BioCryst Pharmaceuticals, Inc.

CLINICAL STUDY PROTOCOL

Protocol No. BCX1812-305

IND No. 69,038

A PHASE 3, RANDOMIZED, OPEN LABEL, ACTIVE-CONTROLLED STUDY TO EVALUATE THE SAFETY, PHARMACOKINETICS AND EFFECTIVENESS OF IV PERAMIVIR COMPARED TO ORAL OSELTAMIVIR IN PEDIATRIC SUBJECTS WITH ACUTE UNCOMPLICATED INFLUENZA

Original Protocol, Version 1.0: 05 November 2014

Amendment 1, Version 2.0: 01 December 2014

Amendment 2, Version 3.0: 21 June 2015

Amendment 3, Version 4.0: 20 October 2016

Amendment 4, Version 5.0: 10 January 2017

Amendment 5, Version 6.0: 05 November 2018

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1. TITLE PAGE

Protocol Number:	BCX1812-305
Study Title:	A Phase 3, randomized, open label, active-controlled study to evaluate the safety, pharmacokinetics and effectiveness of IV peramivir compared to oral oseltamivir in pediatric subjects with acute uncomplicated influenza
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) 919-859-7905 Fax: (+1) 919-851-1416 Email Address: mm@biocryst.com
Principal Investigator:	John A. Vanchiere, M.D., Ph.D. Chief, Pediatric Infectious Diseases Louisiana State University Health Sciences Center - Shreveport
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 6.0: 05 November 2018

1.1. Protocol Approval Signature Page

Protocol No.	BCX1812-305
Protocol Title:	A Phase 3, randomized, open label, active-controlled study to evaluate the safety, pharmacokinetics and effectiveness of IV peramivir compared to oral oseltamivir in pediatric subjects with acute uncomplicated influenza
Version Date:	Version 6.0: 05 November 2018

BioCryst Pharmaceuticals, Inc.

Reviewed and Approved by:

for 12 NOV 2018

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

Date

12 NOV 2018

Elliott Berger, PhD
Senior Vice President, Regulatory Affairs

Date

1.2. Clinical Study Protocol Agreement

Protocol No.	BCX1812-305
Protocol Title:	A Phase 3, randomized, open label, active-controlled study to evaluate the safety, pharmacokinetics and effectiveness of IV peramivir compared to oral oseltamivir in pediatric subjects with acute uncomplicated influenza
Version Date:	Version 6.0: 05 November 2018

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:
Peramivir

Title of Study:
A Phase 3, randomized, open label, active-controlled study to evaluate the safety, pharmacokinetics and effectiveness of IV peramivir compared to oral oseltamivir in pediatric subjects with acute uncomplicated influenza.

Study Center(s): Multi-center

Principal Investigator:
John A. Vanchiere, M.D., Ph.D.
Chief, Pediatric Infectious Diseases
Louisiana State University Health Sciences Center - Shreveport

Studied Period (years):	**Phase of Development:**
Estimated date first subject enrolled: December 2014 Estimated date last subject completed: September 2020	3

Objectives:

Primary:

- To evaluate the safety of intravenous (IV) peramivir (study drug) compared to oral oseltamivir in pediatric subjects with acute uncomplicated influenza.

Secondary:

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

Methodology:

Subjects meeting the inclusion/exclusion criteria may be enrolled into the study. It is expected that most subjects will have the Screening/Baseline visit and the Day 1 treatment visit on the same day.

A subject's duration of participation in this study is expected to be 14 days.

Subjects ≥ 7 years old will be randomized to 1 of 2 treatment arms:

Treatment Group 1: A single dose of intravenous peramivir

Treatment Group 2: Oral oseltamivir given twice daily (BID) for 5 days

(Note: at the date of amendment 3, the dose cohorts for subjects > 7 years old were fully enrolled and no further subjects > 7 years will be enrolled).

Subjects < 7 years old will receive a single dose of intravenous peramivir.

(Note: at the date of amendment 3, the dose cohort for subjects 2-7 years old was partially enrolled under the previous randomization scheme that allocated subjects to peramivir or oseltamivir. Following FDA feedback, remaining subjects to be enrolled in the 2 to <7 years old cohort, the 28 day to < 2 years old cohort, and the birth to < 28-day cohort, will all be assigned to receive treatment with IV peramivir.

Following treatment on study Day 1, subjects will undergo follow-up assessments on Days 3, 7, and 14. The Day 3 visit may be a home visit (performed by a qualified study nurse). Day 7 is required to take place in the clinic, and Day 14 may either be a clinic visit, home visit, or follow-up phone call to the subject/parent/guardian.

All parents/caregivers will record the following information in the Subject Diary:

- Temperature measurements (oral or axillary) will be taken with an electronic thermometer provided by BioCryst, approximately every 12 hours until temperature normalizes for 48 hours (i.e., temperature without antipyretic is < 99.4 orally in children ≥ 6 and < 98.4 axillary in children < 6 years old for 4 measurements).With the exception of the 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.
- Date and time of oral oseltamivir dose administration, if applicable. This should be recorded in the Subject Diary twice a day for 5 days.
- Doses of antipyretic medication and any medications taken for symptomatic relief, each day through the last follow-up assessment.
- The ability of the child or adolescent to return to day care/school and/or resume their normal “pre-illness” daily activity.
- The child or adolescent’s appetite and eating patterns assessed as normal or reduced/abnormal.

All parents/caregivers of subjects 7 years of age and older will record the following additional information in the Subject Diary:

- Assessment of 7 influenza symptoms [cough, sore throat, nasal obstruction, myalgia (muscle aches), headache, feverishness, and fatigue] on a 4-point severity scale (0, absent; 1, mild; 2, moderate; 3, severe) twice daily, beginning pre-dose on Day 1 until symptom resolution or through the last follow-up visit, (whichever comes first).

All parents/caregivers of subjects ≥ 4 years of age to ≤ 6 years of age will record the following additional information in the Subject Diary:

- Assessment of 7 influenza symptoms [cough, sore throat, nasal obstruction, headache, feverishness, fatigue/malaise, and gastrointestinal symptoms (nausea, vomiting or diarrhea)] on a 4-point severity scale (0, absent; 1, mild; 2, moderate; 3, severe) twice daily until symptom resolution or through the last follow-up visit, (whichever comes

first).

All parents/caregivers of subjects ≤ 3 years of age will record the following additional information in the Subject Diary:

- Assessment of 5 influenza symptoms [cough, rhinitis, feverishness, malaise alternating with irritability and gastrointestinal symptoms (nausea, vomiting or diarrhea)] on a 4-point severity scale (0, absent; 1, mild; 2, moderate; 3, severe) twice daily, beginning pre-dose on Day 1 until symptom resolution or through the last follow-up visit, (whichever comes first).

An adequate nasal swab specimen will be collected from all enrolled subjects at Baseline (pre-dose) for virus sub-type identification and quantitative virologic assessments and at the follow-up assessments on study Days 3, 7, and where possible on 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 4 blood samples will be drawn, where possible, during the following time periods, beginning from the end of dosing until release from the site:

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

Note: Subjects ≥ 5 kg will have four 1.0 mL blood draws at the above stated sampling times. Subjects < 5 kg will have two 1.0 mL blood samples; one time immediately following completion of the infusion and one time between 1-3 hours post-infusion. Adverse events and concomitant medications will be monitored at each scheduled visit from the Screening/Baseline assessment to final study visit. Clinical laboratory investigations (chemistries, hematology, and urinalysis) will be collected at Baseline and at the Day 7 visit. 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.

Number of subjects (planned):

Up to 140 subjects will be enrolled in this study according to the following age groups:

- Birth to < 28 days: up to 10 subjects will receive IV peramivir
- 28 days - < 2 years: up to 20 subjects: subjects enrolled after the approval of amendment 3 will receive, IV peramivir
- 2 <4 years: up to 10 subjects: subjects enrolled after the approval of amendment 3 will receive IV peramivir

- 4 - < 7 years:up to 30 subjects: subjects enrolled after the approval of amendment 3 will receive IV peramivir
- 7 - < 13 years:up to 40 subjects, randomized 4:1 to IV peramivir or oral oseltamivir
- 13 - < 18 years:up to 30 subjects, randomized 4:1 to IV peramivir or oral oseltamivir

Criteria for inclusion:

Inclusion criteria:

1. Male and non-pregnant female subjects age birth to 17 years of age.
2. Clinical signs and symptoms consistent with acute influenza infection consisting of an oral temperature ≥ 100°F (37.8°C) or rectal temperature ≥ 101.3ºF (≥ 38.5ºC) with at least one respiratory symptom (cough or rhinitis) OR a positive influenza rapid antigen test. Fever will either be documented at the time of screening or must be reported by the parent or care-giver if treatment with an antipyretic was given within 6 hours of the screening assessment. **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. During the period of approval, clinical symptoms alone will be adequate to meet criteria 2.**
3. Onset of symptoms no more than 72 hours before presentation for screening for subjects < 2 years old.
4. Written informed consent by parents/guardians and assent by subjects ≥ 7 years of age (or as applicable by local IRB or state requirements).
5. Females who have started their menses must either be:
   - Sexually abstinent
   - Using a highly effective form of birth control such as hormone contraception (oral, patch, injection, implant or vaginal ring) or 2 barrier methods (condom with spermicide and diaphragm)

Exclusion Criteria:

1. Age > 17 years.
2. If less than 3 months of age at screening, history of premature birth (< 36 weeks 0 days gestation)
3. Weight less than 3.0 kg
4. Receipt of a live attenuated influenza vaccine (LAIV) within 14 days of presentation.
5. Females who are pregnant (positive urine or serum pregnancy test) or breast-feeding at screening.
6. Onset of symptoms more than 72 hours before presentation for screening for subjects <2 years old.
7. Development of symptoms while hospitalized for another indication
8. Subjects with identified risk factors for influenza complications but with uncomplicated influenza at the time of enrollment are not excluded. This includes lung disease, heart disease, blood disorders such as sickle cell anemia, metabolic disorders and neurologic disease. In addition, mild to moderate immunocompromised status such as due to renal disease, diabetes mellitus or HIV infection with a last known CD4+ count ≥200 cells/µl are not excluded.
9. Presence of severe immunocompromised status due to chronic disease or illness, previous organ transplant, or use of immunosuppressive medical therapy which would include oral or systemic treatment with > 10 mg prednisone or equivalent on a daily basis within 30 days of screening.
10. Complicated influenza characterized by any of the following:
    a. ICU care
    b. Evidence of organ dysfunction
    c. Proven or suspected concomitant bacterial infection
    d. Other known concomitant viral infection that is likely to complicate medical course such as RSV, parainfluenza virus and adenovirus. Co-infection with rhinovirus and enterovirus is allowed.
11. Previous participation in Study BCX1812-305 or participation in a study of any investigational drug or device within the last 30 days.
12. Subjects who cannot comply with all aspects of the study protocol.

Investigational product, dosage and mode of administration:

Subjects assigned to receive peramivir, will receive an age-appropriate single dose of peramivir, diluted appropriately in normal saline, administered as a short intravenous infusion over a minimum of 15 minutes.

- Subjects ≥ 13 years will receive a dose of 600 mg.
- Subjects ≥ 6 months to ≤ 12 years will receive a dose of 12mg/kg (to a maximum dose of 600 mg).
- Subjects < 6 months will receive a dose of 8mg/kg.

