A PHASE II RANDOMIZED AND CONTROLLED INVESTIGATION OF SIX WEEKS OF ORAL VALGANCICLOVIR THERAPY IN INFANTS AND CHILDREN WITH CONGENITAL CYTOMEGALOVIRUS INFECTION AND HEARING LOSS

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STATEMENT OF COMPLIANCE

Each investigator must adhere to the protocol as detailed in this document. Each investigator will be responsible for enrolling only those study participants who have met protocol eligibility criteria. This trial will be conducted in compliance with the protocol, International Conference on Harmonization Good Clinical Practice E6 (ICH-GCP), and the applicable regulatory requirements, including:

- U.S. Code of Federal Regulations applicable to clinical studies (45 CFR 46 and 21 CFR including parts 50 and 56 concerning informed consent and IRB regulations, if under IND, 21 CFR 312).
- Directive 9115071EEC: The Rules Governing Medicinal Products in the European Community.
- Completion of Human Subjects Protection Training. Refer to http://grants.nih.gov/grants/guide/notice-files/NOT-OD-01-061.html; http://cme.cancer.gov/clinicaltrials/learning/humanparticipant-protections.asp

SIGNATURE PAGE

The signature below constitutes my agreement to conduct this protocol "**A Phase II Randomized and Controlled Investigation of Six Weeks of Oral Valganciclovir Therapy in Infants and Children with Congenital Cytomegalovirus Infection and Hearing Loss**" and attachments and provide the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. clinical sites. It is understood that no deviations from the protocol may be made without permission of the Sponsor.

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Signed: _____ Date: _____

Name

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Title

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LIST OF ABBREVIATIONS

ACIP	Advisory Committee for Immunization Practices
ADME	Absorption, Distribution, Metabolism and Elimination
AE	Adverse Event/Adverse Experience
AGA	Appropriate for Gestational Age
AIDS	Acquired Immunodeficiency Syndrome
ANC	Absolute Neutrophil Count
AUC	Area Under the Curve
BBB	Blood-Brain Barrier
BBU	Biostatistics and Bioinformatics Unit
BID	Twice Daily
BSER	Brainstem Evoked Response
CASG	Collaborative Antiviral Study Group
CAVH	Continuous Arterio-Venous Hemofiltration
CAVHD	Continuous Arterio-Venous Hemodialysis
CAVHDF	Continuous Arterio Venous Demodiafiltration
CDC	Centers for Disease Control
CFR	Code of Federal Regulations
CMV	Cytomegalovirus
CNS	Central Nervous System
CrCL	Creatinine Clearance
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CRO	Contract Research Organization
CROMS	Clinical Research Operations and Management Support
CRRT	Continuous Renal Replacement Therapy
CSF	Cerebrospinal Fluid
DAIDS	Division of AIDS
DCC	Data Coordinating Center
DCF	Data Collection Form
DHHS	Department of Health and Human Services
DMID	Division of Microbiology and Infectious Diseases, NIAID, NIH, DHHS
DPOAE	Distortion Product Otoacoustic Emission
DSMB	Data and Safety Monitoring Board
eCRF	Electronic Case Report Form
ESRD	End-stage Renal Disease
EUA	Emergency Use Authorization
FDA	Food and Drug Administration
FWA	Federalwide Assurance

GCP	Good Clinical Practice
GI	Gastrointestinal
GlaxoSmithKline	GSK
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ICU	Intensive Care Unit
IDE	Investigational Device Exemption
IDMS	Isotope Dilution Mass Spectrometry
IEC	Independent or Institutional Ethics Committee
IND	Investigational New Drug Application
IRB	Institutional Review Board
ISM	Independent Safety Monitor
ITT	Intent to Treat
IV	Intravenous
KG	Kilogram
MeDRA	Medical Dictionary for Regulatory Activities
MG	Milligram
MOP	Manual of Procedures
N	Number (typically refers to subjects)
N/A	Not Applicable
NCS	Not Clinically Significant
NDA	New Drug Application
NIAID	National Institute of Allergy and Infectious Diseases, NIH, DHHS
NIH	National Institutes of Health
NOAEL	No Adverse Effect Level
OAE	Otoacoustic Emissions
OCRA	Office of Clinical Research Affairs, DMID, NIAID, NIH, DHHS
OHRP	Office for Human Research Protections
OHSR	Office for Human Subjects Research
ORA	Office of Regulatory Affairs, DMID, NIAID, NIH, DHHS
PCR	Polymerase Chain Reaction
PD	Pharmacodynamic
PHI	Protected Health Information
PI	Principal Investigator
PK	Pharmacokinetics
PO	By Mouth
QA	Quality Assurance
QC	Quality Control
QD	Once Daily

RNA	Ribonucleic Acid
SAE	Serious Adverse Event/Serious Adverse Experience
SAS	Statistical Analysis Software
Scr	Serum Creatinine
SDW	Source Document Worksheet
S&DCC	Statistical and Data Coordinating Center
SMC	Safety Monitoring Committee
SNHL	Sensorineural Hearing Loss
SOP	Standard Operating Procedure
STI	Sexually Transmitted Infections
TEOAE	Transient Evoked Otoacoustic Emission
US	United States
USP	United States Pharmacopeia
VRA	Visual Reinforcement Audiometry
WHO	World Health Organization

PROTOCOL SUMMARY

Title:	A Phase II Randomized and Controlled Investigation of Six Weeks of Oral Valganciclovir Therapy in Infants and Children with Congenital Cytomegalovirus Infection and Hearing Loss
Phase:	II
Population:	Fifty-four male and female infants/toddlers 1 month through 3 years of age (up to the 4th birthday) with sensorineural hearing loss and congenital CMV infection. Up to 20% (n=10) over-enrollment is allowed to replace subjects who drop-out or who have inadequate audiology assessments. Subjects will be randomized 1:1 to Investigational drug or placebo.
Number of Sites:	17 (listed in Section 1)
Study Duration:	3.5 years from enrollment of first study subject
Subject Participation Duration:	6 months
Description of Agent or Intervention:	Investigational Drug: Valcyte (valganciclovir hydrochloride) Powder for oral solution: 16.0 mg/kg twice daily Placebo: Simple Syrup as 60-90% sucrose
Objectives:	Primary: • The primary objective is to assess whether a six week course of oral valganciclovir can stabilize the hearing of children with congenital CMV infection who present with hearing loss. This will be accomplished by evaluating changes in hearing in either ear at 6 months from baseline. Secondary: • To define the following responses as a function of systemic exposure to ganciclovir (active metabolite of valganciclovir): o CMV viral load in blood o CMV viral load in urine o CMV viral load in saliva • To define the safety and tolerability of valganciclovir in enrolled subjects. Tertiary:

- To define the pharmacokinetics of ganciclovir (metabolite) following administration of valganciclovir (prodrug) in enrolled subjects.

Outcome Measures:

Primary Endpoint:

- Change in total ear hearing assessments (improved + no change versus other) between Baseline and Study Month 6

Secondary Endpoints:

- Change in best ear hearing assessments [improved + no change (normal to normal) versus other; improved versus other; worse + no change (abnormal to abnormal) versus other; and worse versus other] between Baseline and Study Month 6
- Change in total ear hearing assessments (improved versus other; worse + no change (abnormal to abnormal) versus other; and worse versus other) between Baseline and Study Month 6
- Detection of viruria by PCR six weeks and six months after trial entry
- The quantitative log reduction in viruria detected after 6 weeks of therapy
- Detection of viremia by PCR six weeks and six months after trial entry
- The quantitative log reduction in viremia detected after 6 weeks of therapy
- Detection of CMV in saliva by PCR six weeks and six months after trial entry
- The quantitative log reduction in CMV viral load in saliva detected after 6 weeks of therapy
- Correlation of change in viral load with change in total ear and best ear hearing at 6 months
- Incidence of unanticipated medically attended visits

occurring from Study Day 1 through two weeks following the last dose of study drug

- Incidence of adverse events which lead to permanent discontinuation of valganciclovir therapy or have an unresolved outcome

Tertiary Endpoints:

- Blood concentrations of ganciclovir after administration of valganciclovir

Description of Study Design:

