Statistical Analysis Plan

Sponsor:	BioCryst Pharmaceuticals, Inc.
Protocol No:	BCX4430-106-DMID18-0013
Protocol Title:	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
PRA Project ID:	BIO139GF-181392
Version Date:	10-April-2019

Approvals

The undersigned have approved this Statistical Analysis Plan for use in this study.

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3.0 Introduction

This Statistical Analysis Plan (SAP) describes the statistical methods that will be used during the analysis and reporting of data collected under BioCryst Pharmaceuticals, Inc., Protocol BCX4430-106.

This SAP should be read in conjunction with the study protocol and electronic case report form (eCRF). This version of the SAP has been developed using the protocol dated 11-Jan-2019 and the final eCRF(s) dated 30-Oct-2018.

An approved and signed SAP is a requirement for database lock.

This SAP covers all results that will be processed by the PRA Early Development Services (EDS) Biostatistics Department.

PRA EDS will perform the final pharmacokinetic (PK) and safety and tolerability analyses.

This SAP supersedes the statistical considerations identified in the protocol; where considerations are substantially different, they are identified. Any post-hoc or unplanned analyses, or substantive changes from the planned analysis in this SAP performed to provide results for inclusion in the clinical study report (CSR), will be clearly identified in the CSR. Changes to planned analyses do not require an updated SAP but should be denoted in the CSR if significant.

4.0 Changes from Previous Version of Approved SAP

Not applicable. This is the first version of the SAP.

5.0 Study Objectives

5.1 Primary Objective

The primary objective of the study is:

- To evaluate the safety and tolerability of single ascending doses (SAD) of galidesivir (BCX4430) administered by intravenous (IV) infusion in healthy subjects.

5.1.1 Primary Endpoints

The primary endpoints of the study are:

- 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).

5.2 Secondary Objective

The secondary objective of the study is:

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

5.2.1 Secondary Endpoints

The secondary endpoints of this study are:

- The PK parameters for galidesivir, including: maximum concentration (C_{max}), last measurable concentration of drug (C_{last}), time to maximum concentration (T_{max}), area under the concentration time curve from time zero to last time (AUC_{last}), area under the concentration time curve from time zero to infinity (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.

- Dose proportionality of galidesivir based upon AUC_{inf}, AUC from time 0 to time "t" (AUC_t), and C_{max}.

6.0 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 enrolled in up to four dose cohorts of 8 subjects each, for a total of 32 subjects. A single dose of study drug will be administered per cohort: 6 subjects will receive galidesivir IV, and 2 subjects will receive matching placebo.

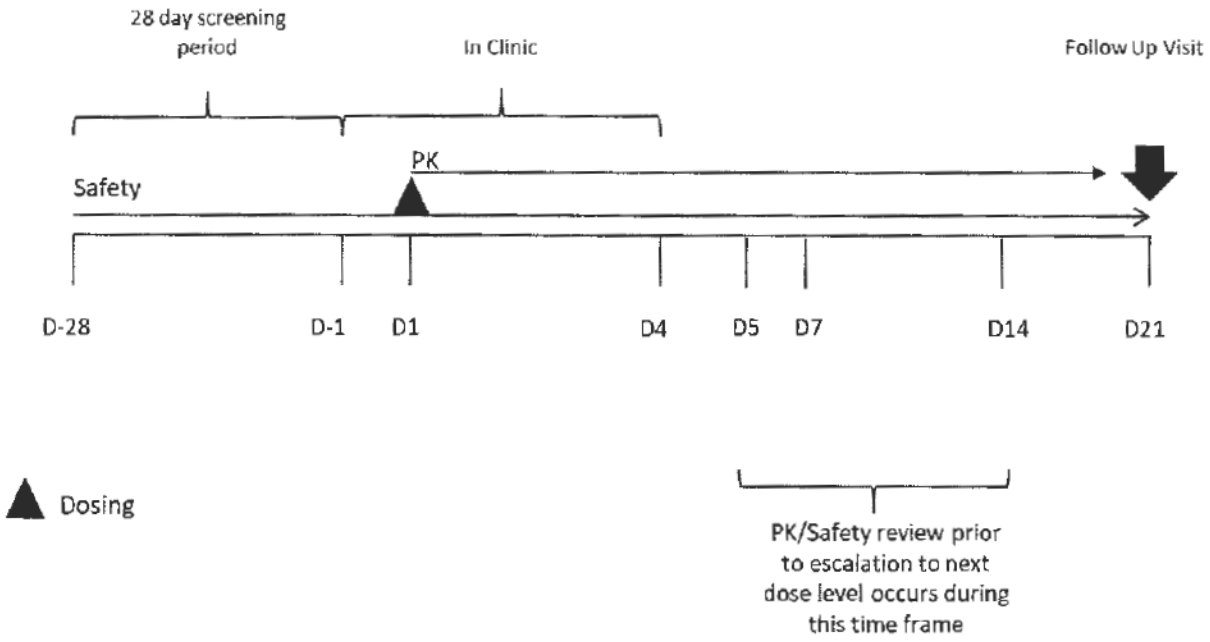
The planned cohorts are as follows:

- 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

Subjects will be randomized within each cohort to receive either galidesivir or placebo. As a safety precaution, on the first day of dosing in each cohort, 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, 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.

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. 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). The study design is shown in Figure 1 (below).

Figure 1 BCX4430-106 Study Design



Abbreviations: D = day; PK = pharmacokinetic.

6.1 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.

6.2 Randomization

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. The randomization schedules will be generated by an unblinded study statistician. 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, and the randomization schedule will be generated so that in each cohort 1 sentinel subject is randomly assigned to receive galidesivir and 1 sentinel subject is randomly assigned to receive placebo. The remainder of the cohort will be randomized such that 5 subjects are assigned to receive galidesivir and 1 subject assigned to receive placebo.

Following confirmation of eligibility, subjects will be identified by a unique 5-digit subject identifier (e.g., 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 (i.e., 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

7.0 Overview of Planned Analysis

7.1 Changes from Protocol

There are no changes from the protocol.

7.2 Interim Analysis and Key Results

An interim PK report will be prepared by Biocryst 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

7.3 Final Analysis

Draft TFLs will be provided after database lock. After Sponsor comments have been incorporated, the TFLs will be finalized and incorporated into the first draft of the CSR.

8.0 Data Review

8.1 Data Management

Data handling and transfer will take place under the PRA Data Management Plan for the study.

8.2 Acceptance of Data for Summarization

Programming of analysis datasets and TFLs may be ongoing during the data management of the study. However, programming of analysis datasets and TFLs will be completed and quality controlled (QC'd) after

database lock. Only quality-assured results released by the Safety Laboratory, Bioanalytical Laboratory, or other external data source will be used for the programming of analysis datasets and TFLs for the final report. Any data values requiring investigation or corrections that are identified while programming the analysis datasets and TFLs will be sent to the project Data Manager. If the issue affects the TFLs the Programmer or Statistician who identified the issue will follow it to resolution.

9.0 Definitions and General Analysis Methods

9.1 Analysis Data Presentation

9.1.1 Rounding

In listings, data will be presented with the same precision as the original data. Derived data will be rounded for presentation purposes.

For all summaries, minimum (min) and maximum (max) will be presented to the same number of decimal places as the original data, the mean and median to 1 decimal greater than the original data, and the standard deviation (SD) to 2 decimals greater than the original data. Frequency percentages and percent coefficient of variation (CV%) will be presented to 1 decimal.

PK parameters will be rounded in the derived datasets as determined by the pharmacokineticist and presented as such in the listings. Each parameter will have a fixed number of decimals (C_{max} and AUC will have 3 significant figures, and half-life and T_{max} will have 1 decimal). In general, the pharmacokineticist will use discretion when deciding the number of decimals for each parameter.

9.1.2 Imputation

Unless otherwise noted, data will not be imputed.

9.1.3 Descriptive Statistics

Unless otherwise indicated, continuous variables will be summarized with the following descriptive statistics: n (number of observations), (arithmetic) mean, SD, min, median, and max.

Categorical data will be summarized with frequencies and percentages. Percentages by categories will be based on the number of subjects exposed within a treatment. Percentages will be rounded to 1 decimal, except 100% which will be displayed without any decimal places. Percentages will not be displayed for zero counts. Categories will be presented in the tables exactly as they appear in the eCRF / database.

9.1.4 Pooling

Placebo subjects will be pooled for summary TFLs for this study.

9.1.5 Unscheduled Measurements

Unscheduled measurements will be included in the listings. In general, except for unscheduled measurements used for baseline, unscheduled measurements will be excluded from the descriptive statistics and statistical analysis by timepoint. For shift tables or tables that summarize worst outcome, unscheduled measurements (occurring after previous timepoint and up to and including each scheduled timepoint) will be included in summary statistics.

9.2 Analysis Data Definitions

9.2.1 Baseline Definition

Unless otherwise stated, baseline for post dose evaluations is defined as the last observation recorded before the first study drug administration for each regimen as indicated in Appendix 2 (Schedule of Assessments). The last observation can be an unscheduled/repeated measurement. Baseline ECGs will

be calculated from an average of the triplicate readings prior to initiation of treatment on Day 1 of each treatment period.

9.2.2 Treatment/Subject Grouping

Throughout this SAP, study drug refers to: BCX4430 galidesivir for IV infusion.

Label	Grouping
Study Drugs	BCX4430 galidesivir for IV infusion
Treatment	Cohort 1: • Regimen A: Galidesivir (Dose 5 mg/kg, Calculated Dose Range 250-500 mg, Concentration 1.0 mg/mL, Dose Volume 250-500 mL), or • Placebo (Dose Volume 250-500 mL) Cohort 2: • Regimen B: Galidesivir (Dose 10 mg/kg, Calculated Dose Range 500-1000 mg, Concentration 1.0-2.0 mg/mL, Dose Volume 500 mL), or • Placebo (Dose Volume 500 mL) Cohort 3: • Regimen C: Galidesivir (Dose 15 mg/kg, Calculated Dose Range 750-1500 mg, Concentration 1.5-3.0 mg/mL, Dose Volume 500 mL), or • Placebo (Dose Volume 500 mL) Cohort 4: • Regimen D: Galidesivir (Dose 20 mg/kg, Calculated Dose Range 1000-2000 mg, Concentration 2.0-4.0 mg/mL, Dose Volume 500 mL), or • Placebo (Dose Volume 500 mL)
Dose Levels	BCX4430: 5 mg/kg, Calculated Dose Range 250-500 mg BCX4430: 10 mg/kg, Calculated Dose Range 500-1000 mg BCX4430: 15 mg/kg, Calculated Dose Range 750-1500 mg BCX4430: 20 mg/kg, Calculated Dose Range 1000-2000 mg [Note: Treatment labels will use mg/kg]

9.2.3 Common Variable Derivations

Variable	Data Type	Definition/Calculation
Change from baseline	All	Post-dose observation minus baseline observation
Analysis study day (prior to dose)	All	Date of measurement minus dose date
Analysis study day (post dose)	All	Date of measurement minus dose date + 1
TEAE	AE	An AE is a treatment-emergent adverse event (TEAE) if the AE start date/time is greater than or equal to the first dose date/time

Abbreviations: AE = adverse event; TEAE = treatment-emergent adverse event.

9.2.4 QC

The analysis datasets and the TFLs will be QC'd according to the PRA EDS QC plan.

9.2.4.1 Critical Data

The QC plan requires datasets be classified as critical or non-critical. As the primary and secondary objectives of this study are to characterize the safety and tolerability of galidesivir as well as PK profile, critical datasets include subject level demographics, PK parameters, concentrations, and AEs.

9.2.5 ADaM Datasets and Metadata

The analysis datasets will be generated in accordance with Clinical Data Interchange Standard Consortium (CDISC) Analysis Data Model (ADaM) Version 2.1.

ADaM-compliant datasets will be delivered to the sponsor. A define.xml file Version 2 with the corresponding metadata will be included. Analysis results metadata are excluded.

9.3 Software

The statistical analysis and reporting will be done using SAS® for Windows™ Version 9.4 or higher (SAS Institute, Inc.).