Reference therapy, dosage and mode of administration:

Subjects randomized to oral oseltamivir will receive an age appropriate dose twice daily for 5 days.

- Subjects ≥ 13 years will receive a 75mg dose administered as a capsule or oral suspension (twice daily for 5 days).
- Subjects 28 days to < 13 years of age will receive a weight-based dose administered as a capsule or oral suspension (twice daily for 5 days).

Note, as of the approval of amendment 3, no additional subjects will be randomized to receive oseltamivir.

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. A review and summary of safety utilizing all collected assessments will be performed by a Data Safety Monitoring Committee (DSMC) after each influenza season as outlined in the DSMC charter.

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 pharmacokinetic parameters.

Effectiveness:

- **Clinical:** Time to resolution of fever; time to resolution of influenza symptoms (per the age appropriate symptoms);
- **Virologic:** Viral shedding; virus susceptibility.

Statistical methods:

Sample Size:

The study is designed to evaluate the safety and pharmacokinetics of IV administration of peramivir in pediatric subjects with influenza. The sample size is adequate to evaluate these objectives. Descriptive comparison between peramivir and oseltamivir treated subjects will be performed where possible. 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 pharmacokinetic parameters in each age group and to identify pharmacokinetically-relevant covariates. Data from the completed pediatric study 0918T0633 of IV peramivir in Japan will be included in this analysis.

Effectiveness:

Clinical and virologic endpoints will be summarized using descriptive statistics.

3. TABLE OF CONTENTS AND LIST OF TABLES

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4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or Specialist Term	Explanation
AAP	American Academy of Pediatrics
ACIP	The Advisory Committee on Immunization Practices
ADL	Activities of Daily Living
AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
AUC	Area Under the Plasma Concentration-Time Curve
BID	Twice Daily
CBC	Complete Blood Count
CDC	US Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CI	Confidence Intervals
CL_{CRRT}	CRRT Clearance
CPK	Creatine Phosphokinase
CrCl	Creatinine Clearance
CRF	Case Report Form
CRRT	Continuous Renal Replacement Therapy
DAIDS	Division of Acquired Immune Deficiency Syndrome
DSMC	Data Safety Monitoring Committee
EIND	Emergency Investigational New Drug
ESRD	End Stage Renal Disease
EUA	Emergency Use Authorization
FDA	US Food and Drug Administration
GCP	Good Clinical Practice
HA	Hemagglutinin
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ICU	Intensive Care Unit

Abbreviation or Specialist Term	Explanation
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
MedDRA	Medical Dictionary for Regulatory Activities
NA	Neuraminidase
NAI	Neuraminidase Inhibitor
NP	Nucleoprotein
NS1	Non-Structural Protein 1
OSE	Oseltamivir Phosphate
OSE-C	Oseltamivir Carboxylate
PA, PB1, PB2	Viral RNA Polymerase Complex
PCR	Polymerase Chain Reaction
PK	Pharmacokinetics
QD	Once Daily
RAT	Rapid Antigen Test
RT-PCR	Reverse Transcriptase Polymerase Chain Reaction
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SCUF	Slow Continuous Ultrafiltration
SD	Standard Deviation
$TCID_{50}$	Tissue Culture Infectious Dose 50%
TEAE	Treatment-Emergent Adverse Event
US	United States
USP	United States Pharmacopeia
WHO	World Health Organization
ZNR	Zanamivir

5. INTRODUCTION

5.1. Influenza Overview

Influenza virus is a member of the orthomyxovirus family and causes an acute viral disease of the respiratory tract. Typical influenza illness is characterized by abrupt onset of fever, headache, myalgia, sore throat, and nonproductive cough (Cox and Subbarao 1999); a significant minority of patients also experience gastrointestinal symptoms of nausea, vomiting, and diarrhea (Novel Swine-Origin Influenza, Dawood et al. 2009). Acute uncomplicated influenza is characterized bronchoscopically by diffuse inflammation and edema of the larynx, trachea, and bronchi; mucosal biopsies show lymphocytic and histiocytic inflammatory infiltrate and desquamation (Walsh, Dietlein et al. 1961).

While the highest morbidity and mortality occurs in the elderly, the highest rate of infection occurs in children (Fiore, Timothy et al. 2012). In healthy adults and children, the illness 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. 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 to influenza in children.

Children are subject to a high burden of influenza related disease. Despite the US Centers for Disease Control and Prevention (CDC's) recommendation that all children 6 months and older get vaccinated against seasonal influenza, in the 2012- 2013 influenza season only 57% of children 6 months to 17 years received vaccination. Coverage was highest in infants and toddlers 6 months to 23 months at 77%, but declined progressively in each subsequent age group. Only 43% of 13-17 adolescents received vaccination (CDC 2013).

Because testing for influenza is not uniformly performed and there are other viruses that can cause lower respiratory tract disease, namely respiratory syncytial virus and parainfluenza virus, it is difficult to know how many children are infected yearly. A population-based surveillance study in cohorts of children ≤ 5 years across 3 counties in the United States (US) over the 2004-2009 influenza seasons was performed, capturing the time period when vaccine recommendations were expanded down to infants 6 months and older (Poehling, Edwards et al. 2013). It was estimated that the rate of hospitalization for influenza was 0.4-1.0 per 1000 children ≤ 5 years. Confirmed influenza infection in the outpatient setting was present in

8-17% of enrolled children who presented for a visit. The rate was somewhat higher in children seen in the emergency department (12%) than in an outpatient clinic (10%). Influenza A was the predominant pathogen causing 70% of influenza infections. Less than half of the infected children had been immunized.

In Europe, a review of the literature from 1970 to 2011 determined that the incidence of influenza was 6.2% in infants ≤ 1 year and 16.7% in all children ≤ 13 years. The rate of hospitalization for influenza was similar to Poehling's US estimate with varying rates among different European countries ranging from 1.5% (for children < 2 years), 0.7% (2-5 years), and 0.4% (6-13 years) in Italy to 0.8% (< 3 years), 0% (3-6 years), and 0% (7-13 years) in Finland (Antonova, Rycroft et al. 2012). Globally, in 2008, about 90 million new cases of influenza and 20 million episodes of influenza-associated acute lower respiratory tract infection occurred worldwide in children aged 0-4 years. That year, estimated deaths worldwide from influenza in children were 28,000 to 111,500 (Nair, Brooks et al. 2011).

Medical resources are highly utilized by children with influenza, due to both initial visits and subsequent complications. Complications of influenza are common, including pharyngitis, otitis media and febrile seizures. While rates vary, some studies have found that almost half of all infections result in bacterial superinfections or seizures (Antonova, Rycroft et al. 2012). In addition, children miss time from school and parents lose time from work. An estimated 1 to 6 days of work are lost by parents caring for children ill with an influenza episode (Neuzil, Hohlbein et al. 2002, Heikkinen, Silvennoinen et al. 2004, Antonova, Rycroft et al. 2012).

During pandemic years, the incidence of influenza increases and may affect children more than older patients. More severe illness and young adult age distribution are consistent features of pandemic influenza, and are linked to more severe lower respiratory tract involvement. Influenza viral pneumonia is more frequent in pandemics (Oseasohn, Adelson et al. 1959, Rello and Pop-Vicas 2009) compared to seasonal epidemics, and more common in children and young adults compared to older patients, most likely related to lack of specific immunity to the newly circulating pandemic strain in those age groups. During the 2009-2010 H1N1 pandemic, 4 times the average number of US children died compared to the previous 5 influenza seasons, rising from an average 82 annually to 344 (Garg, Fry et al. 2012).

Despite increased vaccination efforts and expanded vaccination recommendations, seasonal and pandemic influenza remain significant causes of morbidity and mortality in children, particularly in those less than 2 years of age and those with comorbidities.

5.2. Antiviral therapy for influenza

Two classes of influenza antiviral agents are currently approved in the United States: adamantanes and neuraminidase inhibitors (NAIs). Adamantane antivirals include amantadine, which is approved to treat influenza in adults and children ≥ 1 year old and rimantadine, approved to treat influenza in adults and children ≥ 13 year old. The neuraminidase inhibitors include oseltamivir, which is currently approved for adults and children ≥ 2 weeks of age and zanamivir, an inhaled product, which is approved for adults and children down to age 7.

5.2.1. Treatment in adults

Adamantanes, including amantadine and rimantadine, 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 can reduce the severity and shorten the duration of acute uncomplicated influenza A illness among healthy adults. 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 CDC for treatment of influenza (CDC 2014).

Neuraminidase inhibitors are a newer class of drugs with activity against both influenza A and influenza B viruses. Approved neuraminidase inhibitors include zanamivir (ZNR), administered by inhalation, and oseltamivir phosphate (OSE), an oral prodrug of the active agent, oseltamivir carboxylate (OSE-C). Neither product is specifically approved for use in hospitalized influenza, although oseltamivir is used frequently in both hospitalized adults and children. 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 and children.

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 OSE 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 OSE and ZNR (Jefferson, Jones et al. 2009) and a more recent review focused on OSE (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 OSE 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.

5.2.2. Treatment in children

Adamantane antivirals, although approved for use in children ≥ 1 year old (amantadine) and ≥ 13 year old (rimantadine) are not recommended for either treatment or prophylaxis due to widespread resistance and lack of activity against influenza B. Zanamivir is approved for treatment of influenza in children ≥ 7 years old but is not recommended in those with an underlying respiratory disease such as asthma because of the inhaled route of administration. Oseltamivir is approved for use in infants as young as 2 weeks of age for the treatment of influenza.

Prior to the 2009-2010 pandemic, fewer than 1% of children with influenza were treated with antiviral agents. Even among children hospitalized for influenza, only 2% to 37% (Garg, Fry et al. 2012, Poehling, Edwards et al. 2013) received an antiviral agent. During the pandemic, treatment rates increased markedly and 74% of hospitalized children were treated (Garg, Fry et al. 2012). At the time of the pandemic, OSE was approved for children aged ≥ 1 year and ZNR was approved for children aged ≥ 7 years. Subsequently, in 2012, OSE received approval for use in infants as young as 2 weeks old (Tamiflu® package insert, 2012). It is not clear if these increased rates of treatment have been maintained since the pandemic.

Recommendations regarding the use of antiviral agents were broadened after the H1N1 pandemic. The Advisory Committee on Immunization Practices (ACIP) produced guidelines in 2011 for the use of antiviral agents in influenza. ACIP recommended that antiviral therapy (NAIs but not adamantanes) be initiated as soon as possible for any patients with confirmed or suspected influenza with high severity, hospitalization or risk of complications. Use of antiviral therapy in the outpatient setting when risk factors were not present was left to clinical judgment as long as therapy could be initiated within 48 hours (Fiore, Fry et al. 2011).

The most recent American Academy of Pediatrics (AAP) (Pediatrics 2008) guidelines for the 2013-2014 influenza season are similar to and complement the ACIP's recommendations. The AAP reiterates that oseltamivir remains the drug of choice, simply because zanamivir is difficult to administer in children. Any child hospitalized or at increased risk of complications (see

Section 5.3.1) should receive antiviral therapy, even if influenza is only suspected but not proven and even if the patients present later than 48 hours after onset of symptoms. While the AAP acknowledges that most patients with uncomplicated influenza do not require treatment due to the self-limited nature of the infection, treatment should be offered to any child who would benefit from a decrease in duration of the clinical symptoms (Brady, Byington et al. 2013).

