STATISTICAL ANALYSIS PLAN

Study Title:	A Phase 3, multicenter, single-arm, open-label, study to evaluate the safety, pharmacokinetics and effectiveness of intravenous peramivir in elderly subjects with acute uncomplicated influenza infection and in subjects with acute uncomplicated influenza infection at higher risk for influenza complications
Phase:	3
Protocol No.:	BCX1812-306
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STATISTICAL ANALYSIS PLAN REVIEW AND APPROVAL

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

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TABLE OF CONTENTS

1. INTRODUCTION

This document describes the statistical methods and data presentations to be used in the summary and analysis of data from Protocol BCX1812-306. 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, respectively.

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

1.1. STUDY OVERVIEW

Protocol BCX1812-306 is a multicenter, single-arm, open-label study to evaluate the safety, PK, and effectiveness of a single dose of peramivir administered intravenously (IV) in elderly subjects (≥ 65 years of age) with acute uncomplicated influenza and in younger subjects (< 65 years of age) with acute uncomplicated influenza who are at higher risk for influenza complications. Elderly subjects will not be classified as high or low risk and will be captured as elderly only.

Approximately 120 subjects will be enrolled in this open-label study (a minimum of 80 elderly subjects will be enrolled). A subject's duration of participation in this study is expected to be 14 days and will include up to 4 clinic visits. It is expected that most subjects will have the Screening visit and the Day 1 Treatment visit on the same day. Following treatment on study Day 1, subjects will undergo follow-up assessments on Days 3, 7, and 14 in the clinic. Subjects will be discharged from this study on Day 14. Additional unscheduled visits may be required for subjects who report symptoms of influenza of moderate or severe intensity at Day 14 or have persistent adverse events (AEs) and/or treatment-emergent laboratory findings that require medical monitoring or management.

Eligible subjects will have a positive influenza Rapid Antigen Test (RAT) and/or a Food and Drug Administration (FDA) approved polymerase chain reaction (PCR) test and at least one clinical sign or symptom consistent with influenza OR clinical signs and symptoms consistent with acute influenza infection consisting of an oral temperature ≥ 37.8°C/ 100°F with at least one respiratory symptom of at least moderate severity (cough or rhinitis) and at least one constitutional symptom of at least moderate severity (myalgia, headache, feverishness, or fatigue).

Subjects will receive a single IV dose of 600 mg peramivir (or less if renally impaired), which will occur over 15 to 30 minutes.

An adequate nasal swab specimen will be collected from all enrolled subjects at Baseline (predose) for virus subtype identification and quantitative virologic assessments and at the follow-up assessments on study Days 3, 7, and 14.

Specimens obtained from all subjects on Day 1 and the last specimen that yields influenza virus on culture will also be assessed for susceptibility to neuraminidase inhibitors. A central laboratory will perform all virologic assessments.

Up to 3 blood samples will be drawn to obtain plasma samples for drug concentration determinations, where possible, during the following time periods, beginning from the end of dosing until release from the site on the day of dosing:

- 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

AEs and concomitant medications will be monitored at each scheduled visit from the Screening assessment to final study visit. Clinical laboratory investigations (chemistries, hematology, and urinalysis) will be collected at Baseline, Day 7, and Early Withdrawal visits. Safety and tolerability will be evaluated through assessments of AEs, laboratory analyses (clinical chemistry, hematology, and urinalysis), vital signs, and physical examinations at the time points indicated in the schedule of assessments (see Section 1.2).

