BioCryst Pharmaceuticals, Inc.

CLINICAL STUDY PROTOCOL

Protocol No. BCX1812-306

IND No. 69,038

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

Original Protocol, Version 1.0: 30 June 2015

Protocol Amendment 01, Version 2.0: 03 September 2015

Protocol Amendment 02 (Administrative), Version 3.0: 11 October 2016

Protocol Amendment 03, Version 4.0: 09 August 2017

BioCryst Pharmaceuticals, Inc.
4505 Emperor Boulevard, Suite 200
Durham, NC 27703
Phone: (+1)919-859-1302
Fax: (+1)919-851-1416

1. TITLE PAGE

Protocol Number:	BCX1812-306
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
IND Number:	69,038
EudraCT No.	N/A
Investigational Product:	Peramivir
Indication Studied:	Influenza
Sponsor:	BioCryst Pharmaceuticals, Inc. 4505 Emperor Boulevard, Suite 200 Durham, NC 27703
Development Phase:	3
Sponsor Medical Officer:	Sylvia Dobo, MD Executive Director, Product Safety and Clinical Development Phone: (+1) 773-304-8942 Fax: (+1) 919-851-1416 Email Address: sdobo@biocryst.com
Principal Investigator:	Carol L. Clark, MD Beaumont Health System Emergency Royal Oak, MI
Compliance Statement:	This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and clinical research guidelines established by the Code of Federal Regulations (Title 21, CFR Parts 50, 56, and 312) and ICH Guidelines. Essential study documents are currently archived in accordance with applicable regulations.
Final Protocol Date:	Version 4.0; 09 Aug 2017

1.1. Protocol Approval Signature Page

Protocol No.	BCX1812-306
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Version Date:	Version 4.0; 09 Aug 2017

BioCryst Pharmaceuticals, Inc.

Reviewed and Approved by:

William P Sheridan AUG 09, 2017

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

Date

09 AUG 2017

Elliott Berger, PhD
Senior Vice President, Regulatory Affairs

Date

1.2. Clinical Study Protocol Agreement

Protocol No.	BCX1812-306
Protocol 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
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I have carefully read this protocol and agree that it contains all of the necessary information required to conduct this study. I agree to conduct this study as described and according to the Declaration of Helsinki, International Conference on Harmonization Guidelines for Good Clinical Practices, and all applicable regulatory requirements.

Investigator's Signature Date

Name (Print)

2. SYNOPSIS

Name of Sponsor/Company:
BioCryst Pharmaceuticals, Inc.

Name of Investigational Product:
BCX1812, Peramivir, RAPIVAB™

Title of Study:
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

Study Center(s): Multicenter

Principal Investigator:
Carol L. Clark, MD, MBA, FACP
Beaumont Hospital- Royal Oak
Department of Emergency Medicine

Studied Period (years):	**Phase of Development:**
Estimated date first subject enrolled: October 2015 Estimated date last subject completed: April 2018	3b

Objectives:

Primary:

- To evaluate the safety and tolerability of peramivir administered intravenously (IV) in elderly subjects with acute uncomplicated influenza infection and in subjects with acute uncomplicated influenza infection who are at higher risk for influenza complications.

Secondary:

- To describe the pharmacokinetics (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

Methodology:

This is a multicenter, single-arm, open-label study will evaluate the safety, PK and effectiveness of a single dose of IV peramivir in elderly subjects (≥ 65 years of age) with acute uncomplicated influenza and in subjects with acute uncomplicated influenza at higher risk for influenza complications.

Subjects meeting the inclusion/ exclusion criteria will be enrolled into the study. Following treatment on study Day 1, subjects will undergo in-clinic follow-up assessments on Days 3, 7, and 14.

All subjects/caregivers will record the following information in a subject diary:

- Assessment of the presence and severity of each of the 7 symptoms of influenza on a 4-point severity scale (0, absent; 1, mild; 2, moderate; 3, severe) twice daily 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.
- Temperature measurements (oral) will be taken with an electronic thermometer provided by the

Sponsor, approximately every 12 hours until temperature normalizes for 48 hours (i.e., temperature without antipyretic is < 37.4°C/99.4°F orally for 4 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 analogue scale once daily through Day 14, where 0 = Unable to perform usual activities at all, and 10 = Able to perform all usual activities fully.

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

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). A central laboratory will perform all virologic assessments.

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

Up to 3 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

Adverse events 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, and Day 7 visits. Day 14 clinical laboratory investigations will only be collected if Day 7 labs are in the opinion of the investigator, significantly abnormal or clinically changed from baseline. In additional, clinical laboratory investigations may be conducted at any time for patient management / safety reasons. Safety and tolerability will be evaluated through assessments of adverse events, laboratory analyses (clinical chemistry, hematology, and urinalysis), vital signs and physical examinations at the time points indicated in the schedule of assessments.

A subject's duration of participation in this study is expected to be approximately 14 days and will include up to 4 clinic visits. 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 and/or treatment-emergent laboratory findings that require medical monitoring or management.

Number of subjects (planned):

Approximately 120 subjects will be enrolled. A minimum of 80 elderly subjects (≥ 65 years) will be enrolled.

Criteria for inclusion:

Subjects must meet the following criteria to be eligible for study participation:

1. Male and female subjects age ≥ 18 years.
2. The subject must meet one of the following two criteria:
   a. 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 (see 2b below).

OR

b. Clinical signs and symptoms consistent with acute influenza infection consisting of an oral temperature ≥100°F (37.8°C) 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 [aches and pains], headache, feverishness, or fatigue). **Note: Enrollment at each site by clinical symptoms alone will be approved by the Sponsor at the beginning of each influenza season once influenza has been confirmed in the local community. The Sponsor may withdraw approval for symptomatic screening for any season based upon trends in influenza surveillance data. Prior to Sponsor approval or after approval is withdrawn, Criteria 2 must be met by a positive influenza RAT test and/or PCR. During the period of approval, clinical symptoms alone will be adequate to meet Criteria 2.**

3. Onset of symptoms no more than 48 hours before presentation for screening. However, due to historically delayed presentation for medical care in the adult population, approximately 20% of the elderly population may be enrolled with symptoms starting > 48-hours but ≤ 72-hours prior to presentation for screening. Note: Time of onset of illness is defined as either (1) the time when the temperature (either oral or rectal) was first measured as elevated (at least one °C of elevated temperature), OR (2) the time when the subject experienced the presence of at least one respiratory symptom AND the presence of at least one constitutional symptom together.
4. Either age ≥ 65 years AND/ OR presence of one of the following risk factors:
   a. Pregnancy, including women who are up to 2 weeks post-partum
   b. Resident of a nursing home or long-term care facility
   c. History of chronic lung disease including obstructive pulmonary disease (COPD), persistent asthma or cystic fibrosis
   d. History of heart disease including myocardial infarction, angina requiring treatment, congestive heart failure requiring treatment, arrhythmia including atrial fibrillation and valvular dysfunction
   e. History of blood dyscracias including sickle cell anemia and thalassemia
   f. History of renal impairment (creatinine clearance [CrCl] < 50 mL/min as determined by the Cockcroft-Gault formula) including patients on dialysis
   g. History of liver disease including cirrhosis
   h. Mild to moderate immunocompromised, including: history of human immunodeficiency virus (HIV) disease on stable highly active antiretroviral therapy (HAART) with last known CD4+ count ≥ 200 cells/μL: known neutropenia with ANC > 500 cells/μL; chronic corticosteroid use of < 20 mg/d for any indication.
   i. History of diabetes mellitus (Type I or II)
   j. Morbid obesity (body mass index [BMI] ≥ 40)
   k. American Indian or Alaskan native
5. Written informed consent

Criteria for Exclusion:

Subjects who meet any of the following criteria will be excluded from the study:

1. Subjects who in the opinion of the investigator require hospital admission to treat medical condition(s) which, in the Investigator's opinion, could represent complications of influenza. Note, hospitalization is not an exclusion criterion when it is the usual practice of the treating institution to hospitalize elderly patients with acute uncomplicated influenza.
2. Women who plan to breast-feed for the first 48 hours after study drug administration. However, women who agree to suspend breast feeding for 48 hours after study administration may participate.
3. Employees of the study site, or immediate family members of study site employees
4. Presence of clinically significant signs of acute respiratory distress
5. Clinical evidence of worsening of any chronic medical condition (temporally associated with the onset of symptoms of influenza) which, in the Investigator's opinion, indicates that such finding(s) could

represent complications of influenza.
6. Current clinical evidence, including clinical signs and/or symptoms consistent with a bacterial infection, including: otitis media, bronchitis, sinusitis and/or pneumonia, or active bacterial infection of any body site that requires therapy with oral or systemic antibiotics
7. Immunization against influenza with live attenuated virus vaccine in the previous 14 days
8. History of alcohol abuse or drug addiction within 1 year prior to admission in the study
9. Participation in a study of any investigational drug or device within the last 30 days
10. Previous participation in study BCX1812-305 (pediatric study) or BCX1812-306 (this study)

Presence of any pre-existing illness that, in the opinion of the Investigator, would place the subject at an unreasonably increased risk through participation in this study or would make the subject unable to comply with the protocol

Criteria for evaluation:

Safety:

Safety will be evaluated through assessments of Adverse Events (AEs), laboratory analyses (clinical chemistry, hematology and urinalysis), vital signs, and physical examinations.

Pharmacokinetic:

Plasma peramivir concentrations will be measured by a validated liquid chromatography-tandem mass spectrometry (LC/MS-MS) assay. Concentrations will be utilized in determination of population PK parameters.

Effectiveness:

Clinical:

- Time to alleviation of clinical influenza symptoms
- Time to resolution of fever
- Time to resumption of usual activities
- Incidence of influenza-related hospitalizations
- Incidence of hospital admission (for any reason) post treatment

Virologic:

- Changes in viral shedding measured by quantitative viral titer assay ($TCID_{50}$) and/or quantitative polymerase chain reaction (PCR)
- Change in influenza virus susceptibility to neuraminidase inhibitors

Investigational product, dosage and mode of administration:

Peramivir solution for infusion is a clear, iso-osmotic, sterile, nonpyrogenic solution in 200 mg per 20 mL (10 mg/mL) single-use glass vials. Subjects will receive a single dose of 600 mg peramivir diluted in 0.9 % saline, 0.45% saline, 5% dextrose or lactated Ringer's using the technique described in a separate drug preparation instruction sheet, administered intravenously over a period of 15 to 30 minutes. The drug product should be stored at room temperature (excursion permitted to 59° to 86°F)

Reference therapy, dosage and mode of administration:

Not Applicable

Duration of Treatment:

Following single IV dose of peramivir on Day 1, study duration for all subjects is expected to be approximately 14 days (including all visits). If a subject has one or more persistent or recurrent symptoms of influenza (of the 7 symptoms assessed) of either moderate or severe intensity at the Day 14 visit (± 2 days), or if the subject has an unresolved AE and/or treatment-emergent laboratory finding that requires further medical management, then the subject may be evaluated in further follow-up visits, at the

Investigator's discretion.
Statistical methods: **Sample Size:** The study is designed to evaluate the safety and PK of IV administration of peramivir in elderly subjects (≥ 65 years) with influenza and in subjects with influenza infection at higher risk for influenza complications. The sample size is adequate to evaluate these objectives. Formal hypothesis testing will not be performed. **Safety:** Qualitative analyses will be performed for AE type, frequency and severity, as well as vital sign absolute values, clinical laboratory absolute values, and physical examination findings and their respective changes from Baseline for all subjects. **Pharmacokinetics:** Plasma concentrations and covariates of interest will be evaluated in a meta-population analysis using mixed effect modeling techniques to estimate population PK parameters in each population (≥ 65 years vs < 65 years and at a high risk) and to identify pharmacokinetically-relevant covariates. Data will be compared to available PK data from other adult studies of IV peramivir and included in this analysis. **Effectiveness:** Clinical and virologic endpoints will be summarized using descriptive statistics.

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4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or specialist term	Explanation
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BID	twice a day
BMI	body mass index
CBC	complete blood count
CDC	US Centers For Disease Control And Prevention
CFR	Code Of Federal Regulations
CI	confidence intervals
COPD	chronic obstructive pulmonary disease
CrCl	creatinine Clearance
CRF	case report form
DAIDS	Division Of Acquired Immune Deficiency Syndrome
FDA	US Food And Drug Administration
GCP	Good Clinical Practice
HAART	highly active antiretroviral therapy
HIPAA	Health Insurance Portability And Accountability Act
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Conference On Harmonization
IM	intramuscular
IND	Investigational New Drug
IRB	institutional review board
IRC	Influenza-related complications
ITT	intent to treat (Population)
ITTI	intent to treat infected (Population)
IV	intravenous
LC/MS-MS	liquid chromatography-tandem mass spectrometry
LDH	lactate dehydrogenase

Abbreviation or specialist term	Explanation
MedDRA	Medical Dictionary For Regulatory Activities
PA, PB1, PB2	viral RNA polymerase complex
PCR	polymerase chain reaction
PK	pharmacokinetics
QT	electrocardiographic interval between the beginning of the Q wave and termination of the T wave, representing the time for both ventricular depolarization and repolarization to occur
QTc	QT interval corrected
RAT	rapid antigen test
RBC	red blood cell
RT-PCR	reverse transcriptase polymerase chain reaction
SAE	serious adverse event
SAP	statistical analysis plan
SOP	standard operating procedure
SD	standard deviation
$TCID_{50}$	tissue culture infectious dose 50%
TEAE	treatment-emergent adverse event
US	United States
WBC	white blood cell
WHO	World Health Organization

5. INTRODUCTION

5.1. Influenza Overview

In healthy adults, influenza is usually self-limiting, with resolution of symptoms occurring within 5 to 7 days because immune defenses shut down viral proliferation and shedding, clearing infected cells quickly. In acute uncomplicated influenza, tissue damage is limited, and secondary infections are uncommon. However, influenza is an important cause of morbidity and mortality in certain at-risk populations, and hospital admissions due to influenza-related illness place a seasonal burden on health care facilities. Furthermore, the symptoms of acute uncomplicated influenza are themselves debilitating, with return to normal health and activities delayed for 7 to 11 days (Treanor, Hayden et al. 2000, Kohno, Kida et al. 2010).