Just as with adults, the use of antiviral therapy (primarily OSE) in children has been demonstrated to shorten disease duration, improve complications, and reduce hospital stays. The length of illness is significantly reduced by 1.25 to 1.5 days in health children with confirmed influenza. Complications, particularly otitis media in children less than 5 year of age, are reduced with NAI therapy by 44-85%. Not surprisingly, the use of antibiotics is also reduced when NAIs are initiated promptly (Garg, Fry et al. 2012). In children hospitalized with influenza, if OSE was started within 24 hours of admission, length of stay was reduced by 18%. Intensive care unit (ICU) stay, mortality during hospitalization and readmission within 1 week of discharge were not statistically significantly different in OSE-treated and untreated subjects, which indicates that further study is needed regarding optimal inpatient treatment of children with influenza (Coffin, Leckerman et al. 2011).

5.2.3. Current need

Although OSE, an oral neuraminidase inhibitor pro-drug administered twice daily for 5 days, is widely used for the treatment of influenza, a need still exists for an effective treatment for adult and pediatric influenza patients who present in the urgent care, emergency department and in the hospital who may not be able to tolerate an oral or inhaled product, or where compliance with a 5-day treatment regimen is a concern. Such patients may include those who cannot comply with oral medications, those with poor history of compliance with oral medicines, those with gastrointestinal symptoms such as vomiting and diarrhea associated with influenza that could impair absorption of orally administered drugs, and those with gastrointestinal diseases that could impair drug absorption.

5.3. Previous Experience with Peramivir

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 intravenous doses of peramivir in healthy adult subjects (Study BCX1812-106) demonstrated that intravenous peramivir at a therapeutic dose of 600 mg and at a supratherapeutic dose of 1200 mg was not associated with QTc prolongation or other repolarization abnormalities.

During the 2009 H1N1 pandemic, before the peramivir Emergency Use Authorization (EUA) was issued by the US FDA, BioCryst was providing peramivir to subjects under emergency investigational new drug (EIND) regulations, by request from US physicians. Ultimately, 31 patients received peramivir of which 11 were children. The youngest patient was a 3-month-old girl who was critically ill with influenza, requiring mechanical ventilation and ultimately extra corporeal membrane oxygenation (ECMO). She also went into renal failure and required

continuous veno-venous hemofiltration. It was noted that cardiac contractility markedly improved with peramivir treatment and she ultimately recovered. There were 2 young children treated, a 5-year-old boy and an 8 year old boy, both of whom died. The 5 year old had been hospitalized for 16 days prior to initiation of 10 days of peramivir. He was receiving ECMO and was comatose with heart failure. The patient died on hospital Day 34 when medical support was withdrawn. The 8-year-old boy had numerous underlying medical problems including Noonan syndrome with congenital heart disease and pulmonary hypertension. He had a cardiac arrest at the time of hospitalization and was on ECMO when peramivir was initiated on hospital Day 10. His respiratory status improved on hospital Day 14 but due to severe cerebral ischemia, the family withdrew medical support and he died on hospital Day 35.

There were 8 children aged 10-17 treated under the EIND. A 13 year old boy with a history of asthma died despite improvement in respiratory and hemodynamic parameters after peramivir treatment. A 14-year-old girl with asthma and chronic renal failure also died. The 6 other patients recovered although they all had respiratory failure and were on mechanical ventilation or ECMO, 5 were receiving vasopressor support, and 2 had renal failure. Therapeutic drug monitoring was completed on some of these subjects and the exposure with the 10 mg/kg daily dose was similar to those of adults receiving 600 mg/day (Hernandez, Adiga et al. 2011). Similar to the Japanese pediatric and adolescent experience, no unique safety concerns were identified in this series.

During the 2009 pandemic, the US FDA also issued an Emergency Use Authorization (EUA) for IV peramivir to treat suspected or confirmed 2009 H1N1 influenza virus infection (Sorbello, Jones et al. 2012). Peramivir was provided in response to over 1300 requests, including for children and adolescents. While data are not available on the number of critically ill children treated under the EUA, FDA received adverse event reports on 28 pediatric patients < 18 years.

In addition to clinical trial experience and emergency use experience, peramivir has been approved in Japan for use in children ≥ 28 days old infected with influenza with over 1,000,000 patient exposures, which includes a large proportion of children. A pediatric post-approval observational safety and effectiveness surveillance study was carried out in Japan between October 2010 and February 2012 in a routine pediatric setting and evaluated patients < 15 years of age. A total of 1,254 patients were evaluated at 173 institutions in Japan. This study is described more fully in Section 5.3.3.

5.3.1. Clinical experience in adults

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.

Two additional outpatient studies in adults occurred. Study 0815T0631 was a double-blind, double-dummy study of 1099 subjects from Japan, Taiwan and South Korea who were randomized to receive a single dose of IV peramivir (300 mg or 600 mg) or 5 days of oral OSE BID. For the primary endpoint of time to alleviation of symptoms, both peramivir treatment regimens were non-inferior to OSE. Study 0816T0632 was a double-blind, non-controlled study in high-risk patients with influenza; in this study, 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.

Hospitalized influenza was studied in BCX1812-201, a randomized, double-blind, trial of treatment with OSE 75 mg twice daily for 5 days, or IV peramivir 200 mg once daily, or 400 mg once daily. The study enrolled 122 evaluable subjects and employed an exploratory primary endpoint of "time to clinical stability." Compared to oral OSE given for 5 days, IV doses of peramivir 200 mg and 400 mg had similar effects on the novel exploratory endpoint. Among the secondary endpoints, the median time to resumption of ability to perform usual activities was approximately 4 days shorter for subjects treated with either dose of peramivir compared with OSE. Viral titers decreased rapidly among patients with influenza A after treatment with either OSE 75 mg twice daily or peramivir 200 mg or 400 mg daily. Among subjects with influenza B, numerical trends suggest more rapid reduction in viral titer with peramivir than OSE and greater activity of peramivir 400 mg than peramivir 200 mg.

During the 2009-2010 pandemic, BCX1812-303, an open-label Phase 3 study of peramivir 300 mg BID or 600 mg once daily (QD) enrolled 230 evaluable adult and 4 evaluable adolescent hospitalized subjects with confirmed or suspected influenza infection. The primary endpoint was the reduction in influenza virus titer measured by $\log_{10}$50% tissue culture infective dose ($TCID_{50}$). There were no differences in either the mean or median values in the 300 mg BID or 600 mg QD treatment groups. By 48 hours after the beginning of peramivir treatment, 86% of all subjects with positive baseline titers in the intent to treat infected (ITTI)population had a negative virus titer (80% in the 300 mg BID group and 91% in the 600 mg QD group, as measured by $\log_{10}$ $TCID_{50}$.

BCX1812-301, a Phase 3, multicenter, randomized, double-blind, controlled-study of peramivir evaluated the efficacy and safety of peramivir administered IV in addition to standard of care compared to standard of care alone in subjects who were hospitalized due to influenza. The study failed to demonstrate a significant difference between treatment with placebo and standard of care and treatment with peramivir (600 mg IV, daily for 5 or 10 days) and standard of care for the primary endpoint of time to clinical resolution. A futility analysis was performed, and the study was terminated early at which point 338 evaluable (i.e. ITTI) subjects were enrolled (116 randomized to placebo and 222 randomized to peramivir).

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 rates overall were similar to placebo and OSE. No safety signals have emerged from these trials.

The safety of various doses of peramivir in hospitalized influenza has been evaluated in 355 adults in studies with active or placebo control (BCX1812-201 and 301) and 230 adults in an open label study with 2 different peramivir dosing regimens (BCX1812-303). The hospitalized population was comprised of acutely ill subject; many critically ill infected with both pandemic and seasonal influenza strains. Overall, peramivir had a favorable safety profile. In controlled trials, the most common adverse events in patients receiving various doses of peramivir with and without other NAIs were diarrhea (6.8%), nausea (4.8%), and insomnia (3.9%).The only events reported in ≥ 2% of subjects treated with peramivir 600 mg monotherapy (no additional NAI) and for which the rate was greater than placebo were constipation (4.0% vs. placebo 2.0%), elevated creatine phosphokinase (CPK) (4.0% vs. placebo 0%), insomnia (3.0% vs. 0%), aspartate aminotransferase (AST) increase (3.0% vs. placebo 2.0%), hypertension (2.0 vs. placebo 0%) and hypokalemia (1.0% vs. placebo 0%).

In the open label trial, subjects in both arms receive a total daily dose of 600 mg peramivir (or equivalent in those subjects with renal function adjusted dosing). This trial ran from October 2009 to October 2010 and enrolled primarily subjects infected with pandemic H1N1 virus (74% of the ITTI population). A total of 10% of all subjects in the Safety population died. Nearly half of all deaths were related to respiratory failure reflecting the severity of the pandemic. Most adverse events were attributable to the underlying infection and comorbidities and no clinically relevant differences in safety outcomes were noted between the two dosing regimens. The most common adverse events were constipation (13.0%), diarrhea (12.6%), hypokalemia (9.6%), anemia (7.8%), hypotension (7.8%), nausea (7.8%), peripheral edema (7.8%), insomnia (7.4%) hyperglycemia (6.1%) hypertension (6.1%) and headache (5.2%).

5.3.2. Clinical experience in children

There have been 3 clinical trials that enrolled children. Study 0918T0633 was an open label study in acute uncomplicated influenza. In addition, there were 2 studies in hospitalized influenza that enrolled children, BCX1812-303 and BCX1812-301.

5.3.2.1. Study 0918T0633

Study 0918T0633 was a Japanese non-controlled, open-label study conducted in pediatric subjects with influenza (either inpatient or outpatient) that ran from September 2009 to December 2009. A total of 117 subjects, aged ≥ 28 days to < 16 years, were enrolled of which the ITTI analysis set was 112. The study excluded children with significant comorbidities such as encephalopathy, epilepsy, chronic respiratory disorders, congestive heart failure, immunosuppression and renal failure. Subjects were treated with peramivir 10 mg/kg (maximum dose 600 mg) IV for up to 5 days. This dose was believed to provide children with an adult equivalent of 300 to 600 mg peramivir a day. Two subjects received 2 doses, and the rest received a single infusion. The primary endpoint was the median time to alleviation of influenza defined as mild to no cough or nasal discharge and normal body temperature. Overall the median time was 27.9 hours (95% CI 21.7-31.7) with no differences 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. Normal temperature of < 37.5°C was recovered in a median time of 20.4 hours (95% CI 19.1-20.9). If all influenza symptoms, including cough, sore throat, headache, nasal discharge, fever, myalgia/arthralgia and fatigue were taken into consideration, the median time to alleviation of symptoms was 30.5 hours (95% CI 22.6-45.8) with sore throat taking the longest to resolve. The median time to resuming activities of daily living (ADLs) was 103.0 hours (95% CI 94.9 hours- 119.6 hours) and ranged from 54.7 hours to 126.8 hours in the consecutive age brackets.