PK parameter calculations will primarily be done using Phoenix® WinNonlin® Version 8.1 or higher (Certara, Inc.). Additional PK computations may be performed in SAS.

9.4 Statistical Methods

9.4.1 Statistical Outlier Determination

No statistical outlier analysis is planned.

9.4.2 Predetermined Covariates and Prognostic Factors

There are no predetermined covariates or prognostic factors.

9.4.3 Hypothesis Testing

9.4.3.1 Primary Objective

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

9.4.3.2 Secondary Objective – Dose Proportionality

Dose proportionality for AUC_{inf}, AUC_t, and C_{max} will be evaluated using the power model (including all doses) and also using an ANOVA model where each dose will be compared with a reference dose in a pairwise basis. The mean slope from the power model and the set of pairwise comparisons from the ANOVA method will constitute descriptive evaluations of dose proportionality.

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 k^{th} dose, $S_i^{[1]}$ is random subject effect for the i^{th} subject, and ε_{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. If the 90% CI of the slope of the C_{max} and AUCs contains 1, then dose proportionality is indicated.

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 pairwise basis. The ratio of geometric least squares means (LSM) and the corresponding 90% CI will be estimated for each PK parameter of interest. If the 90% CI for the geometric LSM ratio for a given pairwise comparison falls completely within the 0.8 to 1.25 equivalence region then dose proportionality is indicated.

9.5 TFL Layout

Report layout will be according to the PRA EDS standards, which are International Council for Harmonisation (ICH) E3 compliant. The layout of TFLs will be according to the PRA EDS standards.

TFL shells are provided with and approved as part of this SAP. Small changes to shell layout due to the nature of the data may be required after database lock at the discretion of the PRA project statistician. Other changes to the shells may be out of scope. The TFLs will be provided both individually in revisable text format (RTF) format, with separate files for each table, figure, and listing, and combined in Adobe PDF format. All TFLs will be in letter format.

10.0 Analysis Populations

Analyses	Safety Population	PK Population
Disposition Summaries	✓	
Baseline Characteristics	✓	✓
Safety Assessments	✓	
Plasma Concentrations	✓	
Plasma PK Parameters		✓
Urine PK Parameters		✓
Dose proportionality Analyses		✓

10.1 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.

10.2 Pharmacokinetic Population

The PK population will include all subjects for whom at least 1 PK parameter can be estimated. The PK population will be the primary population for the PK analysis.

11.0 Subject Disposition

The number and percentage of subjects in each analysis population, who complete as well as withdraw from the study prematurely, and a breakdown of the corresponding reasons for withdrawal will be presented for the safety population. A listing of screened subjects and reasons for screen failure will also be presented.

12.0 Protocol Deviations

Important protocol deviations/violations will be listed as well as included in the CSR.

13.0 Demographic and Baseline Characteristics

13.1 Demographics

Subject demographics will be summarized descriptively for all subjects by cohort. The summary will include the subjects' age (in years), sex, race, ethnicity, weight (kg), height (cm), and body mass index (BMI) (in kg/m^2). Demographic characteristics will be summarized for the safety and PK populations.

All demographic data, as collected during the screening visit, will be listed by subject.

13.2 Medical History

Medical history will be categorized by preferred term according to the Medical Dictionary for Regulatory Activities (MedDRA) Version 21.1 and will be listed by subject.

13.3 Screening Results

All screening results (including eligibility criteria) will be listed by subject.

14.0 Prior and Concomitant Medications

Prior and concomitant medications will be categorized by medication group and subgroup according to the World Health Organization (WHO) Drug Dictionary Version September 2018 and listed by subject. Medications with an end date prior to the first dose of study drug will be considered prior medications and will be identified in the listing. Concomitant medications will include records with a start date on the same date or after the first study drug administration, and records with a start date before the date of first study medication that are indicated as ongoing. If a partial date allows a medication to be considered concomitant it will be categorized as such. Records without a start date are assumed to have started before the date of first study drug administration. Records without an end date are assumed to be ongoing.

15.0 Treatment Exposure

The number of subjects who receive study drug will be summarized by cohort and treatment for the safety population. All study drug administration data (including meal data indicating fasting status) will be listed by subject.

Pharmacokinetic Analyses

16.0 Pharmacokinetic Variables

16.1.1 Plasma Variables

- Plasma concentrations of galidesivir.
- Plasma PK parameters of galidesivir.

Venous blood samples will be collected to determine the plasma concentrations of BCX4430. The plasma concentration summaries and figures with mean values described in this section will be created using the safety population. The plasma PK parameter summaries and statistical analyses described in this section will be created using the PK population.

Plasma PK Parameters		
Parameter	**Description**	**Programming Notes**
AUC_{inf}	Area under the concentration versus time curve extrapolated to infinite time, calculated as $AUC_{last} + (C_{last}/\lambda_z)$	AUCINF_obs from WNL If valid lambda_z is not present, then parameter is flagged in listings and will not be used in summary statistics.
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	AUClast from WinNonlin If actual time deviates >20% from nominal time, then AUC_t will be flagged in listings and will not be used in statistical analyses. If valid λ_z is not present, then AUC_t is flagged in listings and will not be used in statistical analyses.
% AUC_{exp}	Percentage of AUC extrapolated between AUC_{last} and AUC_{inf}	AUC_%Extrap_obs from WinNonlin Listed only
C_{last}	Last measurable concentration of drug	Clast from WinNonlin If actual time at T_{last} deviates >20% from nominal time, then parameter is flagged in listings and will not be used in summary statistics.
T_{last}	Time of last measurable concentration of drug	Tlast from WinNonlin If actual time at T_{last} deviates >20% from nominal time, then parameter is flagged in listings and will not be used in summary statistics
C_{max}	Maximum observed concentration of drug	C_{max} from WinNonlin

Plasma PK Parameters		
Parameter	**Description**	**Programming Notes**
$t_{1/2}$	Estimate of the terminal elimination half-life of the drug	HL_Lambda_z from WinNonlin If valid λ_z is not present, then parameter is flagged in listings and will not be used in summary statistics.
CL	CL = Dose/AUC where "Dose" is the dose of the drug and AUC = AUC_{inf}	CL_obs from WinNonlin
λ_z	Terminal elimination rate constant, estimate by linear regression of the terminal elimination phase of the concentration of drug versus time curve	Lambda_z from WinNonlin If Rsq < 0.80 then parameter is flagged in listings and will not be used in summary statistics.
V_z	Volume of distribution of the drug	Vz_obs from WinNonlin If valid λ_z is not present, then parameter is flagged in listings and will not be used in summary statistics.
T_{max}	Time to C_{max}	Tmax from WinNonlin

Note: In all derivations of PK parameters, BQL values at the beginning of the profile will be set to zero, whereas BQL values that occur after the first quantifiable point will be considered missing. Samples that are BQL but are between two samples with detectable concentrations will be excluded from PK analysis.

16.1.2 Urine Variables

- Urine concentrations of galidesivir.
- Urine PK parameters of galidesivir.

Urine samples will be collected to determine the concentrations of galidesivir. The urine PK parameter summaries described in this section will be created using the PK population.

Urine PK Parameters		
Parameter	**Description**	**Programming Notes**
Ct1-t2	Concentration (of the unchanged drug) in the collection interval t1-t2.	Directly from data, no calculation required.
Vt1-t2	Volume of the urine collected in the interval t1-t2	Measured in the clinic, captured on the CRF, no calculation required.

Urine PK Parameters		
Parameter	**Description**	**Programming Notes**
Aet1-t2	Amount of drug excreted unchanged into urine in the interval t1-t2, calculated as the urine volume times the urine concentration for each interval. Intervals: 0-12 h, 12-24 h, 24-48 h, 48-72 h, 72-96 h, 0-96h (cumulative)	Ct1-t2 *Vt1-t2
% $Dose_{excreted,t1-t2}$	Percentage of given dose excreted in the urine as unchanged drug Intervals: 0-12 h, 12-24 h, 24-48 h, 48-72 h, 72-96 h, 0-96h (cumulative)	Aet1-t2/Dose*100 Dose will be converted to match units of Ae
CL_r	Renal clearance of unchanged drug cumulatively over all collection intervals	CLr=Ae0-t1/AUC0-t1 CLr parameter will be calculated according to time matched AUC.

Note: Urine PK parameters will be estimated in SAS based on the recorded urine concentrations and volumes. In estimating the parameters, all missing values will be recorded as missing and all BLQ values will be set to zero. If a missing value is encountered, the cumulative parameters will not be calculated for that subject.

16.2 Pharmacokinetic Summaries

16.2.1 Plasma Concentrations

Plasma concentrations for BCX4430 below the quantifiable limit (BQL) will be set to zero in the computation of mean concentration values. Descriptive statistics including n, arithmetic mean, SD, arithmetic CV%, geometric mean, geometric CV%, geometric n (the number of subjects with an observation who were included in the natural logarithmic transformation) median, min, and max will be used to summarize the plasma concentrations by treatment at each scheduled time point. If more than half of the subjects in a given cell have values BQL, then the descriptive statistics will not be presented and will instead display as BQL for the mean and minimum. Except for n and maximum, all other statistics will be missing. Any value less than BQL will be presented as BQL.

Linear and semi-logarithmic plots of the arithmetic mean and median plasma concentrations by scheduled sampling time will be provided by treatment. These plots will show time in hours. The plots will match the summary table results and will not have an observation at a given time point if more than half of the subjects have values BQL. Mean plots will include SD error bars when plotted on a linear scale and log scale.

Linear and semi-logarithmic plots of the individual plasma concentrations by actual sampling time will be provided by subject (1 subject per page). These plots will show time in hours. Individual plots will use the BQL handling procedure described below for "Plasma Pharmacokinetic Parameters".

All individual subject plasma concentration data will be listed by cohort and treatment.

16.2.2 Plasma Pharmacokinetic Parameters

Plasma PK parameters for BCX4430 will be estimated using non-compartmental methods with WinNonlin®.

The plasma PK parameters will be estimated from the concentration-time profiles. In estimating the PK parameters, BQL values at the beginning of the profile will be set to zero. BQL values that occur after the first quantifiable point will be considered missing. Samples that are BQL but are between two samples with detectable concentrations will be excluded from PK analysis.

Actual sampling times, rather than scheduled sampling times, will be used in all computations involving sampling times. If the actual time or dose time is missing, the scheduled time may be substituted in order to calculate the PK parameter.

Determination of points to be included in λ_z range will follow the Guideline for Defining, Calculating and Summarizing Pharmacokinetic / Pharmacodynamic Parameters (EDSREP 009 R 01) and rule will be noted in table and listing footnotes.

Descriptive statistics (n, arithmetic mean, SD, arithmetic CV%, geometric mean, geometric CV%, median, min, and max) will be used to summarize the calculated PK parameters by treatment. For T_{max}, T_{lag}, and T_{last}, only n, median, min, and max will be presented.

Individual PK parameters AUCt, AUCinf, and Cmax with corresponding geometric means will be shown graphically for each treatment.

All individual subject PK parameters will be listed by treatment and period.

16.2.3 Urine Pharmacokinetic Parameters

Urine PK parameters will be estimated in SAS based on the recorded urine concentrations and volumes. In estimating the parameters, all missing values will be recorded as missing and all BLQ values will be set to zero. If a missing value is encountered, the cumulative parameters will not be calculated for that subject. Summaries of amounts excreted by treatment and scheduled collection interval (Aet1-t2), including cumulative amount excreted, fraction excreted by treatment and scheduled collection interval (% $Dose_{excreted,t1-t2}$), including cumulative fraction excreted, and renal clearance (CL_r) will be provided. Descriptive statistics (n, arithmetic mean, SD, arithmetic CV%, geometric mean, geometric CV%, median, min, and max) will be used to summarize the calculated PK parameters by treatment.

16.2.4 Dose Proportionality Analyses

16.2.4.1 Power Model

The assessment of dose proportionality for the PK parameters of BCX4430 will use a power model approach (including all doses). A model with ln-transformed dose (dose continuous) as a fixed effect and subject as a random effect will be applied to the following ln-transformed PK parameters: AUC_t, AUC_{inf}, and C_{max}. Although there is no formal statistical hypothesis tested for this secondary objective, there will be evidence for dose-proportionality for each PK parameter if the 90% confidence interval (CI) of the fixed slope for ln-dose contains 1. No adjustment for multiplicity will be performed for the set 3 of PK parameters.