The emergence in 2009 of a novel strain of influenza A (H1N1pdm09), reviewed in (Neumann, Noda et al. 2009), led to the first influenza pandemic since the 1960's. Severe illness with rapid evolution to respiratory failure, often in young adults, was reported from many countries including the United States (US) (Jain, Kamimoto et al. 2009, Louie, Acosta et al. 2009, Louie, Yang et al. 2012), Mexico (Dominguez-Cherit, Lapinsky et al. 2009, Perez-Padilla, de la Rosa-Zamboni et al. 2009), Canada (Kumar, Zarychanski et al. 2009), Chile (Cornejo, Tobar et al. 2011), Australia (Investigators, Webb et al. 2011, Muscatello, Barr et al. 2011), Italy (Nicolini, Claudio et al. 2011), South Korea (Jeon, Chung et al. 2011) and Hong Kong (Lee, Chan et al. 2011). Analysis of the pattern of morbidity with age showed a shift to earlier ages for the rates of severe pneumonia, hospitalization, and admission to intensive care (Chowell, Bertozzi et al. 2009, Dominguez-Cherit, Lapinsky et al. 2009, Jain, Kamimoto et al. 2009), as well as an increased incidence of acute respiratory distress syndrome and mortality in previously healthy young to middle-aged adults (Perez-Padilla, de la Rosa-Zamboni et al. 2009). In some countries, around 2% of cases developed severe illness, often with rapid progression to life-threatening pneumonia. Most cases of severe and fatal illnesses reported up to early June 2009 were in adults between the ages of 30 and 50 years (World Health Organization [WHO]). Pregnant women also showed an increased risk of hospitalization and death (Siston, Rasmussen et al. 2010). Globally, the mortality from the pandemic through March to December of 2009 was estimated at 123,000 to 203,000, with the majority of patients under 65 (Simonsen, Spreeuwenberg et al. 2013).

The well-documented morbidity and mortality from the 2009 influenza pandemic, and the emergence of two avian influenza viruses infecting humans in recent years, A/H5N1 (Writing Committee of the Second World Health Organization Consultation on Clinical Aspects of Human Infection with Avian Influenza, Abdel-Ghafar et al. 2008) and A/H7N9 (CDC 2013, Gao, Cao et al. 2013), serve to emphasize the continuing threat that influenza poses to public health as a result of emergence of new viral strains infecting populations with limited herd immunity. Changes in one or more influenza virus virulence determinants [recently reviewed by Tscherne. (Tscherne and Garcia-Sastre 2011)] .

5.2. Antiviral therapy for influenza

Two classes of influenza antiviral agents are currently approved: adamantanes and neuraminidase inhibitors. Adamantanes are thought to interact with the M2 ion channel virus protein. Adamantanes have no activity against influenza B virus. When administered within 48 hours of illness onset, amantadine and rimantadine can reduce the severity and shorten the duration of acute uncomplicated influenza A illness among healthy adults. However, in recent years widespread resistance to adamantanes has been described

in viruses of the H3N2 sub-type (Bright, Medina et al. 2005), and the influenza A (H1N1pdm09) strain also demonstrated adamantane resistance. This class of drugs is currently not recommended by the Centers for Disease Control and Prevention (CDC) for treatment of influenza (Centers for Disease and Prevention 2013).

Neuraminidase inhibitors are a newer class of drugs with activity against both influenza A and influenza B viruses. Approved neuraminidase inhibitors include zanamivir (Relenza®), administered by inhalation, oseltamivir phosphate (Tamiflu®), an oral prodrug of the active agent, oseltamivir carboxylate, and peramivir (Rapivab™), administered intravenously (IV). Influenza neuraminidase is responsible for the release of new viral particles from infected cells and may also assist in the spreading of virus through the mucus within the respiratory tract. When administered within 48 hours of illness onset, neuraminidase inhibitors can reduce the severity and shorten the duration of acute uncomplicated influenza illness among previously healthy adults.

Peramivir is a selective inhibitor of influenza viral neuraminidase with potent activity against influenza A and B subtypes, including influenza A (H1N1pdm09) (CDC 2009) and the recently described novel avian influenza A (H7N9) virus (Cao, Xiao et al. 2013, Gao, Cao et al. 2013). Although oseltamivir is widely used for the treatment of influenza, a need still exists for an effective treatment for influenza patients who present in the urgent care and emergency room settings, and in patients for whom compliance with effective delivery of an oral medication is of concern (e.g., patients with vomiting and diarrhea). Peramivir has been studied for the treatment of influenza in 2 settings: as a single dose treatment in acute uncomplicated influenza, and as a multiple dose treatment in patients who are hospitalized due to influenza.

5.3. Previous Experience with Peramivir

Peramivir hydrate for injection was first approved in Japan on 13 January 2010 under the trade name Rapiacta® by Shionogi & Co., Ltd. for the treatment of viral infection with influenza type A and type B. Marketing authorization for the treatment of children and infants ≥ 28 days of age was obtained in Japan in October, 2010. Peramivir was recently approved in the United States (US) in 2014 for the treatment of acute uncomplicated influenza in patients ≥ 18 years and older who have been symptomatic for no more than 2 days.

BioCryst Pharmaceuticals, Inc. and its partner, Shionogi & Co., Ltd have completed a total of ten Phase 2 and Phase 3 clinical studies to evaluate the efficacy and safety of peramivir in the treatment of influenza. Seven studies exclusively or predominantly enrolled patients with acute uncomplicated influenza, including 1 in children. The remaining 3 studies were conducted in subjects who were hospitalized with influenza, 2 of which allowed children or adolescents to enroll. A thorough QT/QTc study of single IV doses of peramivir in healthy adult subjects (Study BCX1812-106) demonstrated that intravenous peramivir at a therapeutic dose of 600 mg and at a supra-therapeutic dose of 1200 mg was not associated with QTc prolongation or other repolarization abnormalities.

5.3.1. Clinical Experience in Adults

5.3.1.1. Peramivir Efficacy

The pivotal study for the use of IV peramivir to treat subjects with acute uncomplicated influenza is Study 0722T0621, a Phase 2 double-blind, placebo-controlled, single dose study that enrolled 300 Japanese adult subjects with confirmed influenza. Both dosages of peramivir evaluated (single IV doses of 300 or

600 mg) significantly shortened the time to alleviation of influenza symptoms (duration of influenza, the primary endpoint) compared with placebo.

Studies BCX1812-211, BCX1812-311, and BCX1812-212 provide supportive data for the use of single parenteral doses of peramivir to treat influenza in the outpatient setting; in these studies, peramivir was administered as a single dose via bilateral intramuscular (IM) injections to subjects with influenza. Exposure to peramivir by IM administration is bioequivalent to exposure from IV administration (BCX1812-111 and BCX1812-113).

Study BCX1812-211 was a Phase 2, randomized study that enrolled 344 subjects with acute, uncomplicated influenza who received placebo, 150 mg peramivir or 300 mg peramivir as a single, divided IM dose. Study BCX1812-311 was similar in design and was planned as a Phase 3 study, but was terminated early after 82 subjects had enrolled and were randomized 2:1 to receive placebo or 300 mg peramivir in a single, divided IM dose. The study was terminated in order to study higher doses using a product with a higher concentration in subsequent studies. These 2 studies had almost identical eligibility criteria, had identical primary and secondary efficacy endpoints, and were conducted in successive influenza seasons. When the results from studies BCX1812-211 and BCX1812-311 were retrospectively combined in a post-hoc analysis, both primary and secondary endpoints for peramivir-treated subjects were improved compared to placebo.

Study BCX1812-212 was a placebo-controlled study of 405 subjects who were randomized 1:1 to receive either placebo or 600 mg of peramivir as a single divided IM dose. This study was conducted during a season in which the dominant circulating strain of influenza A showed reduced susceptibility to peramivir, and the results showed a non-significant trend favoring peramivir in the primary endpoint of time to alleviation of symptoms.

Three studies are included as additional efficacy studies. Study 0815T0631was a double-blind, double-dummy study of 1099 subjects from Japan, Taiwan or South Korea who were randomized to receive a single dose of IV peramivir (300 mg or 600 mg) or 5 days of oral oseltamivir twice daily (BID). For the primary endpoint of time to alleviation of symptoms, both peramivir treatment regimens were non-inferior to oseltamivir. Study 0816T0632 was a double-blind, non-controlled study in Japan that enrolled 42 high-risk inpatients or outpatients with influenza; in this study, subjects were randomized to receive 300 mg or 600 mg peramivir. The duration of influenza illness was shorter among subjects who received 600 mg doses of peramivir compared with those in the 300 mg treatment group, although the 90% confidence intervals (CI) overlapped. Finally, Study 0918T0633 was a non-controlled, open-label study conducted in Japan in 117 pediatric subjects with influenza (either inpatient or outpatient). For the primary endpoint of duration of influenza illness, no differences were noted between the age groups of 28 days to < 2 years, 2 to < 6 years, 6 to < 12 years, and 12 to < 16 years of age.

5.3.1.2. Peramivir Safety

Safety of various doses of peramivir in acute uncomplicated influenza has been evaluated in 1453 adults. The most frequently observed treatment emergent AEs (TEAEs) across all adult subjects with acute uncomplicated influenza treated with various doses of peramivir were diarrhea (7.4%), decreased neutrophil count (5.5%), and increased blood glucose (5.0%). The only events reported in ≥ 2% of subjects treated with peramivir 600 mg and for which the rate was greater than placebo were diarrhea (7.6% vs. placebo 7.0%), decreased neutrophil count (5.7% vs. placebo 0.0%), hyperglycemia (5.3% vs. placebo 4.8%) and urine leukocytes (2.8% vs. placebo 1.8%). Adverse event (AE) rates overall were similar to placebo and oseltamivir. No safety signals have emerged from these trials.

5.4. Rationale for Study

There is disagreement on the degree of benefit risk provided by NAIs. A 2012 systematic meta-analysis (Hsu, Santesso et al. 2012) supports the conclusion that early treatment with neuraminidase inhibitors such as oseltamivir is associated with reduced mortality and reduced rates of hospital admission. Another independent meta-analysis of 11 randomized clinical trials also found that oseltamivir reduced the risk of lower respiratory tract complications and the use of antibiotics (Hernan and Lipsitch 2011). Mortality benefits were supported by a meta-analysis of hospitalized patients with H1N1 pandemic influenza, although the benefit was not seen in children (Muthuri, Venkatesan et al. 2014). This is in contrast to 2 Cochran reviews, one reviewing both oseltamivir and zanamivir (Jefferson, Jones et al. 2009) and a more recent review focused on oseltamivir (Jefferson, Jones et al. 2014), that found only modest efficacy as measured by time to alleviation of symptoms and no reduction in lower respiratory tract complications. The 2014 review indicated that while there was modest efficacy in healthy adults and children, children with asthma did not benefit. There was no change in the hospital admission rate for adults and insufficient data in children. While oseltamivir did appear to reduce the incidence of unverified pneumonia in adults, there was no decrease in the incidence for children. The review also asserted that there was no decrease in the common complications of influenza such as bronchitis, otitis media and sinusitis.

The CDC responded (CDC 2014) by reiterating their recommendation of the use of antiviral treatment of patients with influenza in certain populations.

The CDC recommendation is as follows:

> Antiviral treatment is recommended as early as possible for any patient with confirmed or suspected influenza who is hospitalized; has severe, complicated, or progressive illness; or is at higher risk for influenza complications. Persons at higher risk for influenza complications recommended for antiviral treatment include: children aged younger than 2 years; adults aged 65 years and older; persons with chronic pulmonary (including asthma), cardiovascular (except hypertension alone), renal, hepatic, hematological (including sickle cell disease), metabolic disorders (including diabetes mellitus), or neurologic and neurodevelopment conditions (including disorders of the brain, spinal cord, peripheral nerve, and muscle such as cerebral palsy, epilepsy [seizure disorders], stroke, intellectual disability [mental retardation], moderate to severe developmental delay, muscular dystrophy, or spinal cord injury); persons with immunosuppression, including that caused by medications or by human immunodeficiency virus (HIV) infection; women who are pregnant or postpartum (within 2 weeks after delivery); persons aged younger than 19 years who are receiving long-term aspirin therapy; American Indians/Alaska Natives; persons who are morbidly obese (i.e., body-mass index is equal to or greater than 40); and residents of nursing homes and other chronic-care facilities.

It is apparent that the definitions of high risk in this context is empirical, and subject to further modifications as additional risk factors are identified in seasonal and pandemic influenza outbreaks.

There remains a significant unmet need for influenza therapies for patients who are specifically at an increased risk of complications. Peramivir has demonstrated efficacy and safety when used in acute uncomplicated influenza in adults in the general population. This study aims to develop additional data on the safety, pharmacokinetics and effectiveness of IV peramivir in patient groups that are at risk of complications from influenza. In particular, this study will target elderly adults (≥ 65 years of age) as well as other groups at increased risk of complications (e.g., pregnant women, residents of long term care facilities, American Indians and Alaskan Natives) and adults with comorbidities that increase the risk of

complications (e.g., adults with asthma, heart disease, diabetes). A complete list of chronic health conditions is provided in the inclusion criteria in Section 8.1.

6. TRIAL OBJECTIVES AND PURPOSE

6.1. Primary objective

- To evaluate the safety and tolerability of peramivir administered intravenously in elderly subjects with acute uncomplicated influenza and in subjects with acute uncomplicated influenza who are at higher risk for influenza complications

6.2. Secondary Objectives

- To describe the pharmacokinetics 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

7. INVESTIGATIONAL PLAN

7.1. Endpoints

7.1.1. Primary Endpoint

The primary endpoint of this study will be safety and include the assessment of AEs, laboratory abnormalities (clinical chemistry, hematology and urinalysis), vital signs and physical examinations.

7.1.2. Secondary Endpoints

Secondary endpoints will include:

- Pharmacokinetic (PK) analyses
- Change (reduction) in influenza virus titer by $\log_{10}$ $TCID_{50}$/mL and by reverse transcriptase polymerase chain reaction (RT-PCR)
- Time to alleviation of clinical symptoms of influenza (per age appropriate symptoms).
- Time to resolution of fever
- Incidence of influenza-related complications
- Incidence of hospital admission post treatment
- Changes in viral shedding measured by quantitative viral titer assay ($TCID_{50}$) and/or quantitative PCR
- Change in influenza virus susceptibility to neuraminidase inhibitors

7.2. Overall Study Design and Plan

This is a multicenter, single-arm, open-label study to evaluate the safety, PK and effectiveness of a single dose of IV peramivir in elderly subjects (≥65 years of age) with acute uncomplicated influenza and in subjects with acute uncomplicated influenza at higher risk for influenza complications.

A subject's duration of participation in this study is expected to be 14 days and will include up to 4 clinic visits. Following treatment on study Day 1, subjects will undergo follow-up assessments on Days 3, 7, and 14 in the clinic. Additional, unscheduled visits may be required for subjects who report symptoms of influenza of moderate or severe intensity at Day 14 or have persistent AEs and/or treatment-emergent laboratory findings that require medical monitoring or management.

7.3. Study Measurements and Visit Schedule

The schedule of assessments for this study is presented in Table 1.

Table 1. BCX1812-306: Schedule of Assessments

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						

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**
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 (i.e. temperature without antipyretic is < 37.4^{o}C/ 99.4^{o}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 patient 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.

8. SELECTION AND WITHDRAWAL OF SUBJECTS

Subjects must meet all of the inclusion criteria and none of the exclusion criteria to be eligible to participate in the study.

8.1. Subject Inclusion Criteria

1. Male and female subjects age ≥ 18 years.
2. The subject must meet one of the following two criteria:

   a. A positive influenza Rapid Antigen Test (RAT) and/or a FDA-approved PCR test and at least one clinical sign or symptom consistent with acute influenza infection as listed in 2b below.

