STATISTICAL ANALYSIS PLAN

Study Title:	A Phase 3, Randomized, Open Label, Active-Controlled Study to Evaluate the Safety, Pharmacokinetics and Effectiveness of IV Peramivir Compared to Oral Oseltamivir in Pediatric Subjects with Acute Uncomplicated Influenza
Phase:	3
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CONFIDENTIAL AND PROPRIETARY INFORMATION

STATISTICAL ANALYSIS PLAN REVIEW AND APPROVAL

This Statistical Analysis Plan has been prepared in accordance with team reviewers' specifications.

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1. GLOSSARY OF ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the curve
BCX-1812	Peramivir
BUN	blood urea nitrogen
CI	confidence interval
CRF	case report form
DAIDS	Division of Acquired Immunodeficiency Syndrome, National Institute of Allergy and Infectious Diseases, National Institutes of Health
FDA	Food and Drug Administration
HGB	hemoglobin
IRC	influenza-related complications
ITT	intent-to-treat
ITTI	intent-to-treat infected
MedDRA	Medical Dictionary for Regulatory Activities
PCR	polymerase chain reaction
PK	Pharmacokinetic
RAT	rapid antigen test
SD	standard deviation
$TCID_{50}$	Tissue-culture infective $dose_{50}$
TEAEs	treatment-emergent adverse events
TWAUC	time-weighted area under the curve
WHO	World Health Organization

2. INTRODUCTION

This document describes the statistical methods and data presentations to be used in the summary and analysis of data from Protocol BCX1812-305. Background information is provided for the overall study design and objectives. The reader is referred to the study protocol and case report forms (CRFs) for details of study conduct and data collection.

This document describes all analyses of safety, clinical effectiveness, pharmacokinetics and virology analyses. Pharmacokinetic and virology analyses will be written as separate reports from the clinical study report.

2.1. STUDY OVERVIEW

Protocol BCX1812-305 is a multicenter, randomized, open-label, active-controlled study to evaluate the safety, pharmacokinetics and effectiveness of a single dose of intravenous (IV) peramivir (600 mg IV or 12 mg/kg IV depending on age) compared to oral oseltamivir (dosed BID for 5 days) in children with uncomplicated acute influenza. Approximately 140 subjects will be enrolled. Up to 10 subjects ages from birth to <– 28- days will be enrolled and will receive a single dose of intravenous (IV) peramivir 12 mg/kg. Up to 20 subjects 28 days to less than 2 years old will be enrolled. Subjects enrolled in this cohort prior to version 4.0 of the protocol will be randomized 4:1 (4 IV peramivir: 1 oral oseltamivir) whereas subjects enrolling in this cohort under version 4.0 or higher of the protocol will receive IV peramivir 12mg/kg. Up to 110 subjects 2 years to < 18 years of age will be randomized 4:1 (4 IV peramivir: 1 oral oseltamivir) according to the following age groups:

- 2 years - < 7 years: up to 40 subjects
- 7 years - < 13 years: up to 40 subjects
- 13 years - < 18 years: up to 30 subjects

Eligible subjects with have clinical signs and symptoms consistent with acute influenza infection consisting of an oral temperature ≥ 100°F or rectal temperature ≥ 101.3°F with at least one respiratory symptom (cough or rhinitis) OR a positive influenza rapid antigen test (RAT). Enrollment of eligible subjects based on clinical symptoms alone will be approved by the Sponsor at the beginning of each influenza season.

The formulation of the peramivir drug to be used in this study contains peramivir at a concentration of 10 mg/mL. The peramivir 10 mg/mL stock solution will be diluted in saline using aseptic techniques with a maximum volume of 100 mL. Oseltamivir will be prepared and administered in accordance with the manufacturer's instructions.

Subjects will record temperature, influenza symptoms, date and time of oral oseltamivir dose administration (if applicable), the ability to return to day care/school and/or resume their normal daily activities, appetite and eating patterns, and doses of symptomatic relief medication in a Subject Diary. Temperature measurements will be taken every 12 hours until temperature

normalizes for 48 hours (i.e., temperature without antipyretic is < 99.4 orally in children ≥ 6 and < 98.4 axillary in children < 6 years old for 4 measurements). Subjects 7 years of age and older will have the following 7 influenza symptoms recorded using a 4-point severity scale twice daily beginning pre-dose on Day 1 assessment until symptom resolution and through the last follow-up visit (whichever comes first): cough, sore throat, nasal obstruction, myalgia, headache, feverishness, and fatigue. Subjects ≥ 4 and ≤ 6 years of age will have the following 7 influenza symptoms recorded using a 4-point severity scale twice daily beginning pre-dose on Day 1 assessment until symptom resolution and through the last follow-up visit (whichever comes first): cough, sore throat, nasal obstruction, myalgia, headache, feverishness, fatigue/malaise, and gastrointestinal symptoms (nausea, vomiting, or diarrhea). Subjects 28 days to < 4 years old will have the following 5 influenza symptoms recorded using a 4-point severity scale twice daily beginning pre-dose on Day 1 assessment until symptom resolution and through the last follow-up visit (whichever comes first): cough, rhinitis, feverishness, malaise/irritability, and gastrointestinal symptoms (nausea, vomiting, or diarrhea).

Subjects will undergo follow-up assessments on Days 3, 7, and 14. The Day 3 visit may be a home visit (performed by a qualified study nurse). Day 7 is required to take place in the clinic, and Day 14 may either be a clinic visit, home visit, or follow-up phone call to the subject/parent/guardian.