The SAS pseudo code for the power model is as follows:

```
data adpp;
set adpp;
ln_auc = log(auc);
ln_dose = log(dose);
run;

proc mixed data=adpp method=reml;
by parameter;
class subject;
model ln_auc = ln_dose / ddfm=kr cl alpha=0.1;
random subject;
run;
```

16.2.4.2 ANOVA Model Pairwise Comparisons

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. Pairwise

comparisons of the ratio of GLS means and the corresponding 90% CI will be estimated for each PK parameter of interest. Although there is no formal statistical hypothesis tested for this secondary objective, if the 90% CI for the geometric LSM ratio falls completely within the 0.8 to 1.25 equivalence region then dose proportionality is indicated for the specific comparison. No adjustment for multiplicity will be performed for the set of descriptive pairwise comparisons.

The SAS PROC MIXED pseudo code for the pairwise comparison for the ANOVA model is as follows:

```
data adpp;
set adpp;
ln_auc_dose = log(auc)/dose;
run;

ods output diffs=diffs;
ods output lsmeans=lsmeans;
proc mixed data=adpp method=reml;
by parameter;
class dose;
model ln_auc_dose = dose / ddfm=kr;
lsmeans dose /  pdiff alpha=0.1 cl;
run;
```

17.0 Safety Analyses

The safety summaries described in this section will be created using the safety analysis population. Safety analyses will be performed separately for each cohort.

17.1 Safety Variables

The following safety variables will be included:

- Adverse events
- Clinical laboratory evaluations
  - Cardiac markers (troponin and creatine kinase-MB [CK-MB])
  - Chemistry
  - Coagulation
  - Hematology
  - Urinalysis
  - Serology
  - Pregnancy
  - Alcohol breath test and urine drug screen
- Vital signs
  - Systolic blood pressure
  - Diastolic blood pressure
  - Pulse rate
  - Oral body temperature
- Electrocardiograms
  - Heart rate
  - RR interval
  - PR interval
  - QRS duration
  - QT interval
  - QT interval corrected using Fredericia's method (QTcF)
- Physical examination findings

17.1.1 Adverse Events

An AE is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation participant that does not necessarily have a causal relationship with treatment. TEAEs are those which occur during or after the administration of the first dose of study drug. All TEAE summaries will be presented alphabetically by system organ class, with preferred terms sorted in decreasing order of frequency within each system organ class based on MedDRA Version 21.1.

The following missing data will be imputed (for calculations only) as defined:

- Missing AE start and / or end times for the calculation of onset and duration will be assumed to be at 00:01 for a start time and 23:59 for end times
- Missing AE severity or relationship will be assumed to be severe or related, respectively
- Missing AE start times for the determination of treatment emergence will be assumed to occur after treatment unless partial date documents the AE as happening prior to treatment
- Missing AE start times for the determination of treatment assignment will be assumed to occur after treatment on the recorded date 1 minute after dosing
- Missing AE start date will be assumed to be after treatment for the determination of TEAE but will not be attributed to a specific study drug

A summary of the number and percentage of subjects reporting AEs, TEAEs, serious AEs (SAEs), and who discontinue study drug due to an AE will be provided by cohort and overall for the study.

A summary of the number and percentage of subjects reporting each TEAE will be provided by cohort and treatment, and overall. Counting will be done by subject, not by event; subjects will only be counted once within each system organ class or preferred term.

A summary of the number and percentage of subjects reporting each TEAE will be provided by relationship to treatment (BCX4430 formulation, as recorded on eCRF) and by cohort and treatment, and overall. Subjects with multiple events will be counted under the category of their most-related event within each system organ class or preferred term.

A summary of the number and percentage of subjects reporting each TEAE will be provided by severity (as recorded on eCRF) and by cohort and treatment, and overall within each cohort. Subjects with multiple events will be counted under the category of their most severe event within each system organ class or preferred term.

All AEs (including non-treatment-emergent AEs) recorded on the eCRF will be listed by subject.

A separate listing of AEs leading to study drug discontinuation will be provided by subject.

17.1.2 Deaths and Serious Adverse Events

A listing of deaths and a listing of SAEs will be provided by subject.

17.1.3 Laboratory Data

Clinical laboratory data will be presented using units from the study data tabulation model (SDTM) Controlled Terminology.

A descriptive statistics summary of continuous laboratory results and derived changes from baseline for cardiac markers, chemistry, coagulation, hematology, and urinalysis will be provided by cohort and scheduled timepoint.

Laboratory abnormalities outside of the normal laboratory reference ranges and associated grades (according to study specific DMID criteria specified in the 2014 DMID Adult Toxicity Grading Scale in Appendix 5) 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 severity grading will be provided by the PI. The number and percentage of subjects experiencing treatment-emergent graded toxicities will be summarized.

A shift table describing the change in continuous clinical laboratory values from baseline to follow-up (number and percentage of subjects) will also be provided. The following categories will be used: Normal, DMID Grade 1, DMID Grade 2, DMID Grade 3, DMID Grade 4.

All laboratory data will be listed by subject, including laboratory variables not listed in the protocol.

A separate listing of out-of-range values will also be provided. Normal ranges will be used directly from the clinical laboratory and will be included in the listings for reference. Flags for high and low values will be provided in the listings.

17.1.4 Vital Signs

A descriptive statistics summary of vital signs and derived changes from baseline will be provided by cohort and treatment, and scheduled timepoint. Baseline is defined as measurement prior to initiation of treatment on Day 1 of each treatment period, where available.

All vital signs data will be listed by subject.

17.1.5 Electrocardiograms

A descriptive statistics summary of 12-lead ECG parameters and derived changes from baseline will be provided by cohort and treatment, and scheduled timepoint. Where triplicate ECGs are taken, the average parameter values of the triplicates will be reported. Baseline is defined as the average of triplicate measurements prior to initiation of treatment on Day 1 of each treatment period, where available.

A summary table for QTcF categories (<=450 msec, >450 to <= 480 msec, >480 to <=500 msec, and > 500 msec) by cohort and treatment, and timepoint will be presented. The table will also summarize the number and percentage of subjects with change from baseline for categories of <= 30 msec, 30 msec to <= 60 msec, and > 60 msec.

All 12-lead ECG parameters, physician's conclusions, and corresponding abnormalities and will be listed by subject.

Descriptive statistics will be provided to summarize mean ECG parameters (observed and changes from baseline) by treatment, visit, and scheduled time.

17.1.6 Cardiac Telemetry

A listing of the cardiac telemetry data will include the start and stop times of telemetric observation, the occurrence of any arrythmia or tachycardia of Grade 2 or higher (i.e. heart rate greater than 115 beats per minute), and the clinical evaluation of clinical significance of any arrythmia or tachycardia.

17.1.7 Echocardiograms

A listing of the echocardiogram data will include the date and time of the assessment, the ejection fraction, and any clinical finding confirmed by cardiologist.

17.1.8 Physical Examination

All physical examination data will be listed by subject.

References

SAS Institute, Inc., SAS® Version 9.4 software, Cary, NC.

Clinical Study Protocol. A Phase 1 Drug Interaction Study to Evaluate the Effect of BCX4430 on the Pharmacokinetics of Danazol, Amlodipine and Desipramine in Healthy Subjects. Version 1.0, Final, 07 Mar 2018.

Gough K, Hutchison M, Keene O, Byrom B, Ellis S, Lacey L, McKellar J. (1995). Assessment of dose proportionality: Report from the statisticians in the pharmaceutical industry / pharmacokinetics UK joint working party, Drug Information Journal, Vol. 29:1039-1048.

Patroneva A , Connolly SM, Fatato P , et al. (2008). An assessment of drug-drug interactions: the effect of desvenlafaxine and duloxetine on the pharmacokinetics of the CYP2D6 probe desipramine in healthy subjects. Drug Metab Dispos 36(12): 2484-2491.

Vincent J , Harris SI, Foulds G , et al. (2000). Lack of effect of grapefruit juice on the pharmacokinetics and pharmacodynamics of amlodipine. Br J Clin Pharmacol 50(5): 455-463.

Appendix 1: Glossary of Abbreviations

Glossary of Abbreviations:	
AE	Adverse event
ADaM	Analysis data model
AUC	Area under the concentration-time curve
AUC_{inf}	Area under the concentration versus time curve extrapolated to infinite time
AUC_t	Area under the concentration time curve from time 0 to time t (hours)
$AUC_{\%extrap}$	Percentage of AUC extrapolated between AUC_t and AUC_{inf}.
BQL	Below the quantifiable limit
CI	Confidence interval
C_{last}	Concentration observed at the last quantifiable time point.
CL/F	Apparent oral clearance after administration of the drug
C_{max}	Maximum plasma concentration.
CSR	Clinical study report
CRU	Clinical research unit
CV	Coefficient of variation
DMID	Division of Microbiology and Infectious Disease
ECG	Electrocardiogram
eCRF	Electronic case report form
EDS	Early Development Services
LSM	Least squares means
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
PK	Pharmacokinetic
QC'd	Quality controlled
SAP	Statistical analysis plan
SAE	Serious adverse event
SD	Standard deviation
TEAE	Treatment-emergent adverse event
TFL(s)	Tables, figures and listings
T_{lag}	Elapsed time from dosing at which analyte was first quantifiable in a concentration vs. time profile
T_{last}	Time of C_{last}
T_{max}	Time of C_{max}

$T_{1/2}$	Terminal phase half-life expressed in time units
Vz/F	Apparent volume of distribution of the drug.
WHO	World Health Organization
λ_z	Terminal elimination rate constant

Appendix 2: Schedules of Assessments from Protocol

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 (Discharge)	Day 5, Day 7, 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
Concomitant medications	X	X	X	X	X	X	X	X	X
ECG	X[c]		X[c]	X[d]	X[d]	X[d]	X[d]		X[d]
Cardiac telemetry			X[e]	X[e]					

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 (Discharge)	Day 5, Day 7, Day 14[n]	Day 21 + 2
ECHO[f]	X[f]					X[f]			
Vital signs	X	X	X[g]	X[g]	X[g]	X	X		X
Pregnancy test[h]	X	X							X
FSH[i]	X								
Clinical chemistry/ hematology	X	X[m]		X	X	X	X		X
Urinalysis	X	X[m]			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
Urine for galidesivir PK analysis[l]			X	X	X	X	X		
AE assessment		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 4 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. 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 -1 for eligibility determination. An ECHO should also be performed on Day 3. An acceptable window for the Day 3 ECHO is up until Day 4 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.
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 5 (+1), Day 7 (+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.