Adverse events were experienced by 62.4% of subjects. In the various age brackets (28 days to < 2 years, 2 to < 6 years, 6 to < 12 years, and 12 to < 16 years of age) the incidence for AEs ranged from 54.1 to 75% and tended to be higher for patients under 12 years. No deaths occurred but 2 subjects experienced serious adverse events (SAEs): influenzal pneumonia in one and pneumonia and encephalopathy in the other. Both children recovered. Most AEs were mild to moderate (79.5%). Overall, the most frequent TEAEs were decreased neutrophil count (21.4%), diarrhea (16.2%), vomiting (9.4%), and increased eosinophil count (7.7%). Of note, there were 3 subjects (2.6%) who experienced abnormal behavior.

5.3.2.2. BCX1812-303

BCX1812-303 was initiated in October 2009 at the request of the FDA due to the 2009 H1N1 pandemic. Originally allowing children ≥ 12 year old to enroll, by December 2009 the protocol was amended to allow children as young as 6 to enroll and receive 10 mg/kg day either in a single or divided dose. Although at the time there was no clinical data on treating children with peramivir, the juvenile animal toxicology studies and the experience with the EIND in which 11 children, one as young as 3 months old, received peramivir indicated that peramivir was generally safe and well tolerated in children. Four adolescents were enrolled; all aged 14-16 years of age. Only 1 subject, a 14-year-old American Indian/Alaskan native girl, was positive for influenza (2009 H1N1 strain) and she was randomized to 5 mg/kg (195 mg) twice a day for 5 days. Her time to clinical resolution was 28.8 hours (study mean was 92 hours) and her time-weighted changes from Baseline in $\log_{10}$ $TCID_{50}$ at 48 hours was similar to the overall mean and median (-1.51). Her only AEs occurred at follow-up when she developed a mild upper lip lesion on study Day 11 and a mild decrease in body temperature on study Day 13. Both events were assessed as unlikely related to peramivir and both events resolved.

Three subjects were found to be negative for influenza. A 16-year-old Asian girl received 5 days of peramivir 5 mg/kg (300 mg) bid and experienced no AEs. A 15-year-old Hispanic boy received 5 days of 10 mg/kg (600 mg) daily and had no AEs. A 14-year-old white girl had septic shock at baseline and required vasopressor support. She received 5 mg/kg (260 mg) BID for 2 days. Once her influenza results were noted to be negative, her parents withdrew consent and she discontinued the study. Her only AE was moderate sedation assessed as unlikely related to peramivir but due to the use of sedative drugs.

5.3.2.3. BCX1812-301

BCX1812-301 was initiated in November 2009 as a randomized, double-blind, controlled study to evaluate the efficacy and safety of peramivir administered intravenously in addition to standard of care compared to standard of care alone in subjects who are hospitalized due to influenza. Originally allowing children ≥ 12 year old to enroll, by August 2010 the protocol was amended to allow children as young as 6 to be randomized to placebo or 10 mg/kg/day of peramivir for those ≥ 12 to < 18 years and 12 mg/kg/day for those ≥ 6 to < 12 years. Overall there were 4 children 6-11 years old and 11 adolescents 12-17 years old who enrolled. Of these children, 9 were randomized to peramivir (2 children and 7 adolescents). One of these subjects withdrew consent prior to receiving any peramivir and 1 withdrew consent on study Day 2 at the time of hospital discharge. Of the 8 subjects who received peramivir, all were influenza positive: 5 tested positive for H2N2 and 3 had the 2009 H1N1 strain. All received OSE from the time of hospital admission as a part of the standard of care, except for 1 subject, a 14 year old boy with a history of asthma and epilepsy who received peramivir monotherapy for the first 5 days but did not meet the protocol defined criteria for clinical resolution. He received another 5 days of peramivir and also initiated OSE BID for 5 days on study Day 5.

The overall time to clinical resolution in the pediatric population treated with peramivir 10 mg/kg/day was a mean of 39.6 hours (range 7.9 to 85.2 hours) and time to alleviation of clinical symptoms of influenza was a mean of 81.5 hours (range 38.0 to 121.8). Time to hospital discharge, a tertiary endpoint, was a mean of 4.5 days (range 2.0-10.0 days). Although the study did not meet its overall primary endpoint and was terminated after a futility analysis, these means compare favorably to the overall results of 53.9 hours mean time to clinical resolution, 81.3 hours mean time to alleviation of clinical symptoms and 5.3 days mean time to hospital discharge.

Only 2 of the pediatric subjects experienced AEs. A 17 year old boy developed mild phlebitis on study Day 3 that was assessed by the Investigator as possibly related. He recovered in 1 day without sequelae. The other subject was a 16 year old boy who developed mild nausea and mild gastritis on study Day 6. The nausea resolved the same day and the gastritis resolved on study Day 12. He also experienced cystitis on study Days 10-14 and laryngitis on study Days 10 to 28. None of the events were assessed as related to peramivir and all the events resolved.

5.3.3. Post marketing experience in children

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. Since that time 3 post marketing surveillance studies

have been performed, including one exclusively enrolling pediatric patients. The other 2 studies (one in routine use and one in high risk patients) allowed enrollment of subjects ≥ 15 years old and any age child respectively.

The pediatric post-approval observational safety and effectiveness surveillance study was carried out between October 2010 and February 2012 in a routine pediatric setting and evaluated patients < 15 years of age. A total of 1,254 patients were evaluated at 173 institutions in Japan. The safety evaluable population was 1,199 and the efficacy evaluable population was 1186. Most patients (79.4%) had type A influenza and 13.2% of the patients were considered high risk.

There were 654 (54.5%) male and 545 (45.5%) female patients in the safety evaluable group. Fifty-four patients (4.5%) were < 1 year of age, including 1 patient who was < 4 weeks of age. Forty-four percent of the patients (527) were ≥ 1 to < 7 years of age, and 51.4% (616 patients) were ≥ 7 to < 15 years of age. A special safety analysis compared patients < 2 years of age and those ≥ 2 years of age, and found that there were no significant differences in the incidence of AEs or the types of AEs in infants and toddlers versus older children.

Almost all patients (1008, 84.1%) received peramivir within 1 day of the start of influenza symptoms. Most patients were treated in an outpatient setting, but 138 (11.5%) were hospitalized for influenza, and 11 patients had serious influenza, defined as either influenza encephalopathy or the need for mechanical ventilation. Almost all patients (96.7%) received only 1 day of treatment with peramivir.

A total of 92 patients experienced 115 AEs deemed related to peramivir by the prescribing physicians. There were no fatal AEs reported. Fourteen of the AEs were serious including 5 SAEs of abnormal behavior, 5 SAEs of neutropenia (2 severe), and individual SAEs of loss of consciousness, erythema multiforme, rash, and peripheral edema. The events of erythema multiforme occurred in a child with ocular pruritus prior to peramivir treatment. After treatment with peramivir, a rash developed on his face, neck, hands, and buttocks. He was treated with an anti-allergy medication but symptoms worsened 2 days after receiving peramivir, and the patient was diagnosed with exudative erythema multiforme. The event resolved with topical steroids and anti-allergy medication in 4 days.

Most of the AEs (87.0%) occurred within 3 days after the start of treatment with peramivir. Almost all AEs recovered or improved (93.9%), the rest had unknown outcomes. The AE durations were brief, with 80.9% resolving or improving within 3 days of onset. The most common AEs were diarrhea (2.5%), abnormal behavior (2.3%), vomiting (0.7%), and nausea (0.7%). Over half of the events of abnormal behavior occurred in children with either high risk factors or complication of influenza such as seizures or bacterial infections. There were no noticeable differences in AE incidence between the various pediatric age ranges. The sole enrolled newborn (< 4 weeks of age) did not experience any AEs. Patients aged ≥ 4 weeks to < 1 year had a 9.4% incidence of AEs; those ≥ 1 to < 7 years of age had a 7.2% incidence of AEs; and children ≥ 7 to < 15 years of age had an 8.0% incidence of AEs.

The reported adverse events were similar to events seen during development. There was a lower incidence of adverse events and no individual events were reported at an incidence greater than that during development. No new safety signals were found as a result of this post-approval safety surveillance study.

Effectiveness was assessed by time to alleviation of symptoms, which represented the day when all 7 symptoms of influenza (cough, sore throat, headache, nasal congestion, fever, achiness, and fatigue) were reported as none or mild. The median time to alleviation of symptoms was 3 days. The median time to resolution of fever was also 3 days. Since the assessment of symptoms and temperature was done only once daily, the actual time to resolution may have been less than reported.

In the routine use post-approval observational safety and effectiveness surveillance study, the safety set included 69 children < 15 years old. The AE incidence was 7.3% compared to the adult population's rate of 4.1%, However, there were only 6 AEs reports in total; diarrhea (3 events), vomiting, insomnia, and urticaria. The median time to alleviation of symptoms (same definition as used in the pediatric post-approval study) was 3 days and the median time to resolution of fever was 2 days. Overall, the adverse events and effectiveness measure was similar to previous investigations. There were no new safety signals found as a result of this post-approval study of routine peramivir use.

In the high risk post-approval observational safety and effectiveness surveillance study there were 181 children < 15 years old evaluated of which 26 were < 2 years old. All the children had high-risk co-morbidities. Overall, the incidence of AEs was 7.2% in children < 15 years old. The median time to alleviation of symptoms was 3.0 days and the median time to resolution of fever was also 3.0 days. Patients ≥ 15 to < 65 years old had an AE incidence of 15.2% and those ≥ 65 years old had an incidence of 14.0%. The pediatric effectiveness measures were identical to both the adult (15 to < 65 years old) and elderly (≥ 65 years old) populations.

Children < 2 years of age had additional analyses. The only AE in a child < 2 years of age was a SAE of neutropenia occurring in a low-birth weight infant with a history of neonatal asphyxia and intracranial hemorrhage with resultant hydrocephalus who developed a neutrophil count of 636/μL 3 days after receiving peramivir. The event resolved 2 months later without treatment. The median time to alleviation of symptoms was 3.5 days and the median time to resolution of fever was 2.0 days in this subgroup of children < 2 years of age. Overall, the adverse events and effectiveness outcomes were similar to previous investigations, despite this being a high risk population. There were no new safety signals found as a result of this post-approval study of peramivir use in high-risk patients.

5.4. Rationale for Study

There remains a significant unmet need for influenza therapies in children. Currently, the only available options are oral or inhalation, both of which have limitations, both in terms of administration and viral resistance. Peramivir has demonstrated efficacy and safety when used in acute uncomplicated influenza in adults. However, there is significant clinical and real world experience with pediatric use indicating that there is both efficacy and safety when used in healthy and high-risk children as young as 28 days. Most children treated to date have been Asian, so the current study will provide valuable information in other racial and ethnic groups.

Because children bear a larger burden of infection during seasonal influenza and are at greater risk for complications during pandemics, new treatments for children are needed. During the last pandemic of 2009-2010, the rates of hospitalization, admission to intensive care units, and invasive life support were higher than for past seasonal influenza with the highest proportion of seriously ill patients being children and young adults (Dominguez-Cherit, Lapinsky et al. 2009,

Jain, Kamimoto et al. 2009, WHO 2009). The approved dose of peramivir in adults is a single dose of 600 mg because of improved efficacy without an increase in safety risk. Population pharmacokinetic modeling performed by the FDA (July 2009) based on the Shionogi Studies 0816T0633 (children and adolescents) and 0722T0621 (adults) supports a target dose of 12 mg/kg/day in children (6 to 12 years) to attain exposures similar to that in adults who receive a 600 mg IV dose.