An adequate nasal swab specimen will be collected from all enrolled subjects on Day 1 prior to dosing and at the follow-up assessments on study Days 3, 7, and 14 for virus sub-type identification and quantitative virologic assessments. Specimens from all subjects yielding influenza virus will also be assessed for susceptibility to neuraminidase inhibitors (Day 1 and last specimen yielding influenza virus on culture).

Plasma samples for determination of drug concentration on subjects randomized to peramivir will be drawn as follows:

Up to 4 blood samples will be drawn, where possible, during the following time periods, beginning from the end of dosing until release from the site:

- One time point immediately following completion of the infusion
- One time point from 30 minutes to 1 hour post-infusion
- One time point from 1 hour to 3 hours post-infusion
- One time point from 3 hours to 6 hours post-infusion

Adverse events, physical examinations, laboratory tests, concomitant medications, and vital signs will be used to monitor subject safety, while daily subject-rated assessments of influenza symptoms and viral titers will be measured to determine effectiveness. The primary safety endpoints include the incidence of treatment-emergent adverse events and treatment-emergent changes in clinical laboratory test. The secondary effectiveness endpoints include the time to alleviation of clinical symptoms of influenza (per age appropriate symptoms), defined as the start of the time period when all of the symptoms assessed are either absent or are present at no more than mild severity level and at this status for a 21.5 hour (24 hours – 10%) period, time to resolution of fever, change

in influenza virus titer by $\log_{10}$ tissue culture infective $dose_{50}$/mL ($TCID_{50}$), and change in viral sensitivity.

2.2. SCHEDULE OF EVENTS/STUDY VISITS

Assessments	Screening [1]	Baseline[1] Pre-Dose	Day 1[1] Post-Dose	Day 3[2]	Day 7 (±2 day)	Day 14[2] (±3 day)	End of Study Early Withdrawal[3]
Informed Consent	X						
Inclusion/Exclusion Criteria	X						
Pregnancy Test (Urine)[4]	X				X		X
Medical History	X						
Body Temperature[5]	X	X	X	X	X	X	X
Physical Exam		X					
Influenza-related complications (IRC) checklist[6]		X		X	X	X	X
Vital Signs[7]		X		X	X	X	X
Concomitant Medications Review[8]	X	X	X	X	X	X	X
Clinical Chemistries and Hematology[9]		X			X		X
Urinalysis[9]		X			X		X
Assessment of influenza symptoms/ activities of daily living/ eating habits[10]		X	X	X	X	X	X
Subject Diary Completion/ Review[11]		X	X	X	X	X	X
Nasal swabs for Virology Analysis[12]		X		X	X	X	X
Study Drug Administration[13]		X					
Serum sample for influenza antibody analysis[14]		X			X		
Pharmacokinetic (PK) Sampling[15]			X				
Adverse Events			X	X	X	X[16]	X[16]

Study Measurements and Visit Schedule Figure Legend on Next Page

Study Measurements and Visit Schedule Figure Legend

[1] It is expected that the date of Screening, Baseline, and Day 1 (date of administration of study drug) will be the same.

[2] The Day 3 visit may be performed as a clinic visit or home visit (conducted by a qualified study nurse). The Day 14 visit may be performed as a home visit, clinic visit, or phone call. In the event the Day 14 assessment is a phone call the parent/caregiver will be requested to mail the completed diary card back to the site.

[3] An Early Withdrawal assessment should be conducted for subjects who withdraw before Day 7. For subjects who withdraw between Day 7 and Day 14 a telephone assessment should be completed, where possible.

[4] Urine pregnancy test will be performed for any female post-menarche.

[5] The screening temperature may be performed per the site's standard method, which will be recorded. For subsequent visits, the parent/guardian will record oral or axillary temperature with the electronic thermometer provided by BioCryst. Thereafter, the parent/caregiver will record temperature in the Subject Diary approximately every 12 hours until temperature is normal for 48 hours without antipyretic.

[6] If an IRC is suspected then a targeted physical examination and if needed, diagnostic testing will be conducted to record the actual presence/absence of the IRC.

[7] Vital sign measures will include blood pressure (in children <2 only if clinically indicated), pulse rate and respiration rate. Vital signs will be recorded at Baseline, and vital signs will be taken once on remaining study visits.

[8] Antipyretic medications will be recorded in the Subject Diary by the parent/caregiver daily from Day 1 through Day 14.

[9] Clinical laboratory assessments performed at Baseline (by a local lab) are for the purpose of establishing a baseline. Subject may be enrolled and begin treatment with study drug prior to receiving results.

[10] The severity of age appropriate influenza signs and symptoms will be recorded by the parent/caregiver in the Subject Diary twice daily, until all symptoms are resolved (Grade 0). Assessments of activities of daily living and eating habits will be recorded once daily until all symptoms are resolved.

[11] On Day 1, the parents/caregivers of subjects and/or adolescent subjects are to be provided training by the study staff on completing the Subject Diary. Instructions will be reviewed with the adolescent subject or parent/caregiver at each study visit.

[12] Swabs for virology analysis will be collected on Day 14 where possible.

[13] Only for those subject randomized to peramivir. The parents/caregivers of subject randomized to the oral oseltamivir arm of the study, will record the date and time of each drug administration, from Day 1 until Day 5 (or last scheduled dose). The first dosing will be administered at the site and documented by the study staff following completion of required predose activities.