Appendix 3: List of End of Text Outputs

List of End of Text Tables and Figures:		
Output	Title	Analysis Population
Section 14.1 – Disposition and Demographic Data		
Table 14.1.1	Summary of Subject Disposition	All Subjects
Table 14.1.2.1	Summary of Demographics	Safety
Table 14.1.2.2	Summary of Demographics	PK
Table 14.1.3	Summary of Study Drug Administration	Safety
Section 14.2 – Plasma Pharmacokinetic Data		
Table 14.2.1	Summary of BCX4430 Plasma Concentrations	Safety
Table 14.2.2	Summary of BCX4430 Plasma Pharmacokinetic Parameters	PK
Table 14.2.3	Summary of BCX4430 Urine Pharmacokinetic Parameters	PK
Table 14.2.3.1	Statistical Analysis of the Dose Proportionality: Power Model	PK
Table 14.2.3.2	Statistical Analysis of the Dose Proportionality: ANOVA Model of Pairwise Comparisons	PK
Figure 14.2.4	Plot of Mean (±SD) BCX4430 Plasma Concentrations vs Time on a Linear Scale	Safety
Figure 14.2.5	Plot of Mean BCX4430 Plasma Concentrations vs Time on a Semi-Log Scale	Safety
Figure 14.2.6	Plot of Median BCX4430 Plasma Concentrations vs Time on a Linear Scale	Safety
Figure 14.2.7	Plot of Individual BCX4430 Plasma Concentrations vs Time on a Linear Scale	Safety
Figure 14.2.8	Plot of Individual BCX4430 Plasma Concentrations vs Time on a Semi-Log Scale	Safety
Figure 14.2.9	Scatter Plot of Individual BCX4430 Plasma Pharmacokinetic Parameters	PK
Section 14.3 – Safety Data		
Table 14.3.1.1	Summary of Adverse Events	Safety
Table 14.3.1.2	Summary of Treatment Emergent Adverse Events by System Organ Class and Preferred Term	Safety
Table 14.3.1.3	Summary of Treatment Emergent Adverse Events by Relationship to BCX4430	Safety
Table 14.3.1.4	Summary of Treatment Emergent Adverse Events by Severity	Safety
Table 14.3.2	Listing of Serious Adverse Events	All Subjects
Table 14.3.3	Listing of Deaths	All Subjects
Table 14.3.4	Listing of Abnormal Laboratory Values	All Subjects
Table 14.3.5.1	Summary of Laboratory Results	Safety
Table 14.3.5.2	Summary of Laboratory Shifts from Baseline	Safety

Table 14.3.5.3	Summary of Treatment Emergent Graded Laboratory Toxicities	Safety
Table 14.3.6	Summary of Vital Signs	Safety
Table 14.3.7.1	Summary of 12-Lead Electrocardiogram Results	Safety
Table 14.3.7.2	Summary of QTcF Categorical Findings	Safety

List of End of Text Listings:	
Output	**Title**
Section 16.2.1 – Disposition	
Listing 16.2.1.1	Subject Disposition
Listing 16.2.1.2	Eligibility Criteria
Section 16.2.2 – Protocol Deviations	
Listing 16.2.2	Important Protocol Deviations
Section 16.2.3 – Excluded Subjects	
Listing 16.2.3	Analysis Populations
Section 16.2.4 – Demographics and Baseline Characteristics	
Listing 16.2.4.1	Subject Demographics
Listing 16.2.4.2	Medical History
Listing 16.2.4.3	Prior and Concomitant Medications
Section 16.2.5 – Compliance	
Listing 16.2.5.1	Study Drug Administration
Listing 16.2.5.2	Meal Administration
Section 16.2.6 – Response Data	
Listing 16.2.6.1	Plasma Concentrations
Listing 16.2.6.2	Plasma Pharmacokinetic Parameters
Listing 16.2.6.3	Urine Pharmacokinetic Parameters
Section 16.2.7 – Adverse Events Data	
Listing 16.2.7.1	Adverse Events
Listing 16.2.7.2	Adverse Events Leading to Study Drug Discontinuation
Section 16.2.8 – Laboratory Data	
Listing 16.2.8.1	Clinical Laboratory Results – Cardiac Markers
Listing 16.2.8.2	Clinical Laboratory Results – Chemistry
Listing 16.2.8.3	Clinical Laboratory Results – Coagulation
Listing 16.2.8.4	Clinical Laboratory Results – Hematology
Listing 16.2.8.5	Clinical Laboratory Results – Urinalysis
Listing 16.2.8.6	Clinical Laboratory Results – Serology
Listing 16.2.8.7	Clinical Laboratory Results – Pregnancy and FSH
Listing 16.2.8.8	Clinical Laboratory Results – Urine Drug and Alcohol Screen
Section 16.2.9-10 – Other Safety Data	

Listing 16.2.9	Vital Signs
Listing 16.2.10	12-Lead Electrocardiogram Results
Listing 16.2.11	Cardiac Telemetry Results
Listing 16.2.12	Echocardiogram Results
Listing 16.2.13	Physical Examination Findings

Other Appendix Outputs:	
Output	**Title**
Appendix 16.1.9.2	Statistical Appendices

Appendix 4: Shells for Post-Text Tables, Figures and Listings

Shells are provided in a separate document.

Appendix 5: 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	8.9-10.4 mg/dL	>ULN – 10.5	10.6 – 11.0	>11.0
	20Y-133Y	8.6-10.3 mg/dL	>ULN – 10.4	10.5 – 10.9	>10.9
Calcium – hypercalcemia mg/dL (Female)	18Y-19Y	8.9-10.4 mg/dL	>ULN – 10.5	10.6 – 10.9	>10.9
	20Y-49Y	8.6-10.2 mg/dL	>ULN – 10.3	10.4 – 10.7	>10.7
	50Y-133Y	8.6-10.4 mg/dL	>ULN – 10.5	10.6 – 10.9	>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	2.5-4.5 mg/dL	2.3 – <2.5	2.0 – < 2.2	<2.0
	65Y-133Y	2.1-4.3 mg/dL	1.9 – <2.1	1.6 – < 1.8	<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	6.3-8.2 g/dL	6.1 – 6.3	5.7 – 6.0	<5.7
	20Y-133Y	6.1-8.1 g/dL	5.9 – 6.1	5.5 – 5.8	<5.5
Alkaline phosphatase – U/L (Male)	18Y-19Y	48-230 U/L	230 – 340	341 – 460	>460
	20Y-133Y	40-115 U/L	115 – 225	226 – 345	>345
Alkaline phosphatase – U/L (Female)	18Y-19Y	47-176 U/L	176 – 286	287 – 406	>406
	20Y-49Y	33-115 U/L	115 – 225	226 – 345	>345
	50Y-133Y	33-130 U/L	130 – 240	241 – 360	>360
AST (Male) U/L	18Y-19Y	12-32 U/L	32 – 93	94 – 163	>163
	20Y-49Y	10-40 U/L	40 – 101	102 – 171	>171
	50Y-133Y	10-35 U/L	35 – 96	97 – 166	>166
AST (Female) U/L	18Y-19Y	12-32 U/L	32 – 93	94 – 163	>163
	20Y-44Y	10-30 U/L	30 – 91	92 – 161	>161
	45Y-133Y	10-35 U/L	35 – 96	97 – 166	>166
ALT (Male) U/L	18Y-19Y	8-46 U/L	46 – 101	102 – 171	>171
	20Y-133Y	9-46 U/L	46 – 101	102 – 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	0.2-1.1 mg/dL	1.2 – 1.9	2.0 - 2.4	>2.4
	20Y-133Y	0.2-1.2 mg/dL	1.3 – 2.0	2.1 – 2.5	>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	12.0-16.9 g/dL	11.5 – 12.0	10.5 – 11.9	<10.5
	19Y-133Y	13.2-17.1 g/dL	12.7 – 13.2	12.2 – 12.7	<12.2
Hemoglobin (Female) - g/dL	18Y	11.5-15.3 g/dL	11.0 – 11.5	9.5 – 10.9	<9.5
	19Y-133Y	11.7-15.5 g/dL	11.2 – 11.7	9.8 – 11.2	<9.8
WBC Increase - cell/mm3	18Y	4,500-13,000/uL	13,001 – 17,000	17,001 – 22,000	>22,000
	19Y-133Y	3,800-10,800/uL	10,801 – 14,800	14,801 – 19,800	>19,800
WBC Decrease - cell/mm3	18Y	4,500-13,000/uL	3,500 – 4,500	2,500 – 3,499	<2,500
	19Y-133Y	3,800-10,800/uL	2,800 – 3,800	1,800 – 2,799	<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				

Document History

Version Date	Modified/Reviewed By	Brief Summary of Changes
21-Jan-2018	Jacqueline Cater Stephannie Kollipara Emily Mick	Created from EDSREP 009 T 01 G.
28-Mar-2018	Jacqueline Cater Emily Mick	Revised according to sponsor comments (using updated protocol and eCRF).

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

Protocol #: **BCX4430-106 / DMID 18-0013**
PRA Study Code: **181392**

Dose Escalation Report

Single Ascending Dose

Cohort 1: 5 mg/kg

Report Date: 07Jan2019

For BioCryst:
Bill Sheridan, MB, BS, Medical Monitor / Chief Medical Officer
Amanda Mathis, PhD, Clinical Pharmacologist

DMID:
Venus S. Shahamatdar, MD, Medical Monitor
Kay M. Tomashek, MD, MPH, DTM, Medical Officer
Carol Ostrye, RN, MPH, Clinical Project Manager

For PRA:
Daniel Dickerson, MD, PhD, Principal Investigator
Jamie Easum, APRN-BC, Co-Lead Sub-Investigator
Lesa Davis, PA-C, Co-Lead Sub-Investigator
Traci Goodwin, Clinical Study Manager
Tim Theisen, Project Manager

Safety Assessment Following Dose Administration of BCX4430 or Placebo to Healthy Volunteers

1.0 Subject Demographics, Dosing Date and Administration Times (All subjects dosed under fed conditions).

Subject #	Screening #	M/F	Age	Dosing Date	Dosing Time	Discharge from Clinical Site (Date)
11001	01-005	M	37	11Dec2018	0900	16Dec2018
11002	01-010	M	27	11Dec2018	0905	16Dec2018
11005	01-013	M	32	13Dec2018	0900	17Dec2018
11006	01-014	M	45	13Dec2018	0905	17Dec2018
11004	01-012	F	48	13Dec2018	0910	17Dec2018
11003	01-006	F	24	13Dec2018	0915	17Dec2018
11008	01-023	F	52	13Dec2018	0925	17Dec2018
11007	01-029	F	32	13Dec2018	0930	17Dec2018

2.0 Adverse Events

Subject #	AE #	Adverse Event	Date of Onset	Time of Onset	Date of Resolution	Time of Resolution	Severity	Relationship to IP
11007	1	Viral Gastroenteritis	26Dec2018	2100	27Dec2018	0900	Mild	Not related

2.1 Adverse Event Comments (summarize findings from above table):

Subject #	AE #	Adverse Event	Comments
11007	1	Viral Gastroenteritis	Subject reports on set of nausea, vomiting and diarrhea with know exposure to family with viral gastroenteritis over the preceding 24-48 hours. Resolved within 48 hours.

3.0 Safety Lab Data: (Summary of significant or notable lab results)

Subj #	Screen #	M/F	Age	Laboratory Collection Date	Lab Test	Result	Range	Toxicity Grading
11001	01-005	M	37	11Dec2018	Total Protein	6.0 g/dL	6.1-8.1 g/dL	1
11002	01-010	M	27	31Dec2018	PT	12.1 sec	9.0-11.5 sec	1
11003	01-006	F	24	13Dec2018	CPK	321 U/L	29-143 U/L	1
11003	01-006	F	24	14Dec2018	CPK	220 U/L	29-143 U/L	1
11003	01-006	F	24	14Dec2018	Glucose	140 mg/dL	65-139 mg/dL	1
11003	01-006	F	24	15Dec2018	CPK	165 U/L	29-143 U/L	1

11003	01-005	F	24	16Dec2018	CPK	152 U/L	29-143 U/L	1
11003	01-005	F	24	16Dec2018	CPK	156 U/L	29-143 U/L	1
11003	01-005	F	24	02Jan2019	CPK	1290 U/L	29-143 U/L	2
11003	01-005	F	24	07Jan2019	CPK	Pending		
11004	01-012	F	49	14Dec2018	Glucose	69 mg/dL	65-139 mg/dL	2
11004	01-012	F	49	16Dec2018	Glucose	61 mg/dL	65-139 mg/dL	2
11006	01-013	M	32	13Dec2018	Phosphate	1.8 mg/dL	2.5-4.5 mg/dL	3
11006	01-013	M	32	14Dec2018	Glucose	142 mg/dL	65-139 mg/dL	1
11006	01-013	M	32	15Dec2018	Glucose	157 mg/dL	65-139 mg/dL	2
11006	01-013	M	32	15Dec2018	Sodium	134 mmol/L	135-146 mmol/L	1
11006	01-013	M	32	16Dec2018	Glucose	141 mg/dL	65-139 mg/dL	1
11006	01-013	M	32	17Dec2018	Sodium	134 mmol/L	135-146 mmol/L	1
11006	01-014	M	45	13Dec2018	Phosphate	2.1 mg/dL	2.5-4.5 mg/dL	2
11006	01-014	M	45	14Dec2018	Phosphate	2.4 mg/dL	2.5-4.5 mg/dL	1
11006	01-014	M	45	15Dec2018	Glucose	148 mg/dL	65-139 mg/dL	1
11006	01-014	M	45	15Dec2018	Phosphate	2.4 mg/dL	2.5-4.5 mg/dL	1
11007	01-029	F	32	14Dec2018	Glucose	62 mg/dL	65-139 mg/dL	1
11007	01-029	F	32	02Jan2019	Hemoglobin	11.6 g/dL	11.7-15.5 g/dL	1
11007	01-029	F	32	02Jan2019	CPK	169 U/L	29-143 U/L	1
11008	01-023	F	62	02Jan2019	ALT	32 U/L	6-29 U/L	1
11008	01-023	F	62	02Jan2019	Amylase	105 U/L	21-101 U/L	1

*N.B. Subject 11004 had elevated CPK at screening and on Day -1.