This is an international, multi-center, double-blind, placebo-controlled evaluation of 6 weeks of valganciclovir treatment for children (up to 4 years of age) with virologically-confirmed congenital CMV infection and hearing loss. Patients who are between 1 month and 4 years of age and who have SNHL are eligible for enrollment on the study. **Enrollment on the study occurs when eligibility is confirmed and the informed consent is signed.** Following the signing of informed consent, the subject's Guthrie card will be retrieved and tested for CMV DNA by PCR unless there is a virologically confirmed diagnosis of congenital CMV infection made within the first 30 days of life. **Randomization on the study occurs when the diagnosis of congenital CMV infection is confirmed**, and the subject then is assigned to either receive 6 weeks of oral valganciclovir or 6 weeks of placebo. Study subjects will be stratified according to age at randomization (1 through 11 months, 12 through 23 months, 24 through 35 months, and ≥ 36 months) and CMV involvement (symptomatic and asymptomatic at birth) as a marker of disease severity. The sample size of randomized, evaluable subjects is 54. Dropouts and subjects with audiology assessments that are inadequate for study comparison will be replaced (up to 20%, or n=10). Baseline study assessments (see Section 7.2) will be performed following randomization. Subjects will be followed for 6 months post randomization. During the six week treatment period, study subjects will be followed every 2 weeks. Subjects will also be seen at approximately one month following the final dose (Study Day 70), and again at Study Months 4 and 6.

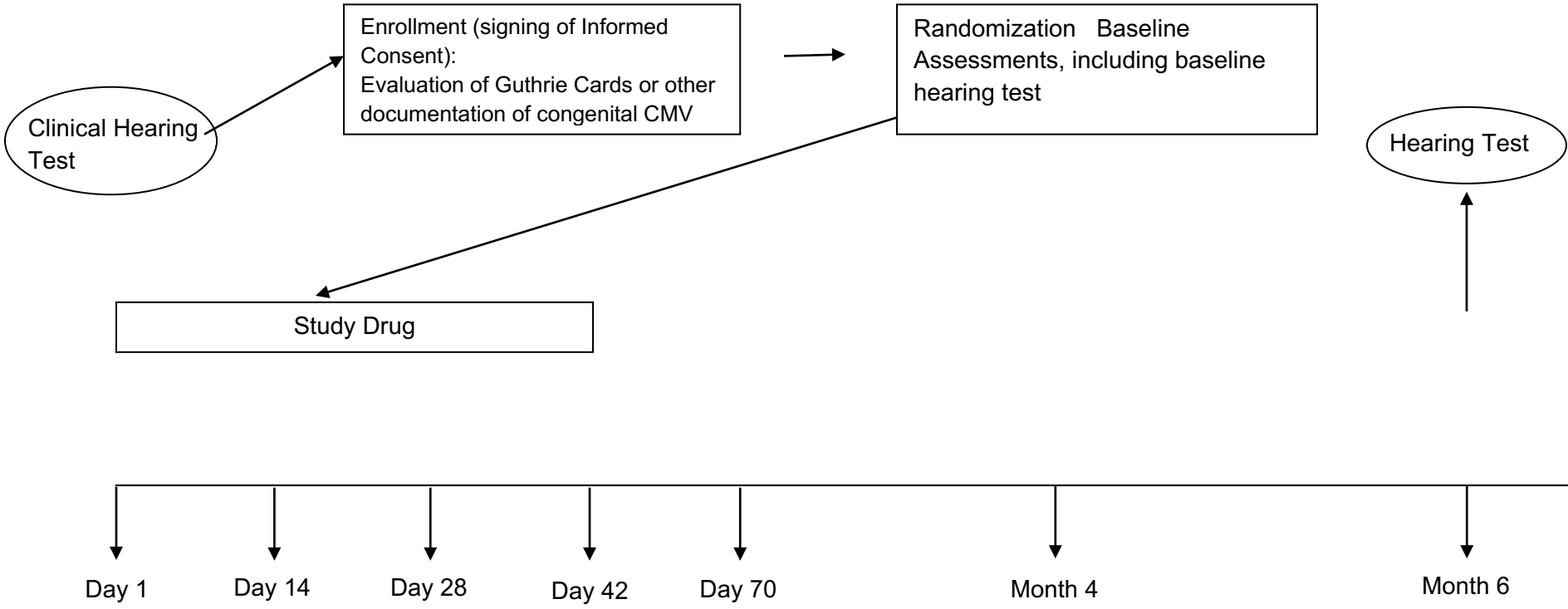
At each of the visits during the treatment phase (Study Days 1, 14, 28, and 42), safety labs will be assessed; viral load

specimens from blood, urine, and saliva will be obtained; adverse events will be assessed; and concurrent medications will be recorded. Ganciclovir concentrations for population pharmacokinetic assessment will be obtained at each study visit while the subject is receiving study medication. Dose adjustments for weight change will occur at study visits during the subject's treatment period, and may also occur at any time during the treatment period as indicated per protocol for neutropenia, thrombocytopenia, or renal impairment. At the Study Day 70 visit, safety labs will be obtained; viral load specimens from blood, urine, and saliva will be obtained; adverse events will be assessed; and concurrent medications will be recorded. Hearing will be assessed at baseline and at Study Month 6.

Changes in whole blood viral load measurements will be correlated with hearing outcomes. In study subjects with increasing whole blood viral loads during the course of treatment, antiviral resistance may be evaluated. A Data and Safety Monitoring Board (DSMB) will be established to oversee the accrual, performance, safety, and efficacy of the trial.

Estimated Time to Complete Enrollment: 3.5 years from enrollment of the first study subject

***Schematic of Study Design**:



Timing of study visits (days, months) for collection of urine, saliva, and blood (together with safety laboratory measurements at Study Days 1, 14, 28, 42 and 70)

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2. BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1. Background Information

Congenital cytomegalovirus (CMV) infection is the most frequent known viral cause of mental retardation,[1] and is the leading non-genetic cause of sensorineural hearing loss in many countries including the United States.[2-4] It also is the most common congenital infection in humans, with approximately 1% of all live births in the United States being infected with CMV (~ 40,000 babies per year).[5] CMV can be acquired *in utero* during any trimester of pregnancy. Of those fetuses infected, approximately 10% will be symptomatic at birth, and ~ 20% of these patients will die in the neonatal period; of the survivors, 90% will have significant neurologic sequelae.[6-11] The majority of these infants will have sensorineural hearing loss, mental retardation, microcephaly, seizures, and/or paresis/paralysis. These impairments frequently result in spastic quadriplegia requiring lifelong dependence on a wheelchair, along with cognitive and speech impairments which dramatically limit their ability to interact with and function in the world. Patients with this degree of neurologic impairment generally have a life expectancy of less than ten to fifteen years.

Children born with congenital CMV infection but without overt symptoms may nevertheless develop sequelae on follow-up, particularly sensorineural hearing loss. A recent systematic review of all prospective studies published worldwide reports that 13.5% of babies with congenital CMV infection develop sensorineural hearing loss on follow-up.[12] Of babies who develop sensorineural hearing loss, more than a quarter of babies born with symptomatic congenital CMV disease and almost 40% of babies born with asymptomatic CMV infection will have delayed-onset hearing loss, as illustrated in the following table:[13]

Characteristics of Audiologic Sequelae in Congenital CMV Infection and Disease

Sequelae	Symptomatic	Asymptomatic
Sensorineural hearing loss	41% (85/209)	7.4% (48/651)
Characteristics of loss		
Unilateral loss	33% (28/85)	52% (25/48)
Bilateral loss	67% (57/85)	48% (23/48)
High frequency loss only	13% (11/85)	38% (18/48)
Delayed-onset loss	27% (23/85)	38% (18/48)
Progressive loss	54% (46/85)	54% (26/48)
Fluctuating loss	29% (25/85)	54% (26/48)
Improvement of loss	21% (18/85)	48% (23/48)

Furthermore, the overwhelming majority who will develop delayed-onset hearing loss do so by 4 years of age:[13]

Cumulative Percentage of Sensorineural Hearing Loss, by Age

Age	Symptomatic	Asymptomatic
Birth – 1 month	43.5%	25.5%
3 months	55.3%	31.4%
6 months	67.2%	43.1%
2 years	82.4%	47.1%
3 years	88.2%	58.8%
4 years	89.4%	72.5%
6 years	95.3%	86.6%
7 – 15 years	100%	100%

The overall societal costs of providing specialized services for surviving infants and children with congenital CMV infections are in the billions of dollars annually.[14] For all of these reasons, the Institute of Medicine assessed the need for a CMV vaccine as the highest of all priorities.[15] However, the prospects for a vaccine to prevent CMV are at least two decades away.