In order to provide recommendations for dosing in subjects less than 6 months of age, an updated population PK model was developed that included all available data from adult and pediatric studies, and data from an interim review of BCX1812-305. Simulations from this model indicate that a dose of 8 mg/kg/day in children from birth to < 6 months of age should provide exposure of peramivir similar to that observed in adult subjects and pediatric subjects who have completed BCX1812-305. In subjects 6 month of age and older, a 12 mg/kg dose is simulated to attain exposures in pediatric subjects similar to that in adults administered a 600 mg IV dose. Simulations indicate that in subjects < 6 months of age, the predicted exposure following an 8 mg/kg dose will not exceed that of adults.

There is ample clinical and real world experience with peramivir. A large number of children have been treated in post-marketing without new safety signals arising, other than those already identified with other NAIs. Events of abnormal behavior have been reported occurring primarily in children and the elderly, often in those with underlying neurologic conditions. In addition, very rare hypersensitivity reactions including, anaphylaxis, erythema multiforme and Stevens-Johnson Syndrome have occurred in the post-marketing setting, although as with all NAIs, it is difficult to know if this is due to concomitant medications, the viral infection, or the NAI. Many studies have reported benefits of NAIs in shortening complications, hospital stays and antibiotic use. Overall it is expected that the benefit risk ratio of peramivir will be favorable in children.

6. TRIAL OBJECTIVES AND PURPOSE

6.1. Primary objective

- To evaluate the safety of IV peramivir compared to oral oseltamivir in pediatric subjects with acute uncomplicated influenza (here within referred to as influenza)

6.2. Secondary Objectives

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

7. INVESTIGATIONAL PLAN

7.1. Endpoints

7.1.1. Primary Endpoint

The primary endpoints of this study will be assessment of adverse events, laboratory analyses (clinical chemistry, hematology and urinalysis), vital signs and physical examinations.

7.1.2. Secondary Endpoints

- Pharmacokinetic analyses.
- Change (reduction) in influenza virus titer by $\log_{10}$ tissue culture infective $dose_{50}$/mL ($TCID_{50}$/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.
- Change in viral sensitivity to the following antiviral drugs: peramivir, oseltamivir, zanamivir.

7.2. Overall Study Design and Plan

This is a multi-center, open label active-controlled study to evaluate the safety, pharmacokinetics and effectiveness of IV peramivir in children.

Up to 140 subjects will be enrolled in this study according to the following age groups:

- Birth to < 28 days: up to 10 subjects will receive IV peramivir
- 28 days - < 2 years: up to 20 subjects: subjects enrolled after the approval of amendment 3 will receive IV peramivir
- 2 – <4 years: up to 10 subjects: subjects enrolled after the approval of amendment 3 will receive IV peramivir
- 4 - < 7 years:up to 30 subjects: subjects enrolled after the approval of amendment 3 will receive IV peramivir
- 7 - < 13 years:up to 40 subjects, randomized 4:1 to IV peramivir or oral oseltamivir
- 13 - < 18 years:up to 30 subjects, randomized 4:1 to IV peramivir or oral oseltamivir

Once an age cohort is filled, enrollment in that cohort will be closed and communicated with all investigators.

A subject's duration of participation in this study is expected to be 14 days.

All subjects will receive either a single dose of IV peramivir (600 mg IV for subjects ≥ 13 years, 12 mg/kg IV for subjects ≥ 6 months - ≤ 12 years, 8 mg/kg for subjects < 6 months IV) or oral oseltamivir, dosed BID for 5 days.

Note, as of the date of amendment 3, no additional subjects will be randomized to receive oseltamivir.

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

7.3. Study Measurements and Visit Schedule

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

Table 1: Study Measurements and Visit Schedule

Assessments	Screening[1]	Baseline[1] Pre-Dose	Day 1[1] Post-Dose	Day 3[2]	Day 7 (+ 2 days)	Day 14[2] (+3 days)	Early Withdrawal[3]
Informed Consent/Assent	X						
Inclusion/Exclusion Criteria	X						
Pregnancy Test (Urine)[4]	X				X		X
Medical History	X						
Body Temperature[5]	X	X	X	X	X	X	X
Physical Exam		X					
Influenza Related Complications (IRC)[6]		X		X	X	X	X
Vital Signs[7]		X		X	X	X	X
Concomitant Medications Review[8]	X	X	X	X	X	X	X
Clinical Chemistries and Hematology[9]		X			X	X[17]	X[17]
Urinalysis[9]		X			X	X[17]	X[17]
Assessment of influenza symptoms/ activities of daily living/ eating habits[10]		X	X	X	X	X	X
Subject Diary Completion/ Review[11]		X	X	X	X	X	X
Nasal swabs for Virology Analysis[12]		X		X	X	X	X
Study Drug Administration[13]		X					
Serum sample for influenza antibody analysis[14]		X			X		
Pharmacokinetic (PK) Sampling[15]			X				
Adverse Events			X	X	X	X[16]	X[16]

1 It is expected that the date of Screening, Baseline, and Day 1 (date of study drug administration) will be the same.
2 The Day 3 visit may be performed as a clinic visit or home visit (conducted by a qualified study nurse). The Day 14 visit may be performed as a home visit, clinic visit, or phone call. In the event the Day 14 assessment is a phone call the parent/ caregiver will be requested to mail the completed diary card back to the site.
3 An Early Withdrawal assessment should be conducted for subjects who withdraw before Day 7. For subjects who withdraw between Day 7 and Day 14 a telephone assessment should be completed, where possible.
4 Urine pregnancy test will be performed for any female post-menarche.

5 The screening temperature may be performed per the site's standard method, which will be recorded. For subsequent visits, the parent/guardian will record oral or axillary temperature with the electronic thermometer provided by BioCryst, Thereafter, the parent/caregiver will record temperature in the Subject Diary approximately every 12 hours until temperature is normal for 48 hours without antipyretic.
6 If an IRC is suspected, then a targeted physical examination and if needed, diagnostic testing will be conducted to record the actual presence/absence of the IRC.
7 Vital sign measures will include blood pressure (in children <2 only if clinically indicated), pulse rate, and respiration rate. Vital signs will be recorded at Baseline, and vital signs will be taken once on remaining study visit days.
8 Antipyretic medications will be recorded in the Subject Diary by the parent/caregiver daily from Day 1 through Day 14.
9 Clinical laboratory assessments performed at Baseline are for the purpose of establishing a baseline. Subjects may be enrolled and begin treatment with study drug prior to receiving results.
10 The severity of age appropriate influenza signs and symptoms will be recorded by the parent/caregiver in the Subject Diary twice daily, until all symptoms are resolved (Grade 0). Assessments of activities of daily living and eating habits will be recorded once daily until all symptoms are resolved.
11 On Day 1, the parents/caregivers of subjects and/or adolescent subjects are to be provided training by the study staff on completing the Subject Diary. Instructions will be reviewed with the adolescent subject or parent/caregiver at each study visit.
12 Swabs for virology analysis will be collected on Day 14 where possible.
13 Only for those subjects randomized to peramivir. The parents/caregivers of subjects randomized to the oral oseltamivir arm of the study, will record the date and time of each drug administration, from Day 1 until Day 5 (or last scheduled dose). The first dosing will be administered at the site and documented by the study staff following completion of required predose activities.
14 A single serum specimen will be collected, where possible, pre-dose on Day 1 and on Day 7 for analysis of influenza antibody titers. Subjects whose weight is < 10kg do not require a serum antibody sample.
15 Only for those subjects randomized to peramivir. A PK sample will be drawn immediately following the end of study drug infusion/administration, between 30 minutes to 1 hour post-infusion, between 1 and 3 hours post-infusion, and between 3 and 6 hours post-infusion. Note: Subjects ≥ 5 kg will have four 1.0 mL blood draws at the above stated sampling times. Subjects < 5 kg will have two 1.0 mL blood samples; one time immediately following completion of the infusion and one time between 1-3 hours post-infusion.
16 Any subject with unresolved moderate or severe intensity influenza symptoms or an unresolved AE and/or treatment-emergent laboratory finding that requires further medical management may be evaluated in further follow-up visits, at the Investigator's discretion.
17 If previous lab results are abnormal and considered clinically significant by the Investigator or significantly changed from baseline, blood specimen collection for clinical chemistry or clinical hematology tests as specified in Sections 11.2.1 and 11.2.2 may be drawn. If previous urinalysis lab results are abnormal and considered clinically significant by the Investigator or significantly changed from baseline, a urine collection for urinalysis may be completed.

8. SELECTION AND WITHDRAWAL OF SUBJECTS

8.1. Subject Inclusion Criteria

1. Male and non-pregnant female subjects age birth to 17 years of age.
2. Clinical signs and symptoms consistent with acute influenza infection consisting of an oral temperature ≥ 100°F (37.8°C) or rectal temperature ≥ 101.3ºF (≥ 38.5ºC) with at least one respiratory symptom (cough or rhinitis) OR a positive influenza rapid antigen test. Fever will either be documented at the time of screening or must be reported by the parent or care-giver if treatment with an antipyretic was given within 6 hours of the screening assessment. **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. During the period of approval, clinical symptoms alone will be adequate to meet criteria 2.**
3. Onset of symptoms no more than 72 hours before presentation for screening for subjects < 2 years old .
4. Written informed consent by parents/guardians and assent by subjects ≥ 7 years of age[1,2]
5. Females who have started their menses must either be:
   - Sexually abstinent
   - Using a highly effective form of birth control such as hormone contraception (oral, patch, injection, implant or vaginal ring) or 2 barrier methods (condom with spermicide and diaphragm)

8.2. Subject Exclusion Criteria

1. Age > 17 years.
2. If less than 3 months of age at screening, history of premature birth (< 36 weeks 0 days gestation)
3. Weight less than 3.0 kg
4. Receipt of a live attenuated influenza vaccine (LAIV) within 14 days of presentation.
5. Females who are pregnant (positive urine or serum pregnancy test) or breast-feeding at screening.

[1] Where permitted by local IRB or state requirements.
[2] If age of assent is limited by local IRB or state requirements, assent must be obtained by all adolescents ≥ 14 years of age. While development varies across individual children, existing data suggest most children are capable of assent by approximately age 14. Wendler, D. S. (2006). "Assent in paediatric research: theoretical and practical considerations." J Med Ethics **32**(4): 229-234.

6. Onset of symptoms more than 72 hours before presentation for screening for subjects < 2 years old.
7. Development of influenza while hospitalized for another indication.
8. Subjects with identified risk factors for influenza complications but with uncomplicated influenza at the time of enrollment are not excluded. This includes lung disease, heart disease, blood disorders such as sickle cell anemia, metabolic disorders and neurologic disease. In addition, mild to moderate immunocompromised status such as due to renal disease, diabetes mellitus or HIV infection with a last known CD4+ count ≥200 cells/µl are not excluded
9. Presence of severe immunocompromised status due to chronic disease or illness, previous organ transplant, or use of immunosuppressive medical therapy which would include oral or systemic treatment with > 10 mg prednisone or equivalent on a daily basis within 30 days of screening.
10. Complicated influenza characterized by any of the following:
    a. ICU care
    b. Evidence of organ dysfunction
    c. Proven or suspected concomitant bacterial infection
    d. Other known concomitant viral infection that is likely to complicate medical course such as RSV, parainfluenza virus and adenovirus. Co-infection with rhinovirus and enterovirus is allowed.