3.1 Actions Taken/Con Meds Administered Related to Adverse Events:

Subject #	AE #	Medication	Dose/Unit	Route	Start Date	Stop Date	Prescribed for:

4.0 Vital Signs Data (summary of clinically significant abnormal vital signs by subject # and time point taken):

Subject #	Screening #	M/F	Age	Date	Time	Values	Grade
							N/A

*There were no vital signs which met the criteria for halting dosing in Section 11.5.2 of the protocol.

5.0 12-Lead ECG Data (summarize clinically significant abnormal changes by subject # and time point taken):

There were no clinically significant ECG findings, and no ECG parameters met the criteria for halting dosing stated in Section 11.5.2 of the protocol.

6.0 Physical Examination Data (summarize clinically significant abnormal changes by subject # and time point performed):

There were no clinically significant physical exam findings noted.

7.0 Subject Discontinuations:

No subjects were discontinued.

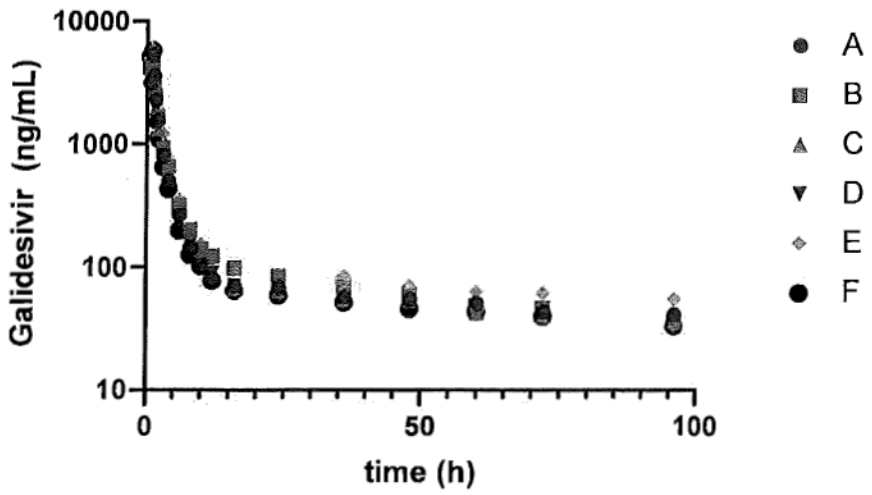
8.0 PK Summary (insert tables, appendices as allowed by sponsor, if available):

Subjects in the table below have been anonymized with an alphabet code. Samples collected through 96 hours post-dose were shipped for analysis, and therefore $AUC_{0\text{-last}}$ in the table below represents 96 hours. Samples were quantifiable through 96 hours in all subjects. The geometric mean(%CV) C_{max}, $AUC_{0\text{-}24}$ and $AUC_{0\text{-last}}$ were 5540 ng/mL (8), 10850 ng.h/mL (11), and 14530 ng.h/mL (12), respectively.

No PK parameters met halting rules, and overall, the PK following a 5 mg/kg single dose administered by IV infusion was in line with anticipated exposure based on modeling and simulation.

Subject Code	T ½ (h)	C_{max}* (ng/mL)	$AUC_{0\text{-}24h}$ (ng.h/mL)	$AUC_{0\text{-last}}$ (ng.h/mL)	$AUC_{0\text{-Inf}}$ (ng.h/mL	%AUC extrap	Cl (mL/h/kg)	Vz (mL/kg)
A	96.9	5420	10000	13660	19440	30	257	35960
B	55.9	4870	11270	15190	18110	16	276	22270
C	191.6	6140	11040	14390	24760	42	202	55830
D	75.3	5510	10460	13730	17110	20	292	31760
E	170.6	5590	12910	17830	31410	43	159	39180
F	92.9	5820	9700	12860	17320	26	289	38680
Geomean	103.6	5540	10850	14530	20810	28	240	35930
%CV	50.2	8	11	12	27	38	22	30

*the timepoint for C_{max} was taken at the end of the 1-hour infusion



9.0 Investigator opinion about safety of IP based upon clinical tolerance of trial during reported period:

Internal review of all available safety data prior to the dose escalation call shows no concerns with proceeding to the next dose level.

10.0 Summary of Discussion at Dose Escalation Call:

Subject 11004 had a grade 2 elevated CPK at her end of study laboratory evaluation. The subject had no physical symptoms associated with this elevated CPK and on review of her previous labs, she had elevated CPK at screening and on Day -1. She is scheduled to have her CPK redrawn today, 07Jan2019. The safety committee had no concerns regarding this laboratory excursion.

Subjects 1105 and 1106 had grade 2 decreases in phosphate which rapidly corrected. Neither subject had signs or symptoms of hypophosphatemia. The safety committee had no concerns regarding these lab excursions. We will continue monitoring for trends.

Based upon safety measures, tolerance, and pharmacokinetic results, the dose of 5 mg/kg was well tolerated. The Safety Committee discussed data and agreed that data supports moving forward with dose escalation without changes to the protocol.

Current Dose Level: 5 mg/kg

Next Dose Level: 10 mg/kg

Protocol changes required prior to next dose level administration (e.g. additional safety monitoring)?

Yes ☐
No ☒

09 Jan 2019

Daniel Dickerson, MD, PhD
Principal Investigator
PRA EDS-Lenexa

Date

Diane Sm Palmer MD MPH
For Bill Sheridan

8 Jan 2019

Bill Sheridan, MB, BS
Medical Monitor
BioCryst Chief Medical Officer

Date

Amanda Mathis

8 Jan 2019

Amanda Mathis
Director, Clinical Pharmacology
BioCryst Pharmaceuticals

Date

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

Protocol #: **BCX4430-106 / DMID 18-0013**
PRA Study Code: **181392**

Dose Escalation Report

Single Ascending Dose

Cohort 2: 10 mg/kg

Report Date: 01Feb2019

For BioCryst: Diane Gesty-Palmer MD, PhD, Medical Monitor/Senior Medical Director

Amanda Mathis, PhD, Clinical Pharmacologist

DMID: Venus S. Shahamatdar, MD, Medical Monitor

Kay M. Tomashek, MD, MPH, DTM, Medical Officer

Carol Ostrye, RN, MPH, Clinical Project Manager

For PRA: Daniel Dickerson, MD, PhD, Principal Investigator

Jamie Easum, APRN-BC, Co-Lead Sub-Investigator

Lesa Davis, PA-C, Co-Lead Sub-Investigator

Traci Goodwin, Clinical Study Manager

Tim Theisen, Project Manager

Safety Assessment Following Dose Administration of BCX4430 or Placebo to Healthy Volunteers

1.0 Subject Demographics, Dosing Date and Administration Times (All subjects dosed under fed conditions).

Subject #	Screening #	M/F	Age	Dosing Date	Dosing Time	Discharge from Clinical Site (Date)
12001	01-045	F	25	09Jan2019	0900	13Jan2019
12002	01-044	M	26	09Jan2019	0905	13Jan2019
12003	01-048	M	28	11Jan2019	0900	15Jan2019
12004	01-052	M	30	11Jan2019	0905	15Jan2019
12005	01-054	M	27	11Jan2019	0910	15Jan2019
12006	01-055	M	46	11Jan2019	0915	15Jan2019
12007	01-057	F	40	16Jan2019	0930	20Jan2019
12008	01-058	M	32	22Jan2019	0900	26Jan2019

2.0 Adverse Events

Subject #	AE #	Adverse Event	Date of Onset	Time of Onset	Date of Resolution	Time of Resolution	Severity	Relationship to IP

2.1 Adverse Event Comments (summarize findings from above table):

Subject #	AE #	Adverse Event	Comments

3.0 Safety Lab Data: (Summary of significant or notable lab results)

Sub #	Screen #	M/F	Age	Laboratory Collection Date	Study Day	Lab Test	Result	Range	Toxicity Grading
12001	01-046	F	25	09Jan2019	1	Hemoglobin	11.0 g/dL	11.7-15.5 g/dL	2
12001	01-046	F	25	10Jan2019	2	Hemoglobin	10.9 g/dL	11.7-15.5 g/dL	2
12001	01-046	F	25	11Jan2019	3	Hemoglobin	11.1 g/dL	11.7-15.5 g/dL	2
12001	01-046	F	25	11Jan2019	3	RBC (UA)	3-10 /HPF (on menses)	</= 2 /HPF	1
12001	01-046	F	25	12Jan2019	4	Hemoglobin	10.7 g/dL	11.7-15.5 g/dL	2
12001	01-046	F	25	12Jan2019	4	RBC (UA)	3-10 /HPF (on menses)	</= 2 /HPF	1
12001	01-046	F	25	13Jan2019	5	RBC (UA)	10-20 /HPF (on menses)	</= 2 /HPF	2
12001	01-046	F	25	13Jan2019	5	Hemoglobin	11.3 g/dL	11.7-15.5 g/dL	1
12001	01-046	F	25	29Jan2019	21	PT	11.6 sec	9.0-11.5 sec	1
12002	01-044	M	26	10Jan2019	2	Glucose (fasting)	58 mg/dL	65-99 mg/dL	2
12003	01-048	M	28	12Jan2019	2	Potassium	5.5 mmol/L	3.5-5.3 mmol/L	2
12003	01-048	M	28	15Jan2019	5	PT	11.7 sec	9.0-11.5 sec	1
12006	01-055	M	48	11Jan2019	1	Hemoglobin	12.9 g/dL	13.2-17.1 g/dL	1
12006	01-055	M	48	11Jan2019	1	Hemoglobin	13.0 g/dL	13.2-17.1 g/dL	1
12006	01-055	M	48	13Jan2019	3	Hemoglobin	12.8 g/dL	13.2-17.1 g/dL	1
12006	01-055	M	48	15Jan2019	5	Hemoglobin	13.1 g/dL	13.2-17.1 g/dL	1
12005	01-054	M	27	15Jan2019	5	PT	11.7 sec	9.0-11.5 sec	1
12005	01-054	M	27	15Jan2019	5	Amylase	102 U/L	21-101 U/L	1
12007	01-057	F	40	16Jan2019	1	Glucose (fasting)	107 mg/dL	65-99 mg/dL	2
12007	01-057	F	40	16Jan2019	1	Calcium	8.5 mg/dL	8.6-10.2 mg/dL	1
12007	01-057	F	40	16Jan2019	1	Albumin	3.5 g/dL	3.6-5.1 g/dL	1
12007	01-057	F	40	16Jan2019	1	Hemoglobin	11.6 g/dL	11.7-15.5 g/dL	1
12007	01-057	F	40	19Jan2019	4	Hemoglobin	11.5 g/dL	11.7-15.5 g/dL	1
12007	01-057	F	40	19Jan2019	4	Glucose (random)	142 mg/dL	65-139 mg/dL	1
12008	01-058	M	32	22Jan2019	1	Hemoglobin	12.9 g/dL	13.2-17.1 g/dL	1
12008	01-058	M	32	23Jan2019	2	Hemoglobin	13.0 g/dL	13.2-17.1 g/dL	1
12008	01-058	M	32	24Jan2019	3	Hemoglobin	13.0 g/dL	13.2-17.1 g/dL	1
12008	01-058	M	32	25Jan2019	4	Hemoglobin	13.0 g/dL	13.2-17.1 g/dL	1

3.1 Actions Taken/Con Meds Administered Related to Adverse Events:

Subject #	AE #	Medication	Dose/Unit	Route	Start Date	Stop Date	Prescribed for:

4.0 Vital Signs Data (summary of clinically significant abnormal vital signs by subject # and time point taken):

Subject #	Screening #	M/F	Age	Date	Time	Values	Grade
12002	01-044	M	26	09Jan2019	1305	54 bpm	1
12002	01-044	M	26	10Jan2019	0910	54 bpm	1

5.0 12-Lead ECG Data (summarize clinically significant abnormal changes by subject # and time point taken): There were no clinically significant ECG findings, and no ECG parameters met the criteria for halting the infusion stated in Section 7.6.3.2 of the protocol.