All subjects or their caregivers will record the following information in a Subject Diary:

- Assessment of the presence and severity of each of 7 symptoms of influenza on a 4-point severity scale (0, absent; 1, mild; 2, moderate; 3, severe) at Screening, then twice daily through Day 13, and prior to the subject's clinic visit on Day 14 or until each symptom is rated as a 0 or 1 for 48 consecutive hours. Diaries will be reviewed at each clinic visit.
- Temperature measurements (oral) will be taken with an electronic thermometer provided by the Sponsor, approximately every 12 hours until temperature normalizes for 48 hours (ie, temperature without antipyretic is < 37.4°C/99.4°F orally for 4 consecutive measurements). With the exception of the Screening/ Baseline measurement, all temperature measurements will be obtained at least 4 hours after, or immediately before, administration of oral acetaminophen or other antipyretic medications, if taken.
- The type, date, and time of medications used for the symptomatic treatment of influenza-related symptoms.
- Assessment of the subject's ability to perform usual activities using a 0 to 10 visual analog scale once daily through Day 14, where 0 = Unable to perform usual activities at all, and 10 = Able to perform all usual activities fully.

1.2. SCHEDULE OF EVENTS/STUDY VISITS

Assessments	Screening[1]	Baseline[1] (Pre-dose)	Day 1 Treatment Day[1]	Day 3	Day 7 (+2 days)	Day 14 (+3 days) / End of Study	Early Withdrawal
Informed Consent	X						
Inclusion/Exclusion Criteria	X						
Medical History/Physical Exam	X			X[6]	X[6]		
Vital Signs[2]	X			X	X	X	X
Body Temperature[3]	X	X	X	X	X	X	X
Clinical Chemistries and Hematology[4]		X			X		X
Urinalysis[4]		X			X		X
Pregnancy Test (Urine or Serum)	X					X	X
Assessment of Influenza Symptoms[5]	X		X	X	X	X	X
Ability to Perform Usual Daily Activities[5]		X		X	X	X	X
Influenza Related Complications (IRC)[7]	X			X[7]	X	X	X
Concomitant Medications Review	X		X	X	X	X	X
Subject Diary Review			X	X	X	X	X
Pharmacokinetic (PK) Sampling			X				
Serum Sample for Influenza Antibody Analysis[8]		X		X	X		X
Swabs for Virology Analysis		X		X	X		X
Rapid Antigen Test (RAT) or FDA-approved PCR Test for Influenza A and B on Nasal Specimen	X						
Study Drug Administration			X				
Adverse Events[9]	X	X	X	X	X	X	X

1 It is expected that the date of Screening, Baseline, and Day 1 (date of study drug administration) will be the same. Day 1 consists of pre and post-dose assessments.
2 Vital sign measures will include blood pressure, pulse rate, and respiration rate. Vital signs will be recorded once during Screening, and vital signs will be taken once on remaining study visit days.
3 The investigator will record oral body temperature at Screening. Thereafter, the subject or care giver will record oral body temperature approximately every 12 hours in the Subject Diary until temperature normalizes for 48 hours (ie, temperature without antipyretic is < 37.4°C/ 99.4°F orally for 4 measurements).
4 Clinical laboratory assessments performed at Screening are for the purpose of establishing a baseline. Subjects may be enrolled and begin treatment with study drug prior to receiving results. These labs may be done at any visit if necessary for subject management or adverse event monitoring purposes.
5 Influenza signs and symptoms will be recorded by the study personnel at Screening, then by the subject or care giver twice daily beginning on Day 1 through Day 13, and prior to the subject's clinic visit on Day 14 or until each symptom is 0 or 1 for 48 hours.
6 Perform a targeted physical exam on Day 3 and Day 7
7 If an influenza related complication (IRC) is suspected the subject will be instructed to return to the clinic as appropriate to confirm the presence or absence of IRCs.
8 A single serum specimen will be collected, where possible, pre-dose on Day 1, Day 3 and on Day 7 for analysis of influenza antibody titers.
9 Adverse events are to be collected from the time of informed consent through the follow-up period ending on Day 14.