    As a note, hospitalization is not an exclusion criterion when it is the usual practice of the treating institution to hospitalize children with influenza. However, the subject must have acute uncomplicated influenza.
11. Previous participation in Study BCX1812-305 or participation in a study of any investigational drug or device within the last 30 days.
12. Subjects who cannot comply with all aspects of the study protocol.

8.3. Withdrawal Criteria

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

- At their parent's/guardian's request;
- At the subject's request if ≥ 7 years old and able to give assent; in cases where a subject is < 7 years of age and expresses a wish to stop the study, the parent/caregiver and the Investigator will use their best judgments to determine what is in the best interest for the child in question;
- 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, although study drug may be stopped, 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. If a subject's participation in this study is terminated, the responsible Investigator at the site will complete a termination form.

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 7 Visit. For subjects who withdraw between Day 7 and Day 14, a telephone assessment should be conducted, where possible.

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

In Study 0816T0633 conducted by Shionogi & Co. Ltd in Japan, 117 pediatric and adolescent patients with type A or type B influenza infection who were ≥ 28 days but < 16 years of age, were treated with 1 to 5 daily doses of IV peramivir in the outpatient setting. The dose of peramivir used in that study (10 mg/kg of body weight to a maximum of 600 mg) was based on pharmacokinetic modeling and target area under the plasma concentration-time curve (AUC). Peramivir, administered IV, was generally safe and well tolerated in this population. Plasma concentrations from the pediatric patients in this study were found to be within the range of plasma concentrations following administration of peramivir at 300 mg or 600 mg in adult patients with influenza, and did not exceed mean plasma concentrations following administration at 800 mg in healthy adults.

The approved dose of peramivir in adults is a single dose of 600 mg. Population pharmacokinetic modeling performed by the FDA (July 2010) based on the Shionogi Studies 0816T0633 (children and adolescents) and 0722T0621 (adults) supports a target dose of 12 mg/kg in children (≤ 12 years) to attain exposures similar to that in adults who receive a 600 mg IV dose. Children 13 and over can be treated with 600 mg/day, the adult dose. Per CDC, the average weight of a 13-year-old boy and girl are 45 kg (99 lbs) and 46 kg (101 lbs) respectively. In adult trials of peramivir in acute uncomplicated influenza, at least 30 subjects with weights between 40 kg (88 lbs) and 50 kg (110 lbs) were treated without additional risk or complication. In addition, peramivir elimination is almost exclusively renal. Renal size reaches adult at age 12 and function (i.e., glomerular filtration rate) reaches that of an adult by age 2. The population PK model built using interim PK data from BCX1812-305 included a renal maturation factor to account for the development of renal function prior to age 2. Simulations support a dose of 8 mg/kg from birth to less than 6 months of age, and 12 mg/kg in subjects 6 months of age and older. Subjects < 6 months of age are not predicted to have higher exposure of peramivir than that of adults.

9.2. Treatments Administered

9.2.1. Peramivir

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 temperatures up to 30°C.

Subjects < 6 months of age at time of consent will receive a single dose of IV peramivir at a dose of 8 mg/kg. Subjects ≥ 6 months - ≤ 12 years of age at time of consent will receive a single dose of IV peramivir at a dose of 12 mg/kg (up to a maximum dose of 600 mg). Subjects ≥ 13 years of age will receive a single dose of 600 mg IV peramivir administered as a short IV infusion over a minimum of 15 minutes. Peramivir must be diluted in normal saline normal saline United States Pharmacopeia (SUP).:

Because of the risk of vasovagal reactions, particularly in children with needle phobia, it is recommended that subjects be in a supine position during peramivir administration. Appropriate post infusion observation should be performed.

9.2.2. Oseltamivir

Oseltamivir will be provided by the site's pharmacy as capsules or powder for oral suspension and prepared and used according to the manufacturer's instructions. Subjects will be dosed according to Table 2 below:

Table 2: Oseltamivir dose regimen by age

Age	Dose regimen
≥ 13 years	75 mg BID for 5 days. Dose may be given as capsules or an oral suspension may be used by patients who cannot swallow a capsule.
7-12 years	Weight based dosing: ≤ 15 kg 30 mg BID for 5 days 15.1 – 23 kg 45 mg BID for 5 days 23.1 – 40 kg 60 mg BID for 5 days > 40 kg 75 mg BID for 5 days Dose may be given as capsules or an oral suspension may be used by subjects who cannot swallow a capsule.

9.3. Randomization and Blinding/ Masking

Subjects ≥ 7 to 17 years of age will be randomized to 1 of 2 treatment arms, at a ratio of 4:1:

Treatment Group 1: A single dose of IV peramivir

Treatment Group 2: Oral oseltamivir given BID for 5 days

Following approval of amendment 3, all subjects < 7 years old will receive a single dose of intravenous peramivir.

As this is an open label study, blinding is not applicable.

9.4. Study Medication Preparation and Administration

9.4.1. Peramivir

The Principal Investigator at each study center will designate a pharmacist (or other qualified study staff member) to prepare IV peramivir as described in a separate study Pharmacy Manual.

Prior to infusion, an appropriate amount of the peramivir 10 mg/mL stock solution will be diluted in saline using aseptic techniques with a maximum volume of 100 mL. Once prepared, solutions of peramivir in saline should be refrigerated and infused within 24 hours of preparation.

In children ≥ 12 months, the total peramivir dose should be diluted to a total volume of 100 mL. For children < 12 months, the following dilution should be followed:

Table 3: Peramivir Dilution for Children < 12 Months of Age

Age		Dosing			
		Anticipated Approximate Volume of Undiluted Drug Product	Volume of Diluted Drug Product Infused	Total mEq of Na Infused	Number of Vials Per Dose
0 - < 28 days (3 kg to 5.5 kg)	Dilute dose to 12 mL total	2.4 to 4.4 mL	12 mL	1.5 to 1.2	1
28 days to < 3 months (3 kg to 7.5 kg)	Dilute dose to 20 mL total	2.4 to 6.0 mL	20 mL	2.7 to 2.2	1
3 months to < 6 months (4.5 kg to 11.2 kg)	Dilute dose to 25 mL total	3.6 to 4.7 mL	25 mL	3.3 to 3.1	1
6 months to < 12 months (4.5 kg to 11.2 kg)	Dilute dose to 25 mL total	7.2 to 13.4 mL	25 mL	2.7 to 1.8	1

The study drug should be given as soon as possible after enrollment and randomization on Day 1. The calendar date and 24-hour clock time (start and end of the IV infusion) will be recorded. If the intravenous line used to administer peramivir is also to be used to administer any other medications, it should be flushed with at least 5 mL of saline before and after peramivir administration. Peramivir should not be piggy-backed to any other medication being administered.

9.4.2. Oseltamivir

Oseltamivir will be prepared and administered in accordance with the manufacturer's instructions.

9.5. 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.

The first dose of oral oseltamivir will be administered in capsule or oral solution form at the site by study staff or other qualified personnel. Details of the first and all subsequent doses (administered at home by the subject/parent/guardian) will be recorded in the Subject Diary. Details will include the date and time of drug administration.

9.6. 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.

9.7. 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.

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

9.8. Concomitant Medications

Administration of a concomitant medication during the study period must be recorded within the subject's medical records. This includes prescription medications as well as over-the-counter medications.

Medications used for the symptomatic treatment of influenza-related symptoms will be discouraged for children 2-5 years of age as per American Academy of Pediatrics guidance and the January 2008 FDA public health advisory. Parents/caregivers will be requested to follow package labeling for over-the-counter cold and influenza symptom relief medications for children 2-5. The use of symptomatic medication will be prohibited in children < 2 years of age. Antipyretics will be permitted in all age groups. Parents/caregivers will record the date, time, and dose of symptomatic medications and antipyretics in the Subject Diary. All other concomitant medications will be transcribed from the source onto the Case Report Form (CRF) by study staff.

Use of concomitant medications will be assessed and recorded at Screening/ Baseline, and daily throughout the duration of the study through the study follow-up visit.

9.8.1. Medications for Chronic Diseases/Conditions

Subjects with chronic medical conditions may continue to receive prescribed treatments during participation in this protocol. The exception is high dose steroids > 10 mg/day (see exclusion criteria, Section 8.2).

9.8.2. Antivirals

There are no known adverse interactions of peramivir with other influenza antivirals (such as oseltamivir, zanamivir, amantadine, and rimantadine); however, their concomitant use is not permitted during administration of study drug and in the post-treatment follow-up period.

9.8.3. Corticosteroids

Corticosteroids at dose < 10 mg a day are allowed during administration of the study drug and throughout study participation.

9.8.4. Antipyretics and Analgesics

Resolution of fever is a major component of some of the clinical effectiveness endpoints 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 dosages of these medications will be recorded in the Subject Diary. To avoid the confounding effects of antipyretic medications, temperature measurements, including those recorded by study staff while in the emergency department or clinic and those recorded by the subjects during the follow-up period, will be taken, whenever possible, at least 4 hours after administration of the antipyretic medication or immediately prior to administration. Following discharge from the hospital, the names and dosages of all other medications will be recorded in the Subject Diary by the parent/ care-giver.

Temperature measurements that are recorded for the purpose of analyzing effectiveness in this study < 4 hours after administration of the antipyretic medication, regardless of the dose, will not be counted in the effectiveness analyses.

9.8.5. Antibiotics

Oral or parenteral antibiotics may be administered, if medically indicated. If such use is a result of proven or suspected influenza-related complication, appropriate assessments should be carried out (see Section 11.4).

10. STUDY CONDUCT

10.1. Overview

Up to 140 subjects will be enrolled in this study according to the following age groups:

- Birth to < 28 days: up to 10 subjects, given IV peramivir
- 28 days to < 2 years: up to 20 subjects: subjects enrolled after the approval of amendment 3 will receive IV peramivir
- 2 - < 4 years: up to 10 subjects: subjects enrolled after the approval of amendment 3 will receive IV peramivir
- 4 - < 7 years:up to 30 subjects: subjects enrolled after the approval of amendment 3 will receive IV peramivir
- 7 - < 13 years:up to 40 subjects, randomized 4:1 to IV peramivir or oral oseltamivir
- 13 - < 18 years:up to 30 subjects, randomized 4:1 to IV peramivir or oral oseltamivir

Once an age cohort is filled, enrollment in that cohort will be closed and communicated with all investigators.

A subject's duration of participation in this study is expected to be 14 days.

Subjects meeting the inclusion/exclusion criteria may be enrolled into the study. It is expected that most subjects will have the Screening/Baseline Visit and the Day 1 Treatment Visit on the same day.

All subjects will receive either a single dose of IV peramivir (600 mg, or12 mg/kg or 8 mg/kg or depending on age) or oral oseltamivir, dosed BID for 5 days. *Note, as of the approval of amendment 3, no additional subjects will be randomized to receive oseltamivir.*

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

All parents/caregivers will record the following information in the Subject Diary.

- Temperature measurements (oral or axillary) will be taken with an electronic thermometer provided by BioCryst, approximately every 12 hours until temperature normalizes for 48 hours (i.e., temperature without antipyretic is < 99.4 orally in children ≥ 6 and < 98.4 axillary in children < 6 years old for 4 measurements). With the exception of the 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.
- Date and time of oral oseltamivir dose administration, if applicable. This should be recorded in the Subject Diary twice a day for 5 days.
- Doses of antipyretic medication and any medications taken for symptomatic relief, each day through the last follow-up assessment.