6.0 Physical Examination Data (summarize clinically significant abnormal changes by subject # and time point performed): There were no clinically significant physical exam findings noted.

7.0 Subject Discontinuations: There were no subject discontinuations throughout this Cohort.

8.0 PK Summary (insert tables, appendices as allowed by sponsor, if available):

Subjects in the table below have been anonymized with an alphabet code. Given the way the cohort dosing was staggered and that samples through only 24 hours post dosing were available for one subject in the cohort, only geometric mean data is presented in order to maintain the blind. If the subject received active, their half-life and clearance parameters are not included in the mean.

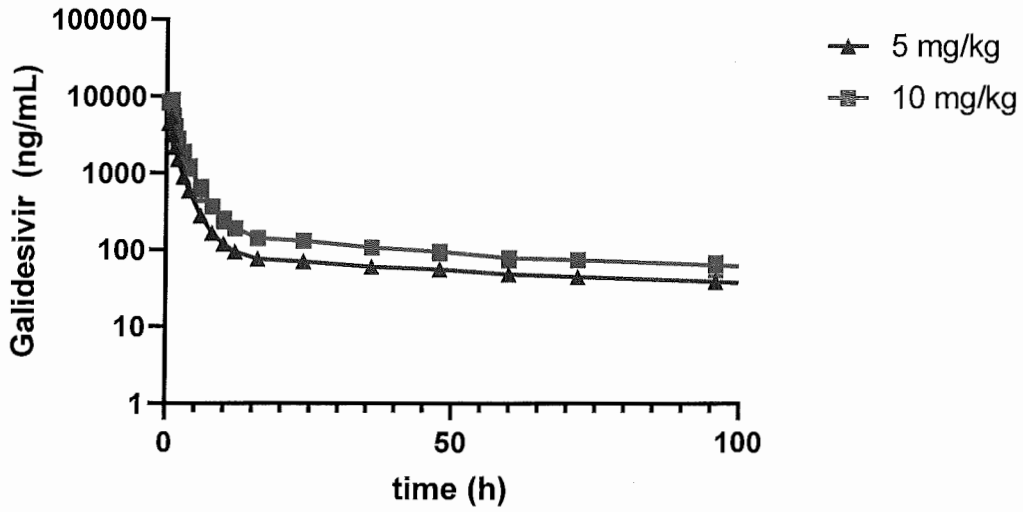
Additionally, the C_{max} for 3 subjects was greater than 10000 ng/mL (the upper limit of quantitation in the assay) and there was not time to re-assay prior to the dose escalation meeting. Therefore, it is possible that the AUC and C_{max} parameters are slightly underestimated. The anticipated geometric mean C_{max} for this cohort was approximately 10000-11000 ng/mL, so it is not anticipated that the C_{max} concentrations are much greater than 10000 ng/mL, or that the AUC parameters are significantly higher than calculated below.

No PK parameters met halting rules, and overall, the PK following a 10 mg/kg single dose administered by IV infusion was in line with anticipated exposure based on modeling and simulation and the exposure in Cohort 1 (5 mg/kg dose). Furthermore, the simulated exposure for the next two dose levels is not anticipated to exceed the PK stopping criteria in the protocol.

	T ½ (h)	C_{max}* (ng/mL)	$AUC_{0\text{-}24h}$ (ng.h/mL)	$AUC_{0\text{-}last}$ (ng.h/mL)	$AUC_{0\text{-}inf}$ (ng.h/mL	%AUC extrap	Cl (mL/h/kg)	Vz (mL/kg)
Geomean	89.1	9240	20400	30200	32400	11.1	285	36600
%CV	21.6	10.6	12.8	14.1	20.9	41.5	14.2	35.4

* 3 subjects had a Cmax > 10000 ng/mL

The figure below shows the mean galidesivir concentration-time profiles for the first two cohorts of this study.



9.0 Summary of Discussion at Dose Escalation Call:

Based upon safety measures, tolerance, and pharmacokinetic results, the dose of 10 mg/kg was well tolerated. The Safety Committee discussed data and agreed that data supports moving forward with dose escalation and with no change to the protocol.

Current Dose Level: **10 mg/kg**

Next Dose Level: **15 mg/kg**

Protocol changes required prior to next dose level administration (e.g. additional safety monitoring)?

Yes ☐

No ☒

04 Feb 2019
Date

Daniel Dickerson, MD, PhD
Principal Investigator
PRA EDS-Lenexa

01 Feb 2019
Date

Diane Gesty-Palmer, MD, PhD
Medical Monitor
BioCryst Sr. Medical Director

01 Feb 2019
Date

Amanda Mathis, PhD
Director, Clinical Pharmacology
BioCryst Pharmaceuticals

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

Protocol #: **BCX4430-106 / DMID 18-0013**
PRA Study Code: **181392**

Dose Escalation Report

Single Ascending Dose

Cohort 3: 15 mg/kg

Report Date: 25Feb2019

For BioCryst: Diane Gesty-Palmer MD, PhD, Medical Monitor/Senior Medical Director

Amanda Mathis, PhD, Clinical Pharmacologist

DMID: Venus S. Shahamatdar, MD, Medical Monitor

Kay M. Tomashek, MD, MPH, DTM, Medical Officer

Carol Ostrye, RN, MPH, Clinical Project Manager

For PRA: Daniel Dickerson, MD, PhD, Principal Investigator

Jamie Easum, APRN-BC, Co-Lead Sub-Investigator

Lesa Davis, PA-C, Co-Lead Sub-Investigator

Traci Goodwin, Clinical Study Manager

Tim Theisen, Project Manager

Safety Assessment Following Dose Administration of BCX4430 or Placebo to Healthy Volunteers

1.0 Subject Demographics, Dosing Date and Administration Times (All subjects dosed under fed conditions).

Subject #	Screening #	M/F	Age	Dosing Date	Dosing Time	Discharge from Clinical Site (Date)
13001	01-064	M	32	05Feb2019	0930	09Feb2019
13002	01-071	F	28	05Feb2019	0935	09Feb2019
13003	01-078	M	27	07Feb2019	0930	11Feb2019
13004	01-080	M	54	07Feb2019	0935	11Feb2019
13005	01-088	M	54	07Feb2019	0940	11Feb2019
13006	01-082	F	34	07Feb2019	0945	11Feb2019
13007	01-089	F	49	07Feb2019	0950	11Feb2019
13008	01-090	F	37	07Feb2019	0955	11Feb2019

2.0 Adverse Events

Subject #	AE #	Adverse Event	Date of Onset	Time of Onset	Date of Resolution	Time of Resolution	Severity	Relationship to IP
13001	1	Back Pain	06Feb2019	1900	08Feb2019	0730	Mild	Not Related
13002	1	Postnasal Drip	05Feb2019	1530	11Feb2019	0800	Mild	Not Related
13003	1	Headache	07Feb2019	1700	08Feb2019	0130	Mild	Possibly
13005	1	Abdominal Bloating	10Feb2019	0700			Mild	Not Related
13005	2	Nausea	10Feb2019	0700	13Feb2019	2000	Mild	Not Related
13005	3	Anorexia	10Feb2019	0700			Mild	Not Related
13007	1	Headache	07Feb2019	1355	10Feb2019	0545	Mild	Possibly
13007	2	Vomiting	08Feb2019	0851	08Feb2019	0852	Mild	Not Related
13007	3	Syncope	13Feb2019	1330	13Feb2019	1310	Mild	Not Related
13007	4	Right Wrist Pain	13Feb2019	1330			Mild	Not Related
13008	5	Urticaria	20Feb2019	1600			Mild	Not Related
13008	1	Headache	07Feb2019	0900	10Feb2019	1900	Mild	Not Related

2.1 Adverse Event Comments (summarize findings from above table):

Subject #	AE #	Adverse Event	Comments
13001	1	Back Pain	Subject complains of aching lumbar back pain secondary to laying in bed. Initially pain rated 6/10 and after adding pillows to lumbar area and heating pad, pain decreased to 3/10. No treatment required.
13002	1	Postnasal Drip	Subject complains of scratchy/itchy/sore throat with accompanying dry cough. No other associated symptoms. Humidifier placed in room and advised increased PO fluids. No treatment required.
13003	1	Headache	Subject complains of aching frontal headache rated 5/10 with no associated symptoms. No medications were required.
13005	1	Abdominal Bloating	Subject complains of abdominal bloating causing pain and discomfort rated 5-7/10. States normal bowel movements but unable to pass gas. Subject states diet here is very different than his usual diet at home where he predominantly eats a low fat diet. Abdominal exam showed positive bowel sounds, tenderness on palpation and tympanic percussion sounds noted in all quadrants. Advised increased ambulation. Continuing to improve as of 20Feb2019.
13005	2	Nausea	Subject states continuous nausea. Smell of food intensifies feelings of nausea. Subject did not consume any food on 10Feb2019 or 11Feb2019. Nausea resolved 13Feb2019.
13005	3	Anorexia	Subject states complete lack of appetite. Subject did not consume any food on 10Feb2019 or 11Feb2019. Appetite improving as of 20Feb2019.
13007	1	Headache	Subject complains of mild, dull, aching frontal headache rated 1/10 on pain scale. Advised ice pack and increased hydration. No medications were required.
13007	2	Vomiting	Subject vomited approximately 30cc of clear liquid. Subject states that she had just finished drinking 48 ounces of water and "it just came back up". No nausea or abdominal pain preceded the vomiting and subject proceeded to eat breakfast immediately after episode.
13007	3	Syncope	Subject states white taking a shower at home she briefly felt lightheaded and then "woke up on the floor". She states she "was only out for a minute". She denies preceding nausea, headache, visual changes or other associated symptoms. She states she felt fine after "waking up". Neuro exam normal at follow up.
13007	4	Right Wrist Pain	Subject fell on right wrist due to syncopal episode in shower. States pain at rest 1/10 and pain with movement 5-6/10. Physical exam showed pain on palpation predominately on dorsal surface, pain on flexion, extension and lateral movement of wrist. Swelling and ecchymosis noted on exam. Subject sent for xrays of wrist. Subject did not complete x-rays due to her personal choice. She reported improvement in swelling and pain with ability to use fully on 20Feb2019. Will monitor.
13007	5	Urticaria	Subject noticed itching around left axilla and shoulder blade region initially, then later noticed "rash" while looking in the mirror. On exam, 7 lesions with wheal/flare response noted (right 4th proximal phalynx, left axilla, 4 X infrascapular region and 1 X inframedial scapula). Lesions are approximately 15-25mm with increase flare to 40mm and wheals approximately 15-20mm after scratching. Subject states ate shrimp for lunch approximately 2.5-3 hours prior to noticing lesions. No oral or respiratory symptoms. Photos taken.

13008	1	Headache	Subject complained of bitemporal headache rated 5/10, at onset, which decreased to 1-2/10 shortly after that. No associated symptoms and no medications were required for treatment.