1.3. GLOSSARY OF ABBREVIATIONS

AE	adverse event
CRF	case report form
FDA	Food and Drug Administration
ITT	intent-to-treat
ITTI	intent-to-treat infected
IV	Intravenous
PCR	polymerase chain reaction
PK	pharmacokinetic
RAT	rapid antigen test
RT-PCR	real time polymerase chain reaction
SAE	serious adverse event
$TCID_{50}$	Tissue-culture infective $dose_{50}$
TEAEs	treatment-emergent adverse events

2. OBJECTIVES

The primary objective is to evaluate the safety and tolerability of peramivir administered IV in elderly subjects with acute uncomplicated influenza and in subjects with acute uncomplicated influenza who are at higher risk for influenza complications.

The secondary objectives for this study are as follows:

- To describe the PK of IV peramivir in elderly and high-risk subjects with acute uncomplicated influenza
- To evaluate the effectiveness of IV peramivir in elderly and high-risk subjects with acute uncomplicated influenza
- To evaluate the incidence of influenza complications, specifically otitis media, sinusitis, bronchitis, or pneumonia requiring antibiotic use diagnosed after initiation of treatment.

3. GENERAL STATISTICAL CONSIDERATIONS

3.1. SAMPLE SIZE AND POWER

The study is designed to evaluate the safety, PK, and effectiveness of IV administration of

peramivir in subjects ≥ 65 years of age with influenza infection and in subjects with influenza infection who are at an increased risk of influenza complications. A sample size of up to 120 subjects, and a minimum of 80 elderly subjects (aged ≥ 65 years), is considered adequate to evaluate the stated objectives. A formal sample size calculation was not performed.

3.2. RANDOMIZATION AND MASKING

As this is a single-arm, open-label study, randomization and masking are not applicable.

3.3. HANDLING OF DATA

3.3.1. Strata and Covariates

There will be no stratification for this study.

3.3.2. Examination of Subject Subsets

All analyses will be presented by age group (≥ 65 years, 65-75 years, >75 years, and < 65 years). Time to resolution of fever, time to alleviation of symptoms, change in tissue-culture infective dose 50 ($TCID_{50}$), viral shedding, real-time PCR (RT-PCR) results, and change of influenza virus susceptibility to neuraminidase inhibitors analyses will be presented by age group and viral subtype at Screening. Additional subgroups defined based on risk of complications may be evaluated.

3.3.3. Multiple Testing and Comparisons

All analyses will be conducted without adjustments for multiple testing.

3.3.4. Missing Data and Outliers

Every effort will be made to obtain required data at each scheduled evaluation from all subjects who have been enrolled. No attempt will be made retrospectively to obtain missing subject reported data (such as influenza symptom severity assessments and temperature) 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. For the subject diary data, the following data conventions will be utilized. Diary completion times will use a 24-hour clock. 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. 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.

3.3.5. 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 (ie, 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.

3.3.6. 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 will be used, as determined by the time collected, if available.

3.3.7. Derived and Transformed Data

$TCID_{50}$ will be $\log_{10}$ transformed prior to performing the analyses.

3.3.8. Definitions and Terminology

Age
Age will be defined as the age in years at time of signing of informed consent for all subjects.

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 (eg, 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 Day 14/End of Study/Early Withdrawal 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 are either absent or are present at no more than mild severity level and at this status for a 21.5 hour period (24 hours less 10%).

Composite Symptom Score
The Composite Symptom Score is defined as the sum of the seven symptoms of influenza (cough, sore throat, stuffy nose, muscle aches, headache, feverishness, fatigue/tired) assessed on a given time point within the subject diary.

Baseline Composite Symptom Score
The Baseline Composite Symptom Score is defined as the sum of the symptoms of influenza recorded by the subject in the diary corresponding to the assessment of a subject's symptoms prior to the initiation of study drug.

Resolution of Fever

A subject has Resolution of Fever if he/she has a temperature < 37.4°C/99.4°F oral 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.

Ability to Perform Usual Activities
The ability to perform usual activities is defined as a subject rating of 10 (able to perform all usual activities fully) on the visual analog scale the subject uses to rate his or her current ability to perform usual activities compared with normal ability.

Time to Event
Time to a given event is defined as the number of hours (days) 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 21.5 hour period (24 hours less 10%) where all symptoms of influenza are recorded as none or mild.