- The ability of the child or adolescent to return to day care/school and/or resume their normal "pre-illness" daily activity will be assessed once daily until the child or adolescent returns to day care/school and/or resume normal "pre-illness" daily activity.
- The child or adolescent's appetite and eating patterns assessed as normal or reduced/abnormal will be assessed once daily until they return to normal "pre-illness" level.

All parents/caregivers of subjects 7 years of age and older will record the following additional information in the Subject Diary:

- Assessment of 7 influenza symptoms (cough, sore throat, nasal obstruction, myalgia [muscle aches), headache, feverishness, and fatigue) on a 4-point severity scale (0, absent; 1, mild; 2, moderate; 3, severe) twice daily, beginning pre-dose on Day 1 until symptom resolution or through the last follow-up visit, (whichever comes first).

All parents/caregivers of subjects ≥ 4 years of age to ≤ 6 years of age will record the following additional information in the Subject Diary:

- Assessment of 7 influenza symptoms [cough, sore throat, nasal obstruction, myalgia (muscle aches), headache, feverishness, fatigue/malaise, and gastrointestinal symptoms (nausea, vomiting or diarrhea)] on a 4-point severity scale (0, absent; 1, mild; 2, moderate; 3, severe) twice daily, beginning pre-dose on Day 1 until symptom resolution or through the last follow-up visit, whichever comes first.

All parents/caregivers of subjects≤ 3 years of age will record the following additional information in the Subject Diary:

- Assessment of 5 influenza symptoms [cough, rhinitis, feverishness, malaise/irritability and gastrointestinal symptoms (nausea, vomiting or diarrhea)] on a 4-point severity scale (0, absent; 1, mild; 2, moderate; 3, severe) twice daily, beginning pre-dose on Day 1 until symptom resolution or through the last follow-up visit, (whichever comes first).

An adequate nasal swab specimen will be collected from all enrolled subjects at Baseline (pre-dose) for virus sub-type identification and quantitative virologic assessments and at the follow-up assessments on study Days 3, 7, and where possible 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 4 blood samples will be drawn, where possible, during the following time periods, beginning from the end of dosing until release from the site

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

- One time point from 1 hour to 3 hours post-infusion
- One time point from 3 hours to 6 hours post-infusion

Note: Subjects ≥ 5 kg will have four 1.0 mL PK blood draws at the above stated sampling times. Subjects < 5 kg will have two 1.0 mL blood samples; one time immediately following completion of the infusion and one time between 1-3 hours post-infusion.

Adverse events and concomitant medications will be monitored at each scheduled visit from the screening/baseline assessment to final study visit. Clinical laboratory investigations (chemistries, hematology, and urinalysis) will be collected at baseline and at the final study visit. 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.

10.2. Schedule of Assessments

10.2.1. Screening Period

The Screening Period begins at the time of consent/assent of the study subject. Subjects whose parents/guardians have provided written informed consent (and assent for subjects ≥ 7 years of age or as permitted by local IRB and state requirements) will be assigned a unique study subject number and the following screening procedures will be conducted:

- Evaluation of study eligibility requirements.
- Urine pregnancy test (females of childbearing potential only).
- Review of medical history and concomitant medications.
- Body temperature (obtained in the site's usual fashion).

Eligible subjects will be enrolled. The study pharmacist will prepare an order for study drug as defined in Section 11.4, which includes the subject's study number.

10.2.2. Treatment Period

Randomization (prior to the approval of amendment 3) 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/Baseline 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. Subjects will receive IV peramivir in a single dose or oral oseltamivir BID for five days. *Note, following the approval of amendment 3, no additional subjects will be randomized to receive oseltamivir.*

10.2.2.1. Day 1/Baseline/Pre-Dose

The following procedures/evaluations will be performed pre-dose at Baseline on Day 1:

- Body temperature just prior to study drug administration (using the study electronic thermometer via the oral or axillary method).

- Physical examination, including assessment of presence of possible influenza-related complications.
- Vital sign measurements (blood pressure (in children < 2 only if clinically indicated), heart rate, respiration rate).
- Review and recording of concomitant medications.
- 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. Subjects whose weight is < 10kg do not require a serum antibody sample.

  (Clinical laboratory specimens collected at Screening are for the purpose of establishing a baseline and the results are not required to determine subject eligibility).
- Urine sample collection for routine urinalysis.
- Determination (and recording in the Subject Diary) of the presence and severity of each of the age specific symptoms of influenza (see Section 10.1). Questions asked of subjects age 6 years and older, if possible.
- Determination [with assistance from the subject (if possible)] of the subject's ability to perform usual daily activities.
- Determination [with assistance from the subject (if possible)] of the subject's appetite and eating patterns assessed as either normal or reduced/abnormal.
- Bilateral adequate nasal swab specimen collection for viral subtyping, culture, quantitative PCR assay and susceptibility to neuraminidase inhibitors.
- Administration of the study medication (at Hour 0) and recording of the calendar date and 24-hour clock time for the start and finish of the IV infusion, if applicable. Each subject will receive peramivir, if ≤ 12 then adjusted for body weight, and oseltamivir adjusted for weight in subjects ≤ 12.

10.2.2.2. Day 1/Post-Dose

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

- For subjects randomized to peramivir: collection of up to 4 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:
  1. One time point immediately following completion of the infusion
  2. One time point from 30 minutes to 1 hours post-infusion
  3. One time point from 1 hour to 3 hours post-infusion
  4. One time point from 3 hours to 6 hours post-infusion

Note: Subjects ≥ 5 kg will have four 1.0 mL blood draws at the above stated sampling times. Subjects < 5 kg will have two 1.0 mL blood samples; one time immediately following completion of the infusion and one time between 1-3 hours post-infusion.

- Training of the parent/ caregiver and the recording of the following in the Subject Diary:
  - Subject's body temperature, obtained at approximately 12-hour intervals each day (and 4 hours from last antipyretic medication administration or immediately prior to administration).
  - Subject's ability to perform usual activities, obtained once daily.
  - Subject's appetite and eating patterns assessed as either normal or reduced/abnormal.
  - The age specific signs and symptoms of influenza (see Section 10.3.2).
- Review and recording concomitant medications.
- Recording of AEs.

10.2.2.3. Day 3

The following procedures/assessments will be performed on Day 3. The Day 3 assessment may be performed in the subject's home by a qualified study nurse, or as a clinic visit.

- Body temperature (using the study electronic thermometer via the oral or axillary method).
- Assessment of presence of possible influenza-related complications.
- Vital sign measurements (blood pressure (in children < 2 only if clinically indicated), heart rate, respiration rate).
- Review of the Subject Diary for completeness and instruction to the parent/caregiver on need to ensure complete recording of required assessments, if needed.
- Determination (and recording in the Subject Diary) of the presence and severity of each of the age specific symptoms of influenza. Questions asked of subjects age 6 years and older, if possible.
- Determination (and recording in the Subject Diary) [with assistance from the subject (if possible)] of the subject's ability to perform usual daily activities.
- Determination (and recording in the Subject Diary) of the subject's appetite and eating patterns assessed as either normal or reduced/abnormal.
- Bilateral adequate nasal swab specimen collection for viral culture and quantitative PCR assay.
- Review and recording of concomitant medications.
- Recording of AEs.

10.2.2.4. 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.

- Urine pregnancy test (females of childbearing potential only).
- Body temperature (using the study electronic thermometer via the oral or axillary method).
- 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. Subjects whose weight is < 10kg do not require a serum antibody sample.
- Urine collection for urinalysis
- Assessment of presence of possible influenza-related complications.
- Vital sign measurements (blood pressure (in children < 2 only if clinically indicated), heart rate, respiration rate).
- Review of the Subject Diary for completeness and instruction to the parent/caregiver on need to ensure complete recording of required assessments, if needed.
- Determination (and recording in the Subject Diary) of the presence and severity of each of the age appropriate symptoms of influenza. Questions asked of subjects age 6 years and older, if possible.
- Determination (and recording in the Subject Diary) [with assistance from the subject (if possible)] of the subject's ability to perform usual daily activities.
- Determination (and recording in the Subject Diary) of the subject's appetite and eating patterns assessed as either normal or reduced/abnormal
- Bilateral adequate nasal swab specimen collection for viral culture, quantitative PCR assay and susceptibility to neuraminidase inhibitors.
- Review and recording of concomitant medications.
- Recording of any AEs.

10.2.2.5. Day 14

The following procedures/assessments will be performed on Day 14 (+ 3 days). The Day 14 assessments will be performed as a clinic visit, home visit (conducted by a qualified study nurse) or, if either of these options are not possible, by phone call. If conducted by phone, the Day 14 assessments will be limited to interview assessment for the presence of possible influenza-related complications, concomitant medication use and AEs. The subject's parent/ caregiver will be asked to return the completed Subject Diary by mail.

- Body temperature (using the study electronic thermometer via the oral or axillary method).
- Assessment of presence of possible influenza-related complications.

- Vital sign measurements (blood pressure (in children < 2 only if clinically indicated), heart rate, respiration rate).
- Review of the Subject Diary for completeness.
- Determination (and recording in the Subject Diary) of the presence and severity of each of age appropriate symptoms of influenza. Question asked of subjects age 6 years and older, if possible.
- Determination (and recording in the Subject Diary) [with assistance from the subject (if possible)] of the subject's ability to perform usual daily activities.
- Determination (and recording in the Subject Diary) of the subject's appetite and eating patterns assessed as either normal or reduced/abnormal
- Bilateral adequate nasal swab specimen collection for viral culture, quantitative PCR assay and susceptibility to neuraminidase inhibitors.
- Review and recording of concomitant medications.
- Recording of any AEs.
- If previous lab results are abnormal and considered clinically significant by the Investigator or significantly changed from baseline, blood specimen collection for clinical chemistry or clinical hematology tests as specified in Sections 11.2.1 and 11.2.2 may be drawn.
- If previous lab results are abnormal and considered clinically significant by the Investigator or significantly changed from baseline, urine collection for urinalysis may be completed.

10.2.2.6. Early Withdrawal

For subjects who withdraw before the Day 7 assessment, the following procedures/assessments will be performed at an Early Withdrawal visit, where possible. Assessments will be performed as a clinic visit or home visit (conducted by a qualified study nurse). For subjects who withdraw between the Day 7 and day 14 assessments, a phone assessment will be performed, where possible. A phone assessment will be limited to interview assessment for the presence of possible influenza-related complications and AEs. The subject's parent/caregiver will be asked to return the completed Subject Diary by mail.

- Urine pregnancy test (females of childbearing potential only).
- Body temperature (using the study electronic thermometer via the oral or axillary method).
- If previous lab results are abnormal and considered clinically significant by the Investigator or significantly changed from baseline, blood specimen collection for clinical chemistry or clinical hematology tests as specified in Sections 11.2.1 and 11.2.2 may be drawn

- If previous lab results are abnormal and considered clinically significant by the Investigator or significantly changed from baseline, urine collection for urinalysis may be completed
- Assessment of presence of possible influenza-related complications.
- Vital sign measurements (blood pressure (in children < 2 only if clinically indicated), heart rate, respiration rate).
- Review of the Subject Diary for completeness.
- Determination (and recording in the Subject Diary) of the presence and severity of each of the age appropriate symptoms of influenza. Questions asked of subjects age 6 years and older, if possible.
- Determination (and recording in the Subject Diary) [with assistance from the subject (if possible)] of the subject's ability to perform usual daily activities.
- Determination (and recording in the Subject Diary) of the subject's appetite and eating patterns assessed as either normal or reduced/abnormal
- Bilateral adequate nasal swab specimen collection for viral culture, quantitative PCR assay and susceptibility to neuraminidase inhibitors.
- Review and recording of concomitant medications.
- Recording of any AEs.

