results

The plasma PK concentration-time profile of galidesivir at all doses was characterized by rapid absorption, an initial rapid distribution and clearance phase, and a slow terminal clearance phase. Time to maximum concentration (T_{max}) after IM administration of galidesivir was typically 15 minutes (the first PK sample was drawn at 5 minutes). PK results from Part 1 of the study are presented in Table 3. Following single doses, galidesivir C_{max}, AUC from time 0 to time "t" (AUC_t), and AUC extrapolated to infinity (AUC_{inf}) values increased in a slightly more than dose-proportional manner over the entire range of 0.3–10.0 mg/kg. The inter-subject variability in exposure (C_{max} and AUC) was low, as reflected in the geometric mean coefficients of variation (CVs) on these parameters.

The geometric mean (CV%) cumulative fraction of the dose appearing unchanged in the urine over 48 hours after single doses ranged from 23.7% (42.2%) to 34.3% (16.5%).

Table 3: Study BCX4430-101 Part 1: Summary of Select Plasma Pharmacokinetic Parameters Following Single Ascending Intramuscular Galidesivir Doses

PK Parameter	Galidesivir					
	0.3 mg/kg (N = 6)[a]	**0.75 mg/kg (N = 6)**	**1.8 mg/kg (N = 6)**	**4.0 mg/kg (N = 6)**	**7.0 mg/kg (N = 6)**	**10 mg/kg (N = 6)**
C_{max} (ng/mL)[a]	167 (30.5) n = 6	562 (37.0) n = 6	1000 (28.6) n = 6	2760 (31.2) n = 6	5760 (25.7) n = 6	7980 (30.6) n = 6
T_{max} (h)[b]	0.75 (0.25, 1.05) n = 6	0.25 (0.25, 0.50) n = 6	0.25 (0.08, 0.25) n = 6	0.25 (0.25, 0.50) n = 6	0.25 (0.25, 0.25) n = 6	0.375 (0.25, 0.50) n = 6
AUC_t (ng.h/mL)[a]	518 (18.6) n = 6	1340 (7.0) n = 6	3890 (8.0) n = 6	10100 (12.1) n = 6	18900 (12.0) n = 6	27100 (17.7) n = 6
AUC_{inf} (ng.h/mL)[a]	527 (9.9) n = 5[c,d]	1650 (11.3) n = 4[c,e]	4770 (6.4) n = 3[f]	11900 (8.7) n = 3[f]	24000 (13.7) n = 6	32900 (21.0) n = 4[e]
$t_{1/2}$ (h)[a]	4.44 (74.8) n = 5[c]	48.1 (44.8) n = 5[c]	81.4 (25.9) n = 6	85.4 (28.2) n = 6	77.9 (12.1) n = 6	73.2 (27.5) n = 6

Abbreviation: AUC_{inf} = area under the concentration-time curve extrapolated to infinity; AUC_t = area under the concentration-time curve from time 0 to time "t"; C_{max} = maximum concentration; CV = coefficient of variation; max = maximum; min = minimum; PK = pharmacokinetic; $t_{½}$ = half-life; T_{max} = time to C_{max}.

[a] Data reported as geometric mean (CV% of geometric mean)

[b] T_{max} reported as median (min, max)

[c] Data from 1 subject were excluded from summary statistics because R^2 was < 7

[d] Data from 1 subject were excluded from summary statistics because the extrapolated portion of AUC was ≥ 25%

[e] Data from 2 subjects were excluded from summary statistics because the extrapolated portion of AUC was ≥ 25%

[f] Data from 3 subjects were excluded from summary statistics because the extrapolated portion of AUC was ≥ 25%

Note: Study medication was administered IM.

PK parameters for Part 3 are presented in Table 4. On Days 1 and 7, over the multiple dose range of 2.5 to 10.0 mg/kg, AUC from time 0 to the end of the dosing interval (AUC_{tau}) demonstrated dose proportionality; the increase in C_{max} with dose was modestly greater than dose proportional with the power model and consistent with dose proportionality with the ANOVA model. Overall, there was an approximately 1.5-fold increase in exposure (AUC) with repeat dosing over 7 days. Assessment of trough concentrations of galidesivir suggested that steady state had not been achieved by Day 7.

Table 4: Study BCX4430-101 Part 3: Summary of Select Plasma Pharmacokinetic Parameters Following 7-Day, Multiple Ascending Intramuscular Galidesivir Regimens (Days 1 and 7)

PK Parameter	2.5 mg/kg Galidesivir N = 7		5.0 mg/kg Galidesivir N = 8		10.0 mg/kg Galidesivir N = 8	
	Day 1	Day 7	Day 1	Day 7	Day 1	Day 7
C_{max} (ng/mL)[a]	1820 (18.7) n = 7	2390 (39.0) n = 7	6840 (12.6) n = 8	6900 (17.4) n = 8	11400 (25.3) n = 8	17500 (83.3) n = 7
T_{max} (h)[b]	0.25 (0.08, 0.50) n = 7	0.25 (0.10, 0.52) n = 7	0.25 (0.25, 0.50) n = 8	0.25 (0.08, 0.25) n = 8	0.25 (0.25, 0.25) n = 8	0.25 (0.08, 0.50) n = 7
C_{tau} (ng/ mL)[a]	33.6 (23.9) n = 7	138 (19.1) n = 7	68.4 (15.9) n = 8	280 (17.8) n = 8	134 (15.7) n = 8	494 (16.6) n = 7
AUC_t (ng.h/mL)[a]	4830 (16.9) n = 7	15100 (16.1) n = 7	12100 (11.6) n = 8	32500 (11.5) n = 8	21600 (10.1) n = 8	62100 (13.9) n = 7
AUC_{tau} (ng.h/mL)[a]	4830 (17.0) n = 7	7620 (17.0) n = 7	12100 (11.6) n = 8	17600 (10.3) n = 8	21700 (10.1) n = 8	34500 (13.6) n = 7
$t_{1/2}$ (h)[a]	NR	104 (15.9) n = 7	NR	85.7 (17.3) n = 8	NR	113 (26.4) n = 7

Abbreviations: AUC_t = area under the concentration-time curve from time 0 to time "t"; AUC_{tau} = area under the concentration-time curve from time 0 to the end of the dosing interval; C_{max} = maximum concentration; C_{tau} = trough concentration; CV = coefficient of variation; max = maximum; min = minimum; IM = intramuscular; NR = not reported; PK = pharmacokinetic; QD once daily; $t_{½}$ = half-life; T_{max} = time to C_{max}.

[a] Data reported as geometric mean (CV% of geometric mean)

[b] T_{max} reported as median (min, max)

Note: Galidesivir was administered QD IM with 20 mg of lidocaine over 7 days. NR = not calculated due to 24 hours not being a reliable time frame from which to estimate half-life and any related parameters. Lambda-based calculations truncated at the dosing interval were not summarized for Day 1.

4.3.1.3. Study BCX4430-101: Safety and Tolerability

Galidesivir was generally safe and well tolerated following single (0.3 to 10.0 mg/kg) and repeat (2.5 to 10.0 mg/kg) IM dosing in healthy subjects. No safety signals were detected. No subject experienced a serious adverse event (SAE) or a Grade 3 TEAE. No TEAE led to study discontinuation in Parts 1 or 2 of the study. Although study drug dosing was discontinued in 1 subject (10.0 mg/kg galidesivir + 20 mg lidocaine) on Day 4 of Part 3 after the subject experienced nausea, vomiting, and abdominal pain, the Investigator made the decision to discontinue the subject due to an intercurrent illness (injection anxiety).

The primary TEAE reported by subjects randomized to galidesivir was injection site pain; injection site pain was reported more often by subjects receiving galidesivir without lidocaine (Part 1: 13 subjects [36.1%] and Part 2: 10 subjects [66.7%]) vs. subjects receiving galidesivir with lidocaine (Part 2: 2 subjects [12.5%] and Part 3: 5 subjects [21.7%]). Investigator-assessed erythema, swelling, pain, and tenderness were infrequently reported, with little or no evidence of a dose relationship.

A Grade 2 TEAE (injection site pain) definitely related to galidesivir was reported by 6 subjects randomized to 4.0 mg/kg galidesivir alone in Part 2. Two subjects experienced Grade 2 TEAEs possibly related to galidesivir: liver enzyme elevation (ALT, Part 2: 4.0 mg/kg galidesivir alone) and nausea, vomiting, and abdominal pain (Part 3: 10.0 mg/kg); the events resolved. As was expected with IM administration, Grade 2 and 3 treatment-emergent CK abnormalities were reported in all three parts of the study; however, these CK abnormalities were observed more often in subjects who received higher galidesivir doses administered without lidocaine. Four subjects from Part 1, Cohort 4 experienced Grade 2 or 3 elevations in potassium. A safety evaluation of the potassium elevations found the elevations not to be associated with clinical evidence of hyperkalemia; there were no ECG changes at time points that coincided with the elevated results, and the subjects were clinically well with no TEAEs at these time points. It was determined that the elevated potassium values were likely due to pseudohyperkalemia.

No clinically significant dose-related trends in laboratory values, vital signs, ECGs, or ECHOs were noted.

4.4. Rationale for Study

Galidesivir is being developed as a parenterally administered nucleoside analog antiviral drug designed to inhibit the activity of a range of viruses associated with high morbidity or mortality, including MARV by disrupting formation of viral RNA by virally-encoded RNA-dependend RNA polymerase enzyme (RdRp). Galidesivir shows concentration-dependent inhibition of viral replication in mammalian cell lines in vitro (Warren, Wells et al. 2014).

Study BCX4430-101, as described in Section 4.3.1, evaluated the exposure of galidesivir following single and multiple dose administration by IM injection. With the IM route of administration, in order to give doses over 10 mg/kg, subjects will have to be given more than 4 injections per day. The IV infusion route of administration will allow the administration of higher doses of galidesivir without numerous injections. This is important because the target population for this drug are patients with bleeding tendencies due to viral hemorrhagic fever.

This Phase 1 study will evaluate the exposure to galidesivir (plasma drug levels) achieved with a range of doses after administration by IV infusion over 60 minutes, will identify a safe dose range of galidesivir administered after a single dose, and will assist in evaluating the therapeutic window of galidesivir. Additionally, this study will provide information about exposure of galidesivir for future studies with multiple dose administration.

4.4.1. Study and Population

Healthy subjects have been selected to minimize variability in factors that may affect the safety, tolerability, and PK profile of galidesivir. In MVD outbreaks, both sexes are affected; therefore, both men and women will be enrolled in the study. It is considered imperative to characterize the safety and PK of galidesivir in women, including those of reproductive age, at this early stage

of development, and therefore considered acceptable to include women in this study, using the strict contraception requirements that are specified in Section 8.1. Both genders will be enrolled in the study.

Reproductive toxicology studies have been conducted (Section Section 4.2.3). Women of childbearing potential may be enrolled in this study if they meet the contraceptive and pregnancy test requirements listed in the inclusion and exclusion criteria.

4.4.2. Rationale for Route of Administration

In nonclinical experiments, galidesivir plasma exposures (AUC) after IM and IV bolus administration were very similar in mice, rats, and cynomolgus monkeys, with concentration-time profiles that were nearly superimposable comparing the two routes across species. Additionally, exposure following IV and IM administration was largely dose proportional in nonclinical species. Although both IM and IV administrations are theoretically feasible routes of administration for galidesivir, based on the effective dose in NHP models of filovirus diseases, the solubility profile of galidesivir requires that multiple daily IM injections would be needed for treatment of MVD and other viral hemorrhagic fevers. The IV route of administration may be more useful for outbreak situations, because it will require fewer needle sticks than multiple IM injections, thus helping to reduce the risk of needle-stick transmission of filovirus infection to health care providers. Therefore, the IV route of administration is being explored in this study.

4.4.3. Rationale for Study Doses

The initial dose levels for galidesivir in this study were selected on the basis of the PK and safety data from Study BCX4430-101 together with target exposures effective in animal models of MVD. The PK of galidesivir was well characterized in Study BCX4430-101 after both single and multiple ascending doses; this enabled the dose selection for this study to be made on the basis of simulated efficacious exposures in models of MVD and other filovirus infections. The simulations of MVD model efficacious exposures were based on pharmacokinetic studies in cynomolgus macaques and corresponding effective doses in the same species in a model of MVD. Simulations of human exposure after IV infusion administration have suggested that exposure will be similar to the observed following the IM administration of galidesivir. The 5 mg/kg dose selected as the starting dose for this study is anticipated to have a C_{max} of approximately 3000 ng/mL and an AUC from time 0 to 24 hours (AUC_{24}) of approximately 10,000 ng.h/mL. The proposed maximum dose for this study, a single dose of 20 mg/kg, is also supported by the nonclinical safety and TK data for IV administration in monkeys and rats, with a no adverse effect level (NOAEL) in monkeys of 30 mg/kg/day with an associated AUC_{24} of 52,500 ng.h/mL; the expected human exposure at a 20 mg/kg dose is approximately 47,000 ng.h/mL.

All planned proposed doses for the study are in Section 7.1. The choice of higher doses to be studied may be modified depending on emerging PK results from the lower dose cohorts.

4.5. Benefit-Risk Analysis

Galidesivir is a parenterally available small molecule nucleoside analog inhibitor of viral RNA polymerase activity, mediated through non-obligate RNA chain termination. Nucleoside analogs

have a proven mode of action in the treatment of multiple human viral infections. As a class, some nucleoside analogs have been associated with serious adverse reactions, including peripheral neuropathy, myopathy, pancreatitis, and lactic acidosis with hepatic steatosis, resulting from mitochondrial toxicity following chronic dosing (Lund, Peterson et al. 2007). There is no evidence in the literature of acute severe adverse reactions resulting from treatment with nucleoside analogs following single doses or up to 1 week of dosing.

- Toxicity studies in the cynomolgus monkey and rat have been conducted with IV infusion administration. Although C_{max} and AUC are lower following IV infusion compared with IM injection, no new findings have been identified from IV infusion toxicology studies. Therefore, the IM studies provide useful toxicological information to develop appropriate monitoring in an IV study.
- Toxicology studies in rats and monkeys summarized in the IB suggest that the primary target organs of galidesivir toxicity following IM administration in the rat were the kidney and liver, with toxicities also observed in the spleen, testes, thymus, heart, hematopoietic system, and injection sites. Target organs of systemic toxicity in the monkey were kidney, liver, lymphoid system, and injection sites. The principal target organ of systemic toxicity in rats and monkeys following IV infusion was the kidneys (Section 4.2.3). Microscopic changes in liver and kidney correlated to monitorable changes in relevant clinical chemistry analytes and were reversible. The large intestine was also a target in rats at the highest dose examined; minimal-to-mild single cell necrosis/degeneration in the cecum (with colon and rectum less frequently affected), with or without concurrent mucosa crypt epithelium hyperplasia/hypertrophy and/or mucosa inflammation. Galidesivir is compatible with human blood and does not cause hemolysis at concentration up to and including 15 mg/mL.
- Clinical chemistry monitoring will be conducted as part of the safety assessments in this study and will include neutrophil gelatinase-associated lipocalin (NGAL), a novel marker for tubular injury, and cystatin C, a biomarker of renal function. The lymphoid system is monitorable via routine blood counts. Testosterone levels will be monitored in male subjects. Although the risk of cardiomyopathy is not clear from animal studies, this study will use laboratory (creatine kinase MB fraction [CK-MB], troponin I), ECG (both 12-lead and telemetry), and radiographic (ie, ECHOs) methods to assess and monitor cardiac health.
- Secondary and safety pharmacology studies summarized in the IB suggest that galidesivir has a low potential to lead to unwanted cellular toxicities or effects in key mammalian functions, such as respiratory, central nervous system, or electrocardiology. Increases in BP and heart rate were observed at IM doses > 10 mg/kg in nonclinical studies in conscious monkeys. Subjects with hypertension will be excluded from the study, and subjects who are enrolled will be monitored for vital signs in addition to the assessments of cardiac health mentioned above.

Given the above considerations, there appears to be a relatively low risk of severe adverse reactions resulting from single dose administration of galidesivir. All cohorts will rely upon the use of sentinel dosing (1 subject receives active drug and 1 subject receives placebo until the

acute safety profile of the investigational drug can be defined). Appropriate safety monitoring for observed nonclinical safety risks will be employed.

4.5.1. Risks/Safety Signals Observed in the First-in-Human Intramuscular Injection Study with Galidesivir

In Study BCX4430-101, healthy volunteers received IM injections of galidesivir, with 6 single ascending dose (SAD) cohorts ranging from 0.3 to 10 mg/kg, and 4 multiple ascending dose (MAD) cohorts (2.5, 4.0 and 10 mg/kg once daily [QD] x 7 days). Subjects received one to four injections, depending on dose.