   OR

   b. Clinical signs and symptoms consistent with acute influenza infection consisting of an oral temperature ≥ 100°F (37.8°C) 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 [aches and pains], headache, feverishness, or fatigue). **Note: Enrollment at each site by clinical symptoms alone will be approved by the Sponsor at the beginning of each influenza season once influenza has been confirmed in the local community. The Sponsor may withdraw approval for symptomatic screening in any season based upon trends in influenza surveillance data. Prior to Sponsor approval or after approval is withdrawn, Criteria 2 must be met by a positive influenza RAT test and/or PCR. During the period of approval, clinical symptoms alone will be adequate to meet Criteria 2.**
3. Onset of symptoms no more than 48 hours before presentation for screening. However, due to historically delayed presentation for medical care in the adult population, approximately 20% of the elderly population may be enrolled with symptoms starting > 48-hours but ≤ 72-hours prior to presentation for screening. Note: Time of onset of illness is defined as either (1) the time when the temperature (either oral or rectal) was first measured as elevated (at least one ºC of elevated temperature), OR (2) the time when the subject experienced the presence of at least one respiratory symptom AND the presence of at least one constitutional symptom together.
4. Either age ≥ 65 years AND/ OR presence of one of the following risk factors:
   a. Pregnancy, including women who are up to 2 weeks postpartum
   b. Resident of a nursing home or long-term care facility
   c. History of chronic lung disease including obstructive pulmonary disease (COPD), persistent asthma or cystic fibrosis
   d. History of heart disease including myocardial infarction, angina requiring treatment, congestive heart failure requiring treatment, arrhythmia including atrial fibrillation and valvular dysfunction
   e. History of blood dyscracias including sickle cell anemia and thalassemia
   f. History of renal impairment (creatinine clearance [CrCl] < 50 mL/min as determined by the Cockcroft-Gault formula) (Cockcroft and Gault 1976), including dialysis.

g. History of liver disease including cirrhosis

h. Mild to moderate immunocompromise, including: history of HIV disease on stable HAART with last known CD4+ count ≥ 200 cells/μL: known neutropenia with ANC > 500 cells/μL; chronic corticosteroid use of < 20 mg/d for any indication.

i. History of diabetes mellitus

j. Morbid obesity (body mass index [BMI] ≥ 40)

k. American Indian or Alaskan native

5. Written informed consent

8.2. Subject Exclusion Criteria

1. Subjects who in the opinion of the investigator require hospital admission to treat medical condition(s) which, in the Investigator's opinion, could represent complications of influenza. Note, hospitalization is not an exclusion criterion when it is the usual practice of the treating institution to hospitalize elderly patients with acute uncomplicated influenza.
2. Women who plan to breast-feed for the first 48 hours after study drug administration. However, women who suspend breast feeding for 48 hours after study administration may participate.
3. Employees of the study site, or immediate family members of study site employees
4. Presence of clinically significant signs of acute respiratory distress.
5. Clinical evidence of worsening of any chronic medical condition (temporally associated with the onset of symptoms of influenza) which, in the Investigator's opinion, indicates that such finding(s) could represent complications of influenza
6. Current clinical evidence, including clinical signs and/or symptoms consistent with a bacterial infection, including: otitis media, bronchitis, sinusitis and/or pneumonia, or active bacterial infection of any body site that requires therapy with oral or systemic antibiotics
7. Immunization against influenza with live attenuated virus vaccine (FluMist®) in the previous 14 days
8. History of alcohol abuse or drug addiction within 1 year prior to admission in the study
9. Participation in a study of any investigational drug or device within the last 30 days
10. Previous participation in study BCX1812-305 (pediatric study) or BCX1812-306 (this study)
11. Presence of any pre-existing illness that, in the opinion of the Investigator, would place the subject at an unreasonably increased risk through participation in this study or would make the subject unable to comply with the protocol.

8.3. Withdrawal Criteria

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

- At the subject's request
- If, in the Investigator's or Sponsor's opinion, continuation in the study would be detrimental to the subject's well-being
- If the subject is not able to comply with the study requirements
- If the Sponsor terminates the study
- If a regulatory authority requires that all study activities be halted

In all cases, the reason for withdrawal must be recorded in the subject's medical records (source documents). If the reason for subject withdrawal is not known, the subject must be followed to establish whether the reason was an AE, and if so, this must be reported in accordance with the procedures outlined in Section 11.1.2. Vigorous attempts should be made for follow-up of all subjects who miss a study visit. In general, subjects will be encouraged to complete the scheduled procedures. The subject will require an Early Withdrawal Visit if withdrawn from the study prior to scheduled study completion.

To the extent possible, all scheduled end-of-study assessments (including the Early Withdrawal Visit) should be performed on all participating subjects who withdraw from the study before the Day 14 Visit.

Subjects withdrawn from the study at any time other than during the screening period will not be replaced.

9. TREATMENT OF SUBJECTS

9.1. Study Drug Dose Rationale

Subjects will be dosed with peramivir at the dosage levels currently approved in the US package insert for peramivir. The standard dose will be a single IV dose of 600 mg for subjects with CrCL ≥ 50 ml/min and reduced for subjects with CrCL < 50 ml/min as described in Section 9.4.

9.2. Study Drug

Peramivir solution for infusion is a clear, iso-osmotic, sterile, nonpyrogenic solution in 200 mg per 20 mL (10 mg/mL) single-use glass vials fitted with rubber stoppers and aluminum flip-off seals. The drug product should be stored at room temperature (excursion permitted to 59° to 86°F).

9.3. Study Drug Preparation and Administration

The Principal Investigator at each study center will designate a pharmacist (or other qualified study staff member) to prepare IV peramivir.

Subjects will receive a single dose of 600 mg peramivir (or less if renally impaired) diluted in 0.9% saline, 0.45% saline, 5% dextrose or lactated Ringer's using the technique described in a separate drug preparation instruction sheet, administered IV over a period of 15 to 30 minutes. The calendar date and 24-hour clock time (start and end of the IV infusion) will be recorded.

The intravenous line used to administer peramivir must be flushed prior to and after peramivir administration. No other medications should be administered through the same IV line during peramivir administration.

9.4. Dose Adjustments for Subjects with Renal Impairment

Table 2 provides dose adjustments based on creatinine clearance for subjects with renal impairment. In subjects with chronic renal impairment maintained on hemodialysis, peramivir should be administered after dialysis at a dose adjusted based on renal function as shown in the table below.

Table 2. Dosage Adjustment for Subjects with Altered Creatinine Clearance

	Creatinine Clearance (mL/min)[a]		
	≥ 50	30 to 49	10 to 29
Recommended Dose (mg)	600 mg	200 mg	100 mg

a Calculated using the Cockroft -Gault equation.

9.5. Study medication accountability

The Investigator/pharmacist must maintain accurate records of the disposition of all study drug received from the Sponsor and administered to the subject (including date and time), and any drug accidentally destroyed. The Sponsor will supply a specific Drug Accountability Form. At the end of the study, information describing study drug supplies (e.g., lot numbers) and disposition of supplies for each subject must be provided, signed by the Investigator or designee, and collected by the Study Monitor. If any

errors or irregularities in any shipment of study medication to the site are discovered at any time, the Sponsor Project Manager must be contacted immediately.

Periodically during the trial and at the end of the study, all medication that was neither dispensed or administered, as well as packaging materials will be collected with supervision of the monitor and returned to the Sponsor or destroyed on site as dictated by the appropriate Standard Operating Procedure (SOP) at the participating site

9.6. Randomization and Blinding/ Masking

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

9.7. Treatment Compliance

Intravenous peramivir will be administered by study staff or other qualified personnel. Details of the infusion (to include date of dose, start time, and stop time) will be recorded by a member of the study staff on Day 1; treatment compliance is expected to be 100% for this study.

9.8. Overdose and Toxicity Management

To date there is no experience with overdose of IV peramivir. If overdose occurs, subjects should receive indicated supportive therapy and evaluation of hematologic and clinical chemistry laboratory tests should be conducted. Peramivir is cleared by hemodialysis; the decision to use hemodialysis should be addressed on a case-by-case basis with the Sponsor.

9.9. Concomitant Medications

With the exception of medications used for the symptomatic treatment of influenza-related symptoms, administration of any dose of a concomitant medication during the study period must be recorded by the study staff within the subject's study source documents (e.g., chart). This includes prescription medications as well as over-the-counter medications.

Medications, such as antipyretics and analgesics, used for the symptomatic treatment of influenza-related symptoms will be recorded separately. Subjects will record the type, date, and time of symptomatic medications in the subject diary supplied by BioCryst including the date and time of administration. Study staff will provide diary completion instructions to subjects during their first study visit.

Use of concomitant medications will be assessed and recorded at Screening, and daily throughout the duration of the study through the study completion visit at Day 14 or later.

9.9.1. Antipyretics and Analgesics

Resolution of fever is an important efficacy endpoint for this study. Accordingly, use of any antipyretics or analgesics with antipyretic properties must be carefully controlled and documented. Antipyretics and analgesics may be administered while the subject is enrolled in this study. The names and times of administration of these medications will be recorded by the subject/caregiver in the subject diary. To avoid the confounding effects of antipyretic medications, temperature measurements recorded by the subjects will be taken, whenever possible, at least 4 hours after administration of the antipyretic medication.

Continuation of low dose aspirin for cardioprophylaxis is allowed.

9.9.2. Medications for Chronic Diseases/Conditions

Subjects with chronic medical conditions may continue to receive prescribed treatments during participation in this protocol. For example, treatment for cardiovascular conditions, endocrine conditions, rheumatologic conditions, respiratory conditions, dermatologic conditions, and neurologic conditions may be continued if not otherwise contraindicated within this protocol.

9.9.3. Antivirals

Subjects must not have received any doses of oseltamivir, zanamivir, amantadine, or rimantadine in the 7 days prior to study drug administration. Concomitant use of oseltamivir, zanamivir, amantadine, and/or rimantadine is not permitted during administration of study drug and during the post-treatment follow-up period. Antivirals for other infections such as HIV or herpes simplex may be taken.

9.9.4. Antibiotics

Oral or parenteral antibiotics may be administered at any time after enrollment if medically indicated. If such use is a result of proven or suspected influenza-related complication, the appropriate assessments should be carried out (see Section 10.2.4).

9.9.5. Immunizations

Subjects must not have received a live attenuated influenza vaccine in the 14 days prior to study drug administration. Immunizations of any kind should not be administered during study participation. Subjects who are candidates for pneumococcal immunization or other immunization should not receive such immunizations during the study period.

10. STUDY CONDUCT

10.1. Overview

Approximately 120 subjects will be enrolled in this open-label study (a minimum of 80 elderly subjects [≥ 65 years] 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. 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 and/or treatment-emergent laboratory findings that require medical monitoring or management.

All subjects will receive a single dose of IV peramivir (600 mg or reduced for renal impairment). Subjects will undergo follow-up clinical assessments on Days 3, 7, and 14.

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

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). 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:

- 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

Adverse events 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 Day 14 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.

All subjects/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 0 or 1 for 48 hours. Symptoms 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 (i.e. temperature without antipyretic is < 37.4°C/ 99.4°F orally for 4 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 analogue scale once daily through Day 14, where 0 = Unable to perform usual activities at all, and 10 = Able to perform all usual activities fully.

10.1.1. Screening Period

The Screening Period begins at the time of consent of the study subject. The Investigator will conduct the following assessments:

- Review of inclusion and exclusion criteria
- Review and record medical history and concomitant medications
- Conduct an assessment for IRC; if an IRC is suspected, then the physical examination will confirm the actual presence/absence of the IRC. If an IRC is present, the subject meets exclusion criteria 6 and is ineligible for the study.
- Measure oral body temperature
- Conduct a RAT or Food and Drug Administration (FDA)-approved PCR test for influenza A and B on an adequate nasal specimen, in accordance with the manufacturer's instructions. The subject must have a positive RAT result and/or a Food and Drug Administration (FDA) approved PCR test and at least one clinical sign or symptom consistent with influenza (see 2b below).

  OR have clinical signs and symptoms consistent with acute influenza infection consisting of an oral temperature ≥ 100°F (37.8°C) 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 [aches and pains], headache, feverishness, or fatigue) (See Section 8.1). **Note: Enrollment at each site by clinical symptoms alone will be approved by the Sponsor at the beginning of each influenza season once influenza has been confirmed in the local community. The Sponsor may withdraw approval for symptomatic screening in any season based upon trends in influenza surveillance data. Prior to Sponsor approval or after approval is withdrawn, Criteria 2 must be met by a positive influenza RAT test and/or PCR. During the period of approval, clinical symptoms alone will be adequate to meet Criteria 2.**

  The subject must have at least 1 respiratory symptom (cough, sore throat or nasal symptoms) of at least moderate severity, in addition to at least 1 constitutional symptom (myalgia, headache, feverishness, or fatigue) of at least moderate severity to be eligible for the study
- Measure vital signs (blood pressure, pulse rate, and respiration rate)
- Perform a complete physical examination. Examination of the breast and urogenital system may be omitted as per the institution's/Investigator's clinical routine.

- Perform a urine or serum pregnancy test (non-pregnant females of childbearing potential only)

Eligible subjects will be enrolled. The study pharmacist/designee will prepare an order for study drug as defined in Section 9.3 , which includes the subject's study number.

10.1.2. Treatment Period

Randomization and study drug administration should begin as soon as possible following determination that the subject is eligible for enrollment at Screening. Therefore, it is anticipated that the date of Screening and Day 1 (date of administration of the first dose of study medication) will be the same day. Day 1 represents the first day of dosing.

10.1.2.1. Baseline (Pre-dose)/Day 1

The following Baseline procedures/evaluations will be performed after Screening and prior to dosing on Day 1:

- Obtain a bilateral adequate nasal swab specimen for viral subtyping, culture, quantitative PCR assay and susceptibility to neuraminidase inhibitors.
- Obtain and record body temperature
- Blood and urine specimen collection for clinical chemistry and clinical hematology tests as specified in Sections 11.2.1 and 11.2.2 and a serum sample for future influenza antibody analysis.

Following completion of the baseline procedures administer study drug:

- Administer study drug (at hour 0) and record the calendar date and 24-hour clock time for the start and finish of the IV infusion.
- Obtain and record body temperature

10.1.2.2. Day 1/Post-dose

The following procedures/evaluations will be performed post-dose on Day 1:

- Collect up to 3 plasma samples, where possible, during the following time periods, beginning from the end of dosing until release from the site. For each plasma sample the calendar date and 24-hour clock time of sample collection will be recorded:
    - 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
- Train the subject/caregiver on the recording of the following in the subject diary:
    - Subject's body temperature, obtained at approximately 12-hour intervals each day until the temperature normalizes for 48 hours (and 4 hours from last antipyretic medication administration or immediately prior to administration).

- Instruct the subject to assess his/her time lost from work, if applicable, and the recording of the subject's ability to perform usual daily activities using a 0 to 10 visual analogue scale.
- Assessment of signs and symptoms of influenza twice daily beginning on Day 1 (see Section10.2.2).

- Review and record concomitant medications
- Obtain and record body temperature
- Review and record AEs

10.1.2.3. Day 3

The following procedures/assessments will be performed on Day 3. The Day 3 assessment will be performed as a clinic visit.