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 (eg, 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 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 a serious adverse event (SAE), which then must be recorded as such (see Protocol Section 11.1.1.2).

All AEs will be recorded on the ADVERSE EVENTS CRF.

Treatment-emergent Adverse Events (TEAEs)
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 AE which was reported to have started on Day 1 without an associated onset time may have occurred after the initiation of study drug. Hence, AEs occurring on Day 1 with no associated onset time are assumed to be treatment-emergent.

Treatment-emergent Laboratory Abnormalities
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 (ie, at least Grade 1) is considered to be treatment-emergent.

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

Prior Medications
Prior medications are those medications taken prior to the initiation of study drug. Subjects will record all medications they are currently taking.

3.4. 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 intent-to-treat infected (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 PK and virology data are not available at the time of the analysis of the clinical data.

4. ANALYSIS POPULATIONS

All subjects enrolled (eg, signed the 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), ITTI, safety, and exposure-response populations.

4.1. INTENT-TO-TREAT POPULATION

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

4.2. INTENT-TO-TREAT INFECTED POPULATION

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

4.3. SAFETY POPULATION

The safety population will include all enrolled subjects who receive any amount of study drug. The safety population will be the primary population for all analyses of safety data.

4.4. 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. STATISTICAL METHODS

Descriptive statistical methods will be used to summarize the data from this study. Data will be summarized by 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 "age group" refers to the following: < 65 years, 65-75 years, > 75 years, and ≥ 65 years. Note that 65-75 years and > 75 years are subsets of the ≥ 65 years group. No formal statistical hypothesis testing is planned.

All data collected during the study will be included in data listings. Unless otherwise noted, the data will be sorted first by age group, subject number, and then by date within each subject number.

The statistical analyses will be conducted with the SAS® software package version 9.4 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.

5.1. 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 will be summarized.

A CONSORT diagram will be produced showing the number of subjects screened, number of screening failures, number of subjects by age group, number in each of the study populations, and number who complete the study.

Demographic data and baseline characteristics including age, gender, race, ethnicity, Baseline Composite Symptom Score, baseline viral titer status, the number subjects who had hypothermia (< 35°C/95°F), normal temperature (35 to < 37.4°C / 95 to < 99.4°F), or fever (≥ 37.4°C/99.4°F) at baseline, height, weight, and body mass index (BMI) will be summarized using descriptive statistics for the ITT, ITTI, safety, and exposure-response populations.

Enrollment by site, eligibility, treatment status, and screening RAT and PCR test results will be summarized by age group and overall.

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

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

5.2. EFFECTIVENESS ANALYSIS

5.2.1. Effectiveness Endpoints

The effectiveness endpoints include:

- Time to resolution of fever
- Time to alleviation of clinical symptoms of influenza
- Change (reduction) in influenza virus titer by $\log_{10}$ $TCID_{50}$/mL
- Change (reduction) in influenza virus titer by RT-PCR results
- Changes in viral shedding measured by quantitative viral titer assay ($TCID_{50}$) and/or quantitative PCR.
- Change in influenza virus susceptibility to neuraminidase inhibitors
- Incidence of influenza-related complications as determined by investigator
- Incidence of hospitalization admission post treatment
- Usage of antipyretic medication
- Change in daily activities per the visual analog scale
- Time to resumption of usual daily activities per the visual analog scale

5.2.2. Effectiveness Analyses

A subject's oral temperature taken by subjects and recorded in the diary by subjects/caregivers will be summarized by age group and overall by study visit. A subject has Resolution of Fever if he/she has an oral temperature < 37.4°C/99.4°F oral 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 using the Kaplan-Meier method with 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, defined as the time from initiation of study drug until the start of the 21.5 hour period (24 hours less 10%) where all symptoms of influenza are recorded as none or mild, will be estimated overall and for each age group using the Kaplan- Meier method. 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 $\log_{10}$ $TCID_{50}$/mL through Day 3, Day 7, and Day 14 will be presented by age group and overall 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 and age group. In addition, the median change from baseline in $TCID_{50}$/mL will be presented by visit and age group.