2.1.1. Retrospective diagnosis of congenital CMV

Clinical investigators are now diagnosing congenital CMV infection retrospectively when older children present with hearing loss by means of PCR testing on stored dried blood spots (DBS; Guthrie cards) which had been obtained during the neonatal period. While the sensitivity of DBS PCR is variable (34-100%), the specificity is high (99-100%) such that a positive result confirms congenital CMV infection while a negative result does not rule out a congenital CMV infection.[16,17] Walter et al.[18] conducted a study using quantitative PCR to extend these results and determine if there was a threshold value of CMV genomes in a DBS above which hearing loss occurred more frequently. Briefly, DBS were created from fresh blood known to be CMV PCR positive at various levels of viral load and tested on multiple occasions. Guthrie cards were also created from fresh blood known to be CMV PCR negative and stored at room temperature adjacent to CMV-positive cards to facilitate any possible cross-contamination. Over a 12 month period, 43 negative DBS gave negative results (specificity 100%) and 39 positive DBS gave positive results (sensitivity 100%). Compared to the viral load found in each fresh whole blood, the viral load from the DBS was initially approximately 2 logs lower but remained stable for at least 2 years. These results show that the sensitivity of DBS is slightly lower than that of whole blood (cut-off 1000 genomes/ml vs 200 genomes/ml) but that DBS retrieved from children of the age required for this study should give reliable results. Additionally, the stored DBS of 39 children (aged 2 months-13 yrs at time of testing) with proven congenital CMV infection and sensorineural hearing loss were retrieved, together with those from 35 children (aged 7months to 15years) with unexplained SNHL. These samples were tested under code by quantitative PCR. The sensitivity was 75% (28/39 known cases of congenital infection) while 23% (8/35) of

cases of unexplained SNHL were PCR positive (similar to results of 20% and 25% previously reported for qualitative PCR). One case of a false-positive reaction was seen (child and mother both CMV seronegative). Importantly, a defined threshold effect was seen when severity of hearing loss was plotted against CMV viral load in DBS. However, the shape of this curve was so steep that, for practical purposes, the detection of any level of viremia could be considered a risk factor for future hearing loss, as previously reported by the NIAID Collaborative Antiviral Study Group (CASG).[19] We conclude from all these results that ongoing CMV replication may be a risk factor for progressive hearing loss and that control of viral replication may be considered a potential pharmacodynamic measure of successful antiviral therapy.

2.1.2. Treatment of Congenital CMV

CYTOVENE-IV (ganciclovir) is indicated for the treatment of CMV retinitis in immunocompromised patients, including patients with acquired immunodeficiency syndrome (AIDS) and for the prevention of CMV disease in transplant recipients at risk for CMV disease.

In adults, VALCYTE (valganciclovir) is indicated for the treatment of CMV retinitis in patients with acquired immunodeficiency syndrome (AIDS) and for the prevention of CMV disease in kidney, heart, or kidney-pancreas transplant patients at high risk.

In pediatric patients, valganciclovir is indicated for the prevention of CMV disease in kidney or heart transplant patients at high risk.

There are no FDA approved therapies for congenital CMV. Both intravenous ganciclovir and oral valganciclovir have been evaluated previously for the treatment of neonates with symptomatic congenital CMV. Several studies conducted by the CASG have indicated that ganciclovir therapy may be beneficial to neonates with congenital CMV.

2.1.2.1. Evaluations of Ganciclovir and Valganciclovir

In one phase III study, 100 neonatal subjects were randomized to receive either 6 weeks of IV ganciclovir or no therapy.[20] The primary study endpoint was improved brain stem evoked response (BSER) audiometry by one gradation between baseline and the 6 month follow-up (or, for those patients with normal hearing at baseline, normal BSER at both timepoints). Measures of clinical and laboratory improvement constituted the secondary endpoints, and growth was the tertiary endpoint of the trial. Audiologic analyses were performed on best evaluable ear ("functional" assessment) and on total evaluable ears ("biologic" assessment). The best ear assessment correlates with functional hearing impairment in daily living (e.g., a person with mild hearing impairment in one ear and severe hearing impairment in the other ear will function essentially as a mildly hearing impaired person).[21,22] Total ear assessment further assesses the biologic effects of ganciclovir therapy. Of these 100 subjects, 42 patients met all study entry

criteria, had both a baseline and 6 month follow-up BSER audiometric exam, and thus were evaluable for the primary endpoint.

Twenty-one (84%) of 25 evaluable ganciclovir recipients either had improvement in hearing in their best ear between baseline and 6 months or had normal hearing at both timepoints, compared with 10 (59%) of 17 evaluable patients in the no treatment group [adjusted P-value = 0.06; OR 5.03 (95% CI: 0.84,45.94)]. Inclusion in the best-ear analysis of two additional patients who did not meet all entry criteria yielded an adjusted P-value of 0.03. None (0%) of 25 ganciclovir recipients had worsening in hearing in their best ear between baseline and 6 months, compared with 7 (41%) of 17 patients in the no treatment group [adjusted P-value < 0.001; OR 21.11 (95% CI: 2.84,∞)]. Five (21%) of 24 ganciclovir recipients had worsening in hearing in their best ear between baseline and ≥ 1 year, compared with 13 (68%) of 19 patients in the no treatment group [adjusted P-value = 0.002; OR 10.26 (95% CI: 1.79,81.92)]. Ganciclovir-treated patients had a more rapid median time to normalization of ALT (19 days) compared with patients in the no treatment group (66 days) (P = 0.03). Ganciclovir-treated patients had a greater degree of weight gain (P = 0.02) and growth in head circumference (P < 0.01) at six weeks following study enrollment than did patients who did not receive antiviral therapy.

Laboratory abnormalities reported during the study, were assessed by the development of Grade 3-4 toxicity utilizing NIAID Division of AIDS (DAIDS) toxicity tables. The most frequent adverse event was neutropenia, which was experienced by a markedly higher proportion of patients on the IV ganciclovir arm of the study.[20] Twenty-nine (63%) of 46 ganciclovir-treated patients developed Grade 3 or 4 neutropenia during the six weeks of study drug administration, compared with 9 (21%) of 43 patients in the no treatment group over the same period of time (P < 0.01). Dose adjustments were required for neutropenia in fourteen (48%)subjects, although only 4 patients had the drug permanently discontinued. The mean time (± SD) of onset of grade 3 or 4 neutropenia for patients receiving ganciclovir was 14.2 (± 12.3) days, and for the no treatment group was 14.3 (± 13.1) days. Neutropenia in ganciclovir-treated patients resolved in 12.8 (± 13.6) days, and in the no treatment group in 14.2 (± 13.5) days. All affected patients resolved their neutropenia. Anemia was also more common in patients who received IV ganciclovir (8%, vs. 3% untreated patients), although the incidence of thrombocytopenia appeared comparable in the two treatment groups (2% i.v. ganciclovir treated patients vs. 3% untreated patients). The incidence of bloodstream infections, hematochezia, and diarrhea was also higher in patients who received IV ganciclovir. The incidence of a Grade 3-4 increase in serum creatinine, alanine amino transferase (ALT), and total bilirubin levels was comparable between groups.

In summary, ganciclovir treatment of neonates with symptomatic congenital CMV disease involving the CNS indicates that ganciclovir therapy both improves hearing function (or maintains normal hearing) and prevents hearing deterioration at 6 months. Furthermore, ganciclovir therapy may prevent hearing deterioration at ≥ 1 year. Ganciclovir recipients also

have a more rapid resolution of their transaminase elevations and a greater degree of short term growth in weight and head circumference compared with untreated patients.

Previous studies of ganciclovir in adult patients indicated that the AUC of ganciclovir is most closely related to virologic treatment success.[23] In adults, valganciclovir, the mono-valyl ester pro-drug of ganciclovir is well absorbed and converted rapidly to ganciclovir. The NIAID CASG therefore conducted a Phase I/II pharmacokinetic/pharmacodynamic investigation of oral valganciclovir in infants with symptomatic congenital CMV disease.[24] Twenty-four subjects under one month of age with symptomatic congenital CMV disease were enrolled. All subjects received antiviral treatment for congenital CMV, either predominantly with IV ganciclovir and with intermittent doses of oral valganciclovir, or predominantly with oral valganciclovir.