- Measure vital signs (blood pressure, pulse rate, and respiration rate)
- Conduct an assessment for IRC; if an IRC is suspected, then the physical examination will confirm the actual presence or absence of the IRC
- Conduct a targeted physical examination
- Measure oral body temperature
- A serum sample for future influenza antibody analysis
- Review the subject diary for completeness and instruct the subject/caregiver on the need to ensure complete recording of required assessments, if needed.
- Collect a bilateral adequate nasal swab specimen for viral culture, quantitative PCR assay and susceptibility to neuraminidase inhibitors.
- Review and record concomitant medications
- Review and record AEs

10.1.2.4. Day 7

The following procedures/assessments will be performed on Day 7 (+ 2 days). The Day 7 assessment will be performed as a clinic visit.

- Measure vital signs (blood pressure, pulse rate, and respiration rate)
- Conduct an assessment for IRC; if an IRC is suspected, the physical examination will confirm the actual presence or absence of the IRC
- Conduct a targeted physical examination
- Measure oral body temperature
- Blood specimen collection for clinical chemistry and clinical hematology tests as specified in Sections 11.2.1 and 11.2.2 and a serum sample for future influenza antibody analysis.
- Collect urine for urinalysis

- Review the subject diary for completeness and instruct the subject/caregiver on the need to ensure complete recording of required assessments, if needed.
- Collect a bilateral adequate nasal swab specimen for viral culture, quantitative PCR assay and susceptibility to neuraminidase inhibitors.
- Review and record concomitant medications
- Review and record AEs

10.1.2.5. Day 14 (End of Study)

The Day 14 assessments will be performed as a clinic visit. The following procedures/assessments will be performed on Day 14 (+ 3 days) or at the time of early withdrawal, where possible:

- Measure vital signs (blood pressure, pulse rate, and respiration rate)
- Measure and record oral body temperature
- Perform a urine or serum pregnancy test (non-pregnant females of childbearing potential only)
- Conduct an assessment for the presence of possible IRC; if an IRC is suspected, a targeted physical exam should be conducted to confirm the absence or presence of the IRC
- Review the subject diary for completeness
- Collect a bilateral adequate nasal swab specimen for viral culture, quantitative PCR assay and susceptibility to neuraminidase inhibitors.
- Review and record concomitant medications
- If Day 7 labs are, in the opinion of the investigator, significantly abnormal or significantly changed from baseline, collect blood specimen for clinical chemistry and/or clinical hematology tests as specified in Sections 11.2.1 and 11.2.2 and a serum sample for future influenza antibody analysis.
- If Day 7 urinalysis is, in the opinion of the investigator, significantly abnormal or significantly changed from baseline, collect urine for urinalysis
- Review and record AEs

10.2. Clinical assessments of Effectiveness

Effectiveness will be evaluated through assessments of body temperature, clinical symptoms of influenza, usual daily activities assessments, incidence of influenza-related complications (see Section 10.2.4) for details), influenza virus titers, and changes in viral sensitivity to other antiviral drugs.

10.2.1. Body Temperature

The Investigator will record oral body temperature at Screening. The baseline temperature will be recorded at the Day 1 visit prior to dosing, regardless of whether the subject had recently taken an antipyretic. Thereafter, the subject or caregiver will record oral body temperatures approximately every 12 hours through Day 14 in the subject diary. Subjects or caregivers will measure their oral temperature with an electronic thermometer (provided by the Sponsor for the study). With the exception of the

baseline measurement, subjects will be instructed to take all temperature measurements at least 4 hours after, or immediately before, administration of oral acetaminophen or other antipyretic medications. The times of each temperature determination will be recorded in the Subject Diary.

10.2.2. Influenza Signs and Symptoms

Subjects will be asked to provide an assessment of 7 influenza symptoms (cough, sore throat, nasal congestion, myalgia [aches and pains], headache, feverishness, and fatigue) on a 4-point severity scale (0, absent; 1, mild; 2, moderate; 3, severe) beginning at Screening then twice daily beginning on Day 1 through Day 13, and prior to the subject's clinic visit on Day 14. Once all symptoms are score a 0 or 1 for at least 48 hours the can discontinue recordings. The definitions to be used to assign severity are as follows:

0, Absent	no symptom present (no cough, no sore throat, etc.)
1, Mild	symptom present and slightly uncomfortable
2, Moderate	symptom is very uncomfortable
3, Severe	symptom is intolerable

The subject diary will be reviewed by study staff at each visit for completion of the record of all required items, with particular emphasis on alleviation of clinical symptoms as well as relapse of symptoms. Study staff will not attempt to ask subjects or caregiver to retrospectively complete missing subject diary data for any scheduled assessments that have not been completed prior to the clinic visit. However, study staff should, however, remind the subject or caregiver to complete the subject diary at all scheduled times.

10.2.3. Assessment of ability to perform usual daily activities

If possible, subjects/caregivers will be asked to provide a daily assessment of the subject's ability to perform usual daily activities using a 0 to 10 visual analogue scale, where 0 = Unable to perform usual activities at all, and 10 = Able to perform usual activities fully. The subject will also assess his/her time lost from work, if applicable. The subject/care giver will be asked to record these assessments in the subject diary once daily from Baseline through Day 13 and prior to the subject's clinic visit on Day 14.

10.2.4. Influenza-Related Complications

Study personnel will evaluate the subject at Screening and Days 3, 7, and 14 for the presence of clinical signs and/or symptoms of the following IRC:

- Sinusitis
- Otitis media
- Bronchitis
- Pneumonia

Note that subjects with clinical signs and/or symptoms consistent with bacterial infections, including: otitis media, bronchitis, sinusitis, and/or pneumonia at screening are not eligible for enrollment in this study (see exclusion criteria in Section 8.2).

If an IRC is suspected, then a targeted physical examination will be conducted to confirm the presence or absence of the IRC. If the Investigator determines that the subject experiences (or is presumed to

experience) an IRC as noted above, he/she will record that assessment and any medication used to treat the condition in the source record and record the IRC and medications in the case report form (CRF). The Investigator will promptly provide appropriate treatment for any suspected or proven IRC. Such information describing IRC signs and/or symptoms should not be reported as AEs. Any reactions at the site of the IV drug administration will be recorded as an AE.

10.2.5. Hospital Admission

In the event that a subject requires admission to a hospital at any time during the study additional information on the hospital admission will be collected. See Section 11.1.5 for serious adverse event (SAE) reporting details.

10.3. Virology Samples

Bilateral mid-nasal swab specimens will be collected for virologic analysis. Samples will be collected at Baseline, Day 3, Day 7, and Day 14.

Virology laboratory tests will include viral sub type characterization from the baseline sample, laboratory culture and analysis by $\log_{10}$ $TCID_{50}$, RT-PCR assay, viral susceptibility to peramivir, oseltamivir, and zanamivir, and genotypic analysis of primary virus isolates.

11. ASSESSMENT OF SAFETY

Safety will be evaluated through assessments of AEs, pregnancy outcomes, laboratory analyses (clinical chemistry, hematology, and urinalysis), vital signs, and physical examinations.

Adverse Events

Adverse events will be assessed and recorded at the indicated time points (see schedule of assessments, Table 1). AEs will be recorded on Screening, Day 1, Day 3, Day 7 and Day 14/Early Withdraw visits. Adverse events will be graded through use of the Division of Acquired Immune Deficiency Syndrome (DAIDS) Tables for Grading Adult and Pediatric Adverse Experiences (see Appendix 16.2). Any Grade 3 and Grade 4 clinical AEs or laboratory abnormalities that are judged to be possibly, probably, or definitely related to study treatment will be promptly (within 72 hours) reported to the study medical monitor unless the event meets criteria for an SAE, in which case they must be reported within 24 hours. Influenza-related complications are not considered AEs unless they meet the criteria for SAEs. Full details on recording and reporting AEs are provided in Section 11.1.2.

11.1.1. Definitions

11.1.1.1. Adverse Event

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.

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 influenza symptoms will be documented 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.

AEs are designated as “non-serious” or “serious.”

11.1.1.2. Serious Adverse Event

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

- Death
- Is life-threatening (subject is at immediate risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe)
- Requires in-subject hospitalization (formal admission to a hospital for medical reasons) or prolongation of existing hospitalization

- Results in persistent or significant disability/incapacity (i.e., there is a substantial disruption of a person's ability to carry out normal life functions)
- Is a congenital anomaly/birth defect

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

Hospitalization, as per the institution's standard of care (SOC) to treat influenza in elderly patients is not considered an SAE and should not be reported as such. Any adverse event that causes a prolongation of an existing hospitalization must be reported as per Section 11.1.5.

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

Reports of AEs are to be collected from the time the subject signs the informed consent through the follow-up period ending on Day 14. The Investigator or designee must completely and promptly record each AE. The Investigator should attempt, if possible, to establish a diagnosis based on the presenting signs and symptoms. In such cases, the diagnosis should be documented as the AE and not the individual sign/symptom. If a clear diagnosis cannot be established, each sign and symptom must be recorded individually. If a final diagnosis is established during evaluation or treatment, the source documents will be updated accordingly.

The Investigator should attempt to follow all unresolved AEs and/or SAEs observed during the study until they are resolved, or are judged medically stable, or are otherwise medically explained.

11.1.3. Definition of Severity

All AEs will be assessed (graded) for severity and classified using the DAIDS criteria for grading AEs (see Section 16.2). Any adverse events not covered by the DAIDS criteria will be assessed and classified into one of 4 clearly defined categories as follows:

Mild:	(Grade 1): Transient or mild symptoms; no limitation in activity; no intervention required. The AE does not interfere with the participant's normal functioning level. It may be an annoyance.
Moderate:	(Grade 2): Symptom results in mild to moderate limitation in activity; no or minimal intervention required. The AE produces some impairment of functioning, but it is not hazardous to health. It is uncomfortable or an embarrassment.
Severe:	(Grade 3): Symptom results in significant limitation in activity; medical intervention may be required. The AE produces significant impairment of functioning or incapacitation.
Life threatening	(Grade 4): Symptoms causing inability to perform basic self-care functions OR Medical or operative intervention indicated to prevent permanent impairment, persistent disability, or death

11.1.4. Definition of Relationship to Study Drug

The Principal Investigator or medically qualified designee must review each AE and make the determination of relationship to study drug using the following guidelines:

Not Related: The event can be readily explained by other factors such as the subject's underlying medical condition, concomitant therapy, or accident, and no temporal relationship exists between the study drug and the event.

Unlikely: The event does not follow a reasonable temporal sequence from drug administration and is readily explained by the subject's clinical state or by other modes of therapy administered to the subject.

Possibly Related: There is some temporal relationship between the event and the administration of the study drug and the event is unlikely to be explained by the subject's medical condition, other therapies, or accident.

Probably Related: The event follows a reasonable temporal sequence from drug administration, abates upon discontinuation of the drug, and cannot be reasonably explained by the known characteristics of the subject's clinical state.

Definitely Related: The event follows a reasonable temporal sequence from administration of the medication, follows a known or suspected response pattern to the medication, is confirmed by improvement upon stopping the medication (dechallenge), and reappears upon repeated exposure (rechallenge, if rechallenge is medically appropriate).

11.1.5. Reporting Serious Adverse Events

Any SAE must be reported by phone or email to the Sponsor medical monitor and in writing via email or fax using the SAE report form within 24 hours of the Investigator's awareness of the SAE. In addition, all SAEs must be recorded on the AE case report form (CRF) in real time.

All additional follow-up evaluations of the SAE must be reported to BioCryst or its designee as soon as they are available.

The SAE report forms should be sent to the following email addresses or fax numbers:

Email: safety@biocryst.com **and** drugsafety@prosarcorp.com

OR

Fax: +1 919 226-5888 **and** +1 866-681-1063

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

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

Any SAEs considered possibly, probably or definitely related to treatment and not in accordance with information in the Investigator's Brochure will be reported to the FDA and other Regulatory Competent

Authorities as applicable via the MedWatch/CIOMS reporting system in accordance with FDA and other applicable regulations.

The Principal Investigator or designee at each site is responsible for submitting the Investigational New Drug (IND) safety report (initial and follow-up) or other safety information (e.g., revised Investigator's Brochure) to the Institutional Review Board (IRB) and for retaining a copy in their files.

11.1.6. Pregnancy

Any pregnancy in an enrolled subject or discovered in a subject during the course of the trial must be reported to BioCryst or designee on the Pregnancy Notification Form (to be supplied by BioCryst) in the same manner as SAEs (see Section 11.1.5). All pregnancies will be followed to an outcome (i.e., miscarriage, elective termination, stillbirth, live birth), and the outcome needs to be reported on the Pregnancy Outcome Form (to be supplied by BioCryst). Pregnancy outcomes of miscarriage, elective termination, stillbirth or birth defects will be considered SAEs and should be reported as per Section 11.1.5.

11.1.7. Reporting DAIDS Grade 3 or 4 events

Any DAIDS Grade 3 and Grade 4 clinical AE or laboratory abnormality that is judged to be possibly, probably, or definitely related to study treatment but does not meet seriousness criteria will be promptly (within 72 hours) reported to the study medical monitor via telephone or email.

11.2. Clinical Laboratory Evaluations

11.2.1. Clinical Chemistry Profiles

Clinical chemistry profiles will include a Chemistry 20 panel (includes sodium, potassium, chloride, total CO_2 [bicarbonate], creatinine, glucose, urea nitrogen, albumin, total calcium, total magnesium, phosphorus, alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, direct bilirubin, lactate dehydrogenase (LDH), total protein, total creatine kinase, and uric acid).

Blood samples for clinical chemistry profiles will be collected at Screening and at Day 7 or early termination visit (if the early termination visit occurs prior to Day 7). Clinically significant results should be reported as AEs. If Day 7 clinical chemistry profiles are, in the opinion of the investigator, significantly abnormal or significantly changed from baseline at Day 7, they should be repeated at the Day 14 visit.

At screening, creatinine clearance will be calculated by the Cockroft-Gault equation (using actual body weight and serum creatinine) (see Appendix 16.1).

11.2.2. Hematology Profiles

Hematology profiles will include complete blood count (CBC) with differential. Blood samples for hematology profiles will be collected at Baseline and at Day 7 or early termination visit (if the early termination visit occurs prior to Day 7). If Day 7 hematology profiles are, in the opinion of the investigator, significantly abnormal or significantly changed at Day 7, repeat at the Day 14 visit.

Clinically significant results should be reported as AEs.

11.2.3. Urinalysis

Urinalysis will include tests for protein, glucose, ketones, blood, urobilinogen, nitrite, pH, and specific gravity and microscopic evaluation (if initial assessment is abnormal) for red blood cells (RBCs) and white blood cells (WBCs).

Urine samples for urinalysis will be collected at Screening, Day 7 and/or at early termination visit (if the early termination visit occurs prior to Day 7). If a urinalysis result for any analyte is, in the opinion of the investigator, significantly abnormal and/or unexplained, repeat testing may be obtained at periodic intervals as deemed appropriate by the Investigator, and should be repeated during the Day 14 visit.

Clinically significant results should be reported as AEs.