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

The RT-PCR results at each visit will be presented by age group and overall 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 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 and viral subtype.

The number and percentage of subjects experiencing influenza related complications will be summarized by age group and overall by complication MedDRA version 18.0 preferred term.

The number and percentage of subjects who are hospitalized due to any TEAE and due to any TEAE related to study drug after initiation of treatment will be summarized by age group and overall.

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.

The change in daily activities will be summarized each day by age group and overall. The ability to perform usual activities is defined as a subject rating of 10 (able to perform all usual activities fully) on the visual analog scale the subject uses to rate his or her current ability to perform usual activities compared with normal ability. The time to return to usual activities will be estimated for each age group and overall using the Kaplan-Meier method. Subjects who do not return to normal activities will be censored at the time of their last non-missing post-baseline assessment.

5.2.3. Exploratory Exposure Response Analyses

Summaries of plasma concentrations of peramivir will be presented by time point and age 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 may be used to complete a separate exposure-response analysis. The methods for the exposure-response analysis will be presented in a separate Statistical Analysis Plan.

5.2.4. Subgroup Analyses

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

5.3. SAFETY

5.3.1. Adverse Events

AEs 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. An overall summary of TEAEs will be generated, showing the number of subjects with at least one AE, SAE, AE related to study drug, AE leading to discontinuation of study, SAE related to study drug, severe or life-threatening AE, and severe or life-threatening AE related to study drug. Summaries of TEAEs will include any AEs reported beginning with the initiation of study drug on Day 1. The occurrence of TEAEs will be summarized by age group using preferred terms, system organ classifications, and severity. Separate summaries of TEAEs, treatment-emergent SAEs, TEAEs related to study drug, events

leading to the discontinuation of study, and events leading to the discontinuation of study drug will be generated by preferred term and system organ classification. TEAEs occurring in ≥10% of subjects will be summarized by preferred term. All AEs reported will be listed for individual subjects showing both verbatim and preferred terms. A separate listing of all SAEs will be generated. All AEs 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 3.3.5 as required to determine whether AEs were treatment-emergent.

5.3.2. Concomitant Medications

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

5.3.3. Clinical Laboratory Assessments

Descriptive summaries of selected (quantitative) clinical laboratory results will be presented by study visit for each age group and overall. The clinical chemistry profile will include: albumin, alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), bicarbonate, direct bilirubin, bilirubin, blood urea nitrogen, calcium, creatine kinase, chloride, creatinine, gamma glutamyl transferase, glucose, potassium, lactate dehydrogenase (LDH), magnesium, phosphate, protein, sodium, and urate. The hematology profile will include: basophils, basophils/leukocytes, eosinophils, eosinophils/leukocytes, hematocrit, hemoglobin, lymphocytes, lymphocytes/leukocytes, erythrocyte mean corpuscular hemoglobin, erythrocyte mean corpuscular hemoglobin concentration, erythrocyte mean corpuscular volume, monocytes, neutrophils, neutrophils/leukocytes, platelets, erythrocytes, and leukocytes. Laboratory abnormalities (toxicities) will be graded according to the Division of AIDS (DAIDS) Table for Grading Adverse Events for Adults and Pediatrics (Published Date: December 2004). The number and percentage of subjects who experience treatment-emergent toxicities will be summarized for each age group and overall. Laboratory toxicity shifts from baseline to Day 7 will be summarized 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.

5.3.4. Other Safety Analyses

Exposure to study drug, including infusion time treatment status, will be summarized by age group

and overall.

Descriptive summaries of vital signs measured by study site personnel will be presented by study visit for each age group and overall.
All physical examination findings will be listed by age group and study visit.

5.4. 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.

In cases where the statistical analysis plan differs from the protocol, the statistical analysis plan will supersede the protocol.

6. 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.