Based on data from a previous phase II study of intravenous ganciclovir in neonates with symptomatic congenital CMV disease, a target AUC_{12} of 27 ugxh/mL (mean AUC_{12}=32.3+13.7 ugxh/mL, range 17.2 to 55.9 ugxh/mL, n=13) was defined following treatment with a 6 mg/kg/dose q 12 hrs.[25] The evaluation of valganciclovir in the same population showed that a median dose of oral valganciclovir of 16 mg/kg provided a ganciclovir AUC_{12} of 27.4 ugxh/mL.[24] The median half-life of valganciclovir in infants ranged between 2.5 to 3 hours. This study also demonstrated that oral bioavailability of valganciclovir oral solution increases in early infancy (from 48% at approximately 4 weeks of life to 64% at approximately 7 weeks of life), and that this increase is proportionate to the increase in renal clearance of ganciclovir during the same period. Thus, oral valganciclovir actually is a more reliable method of delivering ganciclovir to young infants than intravenous ganciclovir, since the increase in oral bioavailability "compensates" for the increase in ganciclovir clearance which occurs in the first few weeks to months of life, thereby providing more consistent ganciclovir blood concentrations over time.

Oral valganciclovir was well tolerated with no vomiting. The primary safety finding was the development of neutropenia. Neutropenia of grade 3 or 4 developed in 38% (n=9) of study subjects treated with oral valganciclovir and/or iv ganciclovir, but only 1 subject discontinued antiviral therapy because of neutropenia.[24] Three subjects developed grade 3 anemia, 1 developed a grade 3 elevation in AST and 1 developed a grade 3 hyperbilirubinemia. Eleven subjects on this study experienced SAEs (46%). One (neutropenia) was assessed to be probably related to receipt of study medication; ten were assessed as unrelated.

2.2. Rationale

Because of the progressive nature of congenital CMV-associated hearing loss, there is a large unmet medical need for treatment options beyond the neonatal period. Data from other CASG investigations support the study of antiviral treatment in infants and toddlers with CMV-associated hearing loss:

- Less than half of the hearing loss due to congenital CMV infection is present at birth.[4,13]

- Children with congenital CMV continue to excrete virus in the urine for three to five years or even longer.[26]
- The quantity of CMV (viral load) found in the urine and blood is greater in those children destined to develop hearing loss.[19,26,27]
- CMV DNA has been detected in the perilymph of children up to four years of age undergoing cochlear implantation for CMV-induced hearing loss.[28]
- Six weeks of IV ganciclovir at 6mg/kg bid given to neonates with congenital CMV disease beginning when they are less than 31 days of age reduces the future incidence of hearing loss.[20]
- Six weeks of intravenous ganciclovir given to neonates with congenital CMV disease beginning when they are less than 31 days of age suppresses viruria, as detected by cell culture, but viruria returns promptly when the drug is stopped, even at the higher dose of 6mg/kg bid.[29]
- The dose of oral valganciclovir that provides the same systemic exposure as the IV ganciclovir dose used in treatment of congenital CMV has been identified, with 16 mg/kg/dose of oral valganciclovir equaling 6 mg/kg/dose of IV ganciclovir.[24]

We hypothesize that six weeks of antiviral therapy can stabilize hearing deterioration in older infants, toddlers, and young children who have developed CMV-associated hearing loss. We will conduct a Phase II study of valganciclovir to test this possibility. We have powered this study to detect a similar difference in audiologic outcomes to that seen when ganciclovir was given for the same duration to neonates and young infants (i.e. worsening of hearing in 41% versus 0% was observed,[20] whereas the more conservative difference of 40% versus 5% has been used for the power calculation for the current study). Since the natural histories of CMV viruria and viremia have not been defined in older children, we anticipate generating valuable data on viral load as a potential biomarker in this population, even if the clinical primary endpoint of hearing is not met. It is possible to envisage utilizing such biomarker data in the development of a future study evaluating a longer duration of valganciclovir or with safer medications.

In the recently completed CASG 112 study of neonates and young infants with symptomatic congenital CMV disease, whole blood viral loads decreased from approximately 3.5 logs to under 2 logs in both groups over the course of the first six weeks of open-label valganciclovir therapy. Viral loads in the two groups of subjects then diverged initially following randomization, but by four months the group randomized to placebo had regained virologic control. By six months the two groups each had approximately 1.5 logs of virus detectable in blood, with the group that had received active drug throughout the six months then experiencing a rebound in viral load as treatment was stopped. Viral load was not assessed beyond month seven. Lower whole blood viral load area-under-the-curve during the first six weeks of therapy was associated with better hearing outcomes at 12 and 24 months in unadjusted ($p=0.005$ and $p=0.003$, respectively) and adjusted ($p=0.044$ and $p=0.023$, respectively) analyses. However, lower whole blood viral load area-under-the-curve from week six to month six was not associated with hearing outcomes in adjusted analyses ($p>0.168$). This suggests that lowering systemic viral load initially aids in improving audiologic outcomes, but that the additional benefit of longer-term treatment for six months may relate to antiviral effects within the inner ear itself, where ongoing viral replication and damage may be impaired with prolonged antiviral therapy. We were not

able to identify specific breakpoints above which the viral load could be used as a biomarker for those patients at higher risk of developmental or hearing sequelae.

Furthermore, we will link this proposed study to the recently introduced national screening programs for hearing loss to demonstrate how CMV screening could be integrated into current diagnostic algorithms employed in the United States and United Kingdom, which offer a potentially cost-effective way to address the unmet medical problem of CMV.

2.3. Potential Risks and Benefits

2.3.1. Potential Risks

The potential risks associated with oral valganciclovir administration relate primarily to the known toxicity of this antiviral agent, neutropenia. Stopping rules are incorporated into this Phase II trial in order to limit exposure of study subjects should the potential risks be unacceptably high.

In addition to neutropenia, the clinical toxicities of valganciclovir include anemia and thrombocytopenia. In animal studies, ganciclovir was carcinogenic, teratogenic, and caused aspermatogenesis. Some additional adverse events reported with valganciclovir are diarrhea, nausea, vomiting and abdominal pain. General disorders reported are pyrexia and fatigue. The most common neurological adverse events reported are headache and insomnia.

The risk associated with blood draws may be discomfort from the needle stick and occasional bruising at the site during or after the blood drawing and rarely an infection. A small clot may form at the site where the needle enters the body.

2.3.2. Known Potential Benefits

Six weeks of intravenous ganciclovir has been proven to protect against hearing deterioration in patients with congenital CMV infection when treatment was initiated during the first month of life.[20] As described above, treatment with oral valganciclovir has the potential benefit of improving hearing outcomes in children with congenital CMV infection and hearing loss who are 1 month through 3 years of age.

3. OBJECTIVES

3.1. Study Objectives

Primary:

- The primary objective is to assess whether a six week course of oral valganciclovir can stabilize the hearing of children with congenital CMV infection who present with hearing loss. This will be accomplished by evaluating changes in hearing in either ear at 6 months from baseline.

Secondary:

- To define the following responses as a function of systemic exposure to ganciclovir (active metabolite of valganciclovir):
  - CMV viral load in blood
  - CMV viral load in urine
  - CMV viral load in saliva
- To define the safety and tolerability of valganciclovir in enrolled subjects.

Tertiary:

- To define the pharmacokinetics of ganciclovir (metabolite) following administration of valganciclovir (prodrug) in enrolled subjects.