11.2.4. Pregnancy Test (Urine or Serum)

Females of childbearing potential will be evaluated for pregnancy at Screening and at the Day 14 or early termination visit (if the early termination visit occurs prior to Day 14) assessment using a urine pregnancy test performed locally unless they are already pregnant. If local regulatory guidelines require a serum pregnancy test, then this modality should be completed in addition to the urine test to complete the pregnancy test.

11.3. Vital Signs

Vital sign measurements (blood pressure, heart rate, respiration rate) will be recorded once at Screening and once at each study visit on Days 3, 7, 14 and/or early termination visit.

11.4. Physical Examination

The Investigator will perform a full physical examination at Screening, including the subject's height and weight, and a targeted physical examination on Day 3 and Day 7 and/or early termination. Examination of the breast and urogenital system may be omitted as per the institution's/investigator's clinical routine. At each follow-up visit, study personnel will evaluate the subject for the presence of clinical signs and/or symptoms of influenza-related complications (see Section 10.2.4). If an IRC is suspected, a targeted physical exam should be conducted to confirm the absence or presence of the IRC.

12. PHARMACOKINETIC ASSESSMENTS

Up to 3 plasma samples will be drawn for determination of peramivir drug concentrations. The samples will be drawn, where possible, during the following time periods, beginning from the end 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

Plasma samples will be processed and shipped for analysis in accordance with instructions provided in the Laboratory Manual.

Plasma peramivir concentrations will be measured by a validated liquid chromatography-tandem mass spectrometry (LC/MS-MS) assay.

13. STATISTICS

Descriptive statistical methods will be used to summarize the data from this study. Unless stated otherwise, the term "descriptive statistics" refers to number of subjects, mean, median, standard deviation (SD), minimum, and maximum for continuous data and frequencies and percentages for categorical data.

All statistical analyses will be conducted with the SAS® System, version 9.1.3 or higher.

13.1. Data Collection Methods

The data will be transcribed from the subjects' source documents into the Case Report Form (CRF) approved by BioCryst. The data collection methods may be either a paper CRF or an electronic CRF, at BioCryst's discretion. All documentation supporting the CRF data, such as laboratory or hospital records must be readily available to verify entries in the CRF.

To ensure subject confidentiality, any documents (including laboratory reports, hospital records subsequent to SAEs, etc.) transmitted to BioCryst should not carry the subject's name.

13.2. Statistical Analysis Plans

A statistical analysis plan (SAP) will be created and approved prior to the review of any data. This document will provide a more technical and detailed description of the proposed data analysis methods and procedures.

13.3. Study Hypothesis

There are no hypotheses to be formally tested in this study.

13.4. Sample Size Estimates

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. The sample size is not based on statistical considerations, rather a sample size of up to 120 subjects is considered adequate to evaluate the stated objectives.

13.5. Analysis Populations

The populations defined for analysis will include the intent-to-treat (ITT) population, intent-to-treat infected (ITTI) population, safety population, and an exposure-response population. Additional analysis populations may be defined to evaluate study results. Any additional analysis populations will be defined in the SAP.

- **Intent-To-Treat Population:** The ITT population will include all subjects who are randomized. The ITT population will be used for analyses of accountability and demographics.
- **Intent-To-Treat Infected Population:** The ITTI population will include all subjects who are enrolled, treated, and have influenza confirmed by PCR. The ITTI population will be used for analyses of effectiveness.
- **Safety Population:** The safety population will include all subjects who received any amount of study drug. This population will be used for all safety analyses.

- **Exposure-Response Population:** The exposure-response population will include all subjects in the ITTI population who have a quantifiable plasma concentration of peramivir and at least 1 post-baseline effectiveness assessment. This population will be used for all exposure-response analyses.

13.6. End of Study Analysis

A final analysis is planned to occur after the last subject completes or discontinues the study, and the resulting clinical database has been cleaned, quality checked, and locked.

13.7. General Issues for Statistical Analysis

13.7.1. Multiple Comparisons and Multiplicity

No adjustments are currently planned.

13.7.2. Covariates

Not applicable.

13.7.3. Planned Subgroups

Analyses will be displayed by age group (≥ 65 years vs < 65 years) and viral subtype at Screening. Additional subgroups based on risk of complication may be evaluated. Subgroups will be defined in the SAP.

13.7.4. Missing Data

Every effort will be made to obtain required data at each scheduled visit from all subjects who have been enrolled. In situations where it is not possible to obtain all data, it may be necessary to impute missing data. In assessing the time to event endpoints, subjects who withdraw or never achieve resolution/alleviation, missing data will be censored using the date of subject's last non-missing assessment. Additional details on the handling of missing data will be presented in the SAP.

13.8. Effectiveness

13.8.1. Effectiveness Endpoints

All effectiveness endpoints will be summarized using descriptive statistics overall, and by age group and study day/time, if appropriate.

13.8.2. Effectiveness Analyses

Time to resolution of fever, defined as a temperature < 99.4°F oral with no antipyretic medications taken for at least 12 hours, will be estimated overall and by each age group using the method of Kaplan-Meier. Subjects who do not achieve resolution of fever will be censored at the time of their last assessment.

Time to resolution of influenza symptoms, defined as the time from initiation of study drug until the start of the 21.5-hour period (24 hours- 10%) where all symptoms of influenza are recorded as none or mild, will be estimated overall and for each age group using the method of Kaplan-Meier. Subjects who do not experience alleviation of symptoms will be censored at the time of the last non-missing symptom assessment.

Reduction in viral shedding will be assessed as the change from baseline in $\log_{10}$ $TCID_{50}$/mL and RT-PCR, and will be summarized overall, by age group, and by study visit.

Changes in virus susceptibility to neuraminidase inhibitors between virus cultured at Baseline and the last post-treatment sample from which virus can be cultured will be assessed using virology laboratory tests. Virology laboratory tests will include phenotypic characterizations of influenza virus recovered (hemagglutinin and neuraminidase) and viral susceptibility to peramivir, and genotypic analysis of primary virus isolates. These analyses will be presented overall, and separately by age group and viral subtype.

13.9. Safety Analyses

Adverse Events will be mapped to a Medical Dictionary for Regulatory Activities (MedDRA)-preferred term and system organ classification. The occurrence of treatment-emergent AEs (TEAEs) will be summarized by age group and treatment group using MedDRA-preferred terms, system organ classifications, and severity. All AEs will be listed for individual subjects showing both verbatim and preferred terms. Separate summaries of treatment-emergent SAEs and AEs related to study drug will be generated.

Descriptive summaries of vital signs and clinical laboratory results will be presented by age group, treatment group and study visit. Laboratory abnormalities will be graded according to the DAIDS Table for Grading Adverse Events for Adults and Pediatrics (Publish Date: December 2004 Clarification, 2009, see Section 16.2). The number and percentage of subjects experiencing treatment-emergent graded toxicities will be summarized overall and by age group. Laboratory toxicity shifts from baseline to post-baseline assessments will be summarized overall and by age group.

Previous and concomitant medications will be mapped to a WHO preferred term and drug classification. The number and percent of subjects taking concomitant medications will be summarized using preferred terms and drug classifications.

The number and percent of subjects experiencing influenza related complications will be summarized overall and by age group.

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.

13.10. Exposure Response Analyses

The data from the PK samples will be used together with data from prior trials to complete a separate exposure-response analysis. The methods for the exposure-response analysis will be presented in a separate SAP.

14. STUDY ADMINISTRATION

14.1. Regulatory and Ethical Considerations

14.1.1. Regulatory Authority Approvals

This study will be conducted in compliance with the protocol; Good Clinical Practices (GCPs), including International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use Guidelines; FDA regulatory requirements and in accordance with the ethical principles of the Declaration of Helsinki. In addition, all applicable local laws and regulatory requirements relevant to the use of new therapeutic agents in the countries involved will be adhered to.

The Investigator should submit written reports of clinical study status to their IRB annually or more frequently if requested by the IRB. A final study notification will also be forwarded to the IRB after the study is completed or in the event of premature termination of the study in accordance with the applicable regulations. Copies of all contact with the IRB should be maintained in the study documents file. Copies of clinical study status reports (including termination) should be provided to BioCryst.

14.1.2. Institutional Review Board Approvals

Before initiation of the study at each investigational site, the protocol, the informed consent and assent forms, the subject information sheet, and any other relevant study documentation will be submitted to the appropriate IRB. Written approval of the study must be obtained before the investigational medicinal product is released to the Investigator and the study site may be opened for enrollment. Any necessary extensions or renewals of IRB approval must be obtained, in particular, for changes to the study such as modification of the protocol, the informed consent and assent forms, the written information provided to subjects/caregivers and/or other procedures.

The Investigator will report promptly to the IRB any new information that may adversely affect the safety of the subjects or the conduct of the study. On completion of the study, the Investigator will provide the IRB with a report of the outcome of the study.

14.1.3. Subject Informed Consent

Signed informed consent must be obtained from each subject prior to performing any study-related procedures. The informed consent process should take place under conditions where the subject has adequate time to consider the risks and benefits associated with his/her participation in the study. Subjects will not be screened or treated until the subject has signed an approved informed consent form (ICF) written in a language in which the subject is fluent.

The ICF that is used must be approved both by BioCryst and by the reviewing IRB. The informed consent should be in accordance with the current revision of the Declaration of Helsinki, current ICH and GCP guidelines, and BioCryst policy.

The Investigator must explain to potential subjects the aims, methods, reasonably anticipated benefits, and potential hazards of the trial and any discomfort it may entail. Each subject will be informed that they are free not to participate in the trial and that they may withdraw consent to participate at any time. They will be told that refusal to participate in the study will not prejudice future treatment. They will also be told that their records may be examined by competent authorities and authorized persons but that personal information will be treated as strictly confidential and will not be publicly available.

Subjects must be given the opportunity to ask questions. After this explanation and before entry into the trial, consent should be appropriately recorded by means of the subject's dated signature. The subject should receive a signed and dated copy of the ICF. The original signed informed consent should be retained in the study files. The Investigator shall maintain a log of all subjects for whom consent was signed and indicate if the subject was enrolled into the study or reason for non-enrollment.

14.1.4. Payment to Subjects

Reasonable compensation to study subjects may be provided if approved by the IRB responsible for the study at the Investigator's site.

14.1.5. Investigator Reporting Requirements

The Investigator will provide timely reports regarding safety to his/her IRB as required.

14.2. Study Monitoring

During trial conduct, BioCryst or its designee will conduct periodic monitoring visits to ensure that the protocol and GCPs are being followed. The monitors may review source documents to confirm that the data recorded on CRFs is accurate. The Investigator and treating institution, if applicable, will allow BioCryst monitors or its designees and appropriate regulatory authorities direct access to source documents to perform this verification.

14.3. Quality Assurance

The trial site may be subject to review by the IRB, and/or to quality assurance audits performed by BioCryst, or designee, and/or to inspection by appropriate regulatory authorities.

It is important that the Investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

14.4. Study Termination and Site Closure

BioCryst reserves the right to discontinue the trial prior to inclusion of the intended number of subjects but intends only to exercise this right for valid scientific or administrative reasons. After such a decision, the Investigator must contact all participating subjects immediately after notification. As directed by BioCryst, all study materials must be collected and all case report forms completed to the greatest extent possible.

14.5. Records Retention

To enable evaluations and/or audits from regulatory authorities or BioCryst, the Investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, case report forms and hospital records), all original signed informed consent forms, copies of all case report forms and detailed records of treatment disposition. The records should be retained by the Investigator according to local regulations or as specified in the Clinical Trial Agreement, whichever is longer.

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

14.6. Confidentiality of Information

BioCryst affirms the subject's right to protection against invasion of privacy. Only a subject identification number, initials and/or date of birth will identify subject data retrieved by BioCryst**.** However, in compliance with federal regulations, BioCryst requires the Investigator to permit BioCryst's representatives and, when necessary, representatives of the FDA or other regulatory authorities to review and/or copy any medical records relevant to the study.

BioCryst will ensure that the use and disclosure of protected health information obtained during a research study complies with the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule, where this rule is applicable. The Rule provides federal protection for the privacy of protected health information by implementing standards to protect and guard against the misuse of individually identifiable health information of subjects participating in BioCryst-sponsored Clinical Trials. "Authorization" is required from each research subject (i.e., specified permission granted by an individual to a covered entity for the use or disclosure of an individual's protected health information). A valid authorization must meet the implementation specifications under the HIPAA Privacy Rule. Authorization may be combined in the Informed Consent document (approved by the IRB) or it may be a separate document, (approved by the IRB) or provided by the Investigator or Sponsor (without IRB approval). It is the responsibility of the Investigator and treating institution, if applicable, to obtain such waiver or authorization in writing from the appropriate individual. HIPAA authorizations are required for US sites only.

14.7. Study Publication

All data generated from this study are the property of BioCryst and shall be held in strict confidence along with all information furnished by BioCryst. Independent analysis and/or publication of these data by the Investigator or any member of his/her staff are not permitted without prior written consent of BioCryst. Written permission to the Investigator will be contingent on the review by BioCryst of the statistical analysis and manuscript and will provide for nondisclosure of BioCryst confidential or proprietary information. In all cases, the parties agree to submit all manuscripts or abstracts to all other parties 30 days prior to submission. This will enable all parties to protect proprietary information and to provide comments based on information that may not yet be available to other parties.

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16. APPENDICES

16.1. Appendix 1: Cockcroft-Gault Equation

Creatinine clearance to be calculated using the Cockcroft Gault Equation (Cockcroft and Gault 1976) using actual body weight (BW) and serum creatinine (S_{cr}).

Male: $$CL_{cr}\ (mL/min) = \frac{[140 - age\ (years)] \times BW(kg)}{72 \times S_{cr}\ (mg/dL)}$$

Female: $$CL_{cr}\ (mL/min) = \frac{[140 - age\ (years)] \times BW(kg) \times 0.85}{72 \times S_{cr}\ (mg/dL)}$$

An on-line calculator can also be found at: http://nephron.com/cgi-bin/CGSI.cgi

16.2. Appendix 2: Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events

DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS
VERSION 1.0, DECEMBER, 2004; CLARIFICATION AUGUST 2009

The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events ("DAIDS AE Grading Table") is a descriptive terminology which can be utilized for Adverse Event (AE) reporting. A grading (severity) scale is provided for each AE term.

This clarification of the DAIDS Table for Grading the Severity of Adult and Pediatric AE's provides additional explanation of the DAIDS AE Grading Table and clarifies some of the parameters.

I. Instructions and Clarifications

Grading Adult and Pediatric AEs

The DAIDS AE Grading Table includes parameters for grading both Adult and Pediatric AEs. When a single set of parameters is not appropriate for grading specific types of AEs for both Adult and Pediatric populations, separate sets of parameters for Adult and/or Pediatric populations (with specified respective age ranges) are given in the Table. If there is no distinction in the Table between Adult and Pediatric values for a type of AE, then the single set of parameters listed is to be used for grading the severity of both Adult and Pediatric events of that type.

> **Note:** In the classification of adverse events, the term "**severe**" is not the same as "**serious**." Severity is an indication of the intensity of a specific event (as in mild, moderate, or severe chest pain). The term "**serious**" relates to a participant/event outcome or action criteria, usually associated with events that pose a threat to a participant's life or functioning.