- In the SAD cohorts, none of the nonclinical toxicology safety risks were confirmed as clinical safety signals.
- The most common adverse events (AEs) were injection site pain (13/48 subjects [27.1%]), headache (8/48 [16.7%]), and presyncope (3/48 [6.3%]). No other AEs were reported in more than a single subject.
- No significant laboratory abnormalities were noted, although there were several instances of pseudohyperkalemia. These elevated potassium levels were not confirmed upon retest and had no associated symptoms or ECG changes and were determined to be laboratory artifact.
- There were no changes in cardiac enzymes, ECGs, or ECHOs.

The second part of the study evaluated lidocaine co-administration with galidesivir IM injections.

- In the lidocaine 4.0 mg/kg BCX4430 single dose cohort, none of the nonclinical toxicology safety risks were confirmed as clinical safety signals.

In the MAD portion of the study, subjects received 2.5, 5.0 and 10.0 mg/kg of galidesivir along with 20 mg lidocaine in each injection intramuscularly for 7 days. Subjects received 1 to 4 injections daily in order to deliver the complete dose.

- In the MAD cohorts, none of the nonclinical toxicology safety risks were confirmed as clinical safety signals.
- The most common AEs were injection site pain (5 subjects [17.2%]), injection site discomfort (2 [6.9%]), injection site reaction (2 [6.9%]), vessel puncture site bruise (2 [6.9%]), and headache (3 [10.3%]). No other AEs were reported in more than a single subject.
- No significant laboratory abnormalities were noted other than CK elevations consistent with multiple IM injections. In a few subjects, the elevated CK was accompanied by mildly elevated CK-MB without any evidence of cardiac injury, and mildly elevated aspartate aminotransferase (AST), also consistent with IM injections. Also noted were subjects in all 3 MAD cohorts with activated partial thromboplastin time (aPTT) and prothrombin time abnormalities. In Cohort 3, 1 subject had Grade 3, 6 subjects had Grade 2, and 1 subject had Grade 1 aPTT abnormalities. In 4 of 8 subjects, the prothrombin time was also abnormal. In most cases there was no international normalized ratio abnormality and no subject had any clinical symptoms

or bleeding. These results were considered not clinically significant and the cause was considered to be laboratory artifact.

Overall, no safety risks were identified during the Phase 1 study with galidesivir IM injection other than injection site pain, which will not be a concern during IV administration of galidesivir. Given the lack of any injection site changes, such as significant erythema, edema, nodules, necrosis, after IM injection, extravasation of galidesivir infused IV is unlikely to cause injury; however, infusion sites will be closely monitored.

4.5.2. Risks of Potential Adverse Events with Study-Mandated Procedures

Blood will be drawn from study participants for safety and PK assessments, which imparts a small risk of venipuncture injury, infection, and hypotension. To reduce the risk of anemia, < 500 mL of blood will be drawn from any subject during the study (screening through last scheduled follow-up visit), and anemic subjects will not be allowed to enroll in the study or continue participation if they become anemic during the study. The total blood collected for this study for both PK and safety laboratory assessments will be approximately 300 mL.

Venipuncture may cause transient discomfort and may result in fainting. Fainting is usually transient and managed by having the subject lie down and elevate his/her legs. Bruising at the site of the venipuncture may occur but may be prevented or lessened by applying pressure to the site for several minutes. Venipuncture may also cause infection. The use of aseptic (sterile) technique will make infection at the site where blood will be drawn extremely unlikely.

4.5.3. Risks Associated with Infusions

Galidesivir at a concentration of 100 mg/mL will be diluted to a maximum concentration of 5 mg/mL using an LR solution. IV doses of galidesivir will be infused over 60 minutes via an IV catheter at a maximum rate of 8.33 mL/min. Nonclinical local tolerability studies in the rabbit showed that intra-arterial injection of 30 mg/kg and perivascular injection of 7.5 mg/animal caused severe erythema with no microscopic correlate. In Study BCX4430-101, there were no injection site changes such as erythema, edema, nodules, necrosis, etc., after IM injection. Taken together, these findings indicate that it is unlikely that extravasation of galidesivir-infused IV would cause injury; however, infusion sites will be closely monitored.

The pH of the diluted drug in LR that will be infused will be approximately 4.0 to 5.0 (Alcami 2016), which should buffer to a physiologic pH rapidly, making peripheral veins appropriate for infusion. General risks associated with IV infusions include pain, bruising, phlebitis, thrombosis of the cannulated vein, and leaking IV fluid into the tissues near the injection. Careful inspection of the site, including visualization of blood return at the catheter site and an infusion time of 60 minutes (ie, maximum rate of 8.33 mL/minute), will minimize this risk. There is a risk of infection; however, this is a small risk as aseptic technique will be employed to reduce this risk.

4.5.4. Known Potential Benefits

Apart from receiving a medical assessment during the screening process, there is no benefit to the subjects from taking part in this study. The development of galidesivir may be of benefit to the broader population as a potential therapeutic medical countermeasure for the treatment of MVD and other filovirus infections.

5. STUDY OBJECTIVES AND PURPOSE

5.1. Primary Objective

- To evaluate the safety and tolerability of SAD of galidesivir administered by IV infusion in healthy subjects

5.2. Secondary Objectives

- To characterize the plasma PK profile and urinary elimination of SAD of galidesivir administered by IV infusion in healthy subjects

6. ENDPOINTS

6.1. Primary Endpoints

- Safety and tolerability parameters including AEs and SAEs, laboratory abnormalities, vital signs, ECGs, ECHOs, cardiac telemetry, and PE findings

6.2. Secondary Endpoints

- Plasma and urine PK parameters for galidesivir
- Dose proportionality of galidesivir

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

This SAD study will evaluate the safety, tolerability, and PK of single doses of galidesivir vs. placebo administered as IV infusions in healthy subjects in up to four dose cohorts. A single dose of study drug will be administered to 8 subjects per cohort: 6 subjects will receive galidesivir IV, and 2 subjects will receive matching placebo.

The planned cohorts are as follows:

- Cohort 1, Regimen A: 5 mg/kg galidesivir or placebo, IV infusion × 1 dose
- Cohort 2, Regimen B: 10 mg/kg galidesivir or placebo, IV infusion × 1 dose
- Cohort 3, Regimen C: 15 mg/kg galidesivir or placebo, IV infusion × 1 dose
- Cohort 4, Regimen D: 20 mg/kg galidesivir or placebo, IV infusion × 1 dose

Study drug will be infused IV via a calibrated infusion pump over 60 minutes at a maximum rate of 8.33 mL/min.

As a safety precaution, on the first day of dosing in all cohorts, only 2 subjects will be dosed (to be referred to as sentinel subjects). The randomization schedule will be constructed such that 1 of the sentinel subjects dosed on the first day will be randomized to receive galidesivir and 1 will be randomized to receive placebo. The remainder of the cohort (5 subjects receiving galidesivir:

1 receiving placebo) will be dosed at least 2 days after the sentinels, contingent upon satisfactory results from safety assessments of the sentinel subjects.

Following a screening period to determine eligibility, subjects in each cohort will be admitted to the clinical research unit (CRU) on Day -1. Study eligibility will be confirmed upon admission to the CRU, and subjects will remain in the CRU overnight prior to dosing on Day 1. Following administration of the study drug on Day 1, subjects will remain in the CRU for 96 hours to enable collection of PK samples and safety and tolerability data. Subjects will be discharged from the CRU on Day 5, 96 hours after the start of the infusion. Subjects will return to the CRU for PK samples on Day 6 (+1 day), Day 8 (+1 day), and Day 14 (± 1 day). Subjects will return to the CRU for a final follow-up visit on Day 21 (+ 2 days). The study design is shown in Figure 1.

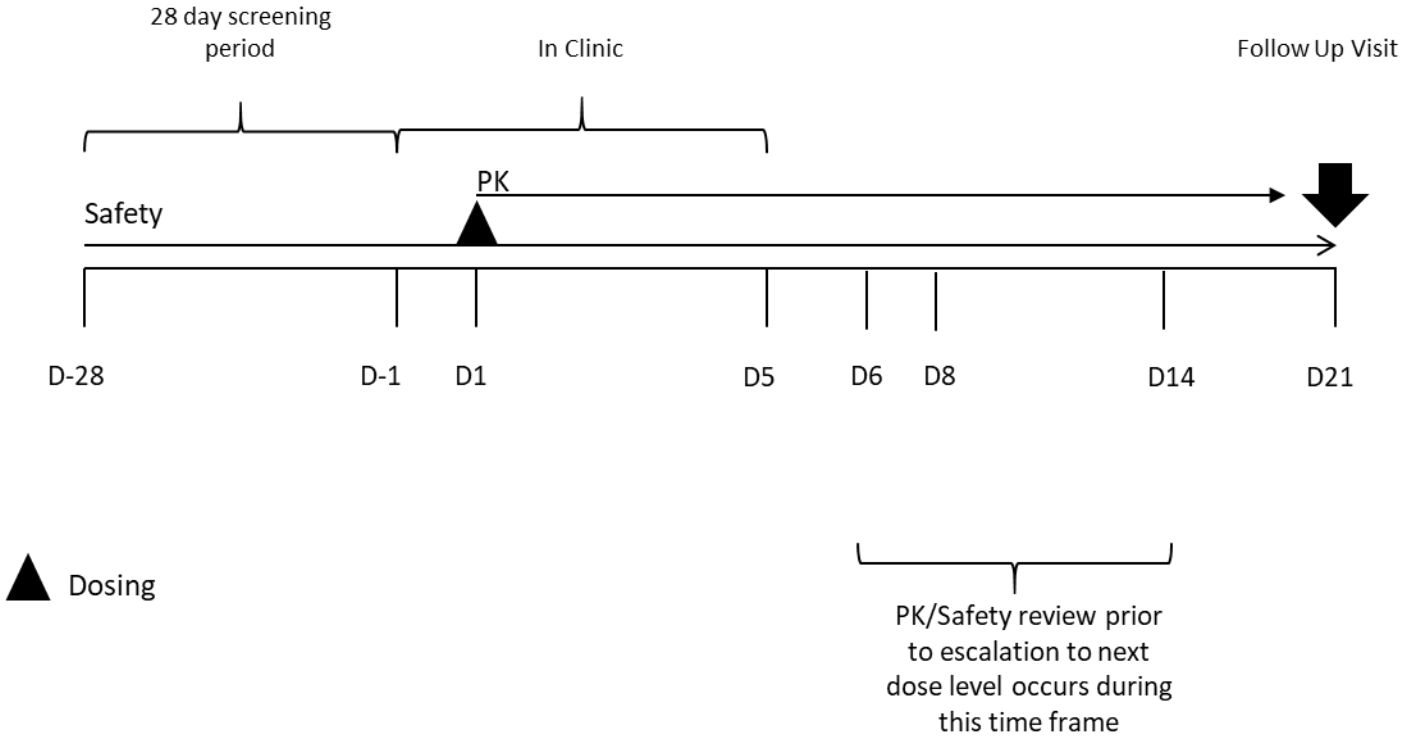
In the event that there are any unresolved safety findings that are ongoing at Day 21, the subject will be followed at additional study visits until the findings are resolved or stabilized. If it is determined that the median half-life is longer than anticipated following IV infusion, or if after obtaining PK data through 96 hours, the AUC_{inf} estimate is > 25% of the AUC from time 0 to the last measurable concentration of drug (AUC_{last}), serial PK sampling may be extended beyond 96 hours in subsequent cohorts, or additional samples may be added in the intervening period between discharge from the CRU and the final follow-up visit (Day 21).

Safety and tolerability will be evaluated through assessments of AEs, laboratory analyses (clinical chemistry, hematology, coagulation, urinalysis, CK-MB, troponin), vital signs, ECGs, ECHOs, cardiac telemetry, and PEs at the time points indicated in the schedule of assessments. PK parameters will be analyzed from the plasma and urine samples collected at the time points indicated in the schedule of assessments (Table 5).

Enrollment of subjects in each sequential higher dose level cohort will occur only after completion of a clinical safety review of laboratory, AE, vital sign, ECG (12-lead and telemetry), and PE data for all subjects up through 96 hours post-dose and plasma PK data through 24 hours, by the Sponsor medical monitor, clinical pharmacologist, and principal investigator (PI) at a dose escalation review meeting. Rules for halting the escalation to the next dose will be followed as defined in Section 7.6.3.2.

Safety and PK data for each cohort will be submitted to the US Food and Drug Administration (FDA) after each cohort is complete. Escalation to the next planned dose may proceed as long as the halting rules are not triggered as defined in Section 7.6.3.2.

Figure 1: BCX4430-106 Study Design



Abbreviations: D = day; PK = pharmacokinetic.

Table 5: Schedule of Assessments

Assessment	Screening	In Clinic (CRU) Study Period							Return to CRU for PK Sample	Follow-up or Early Termination Visit
	Day –28 to –2	Day –1 (Admission)	Day 1 Baseline (Pre-dose)	Day 1 (Post dose)	Day 2	Day 3	Day 4	Day 5 (Discharge	Day 6, Day 8, Day 14[n]	Day 21 + 2
Informed consent	X									
Inclusion/exclusion criteria	X	X								
Medical history	X	X								
Weight/height/BMI	X	X[a]								
Drugs of abuse screen/urine alcohol test/urine cotinine screen	X	X								
HIV/HCV/HBV serology	X									
Physical examination[b]	X	X	X	X	X	X	X	X		X
Concomitant medications	X	X	X	X	X	X	X	X	X	X
ECG	X[c]		X[c]	X[d]	X[d]	X[d]	X[d]	X[d]		X[d]
Cardiac telemetry			X[e]	X[e]						
ECHO[f]	X[f]						X[f]			

Assessment	Screening	In Clinic (CRU) Study Period							Return to CRU for PK Sample	Follow-up or Early Termination Visit
	Day –28 to –2	Day –1 (Admission)	Day 1 Baseline (Pre-dose)	Day 1 (Post dose)	Day 2	Day 3	Day 4	Day 5 (Discharge	Day 6, Day 8, Day 14[n]	Day 21 + 2
Vital signs	X	X	X[g]	X[g]	X[g]	X	X	X		X
Pregnancy test[h]	X	X								X
FSH[i]	X									
Clinical chemistry/ hematology	X	X[m]		X	X	X	X	X		X
Urinalysis	X	X[m]			X	X	X	X		X
aPTT/PT	X	X[m]						X		X
Testosterone[j]		X[m]						X		X
Troponin I		X[m]						X		X
CK-MB		X[m]						X		X
Cystatin C and NGAL		X[m]						X		X
UACR	X	X[m]						X		X
Plasma for galidesivir PK analysis[k]			X[k]	X[k]	X	X	X	X	X	X
Urine for galidesivir PK analysis[l]			X	X	X	X	X	X		
AE assessment		X	X	X	X	X	X	X	X	X
Study drug dosing				X						

Abbreviations: AE = adverse event; aPTT = activated partial thromboplastin time; BMI = body mass index; CK-MB = creatine kinase-MB; CRU = clinical research unit; ECG = electrocardiogram; ECHO = echocardiogram; FSH = follicle-stimulating hormone; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; NGAL = neutrophil gelatinase-associate lipocalin; PK = pharmacokinetic; PT = prothrombin time; UACR = urine albumin-to-creatinine ratio.

a. Weight only.
b. A physical examination consisting of the head and neck, skin, chest (lungs and heart), abdomen (gastrointestinal tract, liver, spleen and kidneys), back, musculoskeletal system, and neurologic system should be conducted at screening and on Day 5 prior to discharge. Breast and genitourinary system do not require examination unless the potential subject indicates a complaint or comorbidity that could result in exclusion. All other physical exams will be symptom directed. The site of infusion should be checked for any changes in skin.
c. Three (3) serial ECGs will be performed at screening and baseline 1–3 minutes apart. Pre-dose ECG should be collected within ≤ 2 hours of the first dose.
d. 12-lead ECGs will be conducted on Day 1 at 2 and 4 hours post dose (post start of the infusion) and on Day 2 at 24 hours post dose (post start of the infusion). An acceptable window is ± 10 minutes from the nominal time point. All subsequent ECGs are daily.
e. Cardiac telemetry will be initiated ≥ 2 hours prior to administration of the dose and will continue for 24 hours after the infusion is started. Subjects may be disconnected for bathroom, hygiene needs, and for 20-minute periods 3 times a day for meals. In addition, subjects may be disconnected for 10 minutes every 2 hours while awake for mild physical exercise such as walking or calf exercises.
f. The ECHO may be performed at any time from screening to Day -2 for eligibility determination. An ECHO should also be performed on Day 4. An acceptable window for the Day 4 ECHO is up until Day 5 discharge.
g. Vital signs (except temperature) will be obtained pre-dose (within 2 hours of dosing) 1, 2, 4, and 8 hours post dose (post start of the infusion) on Day 1, at 24 hours post dose on Day 2 and once per day where indicated. Oral temperature will be obtained at 8 hours post dose on Day 1 and at 24 hours post dose on Day 2. Subjects should be rested for 10 minutes in the supine position prior to vital sign measurements. All times are from the start of the infusion.
h. A serum pregnancy test will be administered at screening to all women; all other pregnancy tests performed during the study may be urine pregnancy tests.
i. An FSH level will be measured in women who report that they have been postmenopausal ≤ 2 years.
j. Free testosterone will be measured in male subjects.
k. Plasma for PK galidesivir analysis will be collected pre-dose, 30 min (halfway through the infusion), 1 h (end of the infusion), 1.25 h, 1.5 h, 2 h, 3 h, 4 h, 6 h, 8 h, 10 h, 12 h,16 h, 24 h, 36 h, 48 h, 60 h, 72 h, and 96 h following the start of the infusion. The pre-dose PK sample must be collected within ≤ 1 hour of the dose. Assessment windows around each PK draw will be ± 2 minutes for sampling times up to 2-hour post dose and from 2-hour post dose onward, ± 10 minutes while subject is confined in the unit. All sample times are from the start of the infusion.
l. For the analysis of urinary excretion of galidesivir, an aliquot of urine will be collected pre-dose (0 hour) and all urine will be collected for the following post dose intervals: 0–12 hours, 12–24 hours, 24–48 hours, 48–72 hours, and 72–96 hours. All sample times are from the start of the infusion.
m. Baseline for study post dose comparisons. NGAL, cystatin C, UACR, testosterone, troponin I, and CK-MB can be collected on Day -1 or Day 1 (pre-dose).
n. Subjects will return to the CRU to have a plasma PK sample collected on Day 6 (+1), Day 8 (+1), and Day 14 (±1). This visit is intended to be a short visit (approximately 1-2 hours) and can take place at any time during the specified window. A plasma PK sample will also be collected at the follow-up visit on Day 21.