3.2. Study Outcome Measures

3.2.1. Primary Outcome Measure

- Change in total ear hearing assessments (improved + no change versus other) between Baseline and Study Month 6

3.2.2. Secondary Outcome Measures

- Change in best ear hearing assessments [improved + no change (normal to normal) versus other; improved versus other; worse + no change (abnormal to abnormal) versus other; and worse versus other] between Baseline and Study Month 6

- Change in total ear hearing assessments (improved versus other; worse + no change (abnormal to abnormal) versus other; and worse versus other) between Baseline and Study Month 6

- Detection of viruria by PCR six weeks and six months after trial entry

- The quantitative log reduction in viruria detected after 6 weeks of therapy
- Detection of viremia by PCR six weeks and six months after trial entry
- The quantitative log reduction in viremia detected after 6 weeks of therapy
- Detection of CMV in saliva by PCR six weeks and six months after trial entry
- The quantitative log reduction in CMV viral load in saliva detected after 6 weeks of therapy
- Correlation of change in viral load with change in total ear and best ear hearing at 6 months
- Incidence of unanticipated medically attended visits occurring from Study Day 1 through two weeks following the last dose of study drug
- Incidence of adverse events which lead to permanent discontinuation of valganciclovir therapy or have an unresolved outcome

3.2.3. Tertiary Outcome Measures

- Blood concentrations of ganciclovir after administration of valganciclovir

4. STUDY DESIGN

This is a Phase II international, multi-center, double-blind, placebo-controlled evaluation of 6 weeks of valganciclovir treatment for children (up to 4 years of age) with virologically-confirmed congenital CMV infection and hearing loss. Patients who are between 1 month and 4 years of age and who have SNHL are eligible for enrollment on the study. **Enrollment on the study occurs when eligibility is confirmed and the informed consent is signed.** Following the signing of informed consent, the subject's Guthrie card will be retrieved and tested for CMV DNA by PCR unless there is a virologically confirmed diagnosis of congenital CMV infection made within the first 30 days of life. **Randomization on the study occurs when the diagnosis of congenital CMV infection is confirmed**, and the subject then is assigned to either receive 6 weeks of oral valganciclovir or 6 weeks of placebo. Study subjects will be stratified according to age at randomization (1 through 11 months, 12 through 23 months, 24 through 35 months, and ≥ 36 months) and CMV involvement (symptomatic and asymptomatic at birth) as a marker of disease severity. The sample size of randomized, evaluable subjects is 54. Dropouts and subjects with audiology assessments that are inadequate for study comparison will be replaced (up to 20%, or n=10). Baseline study assessments (see Section 7.2) will be performed following randomization. Subjects will be followed for 6 months post randomization. During the six week treatment period, study subjects will be followed every 2 weeks. Subjects will also be seen at approximately one month following the final dose (Study Day 70), and again at Study Months 4 and 6.

At each of the visits during the treatment phase (Study Days 1, 14, 28, and 42), safety labs will be assessed; viral load specimens from blood, urine, and saliva will be obtained; adverse events will be assessed; and concurrent medications will be recorded. Ganciclovir concentrations for population pharmacokinetic assessment will be obtained at each study visit while the subject is receiving study medication. Dose adjustments for weight change will occur at study visits during the subject's treatment period, and may also occur at any time during the treatment period as indicated per protocol for neutropenia, thrombocytopenia, or renal impairment. At the Study Day 70 visit, safety labs will be obtained; viral load specimens from blood, urine, and saliva will be obtained; adverse events will be assessed; and concurrent medications will be recorded. Hearing will be assessed at baseline and at Study Month 6.

Changes in whole blood viral load measurements will be correlated with hearing outcomes. In study subjects with increasing whole blood viral loads during the course of treatment, antiviral resistance may be evaluated. A Data and Safety Monitoring Board (DSMB) will be established to oversee the accrual, performance, safety, and efficacy of the trial.

Study Day 1 of the study is the day following randomization that the first dose of study medication is administered. "Study drug" refers to valganciclovir or placebo (for six weeks). Follow-up visits referred to by Study Day will be determined by calendar day from Day 1 (e.g., if Study Day 1 is June 20, then Study Day 7 will be June 26); follow-up visits referred to by Study

Month will be determined by calendar month (e.g., if Study Day 1 is June 20, then Study Month 1 will be July 20).

4.1. Substudies (if applicable)

None.

5. STUDY ENROLLMENT, RANDOMIZATION, AND WITHDRAWAL

5.1. Enrollment

Male and female infants from 1 month through 3 years of age (up to 4th birthday) with sensorineural hearing loss will be eligible for enrollment. **Enrollment on the study occurs when eligibility is confirmed and the informed consent is signed.** Following confirmation of inclusion/exclusion criteria and the signing of informed consent, the subject's Guthrie card will be retrieved and tested for CMV DNA by PCR unless there is a virologically confirmed diagnosis of congenital CMV infection made within the first 30 days of life. Enrollment will be implemented by the web-based enrollment system developed and maintained at the UAB Biostatistics Unit at the University of Alabama at Birmingham.

Clinicians who care for these patients (e.g., audiologists, otolaryngologists, pediatricians) will be made aware of the study so that they can inform the parents and guardians of patients with sensorineural hearing loss about the availability of the study.

5.2. Subject Inclusion Criteria

- Signed informed consent from parent(s) or legal guardian(s)
- Sensorineural hearing loss (≥ 21dB in one or both ears, documented within 12 weeks prior to study entry)
- Children from 1 month through 3 years of age (up to the 4th birthday)

5.3. Subject Exclusion Criteria

- Imminent demise
- Profound sensorineural hearing loss (> 90dB) in both ears
- Patients receiving other antiviral agents or immune globulin
- Gastrointestinal abnormality which might preclude absorption of an oral medication (e.g., a history of necrotizing enterocolitis)
- Documented renal insufficiency, as noted by a creatinine clearance < 10 mL/min/1.73m^2 at time of study enrollment
- Breastfeeding from mother who is receiving ganciclovir, valganciclovir, foscarnet, cidofovir, or maribavir
- Infants known to be born to women who are HIV positive (but HIV testing is not required for study entry).
- Current receipt of other investigational drugs
- Previous receipt of ganciclovir or valganciclovir
- Known hypersensitivity to ganciclovir, valganciclovir, or components of the product

- Inability to attend follow-up hearing and clinical assessments
- Infants with Auditory neuropathy/dyssynchrony.
- Children with another known etiology for SNHL (e.g. connexin 26, syndrome or metabolic disorder associated with SNHL, inner ear malformation and widened vestibular aqueducts, meningitis). Exclusion of each of these conditions is not required for trial enrollment.

5.4. Treatment Assignment Procedures

5.4.1. Randomization Procedures

Randomization on the study occurs when the diagnosis of congenital CMV infection is confirmed, and the subject then is assigned to either receive 6 weeks of oral valganciclovir or 6 weeks of placebo. Study subjects will be stratified according to age at randomization (1 through 11 months, 12 through 23 months, 24 through 35 months, and ≥ 36 months) and CMV involvement (symptomatic and asymptomatic at birth) as a marker of disease severity. Age stratification is justified by the differences in the hearing assessments methods utilized for infants younger than 12 months versus toddlers 12 months and older. Dropouts and subjects with audiology assessments that are inadequate for study comparison will be replaced (up to 20%, or n=10).

Randomization will be implemented by the web-based randomization system developed and maintained at the UAB Biostatistics Unit at the University of Alabama at Birmingham. The generation and maintenance of study randomization codes will be the responsibility of the UAB Biostatistical Unit. The codes will be kept in a secure location in the Biostatistics Unit.

5.4.2. Masking Procedures

Study subjects, investigators, and staff interacting with the study subjects will be masked to treatment. At the time of randomization, the site study pharmacist (who will not be masked to treatment) will prepare oral valganciclovir or oral placebo for distribution to the study subject. To ensure masking of all other study staff and families, study drug will be dispensed in amber bottles, along with amber-colored syringes for drawing up all doses. Additionally, the central audiologist who analyzes the audiology data will be masked to study assignment, as will all personnel at the UAB Central Unit (with the exception of the UAB Study Statistician).

Upon completion of the six month follow-up period for all study subjects, or if the study is stopped early for any reason, the study will be unmasked after all enrolled study participants have completed the Month 6 follow-up assessments and the database is frozen. In an emergency situation, in which knowledge of the treatment assignment will be used to reduce/remove an immediate hazard to a volunteer, the study PI and/or a local site PI will have the ability to access the treatment assignment. In this situation (emergency unblinding) the study/local PI must explain and justify the nature of the event that resulted in the decision to

immediately unblind to the DMID Medical Monitor and the Protocol Chair as soon as possible. This justification will be documented as a protocol deviation, and the IRBs and regulatory agencies will be informed as is appropriate.