Addenda 1-3 Grading Tables for Microbicide Studies

For protocols involving topical application of products to the female genital tract, male genital area or rectum, strong consideration should be given to using Appendices I-III as the primary grading scales for these areas. The protocol would need to specifically state that one or more of the Appendices would be primary (and thus take precedence over the main Grading Table) for items that are listed in both the Appendix and the main Grading Table.

- Addendum 1 - Female Genital Grading Table for Use in Microbicide Studies - PDF
- Addendum 2 - Male Genital Grading Table for Use in Microbicide Studies - PDF
- Addendum 3 - Rectal Grading Table for Use in Microbicide Studies - PDF

Grade 5

For any AE where the outcome is death, the severity of the AE is classified as Grade 5.

Estimating Severity Grade for Parameters Not Identified in the Table

In order to grade a clinical AE that is not identified in the DAIDS AE grading table, use the category "Estimating Severity Grade" located on Page 3.

Determining Severity Grade for Parameters "Between Grades"

If the severity of a clinical AE could fall under either one of two grades (e.g., the severity of an AE could be either Grade 2 or Grade 3), select the higher of the two grades for the AE. If a laboratory value that is graded as a multiple of the ULN or LLN falls between two grades, select the higher of the two grades for the AE. For example, Grade 1 is 2.5 x ULN and Grade 2 is 2.6 x ULN for a parameter. If the lab value is 2.53 x ULN (which is between the two grades), the severity of this AE would be Grade 2, the higher of the two grades.

Values Below Grade 1

Any laboratory value that is between either the LLN or ULN and Grade 1 should not be graded.

Determining Severity Grade when Local Laboratory Normal Values Overlap with Grade 1 Ranges

In these situations, the severity grading is based on the ranges in the DAIDS AE Grading Table, even when there is a reference to the local lab LLN.

For example: Phosphate, Serum, Low, Adult and Pediatric > 14 years (Page 20) Grade 1 range is 2.50 mg/dL - < LLN. A particular laboratory's normal range for Phosphate is 2.1 – 3.8 mg/dL. A participant's actual lab value is 2.5. In this case, the value of 2.5 exceeds the LLN for the local lab, but will be graded as Grade 1 per DAIDS AE Grading Table.

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II. Definitions of terms used in the Table:

Basic Self-care Functions	Adult Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding. Young Children Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).
LLN	Lower limit of normal
Medical Intervention	Use of pharmacologic or biologic agent(s) for treatment of an AE.
NA	Not Applicable
Operative Intervention	Surgical OR other invasive mechanical procedures.
ULN	Upper limit of normal
Usual Social & Functional Activities	Adult Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc. Young Children Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS
VERSION 1.0, DECEMBER, 2004; CLARIFICATION AUGUST 2009

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
ESTIMATING SEVERITY GRADE				
Clinical adverse event NOT identified elsewhere in this DAIDS AE Grading Table	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions OR Medical or operative intervention indicated to prevent permanent impairment, persistent disability, or death
SYSTEMIC				
Acute systemic allergic reaction	Localized urticaria (wheals) with no medical intervention indicated	Localized urticaria with medical intervention indicated OR Mild angioedema with no medical intervention indicated	Generalized urticaria OR Angioedema with medical intervention indicated OR Symptomatic mild bronchospasm	Acute anaphylaxis OR Life-threatening bronchospasm OR laryngeal edema
Chills	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	NA
Fatigue Malaise	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Incapacitating fatigue/ malaise symptoms causing inability to perform basic self-care functions
Fever (nonaxillary)	37.7 – 38.6°C	38.7 – 39.3°C	39.4 – 40.5°C	> 40.5°C
Pain (indicate body site) DO NOT use for pain due to injection (See Injection Site Reactions: Injection site pain) See also Headache, Arthralgia, and Myalgia	Pain causing no or minimal interference with usual social & functional activities	Pain causing greater than minimal interference with usual social & functional activities	Pain causing inability to perform usual social & functional activities	Disabling pain causing inability to perform basic self-care functions OR Hospitalization (other than emergency room visit) indicated

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS
VERSION 1.0, DECEMBER, 2004; CLARIFICATION AUGUST 2009

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Unintentional weight loss	NA	5 – 9% loss in body weight from baseline	10 – 19% loss in body weight from baseline	≥ 20% loss in body weight from baseline OR Aggressive intervention indicated [e.g., tube feeding or total parenteral nutrition (TPN)]
INFECTION				
Infection (any other than HIV infection)	Localized, no systemic antimicrobial treatment indicated AND Symptoms causing no or minimal interference with usual social & functional activities	Systemic antimicrobial treatment indicated OR Symptoms causing greater than minimal interference with usual social & functional activities	Systemic antimicrobial treatment indicated AND Symptoms causing inability to perform usual social & functional activities OR Operative intervention (other than simple incision and drainage) indicated	Life-threatening consequences (e.g., septic shock)
INJECTION SITE REACTIONS				
Injection site pain (pain without touching) Or Tenderness (pain when area is touched)	Pain/tenderness causing no or minimal limitation of use of limb	Pain/tenderness limiting use of limb OR Pain/tenderness causing greater than minimal interference with usual social & functional activities	Pain/tenderness causing inability to perform usual social & functional activities	Pain/tenderness causing inability to perform basic self-care function OR Hospitalization (other than emergency room visit) indicated for management of pain/tenderness
Injection site reaction (localized)				
Adult > 15 years	Erythema OR Induration of 5x5 cm – 9x9 cm (or 25 cm^2 – 81cm^2)	Erythema OR Induration OR Edema > 9 cm any diameter (or > 81 cm^2)	Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage	Necrosis (involving dermis and deeper tissue)
Pediatric ≤ 15 years	Erythema OR Induration OR Edema present but ≤ 2.5 cm diameter	Erythema OR Induration OR Edema > 2.5 cm diameter but < 50% surface area of the extremity segment (e.g., upper arm/thigh)	Erythema OR Induration OR Edema involving ≥ 50% surface area of the extremity segment (e.g., upper arm/thigh) OR Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage	Necrosis (involving dermis and deeper tissue)

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS
VERSION 1.0, DECEMBER, 2004; CLARIFICATION AUGUST 2009

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Pruritis associated with injection See also Skin: Pruritis (itching - no skin lesions)	Itching localized to injection site AND Relieved spontaneously or with < 48 hours treatment	Itching beyond the injection site but not generalized OR Itching localized to injection site requiring ≥ 48 hours treatment	Generalized itching causing inability to perform usual social & functional activities	NA
SKIN – DERMATOLOGICAL				
Alopecia	Thinning detectable by study participant (or by caregiver for young children and disabled adults)	Thinning or patchy hair loss detectable by health care provider	Complete hair loss	NA
Cutaneous reaction – rash	Localized macular rash	Diffuse macular, maculopapular, or morbilliform rash OR Target lesions	Diffuse macular, maculopapular, or morbilliform rash with vesicles or limited number of bullae OR Superficial ulcerations of mucous membrane limited to one site	Extensive or generalized bullous lesions OR Stevens-Johnson syndrome OR Ulceration of mucous membrane involving two or more distinct mucosal sites OR Toxic epidermal necrolysis (TEN)
Hyperpigmentation	Slight or localized	Marked or generalized	NA	NA
Hypopigmentation	Slight or localized	Marked or generalized	NA	NA
Pruritis (itching – no skin lesions) (See also Injection Site Reactions: Pruritis associated with injection)	Itching causing no or minimal interference with usual social & functional activities	Itching causing greater than minimal interference with usual social & functional activities	Itching causing inability to perform usual social & functional activities	NA
CARDIOVASCULAR				
Cardiac arrhythmia (general) (By ECG or physical exam)	Asymptomatic AND No intervention indicated	Asymptomatic AND Non-urgent medical intervention indicated	Symptomatic, non-life-threatening AND Non-urgent medical intervention indicated	Life-threatening arrhythmia OR Urgent intervention indicated
Cardiac-ischemia/infarction	NA	NA	Symptomatic ischemia (stable angina) OR Testing consistent with ischemia	Unstable angina OR Acute myocardial infarction

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS
VERSION 1.0, DECEMBER, 2004; CLARIFICATION AUGUST 2009

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Hemorrhage (significant acute blood loss)	NA	Symptomatic AND No transfusion indicated	Symptomatic AND Transfusion of ≤ 2 units packed RBCs (for children ≤ 10 cc/kg) indicated	Life-threatening hypotension OR Transfusion of > 2 units packed RBCs (for children > 10 cc/kg) indicated
Hypertension				
Adult > 17 years (with repeat testing at same visit)	140 – 159 mmHg systolic OR 90 – 99 mmHg diastolic	160 – 179 mmHg systolic OR 100 – 109 mmHg diastolic	**≥** 180 mmHg systolic OR **≥** 110 mmHg diastolic	Life-threatening consequences (e.g., malignant hypertension) OR Hospitalization indicated (other than emergency room visit)
Correction: in Grade 2 to 160 - 179 from > 160-179 (systolic) and to ≥ 100 -109 from > 100-109 (diastolic) and in Grade 3 to ≥ 180 from > 180 (systolic) and to ≥ 110 from > 110 (diastolic).				
Pediatric ≤ 17 years (with repeat testing at same visit)	NA	91st – 94th percentile adjusted for age, height, and gender (systolic and/or diastolic)	≥ 95th percentile adjusted for age, height, and gender (systolic and/or diastolic)	Life-threatening consequences (e.g., malignant hypertension) OR Hospitalization indicated (other than emergency room visit)
Hypotension	NA	Symptomatic, corrected with oral fluid replacement	Symptomatic, IV fluids indicated	Shock requiring use of vasopressors or mechanical assistance to maintain blood pressure
Pericardial effusion	Asymptomatic, small effusion requiring no intervention	Asymptomatic, moderate or larger effusion requiring no intervention	Effusion with non-life threatening physiologic consequences OR Effusion with non-urgent intervention indicated	Life-threatening consequences (e.g., tamponade) OR Urgent intervention indicated
Prolonged PR interval				
Adult > 16 years	PR interval 0.21 – 0.25 sec	PR interval > 0.25 sec	Type II 2nd degree AV block OR Ventricular pause > 3.0 sec	Complete AV block
Pediatric ≤ 16 years	1st degree AV block (PR > normal for age and rate)	Type I 2nd degree AV block	Type II 2nd degree AV block	Complete AV block

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS
VERSION 1.0, DECEMBER, 2004; CLARIFICATION AUGUST 2009

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Prolonged QTc				
Adult > 16 years	Asymptomatic, QTc interval 0.45 – 0.47 sec OR Increase interval < 0.03 sec above baseline	Asymptomatic, QTc interval 0.48 – 0.49 sec OR Increase in interval 0.03 – 0.05 sec above baseline	Asymptomatic, QTc interval ≥ 0.50 sec OR Increase in interval ≥ 0.06 sec above baseline	Life-threatening consequences, e.g. Torsade de pointes or other associated serious ventricular dysrhythmia
Pediatric ≤ 16 years	Asymptomatic, QTc interval 0.450 – 0.464 sec	Asymptomatic, QTc interval 0.465 – 0.479 sec	Asymptomatic, QTc interval ≥ 0.480 sec	Life-threatening consequences, e.g. Torsade de pointes or other associated serious ventricular dysrhythmia
Thrombosis/embolism	NA	Deep vein thrombosis AND No intervention indicated (e.g., anticoagulation, lysis filter, invasive procedure)	Deep vein thrombosis AND Intervention indicated (e.g., anticoagulation, lysis filter, invasive procedure)	Embolic event (e.g., pulmonary embolism, life-threatening thrombus)
Vasovagal episode (associated with a procedure of any kind)	Present without loss of consciousness	Present with transient loss of consciousness	NA	NA
Ventricular dysfunction (congestive heart failure)	NA	Asymptomatic diagnostic finding AND intervention indicated	New onset with symptoms OR Worsening symptomatic congestive heart failure	Life-threatening congestive heart failure
GASTROINTESTINAL				
Anorexia	Loss of appetite without decreased oral intake	Loss of appetite associated with decreased oral intake without significant weight loss	Loss of appetite associated with significant weight loss	Life-threatening consequences OR Aggressive intervention indicated [e.g., tube feeding or total parenteral nutrition (TPN)]
Comment: Please note that, while the grading scale provided for Unintentional Weight Loss may be used as a guideline when grading anorexia, this is not a requirement and should not be used as a substitute for clinical judgment.				
Ascites	Asymptomatic	Symptomatic AND Intervention indicated (e.g., diuretics or therapeutic paracentesis)	Symptomatic despite intervention	Life-threatening consequences

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Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Cholecystitis	NA	Symptomatic AND Medical intervention indicated	Radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences (e.g., sepsis or perforation)
Constipation	NA	Persistent constipation requiring regular use of dietary modifications, laxatives, or enemas	Obstipation with manual evacuation indicated	Life-threatening consequences (e.g., obstruction)
Diarrhea				
Adult and Pediatric ≥ 1 year	Transient or intermittent episodes of unformed stools OR Increase of ≤ 3 stools over baseline per 24-hour period	Persistent episodes of unformed to watery stools OR Increase of 4 – 6 stools over baseline per 24-hour period	Bloody diarrhea OR Increase of ≥ 7 stools per 24-hour period OR IV fluid replacement indicated	Life-threatening consequences (e.g., hypotensive shock)
Pediatric < 1 year	Liquid stools (more unformed than usual) but usual number of stools	Liquid stools with increased number of stools OR Mild dehydration	Liquid stools with moderate dehydration	Liquid stools resulting in severe dehydration with aggressive rehydration indicated OR Hypotensive shock
Dysphagia-Odynophagia	Symptomatic but able to eat usual diet	Symptoms causing altered dietary intake without medical intervention indicated	Symptoms causing severely altered dietary intake with medical intervention indicated	Life-threatening reduction in oral intake
Mucositis/stomatitis (clinical exam) Indicate site (e.g., larynx, oral) See Genitourinary for Vulvovaginitis See also Dysphagia-Odynophagia and Proctitis	Erythema of the mucosa	Patchy pseudomembranes or ulcerations	Confluent pseudomembranes or ulcerations OR Mucosal bleeding with minor trauma	Tissue necrosis OR Diffuse spontaneous mucosal bleeding OR Life-threatening consequences (e.g., aspiration, choking)
Nausea	Transient (< 24 hours) or intermittent nausea with no or minimal interference with oral intake	Persistent nausea resulting in decreased oral intake for 24 – 48 hours	Persistent nausea resulting in minimal oral intake for > 48 hours OR Aggressive rehydration indicated (e.g., IV fluids)	Life-threatening consequences (e.g., hypotensive shock)