7. REVISION HISTORY

Date	Revision	Rationale

8. 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 (eg, Arial point size 10).
- Identification of analysis population: Every summary table and figure should clearly specify the analysis population being summarized. All listings will be prepared for all subjects enrolled.
- Group headers: In the summary tables, the group headers will identify the age 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 age 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).

9. 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	Eligibility and Treatment Status: Intent-to-Treat Population
Figure 14.1.2.2	BCX1812-306 Study Population Disposition: Intent-to-Treat Population
Table 14.1.3	Populations for Analysis: Intent-to-Treat Population
Table 14.1.4.1	Demographics and Baseline Characteristics: Intent-to-Treat Population
Table 14.1.4.2	Demographics and Baseline Characteristics: Intent-to-Treat Infected Population
Table 14.1.4.3	Demographics and Baseline Characteristics: Safety Population
Table 14.1.4.4	Demographics and Baseline Characteristics: Exposure-Response Population
Table 14.1.5	Summary of Subject Diary Completion: Intent-to-Treat-Infected Population
Table 14.2.1.1	Summary of Oral Temperature Diary Assessments (°C): Intent-to-Treat Infected Population
Table 14.2.1.2	Time to Resolution of Fever: Intent-to-Treat Infected Population
Table 14.2.1.2.X	Time to Resolution of Fever: Viral Subtype: Intent-to-Treat Infected Population
Figure 14.2.1.3	Time to Resolution of Fever (Kaplan-Meier Plot): ITTI Population
Figure 14.2.1.4	Median (95% CI) Time to Resolution of Fever: ITTI Population
Figure 14.2.1.5	Box Plots of Time to Resolution of Fever: ITTI Population
Table 14.2.2.1	Time to Alleviation of Symptoms: Intent-to-Treat Infected Population

Output Number	Output Title
Table 14.2.2.1.X	Time to Alleviation of Symptoms: Viral Subtype: Intent-to-Treat Infected Population
Figure 14.2.2.2	Time to Alleviation of Symptoms (Kaplan-Meier Plot): ITTI Population
Figure 14.2.2.3	Median (95% CI) Time to Alleviation of Symptoms: ITTI Population
Figure 14.2.2.4	Box Plots of Time to Alleviation of Symptoms: ITTI Population
Table 14.2.3.1	Summary of Changes $\log_{10}$ Tissue Culture Infective Dose50 ($TCID_{50}$ /mL) by Study Visit: Subjects with Positive Baseline Titers; Intent-to-Treat Infected Population
Table 14.2.3.1.X	Summary of Changes $\log_{10}$ Tissue Culture Infective Dose50 ($TCID_{50}$ /mL) by Study Visit: Subjects with Positive Baseline Titers: Viral Subtype: Intent-to-Treat Infected Population
Figure 14.2.3.2	Box Plots of Viral Titers ($TCID_{50}$/mL) by Study Visit; Subjects with Positive Baseline Titers: Intent-to-Treat Infected Population
Figure 14.2.3.3	Histograms of Viral Titers ($TCID_{50}$/mL) by Study Visit; Subjects with Positive Baseline Titers: Intent-to-Treat Infected Population
Figure 14.2.3.4	Median (with IQR) Change from Baseline Viral Titers ($TCID_{50}$/mL) by Study Visit: Subjects with Positive Baseline Titers: Intent-to-Treat Infected Population
Table 14.2.4.1	Summary of Viral Shedding by Study Visit; Subjects with Positive Baseline Titers: Intent-to-Treat Infected Population
Table 14.2.4.1.X	Summary of Viral Shedding by Study Visit: Subjects with Positive Baseline Titers: Viral Subtype: Intent-to-Treat Infected Population
Table 14.2.5.1	Summary of RT-PCR Result by Study Visit: Subjects with Positive Baseline RT-PCR: Intent-to-Treat Infected Population
Table 14.2.5.1.X	Summary of RT-PCR Result by Study Visit: Subjects with Positive Baseline RT-PCR: Viral Subtype: Intent-to-Treat Infected Population