[14] A single serum specimen will be collected, where possible, pre-dose on Day 1 and on Day 7 for analysis of influenza antibody titers. .

[15] Only for those subjects randomized to peramivir. A PK sample will be drawn immediately following the end of study drug infusion/administration, between 30 minutes to 1 hour post-infusion, between 1 and 3 hours post-infusion, and between 3 and 6 hours post-infusion.

[16] Any subject with unresolved moderate or severe intensity influenza symptoms or an unresolved AE and/or treatment-emergent laboratory finding that requires further medical management may be evaluated in further follow-up visits, at the Investigator's discretion.

3. OBJECTIVES

The primary objective of the study is to evaluate the safety of IV peramivir compared to oral oseltamivir in pediatric subjects with acute uncomplicated influenza.

The following secondary objectives are planned for this study.

- To describe the pharmacokinetics of IV peramivir in pediatric subjects with influenza.
- To evaluate the effectiveness of IV peramivir compared to oral oseltamivir in pediatric subjects with influenza.
- To evaluate the incidence of influenza complications, specifically otitis media, sinusitis, bronchitis or pneumonia requiring antibiotic use diagnosed after initiation of treatment.

4. GENERAL STATISTICAL CONSIDERATIONS

4.1. SAMPLE SIZE AND POWER

The study is designed to evaluate the safety and pharmacokinetics of IV administration of peramivir in pediatric subjects with influenza. A formal sample size calculation was not performed.

4.2. RANDOMIZATION AND MASKING

Approximately 140 subjects will be enrolled. Up to 10 subjects from birth to < 28 days will be enrolled to receive a single dose of IV peramivir. Up to 20 subjects from 28 days to < 2 years will either be randomized to 1 of 2 treatment arms at a ratio of 4:1 or will receive a single dose of IV peramivir. Up to 110 subjects from 28-days to < 18 years of age will be randomized to 1 of 2 treatment arms at a ratio of 4:1:

- Treatment Group 1: A single dose of IV peramivir
- Treatment Group 2: Oral oseltamivir given BID for 5 days

This is an open label study and as such, blinding is not applicable.

4.3. HANDLING OF DATA

4.3.1. Strata and Covariates

Analyses will be presented by the stratification factor of age group at randomization.

4.3.2. Examination of Subject Subsets

Some analyses will be displayed by viral subtype at Screening.

4.3.3. Multiple Testing and Comparisons

All analyses will be conducted without adjustments for multiple testing.

4.3.4. Missing Data and Outliers

Every effort will be made to obtain required data at each scheduled evaluation from all subjects who have been randomized. No attempt will be made retrospectively to obtain missing subject reported data (such as influenza symptom severity assessments, temperature, and injection site discomfort) that has not been completed by the subject at the time of return of the subject diary to the investigative site. In situations where it is not possible to obtain all data, it may be necessary to impute missing data, as described in the following paragraph.

In assessing the effectiveness endpoint of time to alleviation of symptoms, for subjects who withdraw or who do not experience alleviation of symptoms, missing data will be censored using the date of subject's last non-missing assessment of influenza symptoms. Missing assessments of influenza symptoms will be imputed using the last observation carried forward. For the subject diary data, the following data conventions will be utilized. Missing diary completion times will be imputed as 11:59 for diary entries designated as morning and 23:59 for evening and daily reported values. Entries with values exceeding the 24-hour clock will be handled on a case-by-case basis and reviewed by a member of the clinical project team prior to implementation. In general, values recorded between 24:01 – 24:59 will be interpreted as values past midnight and will be implemented as such. Values recorded as 60:00, 70:00, and 80:00 will be interpreted as 06:00, 07:00, and 08:00, respectively. Should additional data conventions be required, these will be documented in the derived variable specifications and in the final clinical study report. Select exploratory sensitivity analyses may be conducted to ascertain the effect, if any, of these methods. These sensitivity analyses are further described in section 6.2.2.1. Other secondary effectiveness endpoints with time to event data will be censored using the date of subject's last non-missing assessment of the given endpoint.

Unless otherwise specified, no other missing data will be imputed.

4.3.5. Imputation of Incomplete Dates

An incomplete date is any date for which either the day, month or year is unknown, but at least one field is known. An incomplete date occurs when the exact date an event occurred or ended cannot be obtained from a subject. For many of the analyses, a complete date is necessary in order to determine if the event should be included in the analysis (i.e., if the event is treatment-emergent) or to establish the duration of an event. In such cases, incomplete dates will be imputed.

For purposes of imputation, all events with an incomplete end date are assumed to have ended on or before the day the form was completed. In an effort to minimize bias, the project statistician will impute incomplete start dates in a systematic, but reasonable manner. For diary data, missing dates

will be imputed based on the nominal visit day relative to Day 1. For other data, if the month/year is the same as the Day 1 month/year then the date will be set to the date of Day 1. In other cases, missing days will be imputed as the day component of Day 1; missing months/years will be imputed as the month/year of Day 1. A list of incomplete and imputed dates will be prepared by the project statistician or statistical programmer(s) and will be submitted for review by the clinical project manager and sponsor.

4.3.6. By Study Visit Displays

When data are collected serially over time, individual data presentations may include by-visit displays. For these presentations, visits will be presented according to the nominal visit as obtained from the CRF or laboratory data. If assessments are collected with multiple dates or times within a given visit, the result closest to the scheduled visit date will be used for summary presentations. If two measurements have the same distance to the expected date, the earlier value will be used. If a subject has multiple non-missing values on the same date, then the last one is used, as determined by the time collected, if available.