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Pancreatitis	NA	Symptomatic AND Hospitalization not indicated (other than emergency room visit)	Symptomatic AND Hospitalization indicated (other than emergency room visit)	Life-threatening consequences (e.g., circulatory failure, hemorrhage, sepsis)
Proctitis (functional-symptomatic) Also see Mucositis/stomatitis for clinical exam	Rectal discomfort AND No intervention indicated	Symptoms causing greater than minimal interference with usual social & functional activities OR Medical intervention indicated	Symptoms causing inability to perform usual social & functional activities OR Operative intervention indicated	Life-threatening consequences (e.g., perforation)
Vomiting	Transient or intermittent vomiting with no or minimal interference with oral intake	Frequent episodes of vomiting with no or mild dehydration	Persistent vomiting resulting in orthostatic hypotension OR Aggressive rehydration indicated (e.g., IV fluids)	Life-threatening consequences (e.g., hypotensive shock)
NEUROLOGIC				
Alteration in personality-behavior or in mood (e.g., agitation, anxiety, depression, mania, psychosis)	Alteration causing no or minimal interference with usual social & functional activities	Alteration causing greater than minimal interference with usual social & functional activities	Alteration causing inability to perform usual social & functional activities	Behavior potentially harmful to self or others (e.g., suicidal and homicidal ideation or attempt, acute psychosis) OR Causing inability to perform basic self-care functions
Altered Mental Status For Dementia, see Cognitive and behavioral/attentional disturbance (including dementia and attention deficit disorder)	Changes causing no or minimal interference with usual social & functional activities	Mild lethargy or somnolence causing greater than minimal interference with usual social & functional activities	Confusion, memory impairment, lethargy, or somnolence causing inability to perform usual social & functional activities	Delirium OR obtundation, OR coma
Ataxia	Asymptomatic ataxia detectable on exam OR Minimal ataxia causing no or minimal interference with usual social & functional activities	Symptomatic ataxia causing greater than minimal interference with usual social & functional activities	Symptomatic ataxia causing inability to perform usual social & functional activities	Disabling ataxia causing inability to perform basic self-care functions

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

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PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Cognitive and behavioral/attentional disturbance (including dementia and attention deficit disorder)	Disability causing no or minimal interference with usual social & functional activities OR Specialized resources not indicated	Disability causing greater than minimal interference with usual social & functional activities OR Specialized resources on part-time basis indicated	Disability causing inability to perform usual social & functional activities OR Specialized resources on a full-time basis indicated	Disability causing inability to perform basic self-care functions OR Institutionalization indicated
CNS ischemia (acute)	NA	NA	Transient ischemic attack	Cerebral vascular accident (CVA, stroke) with neurological deficit
Developmental delay – **Pediatric ≤ 16 years**	Mild developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Moderate developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Severe developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Developmental regression, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting
Headache	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions OR Hospitalization indicated (other than emergency room visit) OR Headache with significant impairment of alertness or other neurologic function
Insomnia	NA	Difficulty sleeping causing greater than minimal interference with usual social & functional activities	Difficulty sleeping causing inability to perform usual social & functional activities	Disabling insomnia causing inability to perform basic self-care functions
Neuromuscular weakness (including myopathy & neuropathy)	Asymptomatic with decreased strength on exam OR Minimal muscle weakness causing no or minimal interference with usual social & functional activities	Muscle weakness causing greater than minimal interference with usual social & functional activities	Muscle weakness causing inability to perform usual social & functional activities	Disabling muscle weakness causing inability to perform basic self-care functions OR Respiratory muscle weakness impairing ventilation

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

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PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Neurosensory alteration (including paresthesia and painful neuropathy)	Asymptomatic with sensory alteration on exam or minimal paresthesia causing no or minimal interference with usual social & functional activities	Sensory alteration or paresthesia causing greater than minimal interference with usual social & functional activities	Sensory alteration or paresthesia causing inability to perform usual social & functional activities	Disabling sensory alteration or paresthesia causing inability to perform basic self-care functions
Seizure: (new onset) **– Adult ≥ 18 years** See also Seizure: (known pre-existing seizure disorder)	NA	1 seizure	2 **–** 4 seizures	Seizures of any kind which are prolonged, repetitive (e.g., status epilepticus), or difficult to control (e.g., refractory epilepsy)
Seizure: (known pre-existing seizure disorder) **– Adult ≥ 18 years** For worsening of existing epilepsy the grades should be based on an increase from previous level of control to any of these levels.	NA	Increased frequency of pre-existing seizures (non-repetitive) without change in seizure character OR Infrequent break-through seizures while on stable medication in a previously controlled seizure disorder	Change in seizure character from baseline either in duration or quality (e.g., severity or focality)	Seizures of any kind which are prolonged, repetitive (e.g., status epilepticus), or difficult to control (e.g., refractory epilepsy)
Seizure **– Pediatric < 18 years**	Seizure, generalized onset with or without secondary generalization, lasting < 5 minutes with < 24 hours post ictal state	Seizure, generalized onset with or without secondary generalization, lasting 5 – 20 minutes with < 24 hours post ictal state	Seizure, generalized onset with or without secondary generalization, lasting > 20 minutes	Seizure, generalized onset with or without secondary generalization, requiring intubation and sedation
Syncope (not associated with a procedure)	NA	Present	NA	NA
Vertigo	Vertigo causing no or minimal interference with usual social & functional activities	Vertigo causing greater than minimal interference with usual social & functional activities	Vertigo causing inability to perform usual social & functional activities	Disabling vertigo causing inability to perform basic self-care functions

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

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PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
RESPIRATORY				
Bronchospasm (acute)	FEV1 or peak flow reduced to 70 – 80%	FEV1 or peak flow 50 – 69%	FEV1 or peak flow 25 – 49%	Cyanosis OR FEV1 or peak flow < 25% OR Intubation
Dyspnea or respiratory distress				
Adult ≥ 14 years	Dyspnea on exertion with no or minimal interference with usual social & functional activities	Dyspnea on exertion causing greater than minimal interference with usual social & functional activities	Dyspnea at rest causing inability to perform usual social & functional activities	Respiratory failure with ventilatory support indicated
Pediatric < 14 years	Wheezing OR minimal increase in respiratory rate for age	Nasal flaring OR Intercostal retractions OR Pulse oximetry 90 – 95%	Dyspnea at rest causing inability to perform usual social & functional activities OR Pulse oximetry < 90%	Respiratory failure with ventilatory support indicated
MUSCULOSKELETAL				
Arthralgia See also Arthritis	Joint pain causing no or minimal interference with usual social & functional activities	Joint pain causing greater than minimal interference with usual social & functional activities	Joint pain causing inability to perform usual social & functional activities	Disabling joint pain causing inability to perform basic self-care functions
Arthritis See also Arthralgia	Stiffness or joint swelling causing no or minimal interference with usual social & functional activities	Stiffness or joint swelling causing greater than minimal interference with usual social & functional activities	Stiffness or joint swelling causing inability to perform usual social & functional activities	Disabling joint stiffness or swelling causing inability to perform basic self-care functions
Bone Mineral Loss				
Adult ≥ 21 years	BMD t-score -2.5 to -1.0	BMD t-score < -2.5	Pathological fracture (including loss of vertebral height)	Pathologic fracture causing life-threatening consequences
Pediatric < 21 years	BMD z-score -2.5 to -1.0	BMD z-score < -2.5	Pathological fracture (including loss of vertebral height)	Pathologic fracture causing life-threatening consequences
Myalgia (non-injection site)	Muscle pain causing no or minimal interference with usual social & functional activities	Muscle pain causing greater than minimal interference with usual social & functional activities	Muscle pain causing inability to perform usual social & functional activities	Disabling muscle pain causing inability to perform basic self-care functions

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Osteonecrosis	NA	Asymptomatic with radiographic findings AND No operative intervention indicated	Symptomatic bone pain with radiographic findings OR Operative intervention indicated	Disabling bone pain with radiographic findings causing inability to perform basic self-care functions
GENITOURINARY				
Cervicitis (symptoms) (For use in studies evaluating topical study agents) For other cervicitis see Infection: Infection (any other than HIV infection)	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions
Cervicitis (clinical exam) (For use in studies evaluating topical study agents) For other cervicitis see Infection: Infection (any other than HIV infection)	Minimal cervical abnormalities on examination (erythema, mucopurulent discharge, or friability) OR Epithelial disruption < 25% of total surface	Moderate cervical abnormalities on examination (erythema, mucopurulent discharge, or friability) OR Epithelial disruption of 25 – 49% total surface	Severe cervical abnormalities on examination (erythema, mucopurulent discharge, or friability) OR Epithelial disruption 50 – 75% total surface	Epithelial disruption > 75% total surface
Inter-menstrual bleeding (IMB)	Spotting observed by participant OR Minimal blood observed during clinical or colposcopic examination	Inter-menstrual bleeding not greater in duration or amount than usual menstrual cycle	Inter-menstrual bleeding greater in duration or amount than usual menstrual cycle	Hemorrhage with life-threatening hypotension OR Operative intervention indicated
Urinary tract obstruction (e.g., stone)	NA	Signs or symptoms of urinary tract obstruction without hydronephrosis or renal dysfunction	Signs or symptoms of urinary tract obstruction with hydronephrosis or renal dysfunction	Obstruction causing life-threatening consequences

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

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PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Vulvovaginitis (symptoms) (Use in studies evaluating topical study agents) For other vulvovaginitis see Infection: Infection (any other than HIV infection)	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions
Vulvovaginitis (clinical exam) (Use in studies evaluating topical study agents) For other vulvovaginitis see Infection: Infection (any other than HIV infection)	Minimal vaginal abnormalities on examination OR Epithelial disruption < 25% of total surface	Moderate vaginal abnormalities on examination OR Epithelial disruption of 25 - 49% total surface	Severe vaginal abnormalities on examination OR Epithelial disruption 50 - 75% total surface	Vaginal perforation OR Epithelial disruption > 75% total surface
OCULAR/VISUAL				
Uveitis	Asymptomatic but detectable on exam	Symptomatic anterior uveitis OR Medical intervention indicated	Posterior or pan-uveitis OR Operative intervention indicated	Disabling visual loss in affected eye(s)
Visual changes (from baseline)	Visual changes causing no or minimal interference with usual social & functional activities	Visual changes causing greater than minimal interference with usual social & functional activities	Visual changes causing inability to perform usual social & functional activities	Disabling visual loss in affected eye(s)
ENDOCRINE/METABOLIC				
Abnormal fat accumulation (e.g., back of neck, breasts, abdomen)	Detectable by study participant (or by caregiver for young children and disabled adults)	Detectable on physical exam by health care provider	Disfiguring OR Obvious changes on casual visual inspection	NA
Diabetes mellitus	NA	New onset without need to initiate medication OR Modification of current medications to regain glucose control	New onset with initiation of medication indicated OR Diabetes uncontrolled despite treatment modification	Life-threatening consequences (e.g., ketoacidosis, hyperosmolar non-ketotic coma)

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Gynecomastia	Detectable by study participant or caregiver (for young children and disabled adults)	Detectable on physical exam by health care provider	Disfiguring OR Obvious on casual visual inspection	NA
Hyperthyroidism	Asymptomatic	Symptomatic causing greater than minimal interference with usual social & functional activities OR Thyroid suppression therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (e.g., thyroid storm)
Hypothyroidism	Asymptomatic	Symptomatic causing greater than minimal interference with usual social & functional activities OR Thyroid replacement therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (e.g., myxedema coma)
Lipoatrophy (e.g., fat loss from the face, extremities, buttocks)	Detectable by study participant (or by caregiver for young children and disabled adults)	Detectable on physical exam by health care provider	Disfiguring OR Obvious on casual visual inspection	NA

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS
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LABORATORY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
HEMATOLOGY	***Standard International Units are listed in italics***			
Absolute CD4+ count **– Adult and Pediatric > 13 years** (HIV NEGATIVE ONLY)	300 – 400/mm^3 *300 – 400/µL*	200 – 299/mm^3 *200 – 299/µL*	100 – 199/mm^3 *100 – 199/µL*	< 100/mm^3 *< 100/µL*
Absolute lymphocyte count **– Adult and Pediatric > 13 years** (HIV NEGATIVE ONLY)	600 – 650/mm^3 *0.600 x 10^9 – 0.650 x 10^9/L*	500 – 599/mm^3 *0.500 x 10^9 – 0.599 x 10^9/L*	350 – 499/mm^3 *0.350 x 10^9 – 0.499 x 10^9/L*	< 350/mm^3 *< 0.350 x 10^9/L*
Comment: Values in children ≤ 13 years are not given for the two parameters above because the absolute counts are variable.				
Absolute neutrophil count (ANC)				
Adult and Pediatric, > 7 days	1,000 – 1,300/mm^3 *1.000 x 10^9 – 1.300 x 10^9/L*	750 – 999/mm^3 *0.750 x 10^9 – 0.999 x 10^9/L*	500 – 749/mm^3 *0.500 x 10^9 – 0.749 x 10^9/L*	< 500/mm^3 *< 0.500 x 10^9/L*
Infant*†, 2 – ≤ 7 days	1,250 – 1,500/mm^3 *1.250 x 10^9 – 1.500 x 10^9/L*	1,000 – 1,249/mm^3 *1.000 x 10^9 – 1.249 x 10^9/L*	750 – 999/mm^3 *0.750 x 10^9 – 0.999 x 10^9/L*	< 750/mm^3 *< 0.750 x 10^9/L*
Infant*†, ≤1 day	4,000 – 5,000/mm^3 *4.000 x 10^9 – 5.000 x 10^9/L*	3,000 – 3,999/mm^3 *3.000 x 10^9 – 3.999 x10^9/L*	1,500 – 2,999/mm^3 *1.500 x 10^9 – 2.999 x 10^9/L*	< 1,500/mm^3 *< 1.500 x 10^9/L*
Comment: Parameter changed from "Infant, < 1 day" to "Infant, ≤1 day"				
Fibrinogen, decreased	100 – 200 mg/dL *1.00 – 2.00 g/L* OR 0.75 – 0.99 x LLN	75 – 99 mg/dL *0.75 – 0.99 g/L* OR 0.50 – 0.74 x LLN	50 – 74 mg/dL *0.50 – 0.74 g/L* OR 0.25 – 0.49 x LLN	< 50 mg/dL *< 0.50 g/L* OR < 0.25 x LLN OR Associated with gross bleeding

* Values are for term infants. Preterm infants should be assessed using local normal ranges.

† Use age and sex appropriate values (e.g., bilirubin).