7.2. Number of Subjects

It is planned that 32 subjects will be enrolled in the study, with 8 subjects enrolled per cohort. In each cohort, 6 subjects will receive galidesivir and 2 subjects will receive placebo.

Subjects may be replaced as noted in Section 8.5.

7.3. Treatment Assignment

Following confirmation of eligibility, subjects will be identified by a unique 5-digit subject identifier (eg, 11001) in which the first digit indicates the study site identifier, the second digit indicates the cohort number and the final 3 digits indicate the subject number. Any replacement subjects will be identified by replacing the third digit "0" with "9". For example, if Subject 11005 withdraws from the study early, the replacement subject will be numbered 11905 and will receive the same study treatment (ie, active or placebo) as Subject 11005.

Subject numbers will be as follows:

Cohort	Subject Numbers	Replacement Subject Numbers
1	11001 to 11008	11901 to 11908
2	12001 to 12008	12901 to 12908
3	13001 to 13008	13901 to 13908
4	14001 to 14008	14901 to 14908

7.4. Randomization Procedures

The randomization schedules will be generated by an unblinded study statistician. Masking procedures will be as outlined in Sections 7.5 and 9.6 and will be used to blind study drug.

A computer-generated randomization schedule will be used to randomly assign subjects to galidesivir or placebo. Subjects in each of the Cohorts 1 to 4 will be randomized to galidesivir or placebo in a 3:1 ratio (ie, 6 subjects per cohort will be randomly assigned to receive galidesivir and 2 subjects per cohort will be randomly assigned to receive placebo).

As a safety precaution, on the first day of dosing in all cohorts, 2 sentinel subjects will be initially dosed. The randomization schedule will be generated so that in each cohort 1 sentinel subject is randomly assigned to receive galidesivir and 1 is randomly assigned to receive placebo. Contingent upon satisfactory results as determined by the PI from safety assessments 24 hours post-dosing (e.g., AEs, ECGs, etc. as described in Section 7.6) of the sentinel subjects, the remainder of the cohort may be dosed at least 2 days later (with 5 subjects randomly assigned to receive galidesivir and 1 subject randomly assigned to receive placebo).

7.5. Masking Procedures

This is a double-blind study; treatment assignment within a cohort will be blinded to the PI, clinical staff, study subjects, and the data management team, with the exception of the unblinded

dosing team, if required. As described in Section 9.6, once infusion bags are prepared and labeled, the research pharmacist will mask the IV bag and tubing (ie, with the use of an overlay or masking tape) to blind the color of the solution in the IV bag and in the IV line.

An unblinded dosing team may be utilized in this study if required. Members of the unblinded dosing team will not be involved in any assessments on the study and will only be utilized for dose administration.

The PI or designee(s) will confirm subject eligibility. The unblinded pharmacist at the clinical site will receive a copy of the final randomization schedule from the unblinded statistician for preparation of the study drug. The laboratory performing bioanalytical analysis will also be provided this randomization scheme. The clinical pharmacologist will receive a copy of the randomization scheme to prepare interim PK summaries for dose escalation review meetings. The unblinded clinical pharmacologist will attend all dose escalation review meetings.

Prior to database lock and unblinding, all original randomization materials will be held by quality assurance personnel and blinded staff will not have access to the randomization schedule during this time. Disclosure envelopes are held in a locked cabinet in the clinical unit and will be used in the event of an emergency by the PI.

Access to study drug assignment will be immediately available if the PI deems it necessary to break the study blind in the interest of a subject's medical safety, in case of a medical emergency, to meet regulatory safety reporting obligations, or if warranted during scheduled safety reviews. The PI must contact the medical monitor within 24 hours following disclosure of study drug assignment.

Any request for information on the randomization schedule after initial issue must be made using a randomization disclosure form, except in the case of emergency unblinding, which must be recorded on the emergency unblinding form. Details of any disclosure of the randomization schedule will be documented and filed appropriately.

Breaking the blind for a single subject (or the 2 sentinel subjects) will not affect the blind for the remaining subjects; however, the site must appropriately document the process. Data may be unblinded, if required, for an interim review of PK and safety data.

7.6. Dose Escalation and Continuation Criteria

7.6.1. Criteria for Continuing to Dose Within a Cohort after Sentinel Subjects Have Been Dosed

In each cohort, 2 sentinel subjects will be dosed initially. The randomization schedule will be constructed such that 1 of the sentinel subjects dosed on the first day will be randomized to receive galidesivir and 1 will be randomized to receive placebo. After review of the safety data from the 24-hour post-dose period for the sentinel subjects, which includes review of any AEs, any abnormalities in the bedside ECGs, safety laboratory assessments and vital signs, the remainder of the cohort (5 subjects randomized to galidesivir; 1 randomized to placebo) will be dosed at least 2 days after the sentinel subjects.

7.6.2. Dose Escalation Criteria

As described in Section 11.5.2, at the completion of each cohort, the Dose Escalation Committee (DEC) will meet to review the safety and PK data from the cohort. Dose escalation to the subsequent cohort may proceed without consult with the Safety Monitoring Committee (SMC) as long as none of the following criteria are met:

- One or more subjects with a treatment-emergent QT interval corrected by Fridericia's formula (QTcF) > 480 ms (Grade 2 per the National Institutes of Health [NIH] Division of Microbiology and Infectious Diseases [DMID] scale) as determined from bedside ECGs (with repeat ECG). If this occurs, the SMC may consult with an independent cardiologist as needed. If it is deemed acceptable to restart the study following review of the data and discussion with an independent cardiologist, if needed, dosing may resume.
- One or more subjects experiences an increase in BP that requires acute treatment, or has a confirmed systolic BP > 160 mmHg, or a confirmed diastolic BP > 100 mmHg (Grade 3 per DMID scale). Confirmed BP changes require at least 2 measurements at least 2 hours apart, each measured after at least 5 minutes of supine rest.
- Anaphylactic reaction occurs in 1 subject.
- One or more subjects experience a similar Grade 3 treatment-emergent laboratory abnormality or AE that is suspected to be drug-related as determined by the Investigator.
- One subject experiences an SAE.
- A cohort's median AUC_{24} is ≥ 52,500 ng.h/mL, equivalent to the NOAEL exposure in cynomolgus monkeys.

If one of the above safety criteria are met, the SMC will be called to review the safety data from the study. The SMC may make one of two recommendations: to halt the study for further review, or to modify the planned dose escalation to the next dose level. Additionally, the dose escalation may be modified based on review of emerging PK data from any cohort, if needed, in order to refine the escalation to achieve exposure that will not exceed the NOAEL. This review of data may include modeling of planned doses to predict exposure from subsequent cohorts.

7.6.3. Study Drug and Study Halting Rules

7.6.3.1. Infusion Halting Rules

For any individual subject, an infusion must be stopped for the following non-drug related events: the IV line is lost, there is extravasation, or the IV pump malfunctions such that the dose cannot be given in a controlled manner. A 10-minute window is allowed for the infusion, in order to allow for infusion issues to be resolved.

For any individual subject, the infusion must be stopped for any suspected drug-related event such as hypersensitivity (Grade 1 or higher) during infusion.

For any individual subject, the infusion must be stopped for any suspected severe (Grade 3) or serious adverse event during infusion.

The reason for subject discontinuation from the infusion will be recorded in the source documents and electronic Case Report Form (eCRF). In all cases, subjects who discontinue study drug should remain in the study and have all protocol defined study safety assessments performed.

7.6.3.2. Study Halting Rules

Further dosing of other subjects in any cohort will be halted if any of the following criteria are met cumulatively across cohorts; dosing may not recommence unless recommended by the study SMC during the SMC review process:

- The death of a dosed subject for any reason.
- One galidesivir-treated subject experiences an SAE that is considered to be at least possibly related to study drug.
- Two or more subjects experience a Grade 3 AE in the same organ class (systemic toxicity, confirmed clinical laboratory tests, or vital signs) regardless of relatedness to study drug.
- An anaphylactic reaction occurs in 2 subjects.
- One or more subjects experience a confirmed Grade 3 QTcF (QTcF > 500 ms or QTcF increase > 60 ms), or two or more subjects cumulatively have experienced a Grade 2 change in QTcF (>480 msec). If following discussion with an independent cardiologist, it is deemed acceptable to restart the study, dosing will resume. All relevant data will be submitted to the regulatory authorities and Institutional Review Board (IRB).
- Two or more subjects experiences an increase in BP which requires acute treatment, or has a confirmed systolic BP > 160 mmHg, or a confirmed diastolic BP > 100 mmHg. Confirmed BP changes require at least two measurements at least 2 hours apart, each measured after at least 5 minutes of supine rest.

If, following review by the SMC (Section 11.5.3) it is deemed acceptable to restart the study, all relevant data will be submitted to the regulatory authorities and the IRB.

7.7. Criteria for Study Termination

BioCryst reserves the right to terminate the study prior to inclusion of the intended number of subjects but intends only to exercise this right for valid scientific or administrative reasons. Valid scientific reasons may include the development of unacceptable safety or PK findings that do not support continuation of the study. After such a decision, the PI must contact all ongoing subjects immediately after notification. As directed by BioCryst, all study materials must be collected and all (eCRFs completed to the greatest extent possible. Subjects enrolled at the time of study termination would continue to undergo all scheduled assessments as defined in Section 10.

After the start of protocol activities but prior to the commencement of dosing, the study may be terminated by the Sponsor or PI without consultation with the FDA and IRB. Notification of early termination should be provided to the FDA and IRB within 15 days, clearly explaining the reasons for the termination.

If the study is abandoned prior to commencement of any protocol activities, the PI or Sponsor must notify the FDA and IRB by letter outlining the reasons for abandonment of the study.

Once dosing has begun, the study will be completed as planned unless the following criteria are satisfied that require early termination of the study:

- Study halting rules are met and continuing the study would pose an unreasonable risk to subject safety.
- New information regarding the safety of the investigational medicinal product (IMP) that indicates an unreasonable risk for subjects participating in the study.
- Significant violation of Good Clinical Practice (GCP) that compromises the ability to achieve the primary study objectives or compromises subject safety.

If it becomes necessary to consider termination of the study after dosing has begun, dosing may be suspended pending discussion between the Sponsor and PI. Dosing may be suspended immediately on safety grounds.

The study may be terminated or suspended at the request of the FDA, SMC, National Institute of Allergy and Infectious Diseases (NIAID), or IRB.

8. SELECTION AND WITHDRAWAL OF SUBJECTS

8.1. Subject Inclusion Criteria

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

1. Able to provide written, informed consent.
2. Males and non-pregnant, non-lactating females aged 18–55 years.
3. BMI of 19.0 to 32.0 kg/m^2, inclusive.
4. Subject weight ≥ 50 kg (110 lb.) and ≤ 100 kg (220 lb.).
5. Contraception requirements:

   All female subjects must have a negative serum pregnancy test at screening and a negative urine test at Day -1 upon admission to the CRU. Female subjects must meet one of the following requirements:

   a. If the female subject is of childbearing potential, she must agree to practice abstinence, exclusively have female partners, or use acceptable contraception during the study and for 30 days after the infusion ends on Day 1.

      Note: a woman is considered of child bearing potential unless post-menopausal (without menses) for (> 2 years, postmenopausal for ≤ 2 years and has a follicle-stimulating hormone (FSH) >40 mIU/mL at the screening visit, or surgically sterilized via bilateral oophorectomy, or hysterectomy or bilateral tubal ligation or successful Essure placement with documented confirmation test at least 3 months after the procedure.

Note: Acceptable contraception methods are restricted to the following: an intrauterine device (IUD) or intrauterine system (IUS) (implanted any time prior to or during screening), any form of hormonal contraception, use of male or female condom with or without spermicidal foam/gel/film/cream/suppository, use of an occlusive cap (diaphragm, or cervical/vault caps) with spermicidal (foam/gel/film/cream/suppository), or monogamous relationship with a vasectomized partner.

b. If the female subject reports being postmenopausal for ≤ 2 years and has a FSH ≤ 40 mIU/mL at screening visit, she must agree to using acceptable contraception (as proposed above) during the study and for 30 days after the infusion ends on Day 1. Female subjects with a FSH > 40 mIU/mL and history of being postmenopausal ≤ 2 years will not be considered to be of childbearing potential.

Male subjects must comply with the following requirements through the study and for 90 days post dose:

a. If the male subject has female partners of childbearing potential, he must agree to not father a child by using at least one acceptable effective contraceptive method as defined above.
b. Male subjects who declare themselves as sexually abstinent or who exclusively have male partners do not have to comply with contraceptive requirements.
c. Male subjects will agree to not donate sperm for the purposes of reproduction during the study and for 90 days after the dose is administered

6. Has normal vital signs at screening visit at rest, after 10 minutes in the supine position:
   a. Oral temperature < 38°C; no recent hot or cold beverages
   b. Resting heart rate is between 60 and 100 bpm. If a subject is a young, healthy volunteer without cardiac disease or symptomatology, heart rate 45 to 59 bpm will be allowed.
   c. BP: systolic ≥ 90 mm Hg and ≤ 140 mm Hg; diastolic ≥ 40 mm Hg and ≤ 90 mm Hg.
   d. Respiratory rate < 20 respirations per minute
7. Suitable veins for cannulation/multiple venipunctures as assessed by the Investigator or designee at screening.
8. In the opinion of the Investigator, the subject is able and willing to adequately comply with all required study procedures and restrictions for the duration of the study.

8.2. Subject Exclusion Criteria

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

1. Any clinically significant medical conditions or medical history 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*.

*Note: Significant medical history would include, but not be limited to, kidney disease with creatinine clearance < 90 mL/min/1.73m^2, known active liver disease (including steatosis), ischemic heart disease, cardiac conduction disorder, chronic intestinal disease, hypertension (including treated), arrhythmia requiring treatment, diabetes requiring insulin, neuropathy, myopathy, and malignancy (not including squamous cell skin cancer, basal cell skin cancer, or cervical low-grade squamous intraepithelial lesions).

2. Any clinically significant psychiatric condition or history of psychiatric condition that, in the opinion of the Investigator or Sponsor, would interfere with the subject's ability to participate in the study or increase the risk of participation for that subject.
3. Abnormal ECG at the screening visit*.