4.3.7. Derived and Transformed Data

$TCID_{50}$ will be log10 transformed prior to performing the analyses.

4.3.8. Definitions and Terminology

Age
Age will be defined as the age in days for the cohort of subjects <28 days old, months for the cohort of subjects from 28 days - 2 years, or years for the cohorts of subjects greater than 2 years old at the time of randomization. For all subjects, age in years will also be derived and rounded down to the tenth decimal place for the summary statistics that are presented for all subjects combined.

Confirmed Influenza
A subject will be confirmed as having acute influenza infection if any specimen for assay of influenza A or B antigen by RT-PCR obtained during the study is positive.

Baseline Value
For purposes of analysis, the baseline value is defined as the last value obtained prior to initiation of study drug (e.g., the Baseline Pre-Dose value). Should this value be obtained after the injection of study drug, then the most recent value obtained prior to initiation of study drug will be used for the baseline value.

Day 1
Day 1 is the day/time that study drug is initiated.

Study Day
Study Day is defined relative to Baseline (Day 1). Thus, the study day of an event is calculated as:

Study Day = event date – date of Day 1 +1.

Days on Study
Days on Study is the number of days from Day 1 to the date of study completion or early termination as recorded on the EARLY TERMINATION/STUDY COMPLETION CRF.

Days of Subject Diary Completion
Days of Subject Diary Completion is defined as the number of days from Day 1 to the date of last Subject Diary completion. For the purposes of this analysis, the date of last Subject Diary completion is defined as the last date in which the Subject Diary had at least one complete assessment of symptoms recorded.

Alleviation of Symptoms
A subject has Alleviation of Symptoms if all of the assessed symptoms of influenza assessed on his/her subject diary based on age are either absent or are present at no more than mild severity level and at this status for a 21.5 hour (24 hours – 10%) period.

Composite Symptom Score
The Composite Symptom Score is defined as the sum of the symptoms of influenza (per age appropriate symptoms) assessed on a given time point within the subject diary.

Initial Composite Symptom Score
The Initial Composite Symptom Score is defined as the Composite Symptom Score corresponding to the first assessment of a subject's symptoms.

Resolution of Fever
A subject has Resolution of Fever if he/she has a temperature < 99.4°F oral or < 98.4°F axillary and no antipyretic medications have been taken for at least 12 hours. Resolution of Fever is based on information obtained from the individual subject diaries.

Time to Event
Time to a given event is defined as the number of hours from initiation of earliest study treatment until the event occurs. The unit of measurement will vary based upon the endpoint and its respective schedule of assessment.

Time to Alleviation of Symptoms
Time to Alleviation of Symptoms is the number of hours from initiation of study drug to start of the period in which a subject has Alleviation of Symptoms.

Change from Baseline
Change from baseline for a given endpoint is defined as the Study Day X value minus the Baseline Value.

Adverse Event (AE)
According to the protocol, an AE is any untoward medical occurrence in a clinical study subject. No causal relationship with the study drug or with the clinical study itself is implied. An AE may be an unfavorable and unintended sign, symptom, syndrome, or illness that develops or worsens during the clinical study. Clinically relevant abnormal results of diagnostic procedures including abnormal laboratory findings (e.g., requiring unscheduled diagnostic procedures or treatment measures, or resulting in withdrawal from the study) are considered to be AEs.

AEs may be designated as "nonserious" or "serious" (see Protocol Section 11.1.1.1). Surgical procedures are not AEs but may constitute therapeutic measures for conditions that require surgery. The condition for which the surgery is required is an AE, if it occurs or is detected during the study period. Planned surgical measures permitted by the clinical study protocol and the conditions(s) leading to these measures are not AEs, if the condition(s) was (were) known before the start of study treatment. In the latter case the condition should be reported as medical history.

Assessment of age appropriate symptoms of influenza will be documented in a Subject Diary and analyzed as a measure of effectiveness of the study treatment. These symptoms will not be reported as AEs unless the symptom(s) worsen to the extent that the outcome fulfills the definition of an SAE, which then must be recorded as such (see Protocol Section 11.1.1.2). Likewise, a RAT for influenza is required at screening in order to determine eligibility for the study, and therefore a positive RAT is not considered an AE.

All adverse events will be recorded on the ADVERSE EVENTS CRF.

Treatment-emergent Adverse Event
Any event reported on the CRF that occurs on or after the initiation of study drug and not more than 14 days after the last dose of study medication is considered treatment-emergent. Additionally, it is assumed that an Adverse Event which was reported to have started on Day 1 without an associated onset time may have occurred after the initiation of study drug. Hence, Adverse Events occurring on Day 1 with no associated onset time are assumed to be treatment-emergent.

Treatment-emergent Laboratory Abnormality
A treatment-emergent laboratory abnormality is defined as an increase of at least one toxicity grade from the baseline assessment at any post baseline visit up to and including 14 days after the last dose date of study drug. If no assessment is available at baseline, the screening assessment will be used to assign the baseline toxicity grade. If the relevant baseline and screening assessments are

missing, then any graded abnormality (i.e., at least Grade 1) is considered to be treatment-emergent.

Concomitant Medications
Concomitant medications are those medications taken on or after the initiation of study drug.

Previous Medications
Previous medications are those medications taken prior to the initiation of study drug.