3.0 Safety Lab Data: (Summary of significant or notable lab results)

Sub #	Screen #	M/F	Age	Laboratory Collection Date	Study Day	Lab Test	Result	Range	Toxicity Grading
13001	01-064	M	32	07Feb2019	3	Glucose (random)	148 mg/dL	65-139 mg/dL	1
13001	01-064	M	32	08Feb2019	4	Glucose (random)	142 mg/dL	65-139 mg/dL	1
13002	01-071	F	28	05Feb2019	1	Glucose	100 mg/dL	65-99 mg/dL	1
13002	01-071	F	28	07Feb2019	3	Glucose (random)	144 mg/dL	65-139 mg/dL	1
13003	01-078	M	27	07Feb2019	1	Total Protein	6.0 g/dL	6.1-8.1 g/dL	1
13003	01-078	M	27	10Feb2019	4	Glucose (random)	171 mg/dL	65-139 g/dL	2
13004	01-080	M	54	07Feb2019	1	Albumin	3.5 g/dL	3.6-5.1 g/dL	1
13004	01-080	M	54	08Feb2019	2	Glucose (random)	155 mg/dL	65-139 mg/dL	1
13004	01-080	M	54	09Feb2019	3	Glucose (random)	167 mg/dL	65-139 mg/dL	2
13004	01-080	M	54	10Feb2019	4	Glucose (random)	144 mg/dL	65-139 mg/dL	1
13004	01-080	M	54	11Feb2019	5	ALT	47 U/L	9-46 U/L	1
13005	01-088	M	54	07Feb2019	1	Total Protein	6.0 g/dL	6.1-8.1 g/dL	1
13005	01-088	M	54	08Feb2019	2	Total Protein	5.8 g/dL	6.1-8.1 g/dL	2
13005	01-088	M	54	08Feb2019	2	Hemoglobin	12.3 g/dL	13.2-17.1 g/dL	2
13005	01-088	M	54	09Feb2019	3	Glucose (random)	160 mg/dL	65-139 mg/dL	2
13005	01-088	M	54	09Feb2019	3	Total Protein	5.6 g/dL	6.1-8.1 g/dL	2
13005	01-088	M	54	09Feb2019	3	Hemoglobin	12.5 g/dL	13.2-17.1 g/dL	2
13005	01-088	M	54	10Feb2019	4	Glucose (random)	147 mg/dL	65-139 mg/dL	1
13005	01-088	M	54	10Feb2019	4	Sodium	134 mmol/L	134-146 mmol/L	1
13005	01-088	M	54	10Feb2019	4	Total Protein	5.5 g/dL	6.1-8.1 g/dL	2
13005	01-088	M	54	10Feb2019	4	Hemoglobin	12.3 g/dL	13.2-17.1 g/dL	2
13005	01-088	M	54	11Feb2019	5	Glucose	108 mg/dL	65-99 mg/dL	2
13005	01-088	M	54	11Feb2019	5	Total Protein	5.8 g/dL	6.1-8.1 g/dL	2

13005	01-088	M	54	11Feb2019	5	Hemoglobin	12.6 g/dL	13.2-17.1 g/dL	2
13005	01-088	M	54	11Feb2019	5	WBC	10.9 thousand/uL	3.8-10.8 thousand/uL	1
13005	01-088	M	54	13Feb2019	Unsch	Hemoglobin	12.4 g/dL	13.2-17.1 g/dL	2
13005	01-088	M	54	21Feb2019	Unsch	Hemoglobin	11.6 g/dL	13.2-17.1 g/dL	3
13005	01-088	M	54	21Feb2019	Unsch	ALT	72 U/L	9-46 U/L	1
13006	01-082	F	34	07Feb2019	1	Glucose	114 mg/dL	65-99 mg/dL	3
13006	01-082	F	34	08Feb2019	2	Glucose (random)	155 mg/dL	65-139 mg/dL	1
13006	01-082	F	34	10Feb2019	4	Glucose (random)	141 mg/dL	65-139 mg/dL	1
13007	01-089	F	49	07Feb2019	1	Calcium	8.5 mg/dL	8.6-10.2 mg/dL	1
13007	01-089	F	49	07Feb2019	1	Total Protein	5.9 g/dL	6.1-8.1 g/dL	1
13007	01-089	F	49	07Feb2019	1	Albumin	3.5 g/dL	3.6-5.1 g/dL	1
13007	01-089	F	49	07Feb2019	1	Hemoglobin	11.2 g/dL	11.7-15.5 g/dL	1
13007	01-089	F	49	08Feb2019	2	Total Protein	5.8 g/dL	6.1-8.1 g/dL	2
13007	01-089	F	49	08Feb2019	2	Hemoglobin	11.2 g/dL	11.7-15.5 g/dL	1
13007	01-089	F	49	09Feb2019	3	Hemoglobin	11.5 g/dL	11.7-15.5 g/dL	1
13007	01-089	F	49	10Feb2019	4	Hemoglobin	11.3 g/dL	11.7-15.5 g/dL	1
13008	01-090	F	37	07Feb2019	1	Calcium	8.5 mg/dL	8.6-10.2 mg/dL	1
13008	01-090	F	37	07Feb2019	1	Total Protein	6.0 g/dL	6.1-8.1 g/dL	1
13008	01-090	F	37	08Feb2019	2	RBC (UA)	10-20 / HPF (on menses)	</= 2 /HPF	2

3.1 Actions Taken/Con Meds Administered Related to Adverse Events:

Subject #	AE #	Medication	Dose/Unit	Route	Start Date	Stop Date	Prescribed for:

*There were no actions /con meds administered related to adverse events.

4.0 Vital Signs Data (summary of clinically significant abnormal vital signs by subject # and time point taken):

Subject #	Screening #	M/F	Age	Date	Time	Values	Grade

*There were no vital signs which met the criteria for halting dosing in Section 11.5.2 of the protocol.

5.0 12-Lead ECG Data (summarize clinically significant abnormal changes by subject # and time point taken): There were no clinically significant ECG findings, and no ECG parameters met the criteria for halting the infusion stated in Section 7.6.3.2 of the protocol.

6.0 Physical Examination Data (summarize clinically significant abnormal changes by subject # and time point performed): There were no clinically significant physical exam findings noted.

7.0 Subject Discontinuations: There were no subject discontinuations throughout this Cohort.

8.0 PK Summary (insert tables, appendices as allowed by sponsor, if available):

Subjects in the table below have been anonymized with an alphabet code. Samples were quantifiable through 96 hours in all subjects. The geometric mean (%CV) C_{max}, AUC_{0-24}, and AUC_{0-last} were 17700 (16%) ng/mL, 33900 (17%) ng.h/mL, and 44300 (19%) ng.h/mL. No PK parameters met halting rules outlined in the protocol.

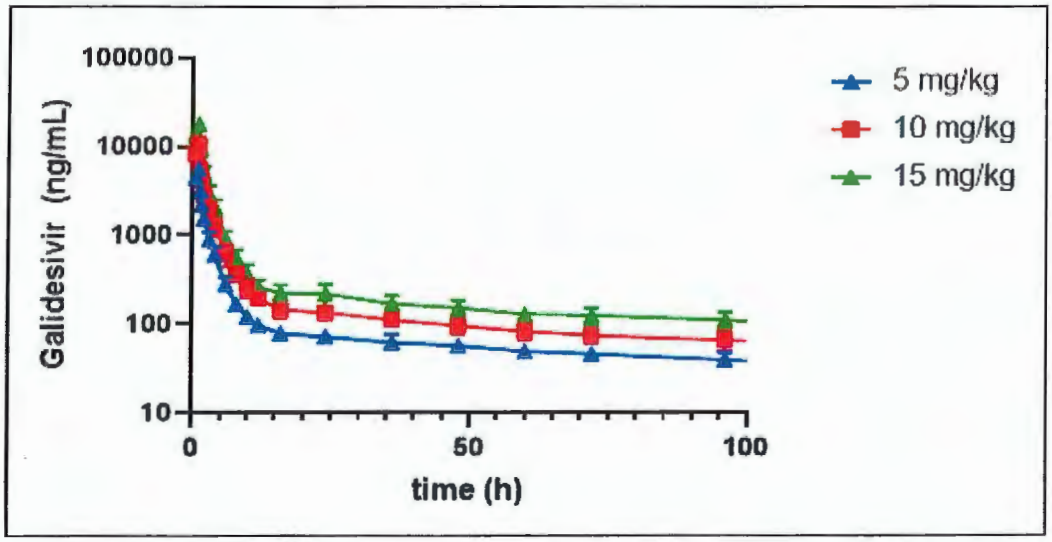
	T ½ (h)	C_{max} (ng/mL)	AUC_{0-24h} (ng.h/mL)	Cl (mL/h/kg)	Vz (mL/kg)
M	126	16500	37700	220	39900
N	81.2	17400	32900	283	33100
O	78	21200	39600	215	24200
P	76.9	18800	29900	298	33000
Q	74	13200	25700	358	38200
R	64.1	20600	40200	237	21900
Geomean	81.4	17700	33900	264	31000
%CV	26	16	17	21	23

Geometric mean summary data from all three cohorts are summarized below. Data from Cohort 1 and 2 have been updated to include all quantifiable PK samples, through the follow up period. Exposure has increased roughly proportional to the increase in dose. Therefore, it can be anticipated that for cohort 4, a 20 mg/kg dose of galidesivir administered by IV infusion would result in a C_{max} of approximately 24000 ng/mL and an AUC_{0-24} of approximately 45000 ng.h/mL, below the stopping criteria (median AUC_{0-24} of 52500 ng.h/mL).

Dose	T ½ (h)	C_{max} (ng/mL)	AUC_{0-24h} (ng.h/mL)	AUC_{0-last}* (ng.h/mL)	Cl (mL/h/kg)	Vz (mL/kg)
5	110 (40)	5540 (8)	10800 (11)	17100 (24)	237 (20)	37700 (13)
10	102 (20)	10300 (21)	20800 (14)	32300 (16)	270 (16)	39800 (29)
15	81.4 (26)	17700 (16)	33900 (17)	44300 (19)	264 (21)	31000 (23)

*Note for cohort 1 and 2, PK has been quantitated through 21 days of sampling. AUC_{0-last} represents a longer period than Cohort 3.

The figure below shows the mean galidesivir concentration-time profiles for the first two cohorts of this study.



9.0 Summary of Discussion at Dose Escalation Call:

Adverse events for subjects 13005 and 13007 were extensively reviewed. Based upon safety measures, tolerance, and pharmacokinetic results, the dose of 15 mg/kg was well tolerated. The Safety Committee discussed data and agreed that data supports moving forward with dose escalation and with no change to the protocol.

Current Dose Level: 15 mg/kg

Next Dose Level: 20 mg/kg

Protocol changes required prior to next dose level administration (e.g. additional safety monitoring)?

Yes ☐
No ☒

27 Feb 2019
Date

Daniel Dickerson, MD, PhD
Principal Investigator
PRA EDS-Lenexa

2-26-2019
Date

Diane Gesty-Palmer, MD, PhD
Medical Monitor
BioCryst Sr. Medical Director

2/26/2019
Date

Amanda Mathis, PhD
Director, Clinical Pharmacology
BioCryst Pharmaceuticals

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

Protocol #: **BCX4430-106 / DMID 18-0013**
PRA Study Code: **181392**

Dose Escalation Report

Single Ascending Dose

Cohort 4: 20 mg/kg

Report Date: 26Mar2019

For BioCryst: Diane Gesty-Palmer MD, PhD, Medical Monitor/Senior Medical Director

Amanda Mathis, PhD, Clinical Pharmacologist

DMID: Venus S. Shahamatdar, MD, Medical Monitor

Kay M. Tomashek, MD, MPH, DTM, Medical Officer

Carol Ostrye, RN, MPH, Clinical Project Manager

For PRA: Daniel Dickerson, MD, PhD, Principal Investigator

Jamie Easum, APRN-BC, Co-Lead Sub-Investigator

Lesa Davis, PA-C, Co-Lead Sub-Investigator

Traci Goodwin, Clinical Study Manager

Tim Theisen, Project Manager

Safety Assessment Following Dose Administration of BCX4430 or Placebo to Healthy Volunteers

1.0 Subject Demographics, Dosing Date and Administration Times (All subjects dosed under fed conditions).

Subject #	Screening #	M/F	Age	Dosing Date	Dosing Time	Discharge from Clinical Site (Date)
14001	01-126	M	39	06Mar2019	0900	10Mar2019
14002	01-124	M	45	06Mar2019	0905	10Mar2019
14003	01-151	F	25	08Mar2019	0900	12Mar2019
14006	01-134	F	28	08Mar2019	0905	12Mar2019
14005	01-161	F	23	08Mar2019	0910	12Mar2019
14004	01-130	M	42	08Mar2019	0915	12Mar2019
14007	01-138	M	21	08Mar2019	0920	12Mar2019
14008	01-157	M	38	08Mar2019	0925	12Mar2019

2.0 Adverse Events

Subject #	AE #	Adverse Event	Date of Onset	Time of Onset	Date of Resolution	Time of Resolution	Severity	Relationship to IP
14001	1	Headache	06Mar2019	1200	07Mar2019	1500	Mild	Possibly

2.1 Adverse Event Comments (summarize findings from above table):

Subject #	AE #	Adverse Event	Comments
14001	1	Headache	Subject states intermittent sharp and throbbing pain in frontal and temporal regions. Rates pain 8/10 at its worst. Subject believes it is due to caffeine withdrawal. Advised increased hydration and rest. Pain resolved without medication.