   *Note: Abnormalities include, but are not limited to, a QTcF > 450 ms in men or > 460 ms in women, a PR > 220 ms, or ventricular and/or atrial premature contractions that are more frequent than occasional, and/or as couplets or higher in grouping, second or third degree heart block, or long QT syndrome.
4. Clinically significant abnormalities found on the screening echocardiogram*.

   *Note: Abnormalities include but are not limited to: ejection fraction (EF) <55% or structural abnormality including valvular and septal defects. Incident mitral valve prolapse (MVP) with none-to-trace regurgitation is not an exclusion.
5. Known family history of sudden death or long QT syndrome, or family or personal history of QT prolongation, or poison/drug induced arrhythmia that required medical intervention.
6. History of or current implanted defibrillator or pacemaker.
7. Any inclusion laboratory test performed at screening with an abnormal result that is DMID Grade 1 or greater. The inclusion tests are defined to be: alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, creatinine, urine protein, hemoglobin, serum potassium, and white blood cell count (Table 6).
8. Any other screening laboratory test (other than the above stated inclusion tests) with an abnormal result that is DMID Grade 2 or higher (Table 6).
9. Current participation in any other investigational drug study or participation in an investigational drug study within 30 days of the Screening visit, or 5.5 half-lives of the investigational drug. Eligible subjects should not have more than 100 mL of blood withdrawn in an investigational study in the 30 days prior to participation in this study.
10. Subject use of any prescription, over-the-counter medications, or herbal supplements* is prohibited during the study. Use of any of the medications specified in Section 9.12 are prohibited in the 30 days prior to the study.

    *Note: an exception is the use of any contraceptive medication allowed under the protocol and up to 2 g/day of acetaminophen for a period of 7 days prior to and during the study. Over-the-counter medications including herbal products not otherwise excluded per Section 9.12 must be stopped 7 days prior to the study.
11. History of drug abuse within the year prior to the screening visit, or current evidence of drug dependence.

    Note: A positive result for any drug listed in Table 8 on the drug screen is exclusionary.
12. Self-reported alcohol intake > 3 drinks/day or a positive alcohol test.
13. A positive cotinine test.

14. Positive serology for human immunodeficiency virus (HIV) or active infection with hepatitis B virus (HBV) or hepatitis C virus (HCV).
15. Pregnant, lactating, or planning to become pregnant during the study or within 30 days of dosing.
16. Donation or loss of > 400 mL of blood within the 3 months prior to screening.
17. History of severe adverse reaction to or known serious hypersensitivity to any drug.
18. Presence or history of severe allergic reaction with generalized urticaria, angioedema, or anaphylaxis requiring treatment, as judged by the Investigator.
19. Employment by the study site, or an immediate family relationship to either study site employees or Sponsor employees.
20. Male subjects with pregnant female partners

Table 6: Screening and Inclusion Laboratory Tests

DMID 2014* Grade ≥ 1 value is exclusionary[1]		**DMID 2014* Grade ≥ 2 value is exclusionary[1]**	
Chemistry	**Hematology**	**Chemistry**	**Hematology**
Alanine aminotransferase (ALT) Aspartate aminotransferase (AST) Bilirubin (total) Serum Potassium creatinine	Hemoglobin White blood cell count[2]	Albumin Amylase Blood glucose Blood urea nitrogen (BUN) Creatine Phosphokinase (CPK) Electrolytes (calcium, sodium, phosphorus) Total serum protein Alkaline phosphatase (ALP)	Eosinophils Lymphocytes Platelets
Urinalysis		**Urinalysis**	**Coagulation**
Protein on dipstick (1+ or higher is exclusionary)		Blood (microscopic)	Prothrombin time (PT) Activated partial thromboplastin time (aPTT)

[1] Laboratory values that are outside the range of eligibility but are thought to be due to an acute condition or due to laboratory error may be repeated once.
[2] Subjects who are of African (e.g., African American) or Middle Eastern descent may have a white blood cell count and/or an absolute neutrophil count that is in the DMID Grade 1 toxicity range and still be eligible for the study if all other study criteria are met.
*Modified DMID 2014 toxicity table

8.3. Additional Study Restrictions

Other protocol restrictions that will occur during their confinement in the CRU are listed below:

- Subjects will abstain from all bergamottin-containing fruits and fruit juices (e.g., Seville oranges, grapefruit, grapefruit juice, pomelos, pomegranate or pomegranate

juice, cranberry or cranberry juice, caffeine or other xanthine-containing foods and beverages from Day -1 until discharge from the CRU on Day 5, 96 hours post dose.

- Subjects should refrain from eating food containing poppy seeds for 2 days prior to Day -1 admission until discharge from the CRU on Day 5, 96 hours post dose.
- Subjects will abstain from alcohol consumption for 2 days prior to Day -1 admission through the follow-up visit on Day 21.
- Subjects will be asked to avoid strenuous exercise from 7 days prior to Day 1 through the last follow-up visit on Day 21.

Protocol restrictions should be reviewed at screening and Day -1 admission to the CRU.

8.4. Subject Withdrawal Criteria

8.4.1. Withdrawal from Study Drug and Study

Reasons for study drug withdrawal (ie, halting of the infusion) are described in Section 7.6.3.1.

Participation in the study is strictly voluntary. Subjects have the right to withdraw from the study at any time, including during the infusion, and for any reason. A subject's participation in the study will be terminated only for the following reasons:

- Subject request to discontinue his or her participation in the study for any reason
- Subject noncompliance, such as a significant protocol deviation
- Discontinuation at the request of the Sponsor, regulatory authority, or IRB

Subjects who withdraw or are withdrawn from the study who received any amount of the study product will be encouraged to continue follow-up (with subjects' consent) for safety. Subjects who withdraw will be asked to complete a final termination visit if they do not wish to be followed per protocol.

8.5. Replacement of Subjects

Replacement subjects may be enrolled as needed for the study to obtain the required number of evaluable subjects. An evaluable subject is defined as a subject who has sufficient PK samples collected to determine PK parameters through 24 hours post-dose and has sufficient safety data (including ECGs, ECHOs, vital signs, PE findings, and clinical lab data) through 24 hours post-dose to allow for the evaluation of the primary objective. At least 5 evaluable subjects who received galidesivir are required per cohort. Replacement subjects will be allowed if PK parameters (through 24 hours post-dose) cannot be determined due to a subject's early discontinuation from the study drug or study.

Subjects who have an IV infusion stopped for non-drug related issues, as described in Section 7.6.3.1, will not continue with dosing but will have all scheduled safety assessments made. These subjects may be replaced as needed. Subjects who have an IV infusion stopped for a safety related issued will not continue with dosing and will be followed as per Section 8.4.1. These subjects may be replaced if needed to fulfill the required number of evaluable subjects.

Subjects who withdraw due to a galidesivir-related AE will not be replaced. Subjects who withdraw for other reasons may be replaced at the discretion of the Investigator and Sponsor to ensure a sufficient number of evaluable subjects at the end of the clinical study.

Following the infusion, one subject per cohort may withdraw prior to the completion of Day 5 without being replaced. Should more than 1 subject from the same cohort who did not meet the above criteria voluntarily withdraw from the study, those subjects may be replaced.

In the event that a replacement subject withdraws, the subject will not be replaced.

9. TREATMENT OF SUBJECTS

9.1. Treatments Administered

Subjects will be administered a single dose of study drug or placebo per dose cohort as shown below:

Table 7: Dosing per Cohort

Cohort/ Regimen	Dose (mg/kg)	Calculated Dose Range[a] (mg)	Galidesivir Concentration[b]/Placebo	Galidesivir/ Placebo Dose Volume (mL)
1/ A	5	250-500	1.0 mg/mL or placebo	250–500
2/ B	10	500–1000	1.0–2.0 mg/mL or placebo	500
3/ C	15	750–1500	1.5–3.0 mg/mL or placebo	500
4/ D	20	1000–2000	2.0–4.0 mg/mL or placebo	500

[a] Based on inclusion criterion No. 4 in Section 8.1, subjects must weigh ≥ 50 kg (110 lb.) and ≤ 100 kg (220 lb.).
[b] Maximum concentration is 4 mg/mL. The lowest concentration of drug used in this study will be 1.0 mg/mL. Rate of infusion and volume infused will be adjusted as required for different concentrations, but the total length of the infusion will remain 60 minutes. Details on calculating infusion volume will be provided in a separate Pharmacy Manual.

Based on PK and safety data emerging from the cohorts, subsequent cohort doses may be modified. Modifications to the planned dose escalation schema may be implemented without modification of the protocol according to the halting/cohort modification rules described in Section 7.6.3. If more than 4 cohorts are required for the SAD, a protocol amendment will be implemented to enable enrollment of further cohorts

9.2. Description of Investigational Medicinal Product

Galidesivir for IV infusion is a sterile, nonpyrogenic solution with a concentration of 100 mg per 1 mL (100 mg/mL) and a pH adjusted to 3.0. The 100 mg/mL solution may appear clear to colorless to brownish. Excipients include Sterile Water for Injection USP/EP, Hydrochloric Acid NF/EP or Sodium Hydroxide NF/EP may be used for pH adjustment. Galidesivir for IV infusion is supplied by BioCryst in 2 mL single-use amber glass vials fitted with rubber stoppers and aluminum flip-off seals. Each 2-mL vial contains a fill volume of 1.2 mL.

The study drug, including IV lines will be masked, as described in Section 7.5 in order to maintain the study blind. Additional details can be found in the study-specific Pharmacy Manual.

Stability of diluted concentrations of galidesivir in 250 mL injection bags has been established for concentrations between 1 and 15 mg/mL. The IV solution is stored at room temperature (15˚C to 25˚C) for up to 24 hours as described in Section 9.5. The pH of the galidesivir solution in LR is between 4.0 and 5.0 (Alcami 2016).

Additional details for the chemical and physical characteristics of galidesivir may be found in the IB.

9.3. Description of Placebo

LR Solution for Injection, USP will be used as the placebo. The volume for infusion should match the volume used in the active treatment in the respective cohort.

LR solution will be provided by PRA Health Sciences.

9.4. Study Drug Packaging and Labeling

Study drug will be labeled with the following information:

- Sponsor name and contact information
- Study protocol number and name of PI
- Lot number
- Description of the contents of the container
- Route of administration
- Conditions for storage
- Statement regarding the investigational (clinical study) use of the drug, which will state “Caution: New Drug – Limited by Federal (United States) law to investigational use.”

9.5. Study Drug Storage

Galidesivir vials (100 mg/mL) are stored at 15˚C to 25˚C (59˚F to 77˚F).

Galidesivir in LR solution is stored at 15˚C to 25˚C (59˚F to 77˚F) for up to 24 hours.

LR solution (placebo) must be stored as per package insert (room temperature [25˚C]). Avoid excessive heat. Protect from freezing.

Study drug will be reconciled and destroyed (or returned) in accordance with the study monitoring plan.

9.6. Study Drug Preparation

Study drug preparation will be performed by a research pharmacist on the same day of study drug administration and must be prepared in a sterile environment (eg, biological safety cabinet or laminar flow hood) using aseptic technique.

Prior to opening the study drug vial, it should be gently mixed by inverting several times and inspected under a bright light to ensure there are no particulates in the vial. Using aseptic technique, an appropriately sized sterile needle and syringe must be used to draw the appropriate dose and volume of galidesivir or placebo. The syringe must not any individual vial more than once. The appropriate dose and volume of galidesivir or placebo will be added to the appropriate amount of LR solution in an infusion bag.

To maintain blinding, once prepared and labeled, the research pharmacist will mask the IV bag and tubing (ie, with the use of an overlay or masking tape) to blind the color of the solution in the IV bag. In addition, the calculated volume for the placebo must match the corresponding calculated volume for the active drug. Additional details can be found in the study-specific Pharmacy Manual.

9.7. Administration

Galidesivir or placebo in LR solution will be administered IV via a peripheral venous catheter inserted into the arm of the subject. Study drug will be infused over 60 minutes via programmable infusion pump. The maximum rate expected for infusion is 8.33 mL/min. The catheter will be maintained and replaced as per institutional policies at the CRU.

An unblinded dosing team may be utilized in this study if required in order to prevent any inadvertent unblinding of study drug while connecting the masked IV bags with the infusion pumps (eg, any drips of the dosing solution during connection of the bag to the infusion pump or a temporary need to remove part of the masking tape or overlay on the IV tubing to make the connection). Members of the unblinded dosing team will not be involved in any assessments on the study and will only be utilized for dose administration. The unblinded dosing team should ensure that the study drug product is blinded to the subject and rest of the study personnel.

In the event that an infusion must be stopped in the middle of dosing for a subject, the subject will not contribute to the PK population, and will be removed from further dosing but will continue to be followed for safety assessments per protocol (Section 7.6.3). If the infusion is stopped for a non-drug related issue such as pump failure, asymptomatic extravasation, then the subject may be replaced as needed.

A physician must be present at the time of study drug administration and present in the unit for a minimum of 4 hours after completion of the infusion.

9.8. Treatment Compliance

IV infusions of galidesivir or matching placebo in LR solution will be administered by the PI or qualified designee licensed to administer study medications. Compliance will be directly observed by study staff. Details of doses administered and dosing times will be recorded by study staff in the subject's source documentation/eCRF. Any episodes of incomplete study drug administration will be recorded.

9.9. Study Drug Accountability

The Investigator must maintain accurate records of the disposition of all study drugs received from the Sponsor, and directly administered to the subject on a drug accountability form (including date and time). The site PI may delegate to the site research pharmacist the responsibility for study product accountability. The site research pharmacist will be responsible for maintaining complete records and documentation of product receipt, accountability, dispensation, temperature and storage conditions, and final disposition of study product. Each investigational product will have a separate drug accountability form. At the end of the study, information describing study drug supplies (eg, lot numbers) and disposition of supplies must be provided, signed by the Investigator or designee, and collected by the study monitor.

9.10. Study Drug Handling and Disposal

At the end of the study, all medication that was not administered and used packaging materials will be returned to the Sponsor or destroyed on site as instructed by the Sponsor following IMP accountability by the study monitor and abiding by appropriate Standard Operating Procedure at the participating institution.

9.11. Concomitant Medications

Any medications used will be recorded in the source document and eCRF.

Emergency equipment and drugs will be available within the CRU as per current standard procedures. In the unlikely event that they are required, their use will be documented.

9.12. Prohibited Medications

Use of the following medications is prohibited 30 days prior to dosing through the Day 21 follow-up visit:

- Medications that are clinically known to induce or inhibit metabolic enzymes or transporters according to the FDA Drug Interaction Guidance (DHHS 2017).
  - A list of metabolic and transporter inducers and inhibitors can be found at: https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm
- Medications that are clinically known or suspected to prolong the QT interval
  - Medications falling into the category of drugs with a risk of torsades de pointes and drugs with a possible risk of torsades de pointes are listed at: https://crediblemeds.org/

Both lists will be provided to the study site by the Sponsor.

In addition, use of investigational agents is prohibited within 90 days of screening through the follow-up visit.

9.13. Food and Drink

Following check-in procedures on Day -1, subjects will be provided with appropriate meals and will fast from all food for approximately 8 hours overnight prior to the morning of Day 1, when subjects will receive a standardized light breakfast 1 hour prior to dosing (standardized means the same breakfast will be administered to all subjects in all cohorts). Water or another beverage will be allowed during the meal prior to dosing. Approximately 4 hours after dosing, a standardized lunch will be served. Dinner should be served approximately 9 hours after the start of dosing. Meals and snacks following dinner on Day 1 may be administered per routine clinic practice.

Water will be provided ad libitum up to 2 hours prior to and 2 hours post the start of dosing.

10. STUDY CONDUCT

10.1. Schedule of Assessments

The schedule of assessments in this study is summarized in Table 5 and described in more detail in Section 11.

Screening procedures are presented in Section 10.1.1. Study procedures are presented in Section Section 10.1.2 . Follow-up procedures conducted on Day 21 will be the same as any early termination visit procedures and are presented together in Section 10.1.3.

10.1.1. Screening

Prospective subjects should be screened within 28 days prior to Day 1. Written informed consent must be obtained from each subject before initiation of any screening assessments or procedures. Each subject will receive a copy of the signed and dated study-specific Informed Consent Form (ICF). Prospective subjects who have signed an ICF and who are interested in participation in the study will then undergo assessments at a screening visit to determine eligibility.