4.4. TIMING OF ANALYSES

If final results to analyze secondary virologic or PK endpoints are delayed unexpectedly and significantly, then analysis of the clinical data will proceed based on cleaned and locked clinical CRF data and virologic data to identify the ITTI population, and analysis of the secondary virologic and PK endpoints will be performed based on available preliminary results. A final analysis of secondary virologic and PK endpoints will be conducted once final data are available.

Secondary analyses to evaluate the exposure response of peramivir, and to assess changes in influenza viral susceptibility to neuraminidase inhibitors following treatment, may be conducted at a later date, if the required pharmacokinetic and virology data are not available at the time of the analysis of the clinical data.

5. ANALYSIS POPULATIONS

All subjects enrolled (e.g., signed informed consent) will be included in the summary of subject disposition and all data listings. The populations for analysis of safety and effectiveness endpoints will include the Intent-to-Treat (ITT), Intent-to-Treat Infected (ITTI), safety populations, and an exposure-response population.

5.1. INTENT-TO-TREAT POPULATION

The ITT population will include all randomized subjects. The ITT population will be the primary population for analyses of demography and subject accountability.

5.2. INTENT-TO-TREAT INFECTED POPULATION

The ITTI population will include all subjects who are enrolled, treated, and have influenza confirmed by RT-PCR. The ITTI population will be used for analyses of effectiveness.

5.3. SAFETY POPULATION

The safety population will include all randomized subjects who receive at least one partial dose/injection of study drug. The safety population will be the primary population for all analyses

of safety data.

5.4. EXPOSURE-RESPONSE POPULATION

The exposure-response population will include all subjects in the ITTI population who have a quantifiable peramivir concentration on day 1 and have at least one post-baseline effectiveness assessment. This population will be used for all exposure-response analyses.

5.5. VIROLOGY POPULATION

The virology population will include all subjects in the ITTI population who have a laboratory-confirmed influenza infection denoted by a positive RT-PCR assay. This population will be used for all virologic analyses.

6. STATISTICAL METHODS

Descriptive statistical methods will be used to summarize the data from this study. Data will be summarized by treatment group, age group, and study day/time, if appropriate. Unless stated otherwise, the term “descriptive statistics” refers to number of subjects (n), mean, median, standard deviation (SD), minimum, and maximum for continuous data and frequencies and percentages for categorical data. The term “treatment group” refers to randomized treatment assignment: single dose peramivir IV or oseltamivir BID for 5 days. The term "age group" refers to the following: 28 days - < 2 years, ≥ 2 years - < 7 years, ≥ 7 years - < 13 years, and ≥ 13 years - < 18 years. All data collected during the study will be included in data listings. Unless otherwise noted, the data will be sorted first by treatment group, age group, subject number, and then by date within each subject number.

The statistical analyses will be conducted with the SAS® software package version 9.2 or higher. All analyses will be subject to formal verification procedures. Specifically, results will be verified utilizing independent programming prior to issuance of the draft statistical report. All documents will be verified by the lead statistician to ensure accuracy and consistency of analyses.

6.1. SUBJECT DISPOSITION, DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Subject disposition will be presented for all subjects. The number of subjects who completed the study and discontinued from the study will be provided. The reasons for early discontinuation also will be presented. Additionally, the number of days on study and study medication will be summarized.

Demographic data and baseline characteristics including age, gender, race, ethnicity, and Initial Composite Symptom Score will be summarized using descriptive statistics for the ITT population.

This information will be reviewed for baseline differences, but no statistical testing will be performed.

Subject diary completion will be summarized included the days of diary completion.

6.2. EFFECTIVENESS ANALYSIS

6.2.1. Effectiveness Endpoints

The effectiveness endpoints include:

- Time to resolution of fever
- Time to alleviation of influenza symptoms
- Change in influenza virus titer by $TCID_{50}$/mL
- Change in RT-PCR results
- Change in virus susceptibility to neuraminidase inhibitors
- Incidence of influenza-related complications
- Usage of antipyretic medication
- Change in daily activities
- Appetite and Eating patterns

6.2.2. Effectiveness Analyses

A subject's oral temperature will be summarized by age group and overall by study visit and treatment group. A subject has Resolution of Fever if he/she has an oral temperature <99.4°F oral or <98.4°F axillary and no antipyretic medications have been taken for at least 12 hours. The time to resolution of fever will be estimated for each age group and overall by treatment group using the method of Kaplan-Meier using temperature and symptom relief medication information obtained from the subject diary data. Subjects who do not have resolution of fever will be censored at the time of their last non-missing post-baseline temperature assessment.

Alleviation of symptoms will be determined by assessment of symptoms as reported on each Subject Diary. The time to alleviation of symptoms will be estimated overall and for individual symptoms for each age group by treatment group using the method of Kaplan-Meier. Subjects who do not experience alleviation of symptoms will be censored at the date of their last non-missing post-baseline assessment.

Change from baseline in $TCID_{50}$/mL through Day 3, Day 7 and Day 14 respectively will be presented by age group and overall by treatment group for subjects with positive viral titers at baseline ($\log_{10}$ $TCID_{50}$/mL > 0.5). A box plot and a histogram of the $TCID_{50}$/mL values will be presented by visit, age group, and treatment group. In addition, the median change from baseline in $TCID_{50}$/mL will be presented by visit, age group, and treatment group.

The number and percent of subjects with positive viral titers at baseline (log_{10} $TCID_{50}$/mL > 0.5) that are shedding virus at each visit will be presented by age group and overall by treatment group.