Unmasking/Unblinding may also occur when the safety of a study participant is in question. In non-emergency situations, a conference call will be held to determine whether or not unmasking of an individual study subject is necessary or appropriate. The conference call will include the Protocol Chair, Protocol Statistician, DMID Medical Monitor and Clinical Project Manager.

5.4.3. Reasons for Withdrawal Before Randomization

The criteria for discontinuation of study participation following enrollment and before randomization include:

- Failure to confirm congenital CMV infection
- Study subject (parent/legal guardian) wishes to withdraw
- Trial termination (by UAB Central Unit, FDA, DMID, NIAID, NIH, UCL, or agreement of all investigators) issued per safety or efficacy criteria
- Any other reason which, in the opinion of the investigator, precludes the study subject's participation in the study. The principal investigator must call the Protocol Chair (or designee) prior to discontinuing a study subject for this reason.

5.4.4. Reasons for Withdrawal After Randomization and During Treatment

The criteria for discontinuations during the treatment portion of the study include:

- Development of a related serious adverse event warranting withdrawal of therapy
- Study subject (parent/legal guardian) wishes to withdraw
- Non-compliance with study procedures or medication schedule that in the opinion of the investigator warrants withdrawal
- Deterioration in general condition for which alternative treatment is indicated and which, in the opinion of the investigator, warrants withdrawal
- Trial termination (by UAB Central Unit, FDA, DMID, NIAID, NIH, UCL, or agreement of all investigators) issued per safety or efficacy criteria

- Any other reason which, in the opinion of the investigator, precludes the study subject's participation in the study. The principal investigator must call the Protocol Chair (or designee) prior to discontinuing a study subject for this reason.

5.4.5. Reasons for Withdrawal After Randomization and After Completion of Treatment

Criteria for discontinuing study subjects from the study after completion of the study medication are:

- Study subject (parent/legal guardian) wishes to withdraw
- Any other reason, which in the opinion of the investigator, should preclude the study subject's continued participation in the study. The investigator must call the Protocol Chair (or designee) prior to discontinuing a study subject for this reason.
- Any subject that is terminated due to loss to follow-up will be considered as withdrawn

5.4.6. Handling of Withdrawals

Study subjects may withdraw voluntarily from participation in the study at any time. Up to 20% (n=10) over-enrollment is allowed to replace subjects who drop-out or who have inadequate audiology assessments. Study subjects also may withdraw voluntarily from receiving the study intervention for any reason. If a study subject withdraws or is discontinued from the study at any time prior to completion of the study, the reason for this decision will be recorded on the electronic case report form (eCRF). SAEs and AEs will be followed according to guidelines in Section 9. The study subject should be encouraged to complete follow-up visits as part of the intent to treat group.

Should a study subject's therapy be discontinued prematurely, all clinical and laboratory evaluations scheduled during the next study visit will be completed on the day the study subject is discontinued. All randomized study subjects will continue to be followed as long as possible and included in the final analysis.

Since the primary endpoint requires comparison of baseline and 6 month audiology assessments, dropouts and subjects with audiology assessments that are inadequate for study comparison (Section 11.4.1) will be replaced. Characteristics of the dropouts and those with missing outcomes will be compared to determine if there is a difference between the two treatment groups. If differences are observed, this will be included in the primary outcome reporting as a limitation.

5.4.7. Termination of Study

The ethics committees, regulatory agencies, UAB Central Unit, or NIH have the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to study subjects
- Study subject enrollment is unsatisfactory.

6. STUDY INTERVENTION/INVESTIGATIONAL PRODUCT

6.1. Study Product Description

Valcyte Powder for Oral Solution (valganciclovir) is indicated for the treatment of CMV retinitis in adult patients with AIDS and for the prevention of CMV disease in adult and pediatric kidney, heart, and kidney-pancreas transplant recipients at high risk. Simple Syrup (Syrup, NF) will be used for the placebo for valganciclovir.

6.1.1. Acquisition

Valcyte Powder for Oral Solution (valganciclovir) will be provided for this study by Genentech/Roche. Simple Syrup (Syrup, NF) for placebo will be purchased from a commercial vendor by the site. Study supply (active drug) will be maintained in a central drug repository as designated by the UAB Central Unit until study enrollment at a site, at which time the supply of study medication will be shipped to the study site pharmacist.

6.1.2. Formulation, Packaging, and Labeling

Valcyte Powder for Oral Solution (valganciclovir) will be supplied as a white to slightly yellow powder for reconstitution. The powder is provided in a round amber glass bottle, containing 12g powder containing 5g valgancyclovir free base. Upon reconstitution, the resulting oral solution contains 50 mg of valganciclovir free base per 1 mL (Total = 100 mL per bottle). The inactive ingredients for the reconstituted oral solution are mannitol, povidone K-30, sodium benzoate, fumaric acid, sodium saccharin, flavoring, and purified or sterile water. The valganciclovir oral solution formulation does not contain lactose anhydrous.

Placebo for Valganciclovir

The placebo for valganiclovir is Simple Syrup (Syrup NF), which contains 60-90% sucrose in purified water. It is supplied as the commercial preparation.

Valganciclovir and Simple Syrup (Syrup NF) will be labeled with the drug identification and dosage. The label will comply with IND regulations, the local requirements of the country in which the study is being conducted and carry the required caution statement. Blinded labeling of study product will be performed by the licensed pharmacist at the time of dispensing. Valganciclovir will be dispensed in its original bottle. Simple Syrup will be transferred to a matching amber bottle. Study products (active or placebo) will be dispensed in a new bottle at each study visit during the six weeks of study drug administration.

6.1.3. Product Storage and Stability

Valganciclovir will be provided as a powder for oral solution. Dry powder is to be stored at 25ºC (77ºC); excursions permitted to 15°C to 30°C (59°F to 86°F). Store reconstituted oral solution at 2° to 8°C (36°F to 46°F) for no longer than 49 days. Do not freeze. Shake bottle well before using.

Simple Syrup placebo is to be stored at 2° to 8°C (36°F to 46°F) for no longer than 49 days following dispensing for the study.

6.2. Dosage, Preparation and Administration of Study Intervention/Investigational Product

Valcyte Powder for Oral Solution (valganciclovir) will be prepared by a licensed pharmacist in accordance with instructions in the package insert. Placebo for valganciclovir (Simple Syrup) will be transferred from the commercial bottle to identical empty amber bottles for dispensing.

Valganciclovir should be dosed at 16mg/kg body weight, unless specific dosage adjustment conditions have been met (see Section 6.3), administered orally twice daily for 6 weeks. Placebo for valganciclovir (Simple Syrup) should be dosed using the same volume that would be required for the active dose, administered orally twice daily for 6 weeks. Dose modifications for neutropenia, thrombocytopenia, renal impairment, and hepatotoxicity are detailed in Section 6.3.

Pharmacy preparation instructions for study product can be found in the protocol-specific Manual of Procedures (MOP), including directions for the reconstitution of the valganciclovir oral solution. Once reconstituted, the oral solution must be stored under refrigeration for no longer than 49 days. Valganciclovir oral solution has been shown not to adhere to syringes or to nasogastric tubing. Valganciclovir oral solution or placebo for valganciclovir should be administered into the patient's mouth by means of a syringe, which will be amber colored and provided by the study. If the patient is unable to swallow, the study product may be administered via the syringe through a nasogastric or gastric tube.

Study product administration should be timed to precede a feeding. If the subject vomits or spits up following the dosing, re-dosing will not be allowed.

6.3. Modification of Study Intervention/Investigational Product for a Participant

Bone marrow suppression secondary to CMV can mimic ganciclovir toxicity. Nevertheless, the dosage of valganciclovir will be reduced or interrupted if any of the following occur.

6.3.1. Neutropenia

If the ANC reproducibly (within one week) decreases to ≤ 500 cells/mm^3, study drug will be held until the ANC recovers to > 750 cells/mm^3, and then administration of the drug will resume at the normal dose. If the ANC again reproducibly (within one week) decreases to ≤ 750 cells/mm^3, the study drug dosage will be reduced by 50% and maintained there as long as the ANC remains > 500 cells/mm^3. If the ANC reproducibly (within one week) decreases to ≤ 500 cells/mm^3 on the 50% dosage, then the study medication will be discontinued. In cases of drug interruption, treatment will not be prolonged beyond the originally scheduled 6 week treatment timeframe.