Output Number	Output Title
Table 14.2.6	Change of Influenza Virus Susceptibility to Neuraminidase Inhibitors: Intent-to-Treat Infected Population
Table 14.2.7	Summary of Influenza-Related Complications and Hospitalizations: Intent-to-Treat Infected Population
Table 14.2.8	Number of Doses of Antipyretic Medications: Intent-to-Treat Infected Population
Table 14.2.9.1	Summary of Subject-Rated Assessment of Ability to Perform Daily Activities: Intent-to-Treat Infected Population
Table 14.2.9.2	Time to Return to Usual Activities: Intent-to-Treat Infected Population
Table 14.3.1.1	Overall Summary of Treatment-Emergent Adverse Events: Safety Population
Table 14.3.1.2	Treatment-Emergent Adverse Events by System Organ Classification, Preferred Term and Greatest Severity: Safety Population
Table 14.3.1.3	Treatment-Emergent Adverse Events by System Organ Classification and Preferred Term: Safety Population
Table 14.3.1.4	Treatment-Emergent Adverse Events Possibly, Probably, or Definitely Related to Study Drug by System Organ Classification and Preferred Term: Safety Population
Table 14.3.1.5	Treatment-Emergent Serious Adverse Events by System Organ Classification and Preferred Term: Safety Population
Table 14.3.1.6	Treatment-Emergent Adverse Events Leading to the Discontinuation of Study by System Organ Classification and Preferred Term: Safety Population
Table 14.3.1.7	Treatment-Emergent Adverse Events Leading to the Discontinuation of Study Drug by System Organ Classification and Preferred Term: Safety Population
Table 14.3.1.8	Treatment-Emergent Adverse Events Occurring in ≥10% of Subjects by Preferred Term: Safety Population

Output Number	Output Title
Table 14.3.4.1.1	Summary of Chemistry Laboratory Values by Study Visit: Safety Population
Table 14.3.4.1.2	Summary of Hematology Laboratory Values by Study Visit: Safety Population
Table 14.3.4.2	Graded Laboratory Toxicities: Safety Population
Table 14.3.4.3.1	Laboratory Shifts from Baseline to Day 7 - Chemistry: Safety Population
Table 14.3.4.3.2	Laboratory Shifts from Baseline to Day 7 - Hematology: Safety Population
Table 14.3.4.3.3	Laboratory Shifts from Baseline to Day 7 - Urinalysis: Safety Population
Table 14.3.5	Study Drug Exposure: Safety Population
Table 14.3.6	Summary of Vital Signs by Study Visit: Safety Population
Table 14.3.7.1	Concomitant Medications by Generic Name and Drug Classification: Safety Population
Table 14.3.7.2	Antipyretic Concomitant Medications by Generic Name and Drug Classification: Safety Population
Table 14.3.7.3	Concomitant Medications Used to Treat Influenza Symptoms by Generic Name and Drug Classification: Safety Population
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 by Time Point: 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

Output Number	Output Title
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: 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: Intent-to-Treat-Infected 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
Listing 16.2.6.5	Viral Titers and Viral Susceptibility: Intent-to-Treat Population
Listing 16.2.6.6	Symptom Relief Medications: Intent-to-Treat Population
Listing 16.2.6.7	Influenza-Related Complications: Intent-to-Treat Population
Listing 16.2.7.1	Adverse Events: Intent-to-Treat Population
Listing 16.2.7.2	Serious Adverse Events: Intent-to-Treat Population

Output Number	Output Title
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 16.2.8.2	Blood and Urine Collection and Pregnancy Tests: Intent-to-Treat Population
Listing 16.2.8.3	Virology Specimen Collection and Influenza Antibodies Analysis: Intent-to-Treat Population
Listing 16.2.8.4	Vital Signs, Height, and Weight: Intent-to-Treat Population
Listing 16.2.8.5	Physical Examinations: Intent-to-Treat Population