The RT-PCR results at each visit will be presented by age group and overall by treatment group for subjects with positive RT-PCR results at baseline.

Change from baseline to last positive value of influenza virus susceptibility to neuraminidase inhibitors will be assessed using virology laboratory tests. Virology laboratory tests will include phenotypic characterizations of influenza virus recovered (hemaglutinin and neuraminidase) and viral susceptibility to zanamivir, oseltamivir, and peramivir, as well as genotyping of virus isolates. These analyses will be presented overall and by age group, treatment group and viral subtype.

The development of any post treatment genotypic changes in neuraminidase and hemagglutinin will be assessed by comparison of sequences from baseline and last positive post-treatment virus samples. These analyses will be presented overall and by age group, treatment group and viral subtype.

The number and percentage of subjects experiencing influenza related complications will be summarized by age group and overall by complication preferred term and treatment group.

The number of doses of antipyretic medications, as recorded in the subject diary, taken throughout the study and by study day will be summarized by age group and overall by treatment group.

The change in daily activities will be summarized each day by treatment group for each age group and overall.

The shift in the assessment of appetite and eating patterns from baseline to each day will be summarized by treatment group for each age group and overall.

6.2.3. Exploratory Exposure Response Analyses

Summaries of plasma concentrations will be presented by time point, age group, and treatment group. Scatter plots will be generated for time to alleviation of influenza symptoms and change from baseline in log_{10} $TCID_{50}$/mL versus peramivir plasma concentration at 30-60 minutes following study drug administration. The data from this trial together with data from prior trials will be used to complete a separate exposure-response analysis. The methods for the exposure-response analysis will be presented in a separate SAP.

6.2.4. Subgroup Analyses

The effectiveness analyses will also be presented by viral subtype at Screening.

6.3. SAFETY

6.3.1. Adverse Events

Adverse events will be mapped to a Medical Dictionary for Regulatory Activities (MedDRA) version 18.0 preferred term and system organ classification. If a subject experiences multiple events that map to a single preferred term, the greatest severity grade and strongest investigator assessment of relation to study medication will be assigned to the preferred term for the appropriate summaries. Should an event have a missing severity or relationship, it will be classified as having the highest severity and/or strongest relationship to study medication. Summaries of treatment-emergent AEs will include any AEs reported beginning with the initiation of study drug on Day 1. The occurrence of treatment-emergent adverse events (TEAEs) will be summarized by treatment group using preferred terms, system organ classifications, and severity. Separate summaries of treatment-emergent serious adverse events, treatment-emergent adverse events related to study drug, and events leading to the discontinuation of study will be generated. All adverse events reported will be listed for individual subjects showing both verbatim and preferred terms. All adverse events that occurred prior to the initiation of study treatment or more than 14 days post-study drug discontinuation will be excluded from the tables but will be included in the listings.

Missing onset dates will be imputed as previously outlined in Section 4.3.5 as required to determine treatment-emergent events.

6.3.2. Concomitant Medications

Previous and concomitant medications, as well as symptom relief medications recorded on the subject diary, will be coded using the World Health Organization (WHO) dictionary (Version: March, 2015). Concomitant medications will be summarized by frequency of drug classification and generic drug name. Previous and concomitant medications will be presented in a data listing. Symptom relief medications will be presented in a data listing.

6.3.3. Clinical Laboratory Assessments

Descriptive summaries of the following selected (quantitative) clinical laboratory results will be presented by study visit and treatment group for each age group and overall: ALT, AST, Serum Creatinine, BUN, HGB, Albumin, and Alkaline Phosphatase. Laboratory abnormalities (toxicities) will be graded according to the DAIDS Table for Grading Adverse Events for Adults and Pediatrics (Publish Date: December 2004). The number and percentage of subjects experiencing treatment-emergent graded toxicities will be summarized by treatment group for each age group and overall. Laboratory toxicity shifts from baseline to Day 7 will be summarized by treatment group for each age group and overall.

All laboratory toxicities that occurred before the initiation of study treatment or more than 14 days post study drug discontinuation will be excluded from the tables but will be included in the listings.

6.3.4. Other Safety Analyses

Descriptive summaries of vital signs will be presented by study visit and treatment group for each age group and overall.

All abnormal physical examination findings will be summarized by study visit and treatment group for each age group and overall.

6.4. PROTOCOL DEVIATIONS

Any deviation from protocol will be listed by subject and date. The type of deviation along with a description and any additional comments about the deviation will be listed.

7. CHANGES IN THE PLANNED ANALYSES

An analysis of the number of doses of antipyretic medications will be prepared.

There are no further changes anticipated to the protocol specified analyses. Should any more deviations occur, these changes will be fully described in the Clinical and Statistical Report.

8. REVISION HISTORY

Date	Revision	Rationale
29JUN2016	Clarification of units for age based on cohort and imputation methods for missing symptom scores. Addition of virology population. Removal of analyses for time weighted area under the curve for $TCID_{50}$. Changed imputation method to last observation carried forward.	Incorporation of review comments from BioCryst.