Administration of granulocyte colony stimulating factor (GCSF) is allowed. All administered GCSF doses will be recorded on the concomitant medication sheet. The decision to utilize GCSF is left to the medical discretion of the participating investigator. The parameters for dose adjustment stated above, based upon ANC, will remain in effect even if the patient is receiving GCSF.

6.3.2. Thrombocytopenia

If the platelet count at baseline was ≥ 100,000/mm^3, then study drug will be held if the platelet count reproducibly (within one week) decreases to ≤ 50,000/mm^3. After the platelet count increases to ≥ 50,000/mm^3, study drug administration at the normal dose will resume.

If the platelet count at baseline was ≤ 100,000/mm^3, then study drug will be held if the platelet count reproducibly (within one week) decreases by 50% from baseline value. After the platelet count increases above 50% from baseline value, study drug administration at the normal dose will resume. If the platelet count again reproducibly (within one week) decreases by 50%, then the study medication will be discontinued. In cases of drug interruption, treatment will not be prolonged beyond the originally scheduled 6 week treatment timeframe.

6.3.3. Renal Impairment

If renal function is normal (creatinine clearance ≥ 60 mL/min/1.73m^2), then administer the full dose of study drug at the same intervals (valganciclovir 16 mg/kg/dose BID)

If renal function is reproducibly impaired (to be confirmed by repeat serum creatinine), then dose adjust as follows:

CrCl 40 to 59 mL/min/1.73m^2:	8 mg/kg/dose PO BID
CrCl 25 to 39 mL/min/1.73m^2:	8 mg/kg dose PO daily

CrCl 10 to 24 mL/min/1.73m^2: 8 mg/kg dose PO every other day.

CrCl <10 mL/min/1.73m^2: Discontinue study medication

When the lab method of Scr determination is **non-IDMS traceable**:
Calculation of creatinine clearance (CrCl) [30]

- Estimated CrCl (mL/min/1.73m^2) = kL / Scr
  - k = proportionality constant
  - L = length (cm)
  - Scr = serum creatinine (mg/dL)
- k values
  - If low birth weight (< 2,500 g), during first year of life: 0.33
  - If term AGA, during first year of life: 0.45
  - If ≥ 1 year of age: 0.55

When the lab method of Scr determination is **IDMS traceable**:
Calculation of creatinine clearance (CrCl)[31]

- Estimated CrCl (mL/min/1.73m^2) = kL / Scr
  - k = proportionality constant
  - L = length (cm)
  - Scr = serum creatinine (mg/dL)
- k values
  - If low birth weight (< 2,500 g), during first year of life: 0.25
  - If term AGA, during first year of life: 0.34
  - If ≥ 1 year of age: 0.41

6.3.4. Hepatotoxicity

If the ALT reproducibly (within one week) increases to > 10 times above baseline, study drug will be held until ALT falls to < 5 times above baseline, at which time study drug will be restarted. If the ALT again increases 10 times above baseline, study drug will be discontinued. In cases of drug interruption, treatment will not be prolonged beyond the originally scheduled 6 week treatment timeframe.

6.4. Accountability Procedures for the Study Intervention/Investigational Product(s)

After receipt of the study products and supplies, the site pharmacist will dispense in an amber bottle that will be supplied by the study and distribute it to the Principal Investigator (or designee) or to the patient's parent or legal guardian. The Principal Investigator will delegate to the site pharmacist responsibility for drug accountability. Each pharmacist will be responsible for and maintain logs of receipt, accountability, dispensation, storage conditions, and disposal of

study drug. These documents will be maintained in a secure and accessible location, but separate from areas accessible to other study staff in order to maintain their blinding. At study completion, the sites will be required to return the drug accountability log to the UAB Central Unit upon request, retaining a copy of the drug accountability form in their study files.

Used and unused study product will not be disposed of or returned until the study monitor reviews and confirms the drug accountability.

- Used or partially used study product will be disposed of by the local site pharmacy in accordance with local regulations after completion of drug accountability by the study monitor.
- All unopened study drug will be returned to the central drug repository from the local site pharmacy or destroyed at the site in accordance with local regulations following the direction from the UAB Central Unit or its designee.

6.5. Concomitant Medications/Treatments

6.5.1. Concomitant Medication Assessment

All concomitant medications will be recorded at each study visit throughout the treatment period (start of blinded study drug administration on Day 1 through Day 70.

6.5.2. Prohibited Therapies

Use of the following concomitant medications during the time of administration of antiviral medication in this clinical trial will not be allowed:

- Cidofovir
- Foscarnet
- Probenecid
- Other Investigational drugs

The following concomitant medications should be used with caution:

- Agents that interfere with renal function
- Agents that interfere with bone marrow function
- Imipenem-cilastatin

The concomitant use of ganciclovir and imipenem-cilastatin has been associated with seizures, and this medication should only be used if the potential benefits outweigh the potential risks.

6.5.3. Drug Interactions

In pharmacokinetic studies, the concomitant use of ganciclovir and didanosine (ddI) has been associated with increases in ddI concentrations of greater than 100%. Accordingly, the possibility of increased ddI toxicity should be considered in patients receiving both medications.

Coadministration of trimethoprim with oral ganciclovir in adults statistically significantly decreased the renal clearance of ganciclovir by 16.3%, and this was associated with a statistically significant decrease in the terminal elimination rate and corresponding increase in half-life by 15%. However, these changes are unlikely to be clinically significant, as the AUC0-8 and Cmax were unaffected. The only statistically significant change in trimethoprim pharmacokinetic parameters when coadministered with ganciclovir was a 12% increase in Cmin. However, this is unlikely to be of clinical significance and no dose adjustment is recommended.

7. STUDY SCHEDULE

The study procedures and evaluations are summarized in Appendix A. Signed informed consent will be obtained at study enrollment and before any study-related procedures. In conducting the informed consent process, the research team will adhere to the standards set forth by their IRB for obtaining informed consent. Study windows are provided in parentheses and apply to all study events described in that subsection, unless a different window is specified for a particular study event.

7.1. Enrollment (Window: Day -90 to Day -1)

Following confirmation that the patient is eligible for study enrollment and obtaining informed consent, if infection with CMV has not been documented within the first 30 days of life then the Guthrie card will be retrieved and analyzed by PCR for CMV DNA; PCR will be performed in the U.K. as part of routine clinical investigation protocols, while in the U.S. it will be performed at the UAB Central Laboratory. If the result is positive or if there is other virologic confirmation of congenital CMV infection, congenital CMV is confirmed. These subjects are eligible for randomization, following which the baseline assessments (see Section 7.2) will be obtained.

Subjects who have signed the informed consent document and therefore are enrolled on the study but who then do not qualify for randomization in the trial (for example, because the Guthrie card PCR was negative) will not be counted toward the final sample size for the study. Consented study participants may receive nominal compensation to offset the cost of travel, parking, meals, etc., for study visits in accordance with local site policies and local IRB approval.

7.2. Randomization (Window Day -30 to Day 1) and Baseline (Window: Day -3 to Day 1)

- Document congenital CMV infection
- Obtain randomization authorization from UAB data center
- Baseline studies will be performed following randomization of the subject on the trial
- Document baseline demographics, selected laboratory parameters, medical history, and baseline conditions (Study Day -30 to Study Day 1) (see Section 8.1.1)
  - Date of birth
  - Gender
  - Race
  - Ethnicity

- Birth weight
- Length at birth, if available
- Head circumference at birth, if available
- Gestational age at birth
- Petechiae at any time from birth through study randomization, if known
- Thrombocytopenia at any time from birth through study randomization, if obtained
- Hepatomegaly at any time from birth through study randomization, if noted
- Splenomegaly at any time from birth through study randomization, if noted
- CSF white blood cell count at any time from birth through study randomization, if obtained
- CSF protein concentration at any time from birth through study randomization, if obtained
- CSF CMV PCR at any time from birth through study randomization, if performed
- Seizures at any time from birth through study randomization, if noted
- Elevated transaminases at any time from birth through study randomization, if obtained
- Elevated bilirubin at any time from birth through study randomization, if obtained
- Neuroimaging abnormalities, if obtained
- Medical history and baseline conditions prior to study randomization, by body system
- Chorioretinitis
- Intrauterine growth restriction
- Urine CMV testing (e.g., viral culture, shell-vial culture, PCR) within 90 days prior to study enrollment, if obtained clinically

- Hematology safety labs (see Sections 6.3 and 8.2.1.1)
  - WBC with differential
  - Hemoglobin
  - Platelet count

- Chemistry safety labs (see Sections 6.3 and 8.2.1.2)
  - ALT
  - Total Bilirubin
  - Creatinine

- Weight and length (see Section 8.1.2)

- Adverse event assessment (see Section 9)

- Concurrent medications assessment (see Section 6.6.1)

- Obtain a new hearing assessment or record results from clinically obtained hearing assessment (may be obtained any time from Study Day -90 to Study Day -1) (see Section 8.1.4)

  - BSER or VRA (to assess neuro-otologic status) and OAEs (DPOAE or TEOAE) will be obtained. If the BSER and/or VRA is abnormal, then bone conduction will be obtained to distinguish between sensorineural hearing loss, conductive loss, or mixed loss. If the OAEs are abnormal, then acoustic immittance measures (tympanometry and acoustic

reflexes) will be obtained to better define the middle or inner ear abnormality (e.g., otitis media).