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

- Review inclusion and exclusion criteria for study eligibility
- Collect demographic data
- Review medical and medication history
- Height, weight, and BMI
- Drug screen, urine alcohol and urine cotinine test
- Blood collection for screening labs (see Table 6 for list of labs), HBV/HIV/HCV serology, FSH (for women who declare that they have been post-menopausal ≤ 2 years)
- Serum pregnancy test for all women
- Urinalysis
- Determine urine albumin to creatinine ratio (UACR)
- Vital signs (heart rate, BP, temperature)

- Physical examination including vein assessment
- 12-lead ECG
- ECHO (Note: ECHO may be performed at any time from screening to Day-2. The ECHO should be done after a subject is otherwise deemed eligible for the study. The ECHO is required to determine eligibility, so it must be conducted prior to Day -1 CRU check-in).

For height and weight measurements, subjects will be allowed to wear indoor clothing, without shoes.

Demographic data will include date of birth, sex, race and ethnicity.

All screening data must be obtained within 28 days prior to administration of study medication, as stipulated above.

Rescreening of ineligible subjects, where there is a reasonable expectation that the subject will become eligible, will be approved or denied on a case-by-case basis by the Investigator. In the case of rescreening, the Investigator may request all or a subset of the required assessments to be redone. Subjects may only be rescreened once and all assessments must be performed/drawn within the required screening window. If a subject is rescreened, the subject must be re-consented.

If a subject has completed all assessments for screening including the ECHO, but are not dosed as part of the cohort (ie, they are a backup subject), the subject may be eligible for a subsequent cohort. For any subsequent cohort that the subject screens for, the subject must complete all screening assessments within the appropriate 28-day window, with the exception of the ECHO, which does not need to be repeated. The ECHO from the original screening may be utilized for eligibility purposes. However if a subject failed screening based on the ECHO, they are not eligible to repeat screening in a later cohort in the hopes they will have a suitable ECHO.

10.1.2. Study Procedures

Subjects will check into the clinic on Day -1 and will remain in the clinic until discharge on Day 5, 96 hours post dose. Subjects will return to the clinic for brief (1 to 2 h duration) visits for PK sampling on Day 6, 8 and 14 and for a final follow-up visit on Day 21.

Subject identity will be confirmed at check-in.

Upon check-in on Day-1, subjects will have the following procedures conducted as outlined in Table 5:

- Review of inclusion and exclusion criteria and prohibited medications
- Medical and medication history
- Weight
- Drug screen, urine alcohol and urine cotinine test
- Urine pregnancy test for all women
- Safety laboratory assessments (clinical chemistry, aPTT/PT, hematology, coagulation)

- Blood drawn for testosterone, troponin I, CK-MB, NGAL, Cystatin C
- Urinalysis
- Determine UACR
- Vital signs (blood pressure and heart rate)
- Physical examination
- Review of AEs and concomitant medications

Note: Testosterone, troponin I, CK-MB, NGAL, Cystatin C samples can be collected on Day-1 or Day 1 prior to dosing; results are not required prior to dosing.

On Day 1, the following procedures will be performed as outlined in Table 5 prior to administration of galidesivir:

- Pre-dose urine and blood samples collected for analysis of galidesivir in urine and plasma
- 12-lead ECG pre-dose in triplicate
- Cardiac telemetry will be initiated at least 2 hours prior to infusion with telemetry data collected for 24 hours post dose
- Vital signs (BP, and heart rate)
- Physical examination
- Review of AEs and concomitant medications

Galidesivir or placebo infusion is administered over one hour with the following procedures performed:

- Blood samples collected for analysis of galidesivir concentrations at the timepoints described in Section 11.2.1
- Urine samples collected for analysis of galidesivir concentrations at the intervals described in Section 11.2.2
- Daily safety laboratory assessments (clinical chemistry and hematology)
- 12-lead ECG post dose at specified timepoints noted in Section Section 11.3.1.4
- Vital Signs (BP, oral temperature, and heart rate)
- Physical examination
- Review of AEs and concomitant medications

Subjects will be discharged on Day 5 96 hours post dose after all assessments and procedures are completed as denoted in Table 5.

Subjects will be asked to return to the clinic for brief visits for collection of PK samples on Days 6 (+1), 8(+1), and 14 (±1). The following procedures will be performed at those visits:

- Blood sample collected for analysis of galidesivir concentrations

- Review of AEs and concomitant medications. If any reported AEs require additional assessments (PE, vital signs, laboratory tests), the required assessments to evaluate the AE should be completed at these visits.

10.1.3. Follow-up/Early Termination Visit

Subjects will return to the clinic on Day 21 +2 for a follow-up visit. If a subject terminates from the study at any point prior to the scheduled follow-up visit, the assessments listed below should be performed at that time.

The following procedures will be performed at the follow-up visit:

- Safety laboratory assessments (clinical chemistry, aPTT/PT, hematology, coagulation)
- Blood drawn for testosterone, troponin I, CK-MB, NGAL, Cystatin C
- Urinalysis
- Determine UACR
- 12-lead ECG
- Vital Signs (blood pressure and heart rate)
- Physical examination
- Review of AEs and concomitant medications
- Blood sample collected for analysis of galidesivir concentrations
- Urine pregnancy test for all women

11. ASSESSMENTS

11.1. Investigator-Completed Assessments

Demographic information, including year of birth, sex, race or ethnicity, 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 and prohibited medications will also be rechecked as outlined in Table 5.

There are times where the protocol requires more than one procedure to be completed at the same time point. In these instances, the following will apply to post dose time points:

- PK samples will take precedence over other procedures and will therefore be collected at the nominal time. An exception to this is the collection of chemistry lab samples which should be collected in the order listed in Section 11.3.1.7.
- Vital signs will be recorded after the nominal time
- ECG recordings will be taken prior to the nominal time (prior to the PK sample)

The Investigator, or a qualified designee, should complete the assessments listed in the protocol.

11.2. Pharmacokinetic Assessments

11.2.1. Blood Sample Collection

Twenty-three blood samples for the measurement of plasma concentrations of galidesivir will be collected at the following time points:

- Pre-dose, halfway through the infusion (30 minutes), 1 hour (end of the infusion) 1.25, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36, 48, 60, 72, and 96 hours post dose.
- Day 6 (+1 day), Day 8 (+1 day), Day 14 (± 1 day)
- Day 21 (+ 2 days) or early termination

Subjects will have a cannula placed for administration of the infusion in one arm, and blood samples for PK will be collected from the other arm, either through direct venipuncture or an indwelling cannula. All cannulas placed will be maintained according to the policies of the unit while in use. All samples are timed from the start of the infusion.

The PK sample collection time points may be modified based on the concentration-time course found in the early cohorts. For subjects randomized to placebo, only the 5-minute post-infusion sample will be analyzed. The pre-dose PK sample must be collected within ≤ 1 hour of the dose. Within the first 2 hours post-dose, an acceptable window around each PK draw is ± 2 minutes. After 2 hours, an acceptable window is ± 10 minutes while the subject is in the unit. For the samples collected when the subjects return to the CRU post-discharge, the appropriate window is as noted above.

11.2.2. Urine Sample Collection

For the analysis of galidesivir, an aliquot of urine will be collected pre-dose (0 hour) and all urine will be collected for the following post-dose intervals: 0–12, 12–24, 24–48, 48–72, and 72–96 hours. A window of ± 30 minutes at the end of each interval is acceptable. For timing of the intervals, time 0 starts at the time of dosing. For the pre-dose sample collection, the urine sample should be collected within 2 hours prior to dosing.

The total volume of all urine collected during each time interval will be recorded in the source documentation/eCRF. For subjects who are randomized to placebo, no urine will be analyzed for galidesivir concentrations.

11.2.3. Sample Analysis

All plasma and urine determination of galidesivir will be analyzed using a validated liquid chromatography-tandem mass spectroscopy assay. Instructions for collection, processing, storage, and shipment of PK samples will be provided to the clinical site in a separate Clinical Sample Processing Manual.

11.3. Assessment of Safety

11.3.1. Safety Parameters

11.3.1.1. Vital Signs

Vital signs include measurements of heart rate, BP, and temperature. BP (systolic and diastolic), pulse rate, and temperature should be taken after the subject has rested in the supine position for at least 10 minutes. Respiratory rate is a required vital sign at Screening for eligibility and should be taken after the subject has rested in the supine position for at least 10 minutes. BP measurements must be obtained with an appropriate cuff size and with the subject's arm supported at the level of the heart. It is acceptable to obtain a pulse rate from the BP or ECG machine. Grade 2 or higher vitals will be repeated in 30 minutes if abnormal.

Pre-dose vital signs must be collected within 2 hours of the IV infusion. Post dose vital signs may be obtained within 10 minutes of the nominal time point. Any abnormality should be graded on a scale from 0 (none) to 3 (severe) using the modified 2014 DMID Adult Toxicity Grading Scale; APPENDIX A) and reported as an AE if appropriate as per Section 11.4.1.1. If the event is more severe than a Grade 3, severity criteria as described in Section 11.4.1.2 should be used to characterize the event.

11.3.1.2. Weight/Height/Body Mass Index

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

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

Weight/BMI will be collected at screening for eligibility determination. Weight will be collected on Day -1 in order to complete the dosing calculations.

11.3.1.3. Physical Examination

A PE consisting of the head and neck, skin, chest (lungs and heart), abdomen (gastrointestinal tract, liver, spleen and kidneys), back, musculo-skeletal system, neurologic system should be conducted at screening and at discharge from the unit. Breast and genitourinary system do not require examination unless the potential subject indicates a complaint or comorbidity that could result in exclusion.

All subsequent PEs may be symptom driven based on the subject's interim medical history.

11.3.1.4. 12-Lead Electrocardiogram

A standard bedside 12-lead ECG machine that calculates heart rate and measures the PR, QRS, QT, RR, and QTc (QTcF) intervals will be utilized. Prior to obtaining an ECG, subjects must rest quietly in a supine position for at least 10 minutes.

Qualified site personnel should review the ECGs and automated findings from the Day 1 pre-dose and post dose ECGs prior to the next day's dosing or scheduled assessments for gross abnormalities and interval measurements of concern (absolute readings and for post dose ECGs,

change from baseline). For all ECGs, the clinical interpretation of the ECG should be recorded directly on a hard copy of the ECGs. Copies of the ECGs may be requested by the Sponsor.

Screening and baseline (Day 1 pre-dose) ECGs will be obtained in triplicate at 1- to 5-minute intervals, with baseline values calculated from an average of the three readings. The pre-dose ECG should be collected within ≤ 2 hours of the first dose. Thereafter, single assessment ECG will be performed on Day 1 at 2 and 4 hours post dose, Day 2 at 24 hours post-dose and on Days 3 and 4 while the subject is in the CRU. An acceptable window is ± 10 minutes from the nominal time point while the subject is in the CRU. An ECG will also be performed at the Day 21 follow-up visit. All ECGs should be obtained per the schedule of assessments in Table 5.

An ECG should be repeated for a change from baseline in QTcF > 30 ms.

An ECG will also be performed if a Grade 3 electrolyte abnormality (such as hyperkalemia) is detected to determine if there are any ECG-related changes and/or arrhythmias. ECGs will also be performed if a subject reports any AE symptoms that are indicative of cardiac signs or symptoms.

11.3.1.5. Cardiac Telemetry

Standard cardiac telemetric monitoring will begin ≥ 2 hours prior to dosing. Telemetry will continue for 24 hours post-dose. Subjects may be disconnected from telemetry for 10-minute intervals every 2 hours while awake during which time they may engage in mild physical activity such as walking or calf exercises. In addition, they may be disconnected for bathroom visits and personal hygiene needs, as well as for three 20-minute periods for meals.

Telemetry will be monitored in real time by qualified personnel, with the assistance of alarms. If no abnormal rhythms are detected during the observation period, this will be recorded in the source documents along with the exact start and stop times of telemetric observation.

The telemetry monitors will be programmed to automatically create a printed tracing of any arrhythmia, including tachycardia of Grade 2 or higher (i.e., heart rate greater than 115 bpm). A rhythms tracing can also be manually printed if the staff notes a rhythm that requires evaluation but did not automatically print. The occurrence of an arrhythmia or tachycardia will trigger the evaluation of the subject. If the tracing is found to be due to artifact (ie, subject motion), the tracing will be noted to be 'not clinically significant' and will be documented in the source documents. The monitor will be programmed to alarm when an abnormal tracing is obtained. Any abnormality that is found to be clinically relevant will be documented in the source documents, recorded as an AE, graded per the modified 2014 DMID toxicity scale (APPENDIX A) and potentially trigger additional evaluations as deemed medically appropriate (eg, an ECG, pharmacologic treatment) by the PI.

11.3.1.6. Echocardiogram

ECHOs will be obtained per the schedule of assessments (Table 5). The ECHO may be performed at any time from screening to Day -2 for eligibility determination. An ECHO will also be performed on Day 4. An acceptable window for the Day 4 ECHO is up until Day 5 discharge.

The ECHO will be performed by trained cardiac sonographers who will provide a real-time assessment of EF and cardiac structure. Subjects must have an EF ≥ 55% and have no structural abnormalities other than incidental MVP with none-to-trace regurgitation. The screening and

subsequent ECHO images will be maintained until the subject has completed the study. Subsequent ECHOs will be performed in a similar manner by a trained sonographer. All ECHOs will be read by a cardiologist. Pre-dose ECHOs will be read prior to dosing. Any new abnormalities identified on post-baseline ECHOs confirmed by the cardiologist will be documented as AEs and graded as per severity grading scale provided in Section 11.4.1.1.

11.3.1.7. Clinical Laboratory Screening and Safety Assessments

Blood and urine samples will be obtained per the schedule of assessments (Table 5). Screening inclusion laboratory tests are listed on Table 6. A list of all laboratory tests that will be performed during the study are provided in Table 8. Laboratory assessments do not require fasting conditions. Acceptable windows for collection of blood samples for laboratory assessments are the same as for the PK samples. Urinalysis (post dose) has an acceptable window of ± 2 hours from the nominal time as designated in Table 5. Samples will be collected into appropriate tubes as specified by the clinical laboratory.

Study eligibility is partially determined by screening laboratory tests. Inclusion laboratory test results must be within acceptable eligibility range for all labs listed in Table 6 at Screening. For all clinical laboratory safety assessments, the laboratory results values obtained on Day -1 establish the baseline for chemistry, hematology, and coagulation laboratory safety results.

Results for Cystatin C, NGAL, and free testosterone (males only) do not need to be obtained prior to initiation of dosing. These tests will be used for baseline measurements for post-dose comparison for evaluation of renal and testicular health following administration of galidesivir.

At time points when multiple samples are taken, the samples will be taken in the following order to minimize the risk of K EDTA contamination of the biochemistry samples.

1. Coagulation
2. Biochemistry / testosterone
3. PK
4. Hematology

Laboratory values drawn after study drug dosing should be assessed within 12 hours of receipt by the PI or qualified designee. Safety laboratory assessments can be taken anytime post-dose on Days 1 to 5 to fit with the clinic and lab schedule. Results from safety laboratory assessments are not required for completing assessments on the following day. Any laboratory findings outside of the normal range should be documented and described in the source documentation. Results from baseline and on-treatment clinical chemistry, hematology, coagulation, and urinalysis tests will be provided to the Sponsor for real-time review.

Laboratory abnormalities outside of the normal laboratory reference ranges and associated grades (according to study specific DMID criteria (modified 2014 DMID Adult Toxicity Grading Scale) see APPENDIX A) should be denoted where possible. For those analyte results that are out of the normal range and do not have an established DMID toxicity criteria, the PI should assess the abnormalities and provide severity grading as defined in Section 11.4.1.2.

All laboratory samples will be analyzed by a local laboratory associated with the site. Reference ranges for each local laboratory will be provided to the Sponsor and included in data listings. For

out-of-range laboratory findings, the interpretation of clinically significant or not clinically significant should be denoted in the source records. Clinically significant laboratory findings in the opinion of the Investigator should be recorded as AEs and handled as described in Section 11.4. Laboratory abnormalities that are not deemed to be clinically significant by the Investigator are not reported as AEs. All laboratory findings will be summarized and reported with appropriate grading, regardless of whether or not they are reported as AEs.

Cystatin C, NGAL, testosterone, CK-MB, troponin and UACR will be analyzed as outlined in the Statistical Analysis Plan. Briefly, changes from baseline will be measured for each analyte. Values outside the normal limits, if applicable, will be graded based on fold changes in comparison to the upper or lower limit of normal. Marked changes in these analytes will be taken as potential indications of impaired organ function and qualitative interpretation will take into account subject incidence, clinical course, and comparison to placebo for the safety analyses in the final study report.