9. PROGRAMMING CONVENTIONS

- Page orientation, margins, and fonts: Summary tables, listings, and figures will appear in landscape orientation. There should be a minimum of a 1.25" boundary on the upper (bound) edge, and a minimum of a 1.0" boundary on the remaining three edges. Output should be printed in Courier New with a point size of 8. Titles may be printed using a larger font (e.g., Arial point size 10).
- Identification of analysis population: Every summary table and figure should clearly specify the analysis population being summarized. Listings will be prepared for all subjects randomized.
- Group headers: In the summary tables, the group headers will identify the treatment group and the within-group sample size for the indicated analysis population. Of note, the header's sample size does not necessarily equal the number of subjects actually summarized within any given summary module; some subjects in the analysis population may have missing values and thus may not be summarized.
- Suppression of percentages corresponding to null categories: When count data are presented as category frequencies and corresponding percentages, the percent should be suppressed when the count is zero in order to draw attention to the non-zero counts.
- Presentation of sample sizes: Summary modules should indicate, in one way or another, the number of subjects actually contributing to the summary statistics presented in any given summary module. As mentioned above, this may be less than the number of subjects in the analysis population.
    - ♦ In the quantitative modules describing continuous variables (and thus presenting sample size, means, and standard deviations), the sample size should be the number of non-missing observations
    - ♦ For categorical variables that are presented in frequency tables, the module should present the total count in addition to the count in each category. Percentages should be calculated using this total as the denominator, and the percentage corresponding to the sum itself (that is, 100%) should be presented so as to indicate clearly to a reviewer the method of calculation.
- Sorting: Listings will be sorted by treatment group, subject number and date, if applicable. If a listing is sorted in a different manner, a footnote will indicate as such.
- General formatting rules: Rounding for all variables will occur only as the last step, immediately prior to presentation in listings, tables, and figures. No intermediate rounding will be performed on derived variables. The standard rounding practice of rounding numbers ending in 0-4 down and numbers ending in 5-9 up will be employed.
- The presentation of numerical values will adhere to the following guidelines:

  - Raw measurements will be reported to the number of significant digits as captured electronically or on the CRFs.
  - Standard deviations will be reported to one decimal place beyond the number of decimal places the original parameter is presented.
  - Means will be reported to the same number of significant digits as the parameter.
  - Calculated percentages will be reported with no decimals.
- Dates will be formatted as DDMMMYYYY. Partial dates will be presented on data listings as recorded on CRFs.
- Time will be presented according to the 24-hour clock (HH:MM).

10. PROPOSED TABLES, LISTINGS, AND FIGURES FOR FINAL ANALYSIS

Output Number	Output Title
Table 14.1.1	Subject Follow-Up and Termination from Study; Intent-to-Treat Population
Table 14.1.2.1	Randomization, Eligibility, and Treatment Status; Intent-to-Treat Population
Figure 14.1.2.2	BCX1812-305 Study Population Disposition; Intent-to-Treat Population
Table 14.1.3	Demographics and Baseline Characteristics; Intent-to-Treat Population
Table 14.1.4	Populations for Analysis; Intent-to-Treat Population
Table 14.1.5	Summary of Subject Diary Completion; Intent-to-Treat-Infected Population
Table 14.2.1.1	Summary of Oral Temperature; Intent-to-Treat Infected Population
Table 14.2.1.2.1.1	Time to Resolution of Fever; Intent-to-Treat Infected Population
Figure 14.2.1.2.1.2	Time to Resolution of Fever (Kaplan-Meier Plot) ; ITTI Population
Figure 14.2.1.2.1.3	Median (95% CI) Time to Resolution of Fever; ITTI Population
Table 14.2.1.2.2	Time to Resolution of Fever by Viral Sub-Type; Intent-to-Treat Infected Population
Table 14.2.2.1.1.1	Time to Alleviation of Symptoms [1]; Intent-to-Treat Infected Population
Figure 14.2.2.1.1.2	Time to Alleviation of Symptoms (Kaplan-Meier Plot) ; ITTI Population
Figure 14.2.2.1.1.3	Median (95% CI) Time to Alleviation of Symptoms; ITTI Population
Table 14.2.2.1.2.1	Time to Alleviation of Symptoms [1] by Viral Sub-Type; Missing Values are Censored at the Last Available Assessment; Intent-to-Treat Infected Population

Output Number	Output Title
Figure 14.2.2.1.2.2	Median (95% CI) Time to Alleviation of Symptoms by Viral Sub-Type; ITTI Population
Table 14.2.3.1.1.1	Summary of Changes $\log_{10}$ Tissue Culture Infective Dose_{50} (TCID_{50} /mL) by Study Visit; Intent-to-Treat Infected Population
Figure 14.2.3.1.1.2	Box Plots of Viral Titers (TCID_{50} /mL) by Study Visit; Subjects with Negative Baseline Viral Titers are Excluded; Intent-to-Treat Infected Population
Figure 14.2.3.1.1.3	Histograms of Viral Titers (TCID_{50} /mL) by Study Visit; Subjects with Negative Baseline Viral Titers are Excluded; Intent-to-Treat Infected Population
Figure 14.2.3.1.1.4	Median (with IQR) Change from Baseline Viral Titers (TCID_{50} /mL) by Study Visit; Subjects with Negative Baseline Viral Titers are Excluded; Intent-to-Treat Infected Population
Table 14.2.3.1.2	Summary of Changes $\log_{10}$ Tissue Culture Infective Dose_{50} (TCID_{50} /mL) by Study Visit and Viral Sub-Type; Intent-to-Treat Infected Population
Table 14.2.3.2.1	Summary of Viral Shedding by Study Visit; Intent-to-Treat Infected Population
Table 14.2.3.2.2	Summary of Viral Shedding by Study Visit and Viral Sub-Type; Intent-to-Treat Infected Population
Table 14.2.3.3.1	Summary of RT-PCR Result by Study Visit; Intent-to-Treat Infected Population
Table 14.2.3.3.2	Summary of RT-PCR Result by Study Visit and Viral Sub-Type; Intent-to-Treat Infected Population
Table 14.2.3.4	Change of Influenza Virus Susceptibility to Neuraminidase Inhibitors by Viral Subtype; Intent-to-Treat Infected Population
Table 14.2.4	Summary of Influenza-Related Complications; Intent-to-Treat Infected Population