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LABORATORY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Hemoglobin (Hgb)				
Comment: The Hgb values in mmol/L have changed because the conversion factor used to convert g/dL to mmol/L has been changed from 0.155 to 0.6206 (the most commonly used conversion factor). For grading Hgb results obtained by an analytic method with a conversion factor other than 0.6206, the result must be converted to g/dL using the appropriate conversion factor for that lab.				
Adult and Pediatric ≥ 57 days (HIV POSITIVE ONLY)	8.5 – 10.0 g/dL *5.24 – 6.23 mmol/L*	7.5 – 8.4 g/dL *4.62–5.23 mmol/L*	6.50 – 7.4 g/dL *4.03–4.61 mmol/L*	< 6.5 g/dL *< 4.03 mmol/L*
Adult and Pediatric ≥ 57 days (HIV NEGATIVE ONLY)	10.0 – 10.9 g/dL *6.18 – 6.79 mmol/L* OR Any decrease 2.5 – 3.4 g/dL *1.58 – 2.13 mmol/L*	9.0 – 9.9 g/dL *5.55 - 6.17 mmol/L* OR Any decrease 3.5 – 4.4 g/dL *2.14 – 2.78 mmol/L*	7.0 – 8.9 g/dL *4.34 - 5.54 mmol/L* OR Any decrease ≥ 4.5 g/dL *> 2.79 mmol/L*	< 7.0 g/dL *< 4.34 mmol/L*
Comment: The decrease is a decrease from baseline				
Infant*†, 36 – 56 days (HIV POSITIVE OR NEGATIVE)	8.5 – 9.4 g/dL *5.24 – 5.86 mmol/L*	7.0 – 8.4 g/dL *4.31 – 5.23 mmol/L*	6.0 – 6.9 g/dL *3.72 – 4.30 mmol/L*	< 6.00 g/dL *< 3.72 mmol/L*
Infant*†, 22 – 35 days (HIV POSITIVE OR NEGATIVE)	9.5 – 10.5 g/dL *5.87 - 6.54 mmol/L*	8.0 – 9.4 g/dL *4.93 – 5.86 mmol/L*	7.0 – 7.9 g/dL *4.34 – 4.92 mmol/L*	< 7.00 g/dL *< 4.34 mmol/L*
Infant*†, ≤ 21 days (HIV POSITIVE OR NEGATIVE)	12.0 – 13.0 g/dL *7.42 – 8.09 mmol/L*	10.0 – 11.9 g/dL *6.18 – 7.41 mmol/L*	9.0 – 9.9 g/dL *5.59- 6.17 mmol/L*	< 9.0 g/dL *< 5.59 mmol/L*
Correction: Parameter changed from "Infant < 21 days" to "Infant ≤ 21 days"				
International Normalized Ratio of prothrombin time (INR)	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.1 – 3.0 x ULN	> 3.0 x ULN
Methemoglobin	5.0 – 10.0%	10.1 – 15.0%	15.1 – 20.0%	> 20.0%
Prothrombin Time (PT)	1.1 – 1.25 x ULN	1.26 – 1.50 x ULN	1.51 – 3.00 x ULN	> 3.00 x ULN
Partial Thromboplastin Time (PTT)	1.1 – 1.66 x ULN	1.67 – 2.33 x ULN	2.34 – 3.00 x ULN	> 3.00 x ULN
Platelets, decreased	100,000 – 124,999/mm^3 *100.000 x 10^9 – 124.999 x 10^9/L*	50,000 – 99,999/mm^3 *50.000 x 10^9 – 99.999 x 10^9/L*	25,000 – 49,999/mm^3 *25.000 x 10^9 – 49.999 x 10^9/L*	< 25,000/mm^3 *< 25.000 x 10^9/L*
WBC, decreased	2,000 – 2,500/mm^3 *2.000 x 10^9 – 2.500 x 10^9/L*	1,500 – 1,999/mm^3 *1.500 x 10^9 – 1.999 x 10^9/L*	1,000 – 1,499/mm^3 *1.000 x 10^9 – 1.499 x 10^9/L*	< 1,000/mm^3 *< 1.000 x 10^9/L*

* Values are for term infants. Preterm infants should be assessed using local normal ranges.

† Use age and sex appropriate values (e.g., bilirubin).

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LABORATORY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
CHEMISTRIES	***Standard International Units are listed in italics***			
Acidosis	NA	pH < normal, but ≥ 7.3	pH < 7.3 without life-threatening consequences	pH < 7.3 with life-threatening consequences
Albumin, serum, low	3.0 g/dL – < LLN *30 g/L – < LLN*	2.0 – 2.9 g/dL *20 – 29 g/L*	< 2.0 g/dL *< 20 g/L*	NA
Alkaline Phosphatase	1.25 – 2.5 x ULN†	2.6 – 5.0 x ULN†	5.1 – 10.0 x ULN†	> 10.0 x ULN†
Alkalosis	NA	pH > normal, but ≤ 7.5	pH > 7.5 without life-threatening consequences	pH > 7.5 with life-threatening consequences
ALT (SGPT)	1.25 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10.0 x ULN	> 10.0 x ULN
AST (SGOT)	1.25 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10.0 x ULN	> 10.0 x ULN
Bicarbonate, serum, low	16.0 mEq/L – < LLN *16.0 mmol/L – < LLN*	11.0 – 15.9 mEq/L *11.0 – 15.9 mmol/L*	8.0 – 10.9 mEq/L *8.0 – 10.9 mmol/L*	< 8.0 mEq/L *< 8.0 mmol/L*
Comment: Some laboratories will report this value as Bicarbonate (HCO_3) and others as Total Carbon Dioxide (CO_2). These are the same tests; values should be graded according to the ranges for Bicarbonate as listed above.				
Bilirubin (Total)				
Adult and Pediatric > 14 days	1.1 – 1.5 x ULN	1.6 – 2.5 x ULN	2.6 – 5.0 x ULN	> 5.0 x ULN
Infant*†, ≤ 14 days (non-hemolytic)	NA	20.0 – 25.0 mg/dL *342 – 428 µmol/L*	25.1 – 30.0 mg/dL *429 – 513 µmol/L*	> 30.0 mg/dL *> 513.0 µmol/L*
Infant*†, ≤ 14 days (hemolytic)	NA	NA	20.0 – 25.0 mg/dL *342 – 428 µmol/L*	> 25.0 mg/dL *> 428 µmol/L*
Calcium, serum, high				
Adult and Pediatric ≥ 7 days	10.6 – 11.5 mg/dL *2.65 – 2.88 mmol/L*	11.6 – 12.5 mg/dL *2.89 – 3.13 mmol/L*	12.6 – 13.5 mg/dL *3.14 – 3.38 mmol/L*	> 13.5 mg/dL *> 3.38 mmol/L*
Infant*†, < 7 days	11.5 – 12.4 mg/dL *2.88 – 3.10 mmol/L*	12.5 – 12.9 mg/dL *3.11 – 3.23 mmol/L*	13.0 – 13.5 mg/dL *3.245 – 3.38 mmol/L*	> 13.5 mg/dL *> 3.38 mmol/L*
Calcium, serum, low				
Adult and Pediatric ≥ 7 days	7.8 – 8.4 mg/dL *1.95 – 2.10 mmol/L*	7.0 – 7.7 mg/dL *1.75 – 1.94 mmol/L*	6.1 – 6.9 mg/dL *1.53 – 1.74 mmol/L*	< 6.1 mg/dL *< 1.53 mmol/L*
Infant*†, < 7 days	6.5 – 7.5 mg/dL *1.63 – 1.88 mmol/L*	6.0 – 6.4 mg/dL *1.50 – 1.62 mmol/L*	5.50 – 5.90 mg/dL *1.38 – 1.51 mmol/L*	< 5.50 mg/dL *< 1.38 mmol/L*
Comment: Do not adjust Calcium, serum, low or Calcium, serum, high for albumin				

* Values are for term infants. Preterm infants should be assessed using local normal ranges.

† Use age and sex appropriate values (e.g., bilirubin).

DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS
VERSION 1.0, DECEMBER, 2004; CLARIFICATION AUGUST 2009

LABORATORY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Cardiac troponin I (cTnI)	NA	NA	NA	Levels consistent with myocardial infarction or unstable angina as defined by the manufacturer
Cardiac troponin T (cTnT)	NA	NA	NA	≥ 0.20 ng/mL OR Levels consistent with myocardial infarction or unstable angina as defined by the manufacturer
Cholesterol (fasting)				
Adult ≥ 18 years	200 – 239 mg/dL *5.18 – 6.19 mmol/L*	240 – 300 mg/dL *6.20 – 7.77 mmol/L*	> 300 mg/dL *> 7.77 mmol/L*	NA
Pediatric < 18 years	170 – 199 mg/dL *4.40 – 5.15 mmol/L*	200 – 300 mg/dL *5.16 – 7.77 mmol/L*	> 300 mg/dL *> 7.77 mmol/L*	NA
Creatine Kinase	3.0 – 5.9 x ULN†	6.0 – 9.9 x ULN†	10.0 – 19.9 x ULN†	≥ 20.0 x ULN†
Creatinine	1.1 – 1.3 x ULN†	1.4 – 1.8 x ULN†	1.9 – 3.4 x ULN†	≥ 3.5 x ULN†

LABORATORY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Glucose, serum, high				
Nonfasting	116 – 160 mg/dL *6.44 – 8.88 mmol/L*	161 – 250 mg/dL *8.89 – 13.88 mmol/L*	251 – 500 mg/dL *13.89 – 27.75 mmol/L*	> 500 mg/dL *> 27.75 mmol/L*
Fasting	110 – 125 mg/dL *6.11 – 6.94 mmol/L*	126 – 250 mg/dL *6.95 – 13.88 mmol/L*	251 – 500 mg/dL *13.89 – 27.75 mmol/L*	> 500 mg/dL *> 27.75 mmol/L*
Glucose, serum, low				
Adult and Pediatric ≥ 1 month	55 – 64 mg/dL *3.05 – 3.55 mmol/L*	40 – 54 mg/dL *2.22 – 3.06 mmol/L*	30 – 39 mg/dL *1.67 – 2.23 mmol/L*	< 30 mg/dL *< 1.67 mmol/L*
Infant*†, < 1 month	50 – 54 mg/dL *2.78 – 3.00 mmol/L*	40 – 49 mg/dL *2.22 – 2.77 mmol/L*	30 – 39 mg/dL *1.67 – 2.21 mmol/L*	< 30 mg/dL *< 1.67 mmol/L*
Lactate	ULN - < 2.0 x ULN without acidosis	≥ 2.0 x ULN without acidosis	Increased lactate with pH < 7.3 without life-threatening consequences	Increased lactate with pH < 7.3 with life-threatening consequences

* Values are for term infants. Preterm infants should be assessed using local normal ranges.

† Use age and sex appropriate values (e.g., bilirubin).

Comment: Added ULN to Grade 1 parameter					
LDL cholesterol (fasting)					
	Adult ≥ 18 years	130 – 159 mg/dL *3.37 – 4.12 mmol/L*	160 – 190 mg/dL *4.13 – 4.90 mmol/L*	≥ 190 mg/dL *≥ 4.91 mmol/L*	NA
	Pediatric > 2 - < 18 years	110 – 129 mg/dL *2.85 – 3.34 mmol/L*	130 – 189 mg/dL *3.35 – 4.90 mmol/L*	≥ 190 mg/dL *≥ 4.91 mmol/L*	NA
Lipase		1.1 – 1.5 x ULN	1.6 – 3.0 x ULN	3.1 – 5.0 x ULN	> 5.0 x ULN
Magnesium, serum, low		1.2 – 1.4 mEq/L *0.60 – 0.70 mmol/L*	0.9 – 1.1 mEq/L *0.45 – 0.59 mmol/L*	0.6 – 0.8 mEq/L *0.30 – 0.44 mmol/L*	< 0.60 mEq/L *< 0.30 mmol/L*
Pancreatic amylase		1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.1 – 5.0 x ULN	> 5.0 x ULN
Phosphate, serum, low					
	Adult and Pediatric > 14 years	2.5 mg/dL – < LLN *0.81 mmol/L – < LLN*	2.0 – 2.4 mg/dL *0.65 – 0.80 mmol/L*	1.0 – 1.9 mg/dL *0.32 – 0.64 mmol/L*	< 1.00 mg/dL *< 0.32 mmol/L*
	Pediatric 1 year – 14 years	3.0 – 3.5 mg/dL *0.97 – 1.13 mmol/L*	2.5 – 2.9 mg/dL *0.81 – 0.96 mmol/L*	1.5 – 2.4 mg/dL *0.48 – 0.80 mmol/L*	< 1.50 mg/dL *< 0.48 mmol/L*
	Pediatric < 1 year	3.5 – 4.5 mg/dL *1.13 – 1.45 mmol/L*	2.5 – 3.4 mg/dL *0.81 – 1.12 mmol/L*	1.5 – 2.4 mg/dL *0.48 – 0.80 mmol/L*	< 1.50 mg/dL *< 0.48 mmol/L*
Potassium, serum, high		5.6 – 6.0 mEq/L *5.6 – 6.0 mmol/L*	6.1 – 6.5 mEq/L *6.1 – 6.5 mmol/L*	6.6 – 7.0 mEq/L *6.6 – 7.0 mmol/L*	> 7.0 mEq/L *> 7.0 mmol/L*
Potassium, serum, low		3.0 – 3.4 mEq/L *3.0 – 3.4 mmol/L*	2.5 – 2.9 mEq/L *2.5 – 2.9 mmol/L*	2.0 – 2.4 mEq/L *2.0 – 2.4 mmol/L*	< 2.0 mEq/L *< 2.0 mmol/L*
Sodium, serum, high		146 – 150 mEq/L *146 – 150 mmol/L*	151 – 154 mEq/L *151 – 154 mmol/L*	155 – 159 mEq/L *155 – 159 mmol/L*	≥ 160 mEq/L *≥ 160 mmol/L*
Sodium, serum, low		130 – 135 mEq/L *130 – 135 mmol/L*	125 – 129 mEq/L *125 – 129 mmol/L*	121 – 124 mEq/L *121 – 124 mmol/L*	≤ 120 mEq/L *≤ 120 mmol/L*
Triglycerides (fasting)		NA	500 – 750 mg/dL *5.65 – 8.48 mmol/L*	751 – 1,200 mg/dL *8.49 – 13.56 mmol/L*	> 1,200 mg/dL *> 13.56 mmol/L*

* Values are for term infants. Preterm infants should be assessed using local normal ranges.

† Use age and sex appropriate values (e.g., bilirubin).

LABORATORY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Uric acid	7.5 – 10.0 mg/dL *0.45 – 0.59 mmol/L*	10.1 – 12.0 mg/dL *0.60 – 0.71 mmol/L*	12.1 – 15.0 mg/dL *0.72 – 0.89 mmol/L*	> 15.0 mg/dL *> 0.89 mmol/L*
URINALYSIS	***Standard International Units are listed in italics***			
Hematuria (microscopic)	6 – 10 RBC/HPF	> 10 RBC/HPF	Gross, with or without clots OR with RBC casts	Transfusion indicated
Proteinuria, random collection	1 +	2 – 3 +	4 +	NA
Proteinuria, 24 hour collection				
Adult and Pediatric ≥ 10 years	200 – 999 mg/24 h *0.200 – 0.999 g/d*	1,000 – 1,999 mg/24 h *1.000 – 1.999 g/d*	2,000 – 3,500 mg/24 h *2.000 – 3.500 g/d*	> 3,500 mg/24 h *> 3.500 g/d*
Pediatric > 3 mo - < 10 years	201 – 499 mg/m^2/24 h *0.201 – 0.499 g/d*	500 – 799 mg/m^2/24 h *0.500 – 0.799 g/d*	800 – 1,000 mg/m^2/24 h *0.800 – 1.000 g/d*	> 1,000 mg/ m^2/24 h *> 1.000 g/d*

* Values are for term infants. Preterm infants should be assessed using local normal ranges.

† Use age and sex appropriate values (e.g., bilirubin).