Table 8: Clinical Safety Laboratory Evaluations

Chemistry	**Hematology**
Albumin Alkaline phosphatase (ALP) # Alanine aminotransferase (ALT) # Aspartate aminotransferase (AST) # Bilirubin (total and direct) # Blood glucose Blood urea nitrogen (BUN) Electrolytes (calcium, sodium, potassium, chloride*, phosporous) Creatine Phosphokinase Creatinine and calculated creatinine clearance# Total serum protein Amylase with reflex lipase	Hemoglobin# Hematocrit* Erythrocytes* White blood cell count#, White blood cell count differential (lymphocytes, monocytes*, neutrophils, eosinophils, and basophils*) Platelets
Urinalysis	**Additional Laboratory Tests**
Bilirubin* Glucose Leukocytes* Ketones* Nitrites* pH* Protein# Urobilinogen* Presence of blood microscopy if dipstick is abnormal (at the discretion of the PI)	Prothrombin time (PT)/international normalized ratio (INR) Activated partial thromboplastin time (aPTT) Hepatitis B surface antigen, hepatitis C antibody, HIV type 1*# Total Testosterone (male subjects only)* Free Testosterone (male subjects only)* Troponin I* CK-MB Cystatin C* Urine Albumin-to-Creatinine ratio (UACR)* Neutrophil gelatinase-associate lipocalin (NGAL)*

*Analytes without established DMID toxicity criteria

#Analytes that are used for screening laboratory tests per Sections 8.1 and 8.2

11.3.1.7.1. Virus Serology

Serology tests for hepatitis B surface antigen, hepatitis C antibody and HIV type 1 will be conducted at Screening. Positive serology results are exclusionary; if subjects have a positive result, they will be informed in private and told about counseling, and positive lab results will be reported per state law.

11.3.1.7.2. Urine Drug Screen and Cotinine Test

A urine drug screen will be conducted at Screening and Day -1. A positive result for a drug of abuse is exclusionary. Tests for the following drugs will be included in the drug screen:

- Amphetamines
- Barbiturates
- Benzodiazepines
- Methamphetamine
- Ecstasy
- Phencyclidine
- Tricyclic antidepressants
- Opiates

Urine alcohol and cotinine tests will also be conducted at Screening and Day -1. A positive result for either test is also exclusionary.

11.3.1.7.3. Pregnancy Screen

A serum pregnancy test should be drawn at Screening for all female subjects, regardless of their contraceptive status or whether they practice abstinence. FSH will be measured at screening in women who declare themselves as postmenopausal for ≤ 2 years to establish childbearing status.

All other pregnancy tests performed during the study may be urine pregnancy tests. A serum pregnancy test should immediately be drawn and sent for analysis following any positive urine pregnancy test.

11.4. Adverse Events and Serious Adverse Events

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

11.4.1. Definition of Adverse Events

11.4.1.1. 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 laboratory findings that are not deemed clinically significant by the Investigator are not considered to be AEs.

This includes the following:

- AEs not previously observed in the subject that emerge during the protocol-specified AE reporting period (see Section 11.4).

- Findings from protocol-mandated interventions. This can include laboratory assessments performed during the clinical study. AEs should only be reported if the abnormalities are changes from baseline and are clinically significant as described above.
- Pre-existing medical conditions judged by the Investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period.

An adverse reaction is defined in Article 2(n) of Directive 2001/20/EC as follows: all untoward and unintended responses to a study drug/IMP related to any dose administered. The definition also covers medication errors and uses outside what is foreseen in the protocol, including misuse and abuse of the product. The definition implies a reasonable possibility of a causal relationship between the event and the study drug/IMP. This means that there are facts (evidence) or arguments to suggest a causal relationship.

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

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

11.4.1.2. Serious Adverse Event

An SAE is an AE occurring during any study phase (ie, baseline, treatment, washout, or follow-up), and at any dose of the investigational product, comparator or placebo, that fulfils one or more of the following:

- Results in death
- It is immediately life-threatening
- It requires inpatient hospitalization or prolongation of existing hospitalization
- It results in persistent or significant disability or incapacity or substantial disruption of the ability to conduct normal life functions
- Results in a congenital abnormality or birth defect
- It is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above.

Important medical events that may not result in death, are not life-threatening, or do not require hospitalization may be considered an 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.

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 event of overdose. 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 a protocol deviation.

Severity of Event: All AEs will be assessed (graded) for severity using the modified 2014 DMID Adult Toxicity Grading Scale (see APPENDIX A). Any AEs not covered by the DMID criteria will be assessed and classified into one of three clearly defined severity categories as follows:

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

Severity refers to the medical perspective of an event whereas seriousness reflects the outcome of the event (ie, hospitalization). Events of mild severity can lead to hospitalization and therefore be serious whereas severe events such as a headache may not meet seriousness criteria.

Changes in the severity of an AE should be documented to allow an assessment of the duration of the event at each level of intensity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

11.4.1.3. Adverse Events of Special Interest

No adverse events of special interest have been identified for galidesivir.

11.4.2. Relationship to Study Drug

The PI or medically qualified designee must review each AE and make the determination of relationship to study drug using the following guidelines. The Sponsor uses five categories of relatedness. The category of "Not Related" and "Likely Not Related" map to the DMID category of "Not Related", whereas the categories of "Possibly Related", "Probably Related" and "Definitely Related" map to the DMID category of "Related". The categories are described below:

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 and the event.
Likely Not 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 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 drug administration, abates upon discontinuation of the drug, 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 administration, follows a known or suspected response pattern to the study drug, is confirmed by improvement upon stopping the study drug (dechallenge), and reappears upon repeated exposure (rechallenge, if rechallenge is medically appropriate).

The clinician's assessment of an AE's relationship to study drug is part of the documentation process. All AEs whether or not deemed related to study drug require reporting. If there is any doubt as to whether a clinical observation is an AE, the event should be reported

11.4.3. Recording Adverse Events

AEs and SAEs will be assessed and recorded from the time of signing of the ICF through the appropriate follow-up period. AEs and SAEs will be followed to adequate resolution or stabilization to new baseline.

11.4.4. Reporting Adverse Events

Any SAE must be reported by phone in real time to the Sponsor Medical Monitor and in writing using the SAE report form within 24 hours of the PI's awareness of the SAE via email or fax (or both). In addition, all SAEs must be recorded on the AE eCRF in real time. All additional follow-up evaluations of the SAE must be reported to BioCryst or its designee as soon as they are available. The SAE report forms should be sent to the following email or fax number (or both):

Email: mmgalidesivir@biocryst.com AND safety@biocryst.com

Fax: +1 919 226-5888

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 PI 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 unreasonable risk profile of the study drug in clinical study, if the relevant information was not already available and provided in the initial report.

BioCryst will in turn do the following in real time:

Contact the DMID medical monitor

Submit the SAE to:

DMID Pharmacovigilance Group (PVG), Clinical Research Operations and Management Support (CROMS), 6500 Rock Spring Dr. Suite 650, Bethesda, MD 20817, USA

SAE Hot Line: 1-800-537-9979 (U.S.) or 1-301-897-1709 (outside U.S.)

SAE FAX Phone Number: 1-800-275-7619 (U.S.) or 1-301-897-1710 (outside U.S.)

SAE Email Address: PVG@dmidcroms.com

The DMID Clinical Project Manager and DMID Medical Monitor will be notified of the SAE by the DMID PVG. The DMID Medical Monitor will review and assess the SAE for potential impact on study subject safety and protocol conduct.

The Independent Safety Monitor (ISM) will be contacted by the PI in real time, and will then assess the event and the subject (see Section 11.5.1).

The Sponsor is responsible for determining regulatory reporting requirements and will provide the PI with reports of suspected unexpected serious adverse reactions (SUSARs). The CRU is responsible for submitting any SUSAR or Investigational New Drug (IND) safety report (initial and follow-up) or other safety information (eg, revised IB) to the IRB and for retaining a copy in its files, unless otherwise instructed.

11.4.5. Regulatory Reporting

A SUSAR is an unexpected serious AE of which the nature or severity is not consistent with the applicable product information (eg, IB) and there is a reasonable possibility that the event was due to use of the study drug or due to a protocol-mandated procedure.

The term “severity” describes the intensity of a specific event and therefore, has to be distinguished from the term “serious”. Reports that add significant information about the specificity, increase of occurrence, or severity of a known, already documented serious adverse reaction constitute unexpected events.

The expectedness of an adverse reaction is determined by the Sponsor in the Reference Safety Information (RSI) on the basis of the events previously observed, not on the basis of what might be anticipated from the pharmacological properties of the study drug/IMP. The RSI is contained

in the IB in a clearly identified section that includes information on the frequency and nature of the adverse reactions. The RSI may change during the conduct of the clinical study and this would be a substantial amendment. For the purpose of SUSAR reporting, the version of the RSI at the moment of occurrence of the SUSAR applies.

It is the responsibility of the Sponsor to determine whether an event requires expedited reporting and to notify the PI of its decision as soon as possible. SUSARs will be subject to expedited reporting.

Where expedited reporting is required, the following procedures should be followed.

Fatal or life-threatening SUSARs:

It is the responsibility of the Sponsor to report fatal or life-threatening SUSARs to the FDA, as soon as possible, but no later than 7 calendar days after the Sponsor first became aware of the reaction.

The PI is required to notify the IRB of any SUSAR as soon as possible, but no later than 7 calendar days after he or she first became aware of the reaction. Any additional relevant information should be sent within 8 days of the report.

Other SUSARs

It is the responsibility of the Sponsor to report other SUSARs to the FDA as soon as possible, but no later than 15 calendar days after it first became aware of the reaction.

The PI is required to notify the IRB of any other SUSAR as soon as possible, but no later than 15 calendar days after he or she first became aware of the reaction.

11.4.6. Periodic Reporting

On an annual basis and as per all local requirements, the Sponsor will provide periodic reports to all competent authorities regarding safety for the product. In the United States, this requirement is met by submitting an IND annual report or a development safety update report (DSUR) to the FDA which will list a summary of most frequent and most serious adverse experiences by body system, a summary of all IND safety reports submitted during the reporting period, a list of subjects who died during participation and cause of death, and a list of subjects who dropped out during the course of the investigation in association with any adverse experience, whether or not thought to be drug related.

11.4.7. Reporting of Pregnancy

Subjects will be instructed that if they/their partner become pregnant during the study this should be reported to the PI immediately. The PI should also be notified of pregnancy occurring after completion of the study for female subjects 30 days after the last dose of study drug and partners of male subjects 90 days after the last dose of study drug. In the event that a subject or subject's partner is subsequently found to be pregnant after the volunteer is included in the study, then consent will be sought from the pregnant female subject or partner of a male subject and, if granted, any pregnancy will be followed and the status of mother and/or child will be reported to the Sponsor after delivery. Any subject who reports pregnancy during the study will be withdrawn from the study.

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. Information related to the pregnancy must be given on a "Pregnancy Confirmation and Outcome" form that will be provided by the Sponsor or its designee so that the pregnancy may be followed and an outcome determined. Any AEs or SAEs experienced by a pregnant subject are to be reported as directed above in Sections 11.4.1.1 and 11.4.1.2. Any complications reported in a subject's pregnant partner should be reported on the Pregnancy Confirmation and Outcome form. All pregnancies must be followed to outcome which occurs when an infant is delivered (live or still born), when there is fetal demise, or when there is an abortion (spontaneous or induced). Any congenital abnormalities in the newborn should be reported as separate SAEs. In addition, abortion (spontaneous or elective), fetal demise and stillbirth are considered SAEs.

A pregnancy that is reported while a subject is on study drug through the visit follow-up time frame will be captured in electronic data capture (EDC) and reported on the Pregnancy Report form for entry into both the clinical database and the safety database. All further follow-up of the pregnancy through resolution (abortion, either elective or spontaneous, fetal demise, still birth, or live birth) will be captured on a Pregnancy Confirmation and Outcome form and entered only into the safety database because these data are not statistically analyzed and would cause the clinical database to remain open, thus preventing adequate analysis of the Phase 1 data.

Pregnancy in a subject that is reported after the final study visit until 30 days after the last study drug dose for female subjects or 90 days after the last study drug dose for partners of male subjects will be reported on the Pregnancy Report form and captured only in the safety database. The pregnancy will not be entered into the clinical database, allowing the database to be locked and the data analyzed. All further follow-up of the pregnancy through resolution (abortion either elective or spontaneous, fetal demise, still birth, or live birth) will be captured on Pregnancy Confirmation and Outcome Forms and entered only into the safety database.

All pregnancy information including any follow up known at that time will be reported in the annual safety reporting required for a product in development. In the United States, this is met by the FDA required IND annual report or the DSUR if waiver is obtained from the FDA. In the European Union this is met by the European Medicines Agency (EMA) required DSUR.

11.4.8. Urgent Safety Measures

If the CRU or any of its staff or contractors becomes aware of an actual or potential urgent safety issue, then the Sponsor must be immediately contacted so that appropriate urgent safety measures can be agreed upon. An urgent safety issue is defined as:

- An immediate hazard to the health or safety of subjects participating in a clinical study
- A serious risk to human health or potentially a serious risk to human health

An urgent safety issue may include issues with an investigational drug or comparators, study procedures, inter-current illness (including pandemic infections), concomitant medications, concurrent medical conditions, or any other issues related to the safe conduct of the study or that pose a risk to study subjects.

In exceptional circumstances of imminent hazard and in order to safeguard the health or safety of individuals, the CRU may take urgent safety measures before informing the Sponsor, but the Sponsor must be informed immediately after the hazard has resolved.

The Sponsor will take responsibility for informing appropriate competent authorities, Investigators, and IRB.

11.4.9. Reporting of Urgent Safety Issues

The Sponsor is required to inform the appropriate competent authorities, Investigators, and IRB within 3 calendar days of the urgent safety issue.

11.4.10. Serious Breaches

It is the responsibility of the Sponsor to notify the licensing authority of any serious breach that is likely to affect, to a significant degree, the safety or mental integrity of the subjects in the study or the scientific value of the study.

11.5. Safety Oversight

Safety oversight will be provided by the means of an ISM, a DEC, and an SMC.

11.5.1. Independent Safety Monitor

The investigative site will have a physician ISM who is not part of the clinical study staff and has no direct study responsibilities. The ISM's responsibility will be the review of all SAEs and if needed, any AEs of special interest. The ISM may use all available data at the site including examination of the subject. The ISM will summarize his/her findings in a report that will be forwarded to the DEC and the SMC within 24 hours of the event.

The ISM must be available during the entire duration of the study or a back-up must be identified and available during the primary ISM's absence.

11.5.2. Dose Escalation Committee

Following the completion of each cohort, the DEC will meet to decide if the required safety parameters have been met. All available safety data for all subjects in a given cohort through 96 hours and PK data through 24 hours post-dose will be reviewed by the Sponsor Medical Monitor, Clinical Pharmacologist, and PI and used in the decision to escalate to the next higher dose. Review meetings will be held following each dose level of Cohorts 1 to 4.

An interim Safety Summary Report will be prepared for review by the DEC that will document the following safety findings for each dose cohort:

- Demographics
- Dosing information, including any subjects who discontinued dosing
- Listing of any SAEs with assessment of severity
- Listing of AEs with assessment of severity
- Listing of any graded clinical chemistry findings

- Listing of all clinical chemistry findings Grade 2 or higher
- Listing of any graded hematology findings
- Listing of all hematology findings
- Listing of any graded urinalysis findings
- Listing of all urinalysis findings
- Listing of vital signs
- Listing of QT findings
- Telemetry findings
- Additional narrative summaries
- Listing of subjects who terminated early
- Listing of PE data

An interim PK report will be prepared for review by the DEC that will document the following PK findings for each dose cohort:

- Preliminary plasma PK parameters (through 24-hours post-dose) based upon nominal times: AUC; C_{max}, T_{max}, terminal elimination half-life ($t_{1/2}$; median, minimum, maximum, geometric mean, coefficient of variation [CV%])
- Predictions of C_{max} and AUC values for the next cohort, where relevant

The interim Safety Summary and PK report documents will form the basis of teleconferences involving the Sponsor and the PI to evaluate each completed cohort in the study. The DEC will use the Dose Escalation Criteria to determine whether escalation as planned per protocol may commence.