Output Number	Output Title
Table 14.2.5	Number of Doses of Antipyretic Medications; Intent-to-Treat Infected Population
Table 14.2.6	Summary of Subject-Rated Assessment of Ability to Perform Daily Activities; Intent-to-Treat Infected Population
Table 14.2.7	Summary of Assessment of Appetite and Eating Patterns; ITTI Population
Table 14.3.1.1	Treatment-Emergent Adverse Events by System Organ Classification, Preferred Term and Greatest Severity; Safety Population
Table 14.3.1.2	Treatment-Emergent Adverse Events Possibly, Probably, or Definitely Related to Study Drug by System Organ Classification and Preferred Term; Safety Population
Table 14.3.1.3	Treatment-Emergent Serious Adverse Events by System Organ Classification and Preferred Term; Safety Population
Table 14.3.1.4	Treatment-Emergent Adverse Events Leading to the Discontinuation of Study by System Organ Classification and Preferred Term; Safety Population
Table 14.3.5.1	Summary of Select Laboratory Values by Study Visit; Safety Population
Table 14.3.5.2	Graded Laboratory Toxicities; Safety Population
Table 14.3.5.3.1	Laboratory Shifts from Baseline: Chemistry; Safety Population
Table 14.3.5.3.2	Laboratory Shifts from Baseline: Hematology; Safety Population
Table 14.3.5.3.3	Laboratory Shifts from Baseline: Urinalysis; Safety Population
Table 14.3.6	Summary of Vital Signs by Study Visit; Safety Population
Table 14.3.7	Abnormal Physical Examinations; Safety Population
Table 14.3.8	Concomitant Medications by Generic Name and Drug Classification; Safety Population

Output Number	Output Title
Table 14.4.1.1	Summary of Plasma Concentrations of Peramivir by Time point; Intent-to-Treat Population
Table 14.4.1.2	Summary of Plasma Concentrations of Peramivir; Exposure Response Population
Figure 14.4.2	Relationship between Time to Alleviation of Influenza Symptoms and Peramivir Plasma Concentrations at 30-60 Minutes Post-Dose; Exposure-Response Population
Figure 14.4.3	Relationship between Viral Change from Baseline and Peramivir Plasma Concentrations at 30-60 Minutes Post-Dose; Exposure-Response Population
Listing 16.2.1	Study Completion; Intent-to-Treat Population
Listing 16.2.2	Protocol Deviations; Intent-to-Treat Population
Listing 16.2.4.1	Inclusion/Exclusion Criteria; Intent-to-Treat Population
Listing 16.2.4.2	Subject Eligibility and Randomization; Intent-to-Treat Population
Listing 16.2.4.3	Demographics; Intent-to-Treat Population
Listing 16.2.4.4	Medical History; Intent-to-Treat Population
Listing 16.2.4.5	Prior and Concomitant Medications; Intent-to-Treat Population
Listing 16.2.5.1	Study Medication Administration; Intent-to-Treat Population
Listing 16.2.5.2	Pharmacokinetic Sample Collection Time and Concentrations; PK Population
Listing 16.2.6.1.1	Summary of Efficacy Variables; ITTI Population
Listing 16.2.6.2	Influenza Symptoms; Intent-to-Treat Population
Listing 16.2.6.3	Temperature; Intent-to-Treat Population
Listing 16.2.6.4	Subject-Rated Assessment of Daily Activities and Assessment of Appetite and Eating Patterns; Intent-to-Treat Population

Output Number	Output Title
Listing 16.2.6.5	Viral Titers and Viral Susceptibility; Intent-to-Treat Population
Listing 16.2.6.6	RT-PCR for Influenza; Intent-to-Treat Population
Listing 16.2.6.7	Symptom Relief Medications; Intent-to-Treat Population
Listing 16.2.6.8	Influenza-Related Complications; Intent-to-Treat Population
Listing 16.2.7	Adverse Events; Intent-to-Treat Population
Listing 16.2.8.1.1	Laboratory Tests - Hematology; Intent-to-Treat Population
Listing 16.2.8.1.2	Laboratory Tests - Chemistry; Intent-to-Treat Population
Listing 16.2.8.1.3	Laboratory Tests - Urinalysis; Intent-to-Treat Population
Listing 16.2.8.1.4	Laboratory Tests - Virology; Intent-to-Treat Population
Listing 16.2.8.1.5	Laboratory Tests - Other; Intent-to-Treat Population
Listing 16.2.8.2	Blood and Urine Collection and Pregnancy Tests; Intent-to-Treat Population
Listing 16.2.8.3	Vital Signs, Height, and Weight; Intent-to-Treat Population
Listing 16.2.8.4	Physical Examinations; Intent-to-Treat Population
Listing 16.2.9.1	Changes in NA Amino Acids from Baseline to Post-Baseline
Listing 16.2.9.2	Changes in HA Amino Acids from Baseline to Post-Baseline
Listing 16.2.9.3	NA Sequence Alignment
Listing 16.2.9.4	HA Sequence Alignment