10.3. Clinical assessments of Effectiveness

Effectiveness will be evaluated through assessments of body temperature, clinical symptoms of influenza, usual daily activities, appetite/eating patterns, incidence of influenza-related complications (see Section 11.4 for details), influenza virus titers, and changes in viral sensitivity to other antiviral drugs.

10.3.1. Body Temperature

Body temperature measurements will be recorded once at Screening/Baseline by the site's normal method, and then via an electronic thermometer provided by the Sponsor twice per day until temperature normalizes for 48 hours without the use of anti-pyretic medication. Acceptable means by which to record body temperature will be oral or axillary measurements. Study staff will record temperature measurements while the subject is on-site. Parents/care givers will be instructed to measure and record the subject's body temperature in the Subject Diary, using the electronic thermometer provided by the Sponsor. To avoid the confounding effects of antipyretic medications, temperature measurements will be taken, whenever possible, at least 4 hours after administration of any antipyretic medication or immediately prior to dosing. Temperature measurements that are recorded for the purpose of analyzing effectiveness in this study < 4 hours after administration of the antipyretic medication, regardless of the dose, will not be counted in the effectiveness analyses. The method of temperature measurement must be recorded.

10.3.2. Influenza Signs and Symptoms

Subjects (or parent/guardian) will be asked to provide an assessment of influenza symptoms on a 4-point severity scale (0, absent; 1, mild; 2, moderate; 3, severe) beginning pre-dose on Day 1 until symptom resolution and through the last follow-up visit, (whichever comes first). These assessments will be recorded on each day that the medical condition allows. Study staff will obtain this assessment pre-dose and post-dose on Day 1, and the subject's trained parent-guardian will then obtain it until returning to the site for the final visit. Influenza signs and symptoms vary by age. In addition, younger children may not be able to verbalize specific symptoms. Therefore, the assessment of influenza symptoms will be based on the subject's age, as follows:

- Parent/guardian of subjects birth to ≤ 3 years of age will provide/record an assessment of 5 influenza symptoms [cough, rhinitis, feverishness, malaise/irritability and gastrointestinal symptoms (nausea, vomiting or diarrhea)]
- Subjects ≥ 4 years of age to ≤ 6 years of age will be asked to provide an assessment of 7 influenza symptoms [cough, sore throat, nasal obstruction, myalgia (muscle aches), headache, feverishness, and gastrointestinal symptoms (nausea, vomiting or diarrhea)].
- Subjects 7 years of age and older will be asked to provide an assessment of 7 influenza symptoms (cough, sore throat, nasal obstruction, myalgia (muscle aches), headache, feverishness, and fatigue).

During the first visit, the study staff will instruct the parent/care giver on completing these assessments and recording responses directly into the Subject Diary. Although the parent/care giver will be recording the responses, the subject should be involved in the assessment of the symptoms.

10.3.3. Assessment of ability to perform usual daily activities

If possible, subjects or parents/care givers will be asked to provide a daily assessment of the subject's ability to perform usual daily activities using a 0-10 visual analogue scale, where 0 = Unable to perform usual activities at all, and 10 = Able to perform usual activities fully. The parent/care giver will be asked to record these assessments in the Subject Diary, with appropriate input from the subjects, once daily from Day 2 until resolution or the final follow-up assessment, whichever comes first.

10.3.4. Assessment of appetite and eating patterns

Subjects or parents/caregivers will be asked to provide a daily assessment of the subject's appetite and eating pattern as either normal or abnormal/reduced. The parent/ caregiver will be asked to record this assessment in the Subject Diary, with appropriate input from subjects, once daily from Day 2 until resolution or the final follow-up assessment, whichever comes first.

10.4. Virology Samples

Bilateral mid-nasal swab specimens will be collected for virologic analysis. Samples will be collected at Baseline, Day 3, Day 7, and, where possible, 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, laboratory analyses (clinical chemistry, hematology, and urinalysis), vital signs, and physical examinations.

11.1. 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 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 1). 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 the age appropriate symptoms 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. Likewise, a RAT for influenza is required at screening in order to determine eligibility for the study, and therefore a positive RAT is not considered an AE.

AEs are designated as “nonserious” 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 pediatric influenza is not considered an SAE and should not be reported as such. Any adverse event the 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 consents to participate 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 Appendix 1). Any adverse events not covered by the DAIDS criteria will be assessed and classified into one of three 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 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: mm@biocryst.com **and** clinicalsafety@propharmagroup.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 serious adverse event 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 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

Pregnancy is not considered an AE but any pregnancy discovered in a subject during the course of the trial must be reported to BioCryst or designee on a pregnancy report form (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). Pregnancy outcomes of miscarriage, elective termination, stillbirth or birth defect will be considered SAEs and should be reported as per 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

For any subject that is hospitalized, clinical chemistry, hematology and urinalysis samples will be analyzed by the local laboratory. Duplicate samples will not be drawn for analysis by the central laboratory.

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 Baseline and at the Day 7 follow-up assessment. Clinically significant results should be reported as AEs.

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 the Day 7 follow-up assessment. Clinically significant results should be reported as AEs.

11.2.3. Urinalysis

Routine urinalysis evaluations will include dipstick evaluations for protein, glucose, ketones, hemoglobin, and specific gravity. If indicated by dipstick results, the urine should be sent for microscopy.

Urinalysis will be conducted on urine samples obtained at Baseline, and at the Day 7 follow-up assessment. 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/Baseline and at the Day 7 follow-up assessment using a urine pregnancy test performed locally.

11.3. Vital Signs

Vital sign measurements (blood pressure (in children < 2 only if clinically indicated), heart rate, respiration rate, temperature) will be recorded once at Baseline and once at each follow-up visit.

11.4. Physical Examination and Influenza-Related Complications Assessment

The Investigator will perform a full physical examination at Baseline, including the subject's height or length and weight. At each follow-up visit, study personnel will evaluate the subject for the presence of clinical signs and/or symptoms of the following influenza-related complications: sinusitis, otitis media, bronchitis and pneumonia.

If the Investigator determines that the subject has (or is presumed to have) one of the influenza-related complications noted above, he/she will note that in the subject's source documents and on the influenza-related complications CRF page. Any medication used to treat the condition must also be recorded (on the concomitant medication page). The Investigator will promptly provide appropriate treatment for any suspected or proven influenza-related complication(s). Signs and symptoms associated with influenza-related complications will not be reported on the adverse event CRF page unless they meet criteria for an SAE.

11.5. Safety Oversight

Since the study is open label, a sponsor-led Data Safety Management Committee (DSMC) will oversee safety. A full review and summary of safety utilizing all collected safety assessments will occur after each influenza season. This will be described in the separate DSMC charter.

12. PHARMACOKINETIC ASSESSMENTS

For subjects randomized to peramivir, up to 4 plasma samples will be drawn for determination of drug concentration. The samples will be drawn, where possible, during the following time periods, beginning from the end of dosing:

1. One time point immediately following completion of the infusion
2. One time point from 30 minutes to 1 hours post-infusion
3. One time point from 1 hour to 3 hours post-infusion
4. One time point from 4 hours to 6 hours post-infusion

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

Note: Subjects ≥ 5 kg will have four 1.0 mL blood draws at the above stated sampling times. Subjects < 5 kg will have two 1.0 mL blood samples; one time immediately following completion of the infusion and one time between 1-3 hours post-infusion.

13. STATISTICS

Descriptive statistical methods will be used to summarize the data from this study. Data will be summarized by treatment group, age group, and study day/time, if appropriate. Unless stated otherwise, the term “descriptive statistics” refers to number of subjects (n), mean, median, standard deviation (SD), minimum, and maximum for continuous data and frequencies and percentages for categorical data. The term “treatment group” refers to treatment assignment: single dose peramivir IV or oseltamivir BID for 5 days. The term "age group" refers to the following: 0 – 28 days; 28 days - < 2 years, ≥ 2 years - < 7 years, ≥ 7 years - < 13 years, and ≥ 13 years - < 18 years. All data collected during the study will be included in data listings. Unless otherwise noted, the data will be sorted first by treatment group, age group, subject number, and then by date within each subject number.

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

13.1. Data Collection Methods

The data will be transcribed from the subjects’ source documents into the 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 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, pharmacokinetics, and effectiveness of IV administration of peramivir compared to oral oseltamivir in pediatric subjects with acute uncomplicated influenza. The sample size is not based on statistical considerations, rather a sample size of up to 140 subjects (approximately 117 randomized to peramivir) 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 RT-PCR. The ITTI population will be used for analyses of effectiveness.
- **Safety Population:** The safety population will include all subjects who received at least one dose 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 one 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 and viral subtype at Screening.

13.7.4. Missing Data

Every effort will be made to obtain required data at each scheduled visit from all subjects who have been randomized. 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 by treatment group, age group, and study day/time, if appropriate.

13.8.2. Effectiveness Analyses

Time to resolution of fever, defined as a temperature < 99.4 oral or < 98.4 axillary with no antipyretic medications taken for at least 12 hours, will be estimated for each age group and overall by treatment 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 for each age group and treatment 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. As the number and type of symptoms varies by age, the analysis of time to resolution of symptoms will not be presented as an overall 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 for each age group, treatment group and 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 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 Appendix 1). The number and percentage of subjects experiencing treatment-emergent graded toxicities will be summarized by age group and treatment group. Laboratory toxicity shifts from baseline to post-baseline assessments will be summarized by age group and treatment 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 by age group and treatment 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 Institutional Review Board (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/ parents/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 parent/caregiver prior to performing any study-related procedures. Similarly, subject assent by subjects ≥ 7 years will be obtained from each child or adolescent prior to performing any study-related procedures. If the local IRB or state requirements limit the age of assent, then assent will be obtained based on those requirements but in all cases assent will be obtained for adolescents 14 and older. Each parent/caregiver should be given both verbal and written information describing the nature and duration of the clinical study. The informed consent process should take place under conditions where the parent/caregiver has adequate time to consider the risks and benefits associated with his/her child's participation in the study. Subjects will not be screened or treated until the parent/caregiver has signed an approved informed consent form (ICF) written in a language in which the subject is fluent.

The ICF and assent form 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 and their parent/ caregiver the aims, methods, reasonably anticipated benefits, and potential hazards of the trial and any discomfort it may entail. Each parent/caregiver will be informed that they are free for their child not to participate in the trial and that they may withdraw consent for their child to participate at any time. They will be told that refusal for their child to participate in the study will not prejudice future treatment. They will also be told that their child's 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.

Parents/caregivers and 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 parent's/caregiver's dated signature. The parent/ caregiver should receive a signed and dated copy of the ICF, and, if applicable, the assent. 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 parents/caregivers of 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' parents/ care givers

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 and assent 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/authorization in writing from the appropriate individual. HIPAA authorizations are required for U.S. 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

Appendix 1: 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.).

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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.

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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.).

DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS
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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)

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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).

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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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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).

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**
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).