Dose Escalation Criteria

The study will proceed to the next planned dose level if **NONE** of the following is met:

- One or more subjects with a treatment-emergent QT interval corrected by Fridericia's formula (QTcF) > 480 ms (Grade 2 per the DMID scale) as determined from bedside ECGs (with repeat ECG). If this occurs, the SMC may consult with an independent cardiologist as needed. If it is deemed acceptable to restart the study following review of the data and discussion with an independent cardiologist, if needed, dosing may resume.
- One or more subjects experiences an increase in BP that requires acute treatment, or has a confirmed systolic BP > 160 mmHg, or a confirmed diastolic BP > 100 mmHg (Grade 3 per DMID scale). Confirmed BP changes require at least 2 measurements at least 2 hours apart, each measured after at least 5 minutes of supine rest.
- Anaphylactic reaction occurs in one subject.

- One or more subjects experience a similar Grade 3 treatment-emergent laboratory abnormality or AE that is suspected to be drug-related as determined by the investigator.
- One subject experiences an SAE.
- A cohort's median AUC_{24} is ≥ 52,500 ng.h/mL, equivalent to the NOAEL exposure in cynomolgus monkeys.

If any of the above criteria are met, escalation to the next planned dose cohort will not proceed until all available study data have been reviewed by the independent SMC, as per Section 11.5.3.

If, following review by the SMC (Section 11.5.3) it is deemed acceptable to restart the study, dosing will resume. All relevant data will be submitted to the regulatory authorities and IRB.

11.5.3. Safety Monitoring Committee

A SMC will be assembled for this study. The SMC membership is determined by NIAID, who is also responsible for the Charter. The SMC will review reports provided by the PI and Sponsor as outlined in the Charter and agreed upon in the organizational meeting.

The SMC will meet to review all available safety and PK data from the study on the following occasions: when study halting criteria are met, when dose escalation could not be approved by the DEC, or when the criteria for not dosing additional subjects in a cohort are met after the sentinel subjects are dosed. A final SMC meeting will occur approximately 6 to 8 months following clinical database lock to review the cumulative unblinded safety data for the study.

Data for all SMC meetings will be provided in a standard summary format. The SMC may be asked to provide recommendations in response to questions posed by DMID. Additionally, following the administration of Cohort 4 and a review of the PK and safety data by the SMC, the Sponsor may make a recommendation to enroll additional cohorts in the SAD to further characterize the safety, tolerability and PK of galidesivir. This additional enrollment will only occur provided that the PK is increasing predictably in proportion with increasing dose, no safety concerns have arisen or stopping criteria have been met, the exposure is below the NOEAL exposure identified in NHP studies, and with recommendation by the SMC. The protocol will be amended to enable the enrollment of any SAD cohorts after Cohort 4.

The recommendations and final minutes of any SMC meeting will be supplied to the Sponsor, FDA and IRB, as applicable.

12. STATISTICS

12.1. Study Hypothesis

No formal study hypothesis will be stated or tested in this Phase 1 study.

12.2. Sample Size Considerations

No formal power or sample size calculations were used to determine cohort sizes. Cohort sizes were based upon experience in other SAD Phase 1 studies. A sample size of 6 subjects receiving

active drug per cohort should provide adequate characterization of PK and safety assessments within this setting.

12.3. Final Analysis Plan

12.3.1. Statistical Methods

A detailed Statistical Analysis Plan (SAP) will be developed and finalized prior to database lock. The SAP will describe the methods of analyses/summaries, including all endpoints, time points, populations, missing data, etc. Any deviation from the analyses outlined in the SAP will be described in the final CSR.

12.3.1.1. Analysis Populations

The analysis populations are defined below. Data from placebo-treated subjects will be pooled across cohorts.

Safety Population

The safety population will include all randomized subjects who received any amount of study drug (ie, a partial infusion). Subjects will be analyzed according to the treatment received. This population will be used for all analyses of accountability, demographics, galidesivir drug concentration, and safety.

Pharmacokinetic Population

The PK population will include all subjects for whom PK parameters can be estimated. The PK population will be the primary population for the PK analysis.

12.3.1.2. Subject Demographic and Disposition Data

Subject disposition will be presented for all subjects. The number of subjects who completed the study and discontinued from the study will be provided. All pertinent subject demographics will be presented using descriptive statistics. The reasons for early discontinuation will be presented.

12.3.1.3. Analysis of Safety Variables

AEs will be mapped to a Medical Dictionary for Regulatory Activities (MedDRA) preferred term (PT) and system organ classification (SOC). Any event reported on the subject's study record that occurs on or after the initiation of study drug is defined as treatment emergent. Additionally, it is assumed that an AE that is reported to have started on Day 1 of a given treatment period without an associated onset time may have occurred after the initiation of study drug. Hence, AEs occurring on Day 1 with no associated onset time will be assumed to be treatment emergent. The occurrence of TEAEs will be summarized by cohort and treatment assignment using MedDRA PTs, SOCs, and severity. Separate summaries of treatment-emergent SAEs and AEs considered to be related to study drug will be generated. All AEs will be listed for individual subjects showing both verbatim and preferred terms.

Descriptive summaries of vital signs, ECG parameters (12 lead and telemetry), ECHOs, and clinical laboratory results will be presented separately for each cohort by study visit and treatment assignment. Laboratory abnormalities will be graded according to the modified DMID criteria (APPENDIX A).

Any graded abnormality that occurs following the initiation of study drug and represents at least one 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 by treatment group. Laboratory toxicity shifts from baseline to post-baseline assessments will be summarized by treatment group.

PE results will be presented in listings. Changes in PE results that are AEs will be reported in AE tables.

Concomitant medications will be coded using the World Health Organization (WHO) Dictionary. These data will be summarized by cohort and treatment assignment.

Subjects receiving placebo will be pooled and reported together across cohorts.

12.3.1.4. Pharmacokinetic Analysis

Concentrations of galidesivir will be determined by validated plasma and urine assays and will be summarized by treatment and displayed in figures. Plasma PK parameters for each subject will be estimated over the sampling interval using noncompartmental analysis (Phoenix WinNonlin Version 7.0 or higher, Certara) and summarized by treatment group using descriptive statistics. The amount and percentage of galidesivir excreted in the urine will be assessed at all doses. If possible, data will be summarized by cohort and dose proportionality assessed.

The PK parameters that will be estimated for galidesivir are listed in Table 9. Additional analyses may be conducted as appropriate.

Table 9: Pharmacokinetic Parameters

Pharmacokinetic Parameter	Definition
AUC_{inf}	Area under the concentration versus time curve extrapolated to infinite time, calculated as $AUC_{last} + (C_{last}/\lambda_z)$
AUC_t	Area under the concentration versus time curve from time zero to time "t"; may be denoted as AUC_{last} if the "t" is the last timepoint with a measurable concentration
% AUC_{exp}	Percentage of AUC extrapolated between AUC_{last} and AUC_{inf}
C_{last}	Last measurable concentration of drug
C_{max}	Maximum observed concentration of drug
$t_{1/2}$	Estimate of the terminal elimination half-life of the drug
CL	CL = Dose/AUC where "Dose" is the dose of the drug and AUC = AUC_{inf}
λ_z	Terminal elimination rate constant, estimate by linear regression of the terminal elimination phase of the concentration of drug versus time curve
V_z	Volume of distribution of the drug
T_{max}	Time to C_{max}
CL_r	Renal clearance of unchanged drug in a specific interval (CL_r [interval]) or cumulatively over all collection intervals
% $Dose_{excreted}$	Percentage of given dose excreted in the urine as unchanged drug

In all derivations of PK parameters, zero will be substituted for concentrations below the quantitation limit (BQL) of the assay. Samples that are BQL, but are between two samples with detectable concentrations will be excluded from PK analysis.

12.3.1.5. Dose Proportionality of Galidesivir

Dose proportionality will be evaluated over all doses and will be based upon AUC_{inf}, AUC_t, and C_{max} using both the power model and the analysis of variance ANOVA method.

12.3.1.5.1. Power Model

The power model is as follows:

Equation 1:

$$\log(Y_{ik}) = S_i^{[1]} + \beta \times \log(Dose_k) + \varepsilon_{ik}$$

where Y_{ik} is the measured response variable, AUC_{inf}, AUC_t, and C_{max}, on the kth dose, $S_i^{[1]}$ is random subject effect for the ith subject, and $\varepsilon_{ik}$is the random error. After exponentiation, the model equation 1 is identical to equation 2 (below).

Equation 2:

$$Y_{ik} = \alpha \times Dose^{\beta}$$

where α includes the error.

Dose proportionality for PK parameters will be assessed by restricted maximum likelihood using SAS PROC MIXED. The mean slope will be estimated from the power model and the corresponding 90% CI calculated.

12.3.1.5.2. Analysis of Variance

Following log-e transformation, dose-normalized PK parameters will be analyzed with an ANOVA model using PROC MIXED. Each dose will be compared with a reference dose on a pair-wise basis. The ratio of GLS means and the corresponding 90% CI will be estimated for each PK parameter of interest.

13. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The study site will maintain appropriate medical and research records for this study, in compliance with International Council for Harmonisation (ICH) E6, Section 4.9 and regulatory and institutional requirements for the protection of confidentiality of subjects.

Source data are all information, original records of clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the study. Examples of these original documents and data records include, but are not limited to, clinical and office charts, laboratory notes, memoranda, subjects' memory aid or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives,

microfilm or magnetic media, x-rays, and subject files and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical study.

The site will permit authorized representatives of the Sponsor, DMID, and regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits, and evaluation of the study safety and progress.

13.1. Study Monitoring

Before an investigational site can enter a subject into the study, a representative of BioCryst (this may include a representative from a contract-research organization) will visit the investigational study site to:

- Determine the adequacy of the facilities
- Discuss with the investigator(s) and other personnel their responsibilities regarding protocol adherence, and the responsibilities of BioCryst or its representatives.

During the study, the representative acting on behalf of BioCryst will have regular contacts with the investigational site for the following:

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

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

Site monitoring of this study will be conducted, as described in the study-specific Site Monitoring Plan, to ensure that human subject protection, study procedures, laboratory, study intervention administration, and data collection processes are of high quality and meet the Sponsor, ICH E6/GCP, and regulatory guidelines.

13.2. Audits and Inspections

Authorized representatives of BioCryst, a regulatory authority, or an IRB may visit the study site to perform audits or inspections, including source data verification. The purpose of a BioCryst audit or inspection is to systematically and independently examine all study-related activities and

documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, GCP guidelines of the ICH, and any applicable regulatory requirements. The investigator should contact BioCryst immediately if contacted by a regulatory agency about an inspection.

13.3. Institutional Review Board

The principal investigator must obtain IRB approval for the investigation. Initial IRB approval, and all materials approved by the IRB for this study including the subject consent form and recruitment materials must be maintained by the investigator and made available for inspection.

14. QUALITY CONTROL AND QUALITY ASSURANCE

Following Phase 1 Unit Clinical's Quality Management, Quality System policy and standard operating procedures, the investigational site is responsible for conducting timely routine quality control and quality assurance activities to internally monitor study progress, compliance with the protocol, applicable regulations, and GCP (E6) guidelines.

The PI will provide BioCryst with direct access to the study site, source data/documents, and reports for the purpose of monitoring and auditing by the Sponsor, and inspection by local and regulatory authorities.

The PI is responsible for ensuring that all study personnel are appropriately trained prior to conducting any protocol procedures, and current and complete documentations are maintained on site.

Clinical site monitors will verify that the clinical study is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements. Data Management and control processes specific to this study, along with all steps and actions taken regarding data management and data quality control, will be described in a Data Management Plan.

An explanation will be given for all missing, unused, and spurious data in the relevant sections of the CSR.

15. ETHICS

15.1. 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 IRB as appropriate. The investigator must submit written approval to BioCryst before he or she can enroll any subject into the study.

The PI is responsible for informing the IRB of any amendment to the protocol in accordance with local requirements. In addition, the IRB must approve all advertising used to recruit subjects for the study. The protocol must be re-approved by the IRB upon receipt of amendments and annually, as local regulations require.

The PI is also responsible for providing the IRB with reports of any reportable serious adverse drug reactions from any other study conducted with the investigational product. BioCryst will provide this information to the PI.

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

The IRB must be registered with the Office for Human Research Protections (OHRP) and must be designated on the research site's Federal Wide Assurance (FWA).The IRB must provide written approval for the protocol and required documents (all handouts and forms given to or signed by the subject, all recruitment tools, all consent forms including screening, study, and pregnancy), prior to initiating any study related procedures, in compliance with the requirements of U.S. 45 CFR 46: Protection of Human Subjects, 21 CFR 56: Institutional Review Boards, and 21 CFR 50: Protection of Human Subjects. The ICF is viewed as an essential document that must be reviewed and approved by an IRB. The Sponsor and PI are responsible for complying with the principles of GCP as specified in the ICH Harmonised Tripartite Guideline for GCP E6 (R2).

15.2. 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 policy on Bioethics.

15.3. Written Informed Consent

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continuing throughout the individual's study participation. Extensive discussion of risks and possible benefits of this therapy will be provided to the subjects. Consent forms describing in detail the study interventions/products, study procedures, and risks are given to the subject and written documentation of informed consent is required prior to starting intervention/administering study product. Consent forms will be IRB-approved and the subject will be asked to read and review the document. Upon reviewing the document, the PI or designee will explain the research study to the subject and answer any questions that may arise. The subjects will sign the ICF prior to any procedures being done specifically for the study including obtaining identifiable data from medical records. The subjects should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The subjects may withdraw consent at any time throughout the course of the study. A copy of the ICF will be given to the subjects for their records. The rights and welfare of the subjects will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

Subjects may be recruited from a generic screening protocol where they have been pre-screened for clinical studies by Phase 1 Unit Clinical and have signed a Generic Screening ICF. Procedures performed as part of the Phase 1 Unit Clinical generic screening protocol will be considered part of the subject's medical history at Phase 1 Unit Clinical and the clinical or laboratory data may be used for screening and eligibility after informed consent for this study has been obtained.

15.3.1. Informed Consent/Assent Process (in Case of a Minor)

Not applicable

15.4. Exclusion of Women, Minorities, and Children (Special Populations)

This study will be limited to adults aged 18 to 55 years due to the early stage of development and absence of any developmental or juvenile toxicity data.

15.5. Subject Confidentiality

Subject confidentiality is strictly held in trust by the participating investigators, their staff, and the Sponsor and their agents. This confidentiality is extended to cover testing of biological samples in addition to the clinical information relating to participating subjects.

The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the Sponsor.

The study monitor or other authorized representatives of the Sponsor may inspect all documents and records required to be maintained by the PI, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the subjects in this study. The clinical study site will permit access to such records.

To protect privacy, the study site has received a Certificate of Confidentiality. With this Certificate, the researchers cannot be forced to release information that may identify the research subject, even by a court subpoena, in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. The researchers will use the Certificate to resist any demands for information that would identify the subject, except as explained below.

The Certificate cannot be used to resist a demand for information from personnel of the United States Government that is used for auditing or evaluation of federally funded projects, like this study, or for information that must be released in order to meet the requirements of the Federal FDA.

A Certificate of Confidentiality does not prevent the subject from voluntarily releasing information about themselves or their involvement in this research. If any person or agency obtains a written consent to receive research information, then the researchers may not use the Certificate to withhold that information.

The Certificate of Confidentiality does not prevent the researchers from reporting without the subject's consent, information that would identify the subject as a participant in the research project regarding matters that must be legally reported including: child and elder abuse, sexual abuse, or wanting to harm him/herself or others.

15.6. Study Discontinuation

See Section 7.7.

15.7. Future Use of Stored Specimens

Not applicable.

15.8. Costs, Subject Compensation, and Research Related Injuries

There is no cost to subjects for the research tests, procedures, and study product while taking part in this study. Procedures and treatment for clinical care may be billed to the subject, subject's insurance or third party. Subjects may be compensated for their participation in this study. Compensation will be in accordance with the local IRB's policies and procedures, and subject to IRB approval.

If it is determined by the study site PI that an injury occurred to a subject as a direct result of the tests or treatments that are performed in this study, then referrals to appropriate health care facilities will be provided to the subject. Study personnel will try to reduce, control, and treat any complications from this study. Immediate medical treatment may be provided by the participating site. No financial compensation will be provided to the subject by the NIAID, NIH to the subject, or by the participating site for any injury suffered due to participation in this study.

16. DATA HANDLING AND RECORDKEEPING

The PI is responsible to ensure the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Black ink is preferred to ensure clarity of reproduced copies, however blue ink is acceptable. When making changes or corrections, cross out the original entry with a single line, and initial and date the change. DO NOT ERASE, OVERWRITE, OR USE CORRECTION FLUID OR TAPE ON THE ORIGINAL.