3.0 Safety Lab Data: (Summary of significant or notable lab results)

Sub #	Screen #	M/F	Age	Laboratory Collection Date	Study Day	Lab Test	Result	Range	Toxicity Grading
14001	01-126	M	39	06Mar2019	1	Total Protein	5.4 g/dL	6.1-8.1 g/dL	3
14001	01-126	M	39	06Mar2019	1	Albumin	3.4 g/dL	3.6-5.1 g/dL	1
14001	01-126	M	39	06Mar2019	1	Hemoglobin	12.6 g/dL	13.2-17.1 g/dL	2
14001	01-126	M	39	07Mar2019	2	Total Protein	6.0 g/dL	6.1-8.1 g/dL	1
14001	01-126	M	39	07Mar2019	2	Hemoglobin	13.1 g/dL	13.2-17.1 g/dL	1

14001	01-126	M	39	08Mar2019	3	Total Protein	5.9 g/dL	6.1-8.1 g/dL	1
14001	01-126	M	39	08Mar2019	3	Hemoglobin	12.9 g/dL	13.2-17.1 g/dL	1
14001	01-126	M	39	09Mar2019	4	Total Protein	5.9 g/dL	6.1-8.1 g/dL	1
14001	01-126	M	39	09Mar2019	4	Hemoglobin	12.9 g/dL	13.2-17.1 g/dL	1
14001	01-126	M	39	10Mar2019	5	PT	11.6 sec	9.0-11.5 sec	1
14001	01-126	M	39	10Mar2019	5	Total Protein	5.9 g/dL	6.1-8.1 g/dL	1
14002	01-124	M	45	06Mar2019	1	Total Protein	5.9 g/dL	6.1-8.1 g/dL	1
14002	01-124	M	45	07Mar2019	2	Total Protein	6.0 g/dL	6.1-8.1 g/dL	1
14002	01-124	M	45	10Mar2019	5	PT	11.8 sec	9.0-11.5 sec	1
14003	01-151	F	25	08Mar2019	1	Calcium	8.2 mg/dL	8.6-10.2 mg/dL	2
14003	01-151	F	25	09Mar2019	2	Calcium	8.5 mg/dL	8.6-10.2 mg/dL	1
14003	01-151	F	25	12Mar2019	5	PT	11.6 sec	9.0-11.5 sec	1
14006	01-134	F	28	08Mar2019	1	Calcium	8.5 mg/dL	8.6-10.2 mg/dL	1
14005	01-161	F	23	09Mar2019	2	WBC	3.1 Thousand/uL	3.8-10.8 thousand/uL	1
14005	01-161	F	23	10Mar2019	3	WBC	3.1 Thousand/uL	3.8-10.8 thousand/uL	1
14005	01-161	F	23	10Mar2019	3	ANC	1389 cells/uL	1500-7800 cells/uL	1
14005	01-161	F	23	11Mar2019	4	WBC	3.0 Thousand/uL	3.8-10.8 thousand/uL	1
14005	01-161	F	23	11Mar2019	4	ANC	1434 cells/uL	1500-7800 cells/uL	1
14005	01-161	F	23	12Mar2019	5	PT	11.6 sec	9.0-11.5 sec	1
14004	01-130	M	42	08Mar2019	1	Absolute Neutrophils	1163 cells/uL	1500-7800 cells/uL	1
14004	01-130	M	42	12Mar2019	5	PT	12.0 sec	9.0-11.5 sec	1
14007	01-138	M	21	10Mar2019	3	Glucose (random)	141 mg/dL	65-139 mg/dL	1
14007	01-138	M	21	11Mar2019	4	Glucose (random)	166 mg/dL	65-139 mg/dL	2
14007	01-138	M	21	12Mar2019	5	PT	12.4 sec	9.0-11.5 sec	1
14008	01-157	M	39	09Mar2019	2	Glucose (random)	175 mg/dL	65-139 mg/dL	2
14008	01-157	M	39	10Mar2019	3	Glucose (random)	170 mg/dL	65-139 mg/dL	2
14008	01-157	M	39	11Mar2019	4	Glucose (random)	149 mg/dL	65-139 mg/dL	1

3.1 Actions Taken/Con Meds Administered Related to Adverse Events:

Subject #	AE #	Medication	Dose/Unit	Route	Start Date	Stop Date	Prescribed for:

*There were no actions /con meds administered related to adverse events.

4.0 Vital Signs Data (summary of clinically significant abnormal vital signs by subject # and time point taken):

Subject #	Screening #	M/F	Age	Date	Time	Values	Grade

*There were no vital signs which met the criteria for halting dosing in Section 11.5.2 of the protocol.

5.0 12-Lead ECG Data (summarize clinically significant abnormal changes by subject # and time point taken): There were no clinically significant ECG findings, and no ECG parameters met the criteria for halting the infusion stated in Section 7.6.3.2 of the protocol.

6.0 Physical Examination Data (summarize clinically significant abnormal changes by subject # and time point performed): There were no clinically significant physical exam findings noted.

7.0 Subject Discontinuations: There were no subject discontinuations throughout this Cohort.

8.0 PK Summary (insert tables, appendices as allowed by sponsor, if available):

Subjects in the table below have been anonymized with an alphabet code. PK presented in this report is based on nominal sampling times. Samples were available through 24 hours in all subjects and were quantifiable through 24 hours. The geometric mean (%CV) C_{max} and AUC_{0-24} were 20500 (16%) ng/mL and 44600(13%) ng.h/mL. No PK parameters met halting rules outlined in the protocol.

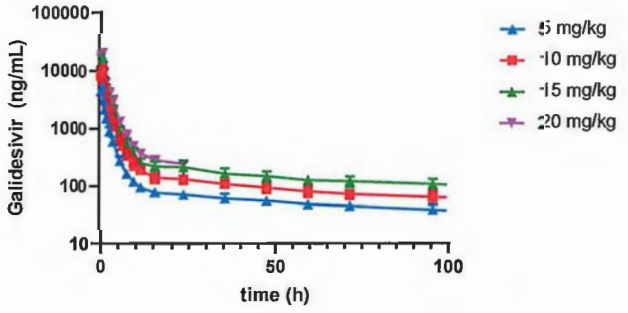
	T ½ (h)	C_{max} (ng/mL)	AUC_{0-24} (ng.h/mL)	Cl (mL/h/kg)	Vz (mL/kg)
S	NR	25500	44200	382	12100
T	NR	19900	39800	487	2610
U	NR	17000	42800	449	2650
V	NR	19900	43900	415	8110
W	NR	24100	51200	357	8190
X	NR	17900	46500	349	13400
Geomean	NR	20500	44600	404	6490
%CV		16.4	8.6	13.4	58

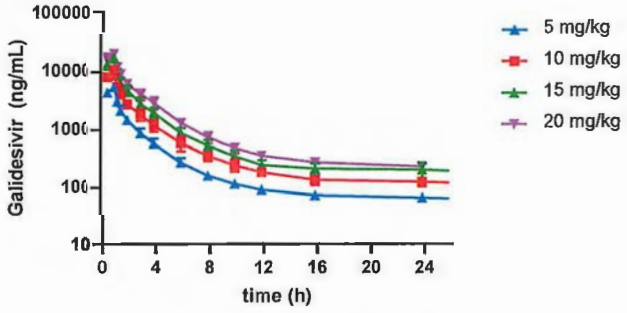
Across cohorts, galidesivir exposure increased roughly proportional to the increase in dose, with a 3.7-fold increase in geometric mean C_{max} and a 4.1-fold increase in AUC_{0-24} with a 4-fold increase in dose.

Dose	T ½ (h)	C_{max} (ng/mL)	AUC_{0-24} (ng.h/mL)	AUC_{0-last}* (ng.h/mL)	Cl (mL/h/kg)	Vz (mL/kg)
5	110 (40)	5540 (8)	10800 (11)	17100 (24)	237 (20)	37700 (13)
10	102 (20)	10300 (21)	20800 (14)	32300 (16)	270 (16)	39800 (29)
15	81.4 (26)	17700 (16)	33900 (17)	59600 (21)	228 (22)	56400 (12)
20	NR	20500 (16)	44600 (9)	44600 (9)	404 (13)	NR

*Note for cohort 1,2 and 3, PK has been quantitated through 21 days of sampling. AUC_{0-last} represents a longer period than Cohort 3.

The figures below shows the mean galidesivir concentration-time profiles for all cohorts of this study. As Cohort 4 only has PK available through 24 hours, the figure on the right shows concentration-time profiles for all cohorts through 24 hours.





9.0 Summary of Discussion at Dose Escalation Call:

Based upon safety measures, tolerance, and pharmacokinetic results, the dose of 20 mg/kg was well tolerated. The Safety Committee discussed data and agreed that data supports safety of 20 mg/kg dose.

The safety committee reviewed previous SAEs and outstanding AEs:

Subject 12007, in Cohort 2, had a pregnancy that resulted in a spontaneous abortion. Hospital records have been obtained but follow-up gynecologic records were never received. The information was reviewed with the safety committee and the final SAE report will be submitted on 27-Mar-2019. The PI deemed that the SAE was unlikely related to study drug due to subject's age and prior history of spontaneous abortion. The Sponsor concurred that the spontaneous abortion was unlikely related to study drug. In addition, this assessment is consistent with the reported preclinical toxicology.

Subject 13005, in Cohort 3, reported to the PI on 26-Mar-2019 that he was in the hospital and had a "mass on his stomach". Hospital records are not yet available. The subject had four adverse events on study that are potentially related to his stomach mass. On day 1 of the study (08-Feb-2019) the subject developed anemia which was worked up and found to be an iron deficiency anemia with a negative stool hemoccult, normal reticulocyte count, and low serum iron. On day 3 of the study (10-Feb-2019) he reported abdominal bloating, nausea, and anorexia.

The stomach mass was reported as an SAE on 26-Mar-2019 and the PI deemed it to be unrelated to study drug because potential mass related adverse events began within days after dosing. All members of the safety committee, including the medical monitor, concur with this assessment.

Subject 13007, in Cohort 3, developed urticaria which was evaluated by a dermatologist and found to be vascular urticaria on biopsy. Following dermatology workup, the subject noted working and sleeping at a facility that was found to have bedbugs. The follow-up dermatology report lists bedbugs as consistent with the subject's vascular urticaria. This adverse event was deemed by PI to not be related to study drug based on subject history and dermatology report.

Current Dose Level: 20 mg/kg

Next Dose Level: NA

Protocol changes required prior to next dose level administration (e.g. additional safety monitoring)?

Yes ☐

No ☒

The protocol has completed enrollment of all cohorts and therefore there will be no further doses administered.

This report is intended to summarize the exposure of BCX4430 observed in cohort 4.

There were no stopping criteria met in any cohort of the study

There were no trends or dose relatedness to any laboratory abnormalities.

Overall, galidesivir was well tolerated and has an acceptable safety profile, supporting further clinical development.

28 Mar 2019
Date

Daniel Dickerson, MD, PhD
Principal Investigator
PRA EDS-Lenexa

28 March 2019
Date

Diane Gesty-Palmer, MD, PhD
Medical Monitor
BioCryst Sr. Medical Director

28 March 2019
Date

Amanda Mathis, PhD
Director, Clinical Pharmacology
BioCryst Pharmaceuticals