16.1. Data Management Responsibilities

All source documents and laboratory reports must be reviewed by the clinical team and data entry staff, who will ensure that they are accurate and complete. AEs must be graded, assessed for severity and causality, and reviewed by the study site PI or designee.

Data collection is the responsibility of the clinical study staff at the site under the supervision of the site PI. During the study, the PI must maintain complete and accurate documentation for the study.

The data coordinating center for this study at the CRO will be responsible for data management, quality review, analysis, and reporting of the study data.

16.2. Data Capture Methods

Clinical data (including AEs and concomitant medications) and clinical laboratory data will be entered into a 21 CFR Part 11-compliant Data Entry System. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate.

16.3. Types of Data

Data for this study will include safety, laboratory, and PK data.

16.4. Timing/Reports

Data from each cohort will be reviewed in a Dose Escalation Committee meeting in accordance with the procedures described in Section 11.5.2.

16.5. Inspection of Records

BioCryst will be allowed to conduct site visits to the investigation facilities for 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.

16.6. Retention of Records

To enable evaluations and/or audits from regulatory authorities or BioCryst, the PI agrees to keep records, including the identity of all participating subjects (sufficient information to link records, eCRFs, and medical/hospital records), all original signed ICFs, all eCRFs, and detailed records of study drug accountability and treatment disposition. Study documents will be retained for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. The records should be retained by the PI according to local regulations or as specified in the Clinical Trial Agreement, whichever is longer.

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

16.7. Protocol Deviations

A protocol deviation is any noncompliance with the clinical study protocol, GCP, or Manual of Procedures requirements. The noncompliance may be either on the part of the subject, the PI, or the study site staff. Deviations from the protocol will be recorded in the source workbook as noted by the clinical staff. The Sponsor will be informed of the deviation. As a result of applicable deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH E6:

4.5 Compliance with Protocol, Sections 4.5.1, 4.5.2, and 4.5.3

5.1 Quality Assurance and Quality Control, Section 5.1.1

5.20 Noncompliance, Sections 5.20.1, and 5.20.2.

Protocol deviations must be sent to the local IRB per the IRB guidelines. The study site PI/study staff is responsible for knowing and adhering to the IRB requirements.

17. 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. Independent analysis and/or publication of these data by the PI or any member of his/her staff are not permitted without prior written consent of BioCryst. Written permission to the PI will be contingent on the review by BioCryst of the statistical analysis and manuscript and will provide for nondisclosure of BioCryst confidential or proprietary information. In all cases, the parties agree to submit all manuscripts or abstracts to all other parties 30 days prior to submission. This will enable all parties to protect proprietary information and to provide comments based on information that may not yet be available to other parties.

All investigators funded by the NIH must submit or have submitted for them to the National Library of Medicine's PubMed Central (http://www.ncbi.nlm.nih.gov/pmc/) an electronic version of their final, peer-reviewed manuscripts upon acceptance for publication, to be made publicly available no later than 12 months after the official date of publication. The NIH Public Access Policy ensures the public has access to the published results of NIH funded research. It requires investigators to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication. Further, the policy stipulates that these papers must be accessible to the public on PubMed Central no later than 12 months after publication.

Refer to the following:

- NIH Public Access Policy, http://publicaccess.nih.gov/
- NIH Office of Extramural Research (OER) Grants and Funding, http://grants.nih.gov/grants/oer.htm

As of January 2018, all clinical studies supported by the NIH must be registered on ClinicalTrials.gov, no later than 21 days after the enrollment of the first subject. Results of all clinical studies supported by the NIH, generally, need to be submitted no later than 12 months following the primary completion date. A delay of up to 2 years is available for studies that meet certain criteria and have applied for certification of delayed posting.

As part of the result posting a copy of this protocol (and its amendments) and a copy of the SAP will be posted on ClinicalTrials.gov.

For this study the responsible party is BioCryst which will register the study and post results.

The responsible party does not plan to request certification of delayed posting.

Refer to the following:

- Public Law 110-85, Section 801, Clinical Trial Databases
- 42 CFR Part 11
- NIH NOT-OD-16-149

18. LIST OF REFERENCES

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APPENDICES

APPENDIX A: TOXICITY TABLE – MODIFIED DMID ADULT TOXICITY TABLE, 2014

Clinical Adverse Events			
VITAL SIGNS	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**
Fever (°C) **	38.0 – 38.4	38.5 – 38.9	≥39.0
(°F) **	100.4 – 101.1	101.2 – 102.0	>102.0
** Oral temperature; no recent hot or cold beverages or smoking. A protocol should select either °C or °F for inclusion.			
Tachycardia - beats per minute	101 – 115	116 – 130	> 130 or ventricular dysrhythmias
Bradycardia - beats per minute	50 – 54 or 45-50 bpm if baseline <60 bpm	45 – 49 or 40-44 if baseline <60bpm	< 45 or <40bpm if baseline <60bpm
Hypertension# (systolic)- mm Hg	141-150	151-160	> 160
Hypertension# (diastolic) - mm Hg	91-95	96-100	> 100
# Assuming supine position, 10 min at rest conditions, not sleeping subjects, measurements on the same arm and several concordant results.			

Hypotension (systolic) - mm Hg	85-89	80-84	< 80
Tachypnea – breaths per minute	23-25	26-30	>30
CARDIOVASCULAR	**Grade 1**	**Grade 2**	**Grade 3**
Arrhythmia		asymptomatic, transient signs, no Rx required	recurrent/persistent; symptomatic Rx required
QTcF interval prolonged (msec)	Asymptomatic, QTcF >450-480 msec	Asymptomatic, QTcF >480-500 msec OR increase in interval 30-60 msec from baseline	Asymptomatic, QTcF >500 msec OR increase in interval >60 msec from baseline
Hemorrhage, Blood Loss	Estimated blood loss ≤ 100 mL	Estimated blood loss > 100 mL, no transfusion required	Transfusion required
RESPIRATORY	**Grade 1**	**Grade 2**	**Grade 3**
Cough	Transient- no treatment	Persistent cough;	Interferes with daily activities
Bronchospasm, Acute	transient; no treatment; 71% - 80% FEV1 of peak flow	requires treatment; normalizes with bronchodilator; FEV1 60% - 70% (of peak flow)	no normalization with bronchodilator; FEV1 <60% of peak flow
Dyspnea	Does not interfere with usual and social activities	Interferes with usual and social activities, no treatment	Prevents daily and usual social activity or requires treatment
GASTROINTESTINAL	**Grade 1**	**Grade 2**	**Grade 3**
Nausea	No interference with activity	Some interference with activity	Prevents daily activities
Vomiting	No interference with activity or 1 - 2 episodes/24 hours	Some interference with activity or > 2 episodes/24 hours	Prevents daily activity or requires IV hydration

Diarrhea	2 - 3 loose or watery stools or < 400 gms/24 hours	4 - 5 loose or watery stools or 400 - 800 gms/24 hours	6 or more loose or watery stools or > 800gms/24 hours or requires IV hydration
SYSTEMIC	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**
Allergic Reaction/Hypersensitivity	pruritus without rash	localized urticaria	generalized urticaria; angioedema or anaphylaxis
Headache	No interference with activity	Repeated use of non-narcotic pain reliever > 24 hours or some interference with activity	Significant; any use of narcotic pain reliever or prevents daily activity
Fatigue	No interference with activity	Some interference with activity	Significant; prevents daily activity
Myalgia	No interference with activity	Some interference with activity	Significant; prevents daily activity
All Other conditions	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**
Illness or clinical adverse event (as defined according to applicable regulations)	Transient or mild symptoms; no limitation in activity; no intervention required. The AE does not interfere with the participant's normal functioning level. It may be an annoyance.	Symptom results in mild to moderate limitation in activity; no or minimal intervention required. The AE produces some impairment of functioning, but it is not hazardous to health. It is uncomfortable or an embarrassment.	Symptom results in significant limitation in activity; medical intervention may be required. The AE produces significant impairment of functioning or incapacitation.

Laboratory Adverse Events					
Blood, Serum, or Plasma *	**Reference Range ****		**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**
Sodium – Hyponatremia mEq/L	135-146 mmol/L		134 – <LLN	132 – 133	<132
Sodium – Hypernatremia mEq/L	135-146 mmol/L		>ULN – 147	148 – 149	>149
Potassium – Hyperkalemia mEq/L	3.5-5.3 mmol/L		>ULN – 5.4	5.5 – 5.6	>5.6
Potassium – Hypokalemia mEq/L	3.5-5.3 mmol/L		<LLN-3.4	<3.4 – 3.3	<3.3
Glucose – Hypoglycemia mg/dL	65-99 mg/dL		62 – 64	52 – 62	<52
Glucose – Hyperglycemia Fasting – mg/dL	65-99 mg/dL		>ULN - 100	101 – 110	>110
Glucose – Hyperglycemia Random – mg/dL	65-139 mg/dL		140 – 159	160 – 200	>200
Blood Urea Nitrogen mg/dL	7-25 mg/dL		26 – 29	30 – 34	>34
Creatinine (Male) – mg/dL	18Y-19Y	0.60-1.26 mg/dL	>ULN – 1.36	>1.36 – 1.56	>1.56
	20Y-49Y	0.60-1.35 mg/dL	>ULN – 1.45	>1.45 – 1.65	>1.65
	50Y-59Y	0.70-1.33 mg/dL	>ULN – 1.43	>1.43 – 1.63	>1.63
Creatinine (Female)- mg/dL	18Y-19Y	0.50-1.00 mg/dL	>ULN – 1.10	>1.10 – 1.30	>1.30
	20Y-49Y	0.50-1.10 mg/dL	>ULN – 1.20	>1.20 – 1.40	>1.40
	50Y-59Y	0.50-1.05 mg/dL	>ULN – 1.15	>1.15 – 1.35	>1.35
Calcium – hypocalcemia mg/dL (Male)	18Y-19Y	8.9-10.4 mg/dL	8.8 – <LLN	8.3 – 8.7	<8.3
	20Y-133Y	8.6-10.3 mg/dL	8.5 – <LLN	8.0 – 8.4	<8.0
Calcium – hypocalcemia mg/dL (Female)	18Y-19Y	8.9-10.4 mg/dL	8.8 – <LLN	8.3 – 8.7	<8.3
	20Y-49Y	8.6-10.2 mg/dL	8.5 – <LLN	8.0 – 8.4	<8.0

	50Y-133Y	8.6-10.4 mg/dL	8.5 – <LLN	8.0 – 8.4	<8.0
Calcium – hypercalcemia mg/dL (Male)	18Y-19Y 20Y-133Y	8.9-10.4 mg/dL 8.6-10.3 mg/dL	>ULN – 10.5 >ULN – 10.4	10.6 – 11.0 10.5 – 10.9	>11.0 >10.9
Calcium – hypercalcemia mg/dL (Female)	18Y-19Y 20Y-49Y 50Y-133Y	8.9-10.4 mg/dL 8.6-10.2 mg/dL 8.6-10.4 mg/dL	>ULN – 10.5 >ULN – 10.3 >ULN – 10.5	10.6 – 10.9 10.4 – 10.7 10.6 – 10.9	>10.9 >10.7 >10.9
Magnesium – hypomagnesemia mg/dL	1.5-2.5 mg/dL		1.3 – 1.5	1.1 – 1.2	<1.1
Phosphorous – hypophosphatemia mg/dL	18Y-64Y 65Y-133Y	2.5-4.5 mg/dL 2.1-4.3 mg/dL	2.3 – <2.5 1.9 – <2.1	2.0 – < 2.2 1.6 – < 1.8	<2.0 1.6
CPK – U/L (male)	<196		196 – 1000	1001-1500	>1500
CPK – U/L (female)	<143		143 – 1000	1001-1500	>1500
Albumin – Hypoalbuminemia g/dL	3.6-5.1 g/dL		3.0 – 3.5	2.7 – 2.9	<2.7
Total Protein – Hypoproteinemia g/dL	18Y-19Y 20Y-133Y	6.3-8.2 g/dL 6.1-8.1 g/dL	6.1 – 6.3 5.9 – 6.1	5.7 – 6.0 5.5 – 5.8	<5.7 <5.5
Alkaline phosphatase – U/L (Male)	18Y-19Y 20Y-133Y	48-230 U/L 40-115 U/L	230 – 340 115 – 225	341 – 460 226 – 345	>460 >345
Alkaline phosphatase – U/L (Female)	18Y-19Y 20Y-49Y 50Y-133Y	47-176 U/L 33-115 U/L 33-130 U/L	176 – 286 115 – 225 130 – 240	287 – 406 226 – 345 241 – 360	>406 >345 >360
AST (Male) U/L	18Y-19Y 20Y-49Y 50Y-133Y	12-32 U/L 10-40 U/L 10-35 U/L	32 – 93 40 – 101 35 – 96	94 – 163 102 – 171 97 – 166	>163 >171 >166
AST (Female) U/L	18Y-19Y 20Y-44Y 45Y-133Y	12-32 U/L 10-30 U/L 10-35 U/L	32 – 93 30 – 91 35 – 96	94 – 163 92 – 161 97 – 166	>163 >161 >166
ALT (Male) U/L	18Y-19Y 20Y-133Y	8-46 U/L 9-46 U/L	46 – 101 46 – 101	102 – 171 102 – 171	>171 >171
ALT (Female) U/L	18Y-19Y	5-32 U/L	32 – 87	88 – 157	>157

	20Y-133Y	6-29 U/L	29 – 84	85 – 154	>154
Bilirubin (serum total) mg/dL	18Y-19Y 20Y-133Y	0.2-1.1 mg/dL 0.2-1.2 mg/dL	1.2 – 1.9 1.3 – 2.0	2.0 - 2.4 2.1 – 2.5	>2.4 >2.5
Bilirubin – when ALT ≥105 (Hy's law)			1.3 – 1.5	1.6 – 2.0	>2.0
Amylase- U/L	21 – 101 U/L		102 – 177	178 – 278	>278
Lipase- U/L	7 – 60 U/L		60 – 165	166 – 250	>250
Hemoglobin (Male) - g/dL	18Y 19Y-133Y	12.0-16.9 g/dL 13.2-17.1 g/dL	11.5 – 12.0 12.7 – 13.2	10.5 – 11.9 12.2 – 12.7	<10.5 <12.2
Hemoglobin (Female) - g/dL	18Y 19Y-133Y	11.5-15.3 g/dL 11.7-15.5 g/dL	11.0 – 11.5 11.2 – 11.7	9.5 – 10.9 9.8 – 11.2	<9.5 <9.8
WBC Increase - cell/mm3	18Y 19Y-133Y	4,500-13,000/uL 3,800-10,800/uL	13,001 – 17,000 10,801 – 14,800	17,001 – 22,000 14,801 – 19,800	>22,000 >19,800
WBC Decrease - cell/mm3	18Y 19Y-133Y	4,500-13,000/uL 3,800-10,800/uL	3,500 – 4,500 2,800 – 3,800	2,500 – 3,499 1,800 – 2,799	<2,500 <1,800
Lymphocytes Decrease - cell/mm3	18Y 19Y-133Y	1200-5200 cells/uL 850-3900 cells/uL	950 – 1,200 600 – 850	700 – 949 450 – 599	<700 <450
Neutrophils Decrease - cell/mm3	18Y 19Y-133Y	1800-8000 cells/uL 1500-7800 cells/uL	1,300 – 1,799 1,000 – 1,499	1,049 – 1,299 750 – 999	<1,049 <750
Eosinophils - cell/mm3	15-500 cells/uL		500 – 750	751 – 1600	>1600
Platelets Decreased - cell/mm3	140,000 – 400,000/ uL		130,000 – 140,000	110,000 – 129,999	<110,000
PT – seconds (prothrombin time)	9.0-11.5 seconds		> ULN-14.4	14.5 – 15.7	>15.7
PTT – seconds (partial thromboplastin time)	22-34 sec		>ULN-34.1	34.2– 42.0	>42.0
Fibrinogen increase - mg/dL	175-425 mg/dL		>ULN – 425	426 – 525	>525
Fibrinogen decrease - mg/dL	175-425 mg/dL		<LLN – 175	160 – 174	<160

Urine *		**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**
Protein		1+	2+	>2+
Glucose		1+	2+	>2+
Blood (microscopic) - red blood cells per high power field (rbc/hpf)		5-10	11-50	> 50 and/or gross blood
	* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters.			
	* Institutional normal reference ranges should be provided to demonstrate that they are appropriate.			
	** Reference ranges are from Quest Diagnostics. Any age range that is not specified is 18Y – 133Y			