- Virology specimens for CMV viral load (see Section 8.2.2.1)
- Confirm that Study Day 1 safety labs allow for dosing of study medication (see Section 6.3); if so, begin study medication on Study Day 1
- Updated results of any etiological investigations for SNHL.

7.3. Treatment (Day 1 through Day 42)

Administer study medication twice daily

7.4. Follow-up

7.4.1. Day 14 (± 2 days)

- Hematology safety labs (see Sections 6.3 and 8.2.1.1)
  - WBC with differential
  - Hemoglobin
  - Platelet count
- Chemistry safety labs (see Sections 6.3 and 8.2.1.2)
  - ALT
  - Total Bilirubin
  - Creatinine
- Weight and length (see Section 8.1.2)
- Verbally assess previous administration of study medication by parents/ guardians
- Adjust dose of study medication for weight change, if needed
- Adverse event assessment (see Section 9)
- Concurrent medications assessment (see Section 6.6.1)
- Virology specimen for CMV viral load (see Section 8.2.2.1)
- Pharmacokinetic specimen for ganciclovir concentration (see Section 8.2.2.2)
- Updated results of any etiological investigations for SNHL.

7.4.2. Day 28 (± 2 days)

- Hematology safety labs (see Sections 6.3 and 8.2.1.1)
  - WBC with differential
  - Hemoglobin
  - Platelet count
- Chemistry safety labs (see Sections 6.3 and 8.2.1.2)
  - ALT
  - Total Bilirubin
  - Creatinine
- Weight and length (see Section 8.1.2)
- Verbally assess previous administration of study medication by parents/ guardians
- Adjust dose of study medication for weight change, if needed
- Adverse event assessment (see Section 8.1.3)
- Concurrent medications assessment (see Section 6.6.1)
- Virology specimen for CMV viral load (see Section 8.2.2.1)
- Pharmacokinetic specimen for ganciclovir concentration (see Section 8.2.2.2)
- Updated results of any etiological investigations for SNHL.

7.4.3. Day 42 (± 2 days)

- Hematology safety labs (see Section 8.2.1.1)
  - WBC with differential
  - Hemoglobin
  - Platelet count
- Chemistry safety labs (see Section 8.2.1.2)
  - ALT
  - Total Bilirubin
  - Creatinine
- Verbally assess previous administration of study medication by parents/ guardians
- Discontinue study medication after Study Day 42 dosing complete
- Adverse event assessment (see Section 9)

- Concurrent medications assessment (see Section 6.6.1)
- Virology specimen for CMV viral load (see Section 8.2.2.1)
- Pharmacokinetic specimen for ganciclovir concentration (see Section 8.2.2.2)
- Updated results of any etiological investigations for SNHL.

7.4.4. Day 70 (± 4 days)

- Hematology safety labs (see Section 8.2.1.1)
  - WBC with differential
  - Hemoglobin
  - Platelet count
- Chemistry safety labs (see Section 8.2.1.2)
  - ALT
  - Total Bilirubin
  - Creatinine
- Adverse event assessment (see Section 9)
- Concurrent medications assessment (see Section 6.6.1)
- Virology specimen for CMV viral load (see Section 8.2.2.1)
- Updated results of any etiological investigations for SNHL.

7.4.5. Month 4 (± 7 days)

- Virology specimen for CMV viral load (see Section 8.2.2.1)
- Updated results of any etiological investigations for SNHL.

7.4.6. Month 6 (± 7 days)

- Virology specimen for CMV viral load (see Section 8.2.2.1)
- Hearing assessment (see Section 8.1.4) (to be obtained -14 days to +30 days from Study Month 6)
  - BSER or VRA (to assess neuro-otologic status) and OAEs (DPOAE or TEOAE) will be obtained. If the BSER and/or VRA is abnormal, then bone conduction will be obtained to

distinguish between sensorineural hearing loss, conductive loss, or mixed loss. If the OAEs are abnormal, then acoustic emittance measures (tympanometry and acoustic reflexes) will be obtained to better define the middle or inner ear abnormality (e.g., otitis media).

- Updated results of any etiological investigations for SNHL.

7.5. Final Study Visit

At the last clinic visit, the study subject's parent or guardian should be notified that this is the last contact/visit for the study. If the family would like to know results of the study, they will be asked to provide contact information (if different to information previously recorded) so that at a later date (after study results analyzed, the study staff can contact the parent or guardian.

7.6. Early Termination Visit

Study subjects may withdraw voluntarily from participation in the study at any time. Study subjects may also withdraw voluntarily from receiving the study intervention for any reason. If a study subject withdraws or is discontinued from the study at any time prior to completion of the study, the reason for this decision will be recorded on the CRFs. The remaining follow-up evaluations will be conducted if patient consent is obtained. SAEs and AEs will be followed according to guidelines in Section 9. The study subject should be encouraged to complete follow-up visits as part of the intent to treat group.

Should a study subject's therapy be discontinued prematurely, all clinical and laboratory evaluations scheduled during the next study visit will be completed on the day the study subject is discontinued. All key endpoints will be evaluated and all randomized study subjects will continue to be followed as long as possible and included in the final analysis.

7.7. Unscheduled Visit

Should an unscheduled visit occur, it would likely be due to an adverse event. At this visit, the study subject will be assessed as standard of care. Recording of SAEs or AEs will be done according to Section 9.0 of this protocol.

8. STUDY PROCEDURES/EVALUATIONS

The study procedures and evaluations are summarized in Appendix A. Allowable windows for each study visit have been described previously. Some assessments and medical history information may be collected from the subject's medical charts as outlined below.

8.1. Clinical Evaluations

8.1.1. Baseline Demographics

To characterize the study subjects, information will be recorded at the baseline study visit (Day -30 to Day 1, unless broader window allowed below) following the obtaining of informed consent. Data collected will include basic demographics and selected laboratory parameters. The following information will be collected from the subjects medical records to the extent the information is available: date of birth; gender; race; ethnicity; birth weight; length at birth; head circumference at birth; and gestational age at birth. The degree of CMV disease involvement at birth will be recorded, if known, including: neuroimaging abnormalities; petechiae at any time from birth through study randomization; thrombocytopenia at any time from birth through study randomization; hepatomegaly at any time from birth through study randomization; splenomegaly at any time from birth through study randomization; CSF white blood cell count at any time from birth through study randomization; CSF protein concentration at any time from birth through study randomization; CSF CMV PCR at any time from birth through study randomization; seizures at any time from birth through study randomization; elevated transaminases at any time from birth through study randomization; elevated bilirubin at any time from birth through study randomization. Medical history and baseline conditions prior to study randomization will be recorded by body system.

8.1.2. Growth

To adjust study medication for weight gain, weight will be recorded at multiple study visits. To assess renal function, length will be recorded at multiple study visits for use in calculating creatinine clearance.

8.1.3. Adverse Event Assessment

At each study visit from the receipt of first dose of study drug and continuing through four weeks following the final dose of study drug, the study subject will be assessed for any adverse events (see Section 9).

8.1.4. Hearing Assessment

At the study visits on Week 0 (window: Study Day -90 to Study Day -1) and Month 6 (window: -14 days to +30 days), age-appropriate assessments of hearing will be performed. Results of hearing assessments conducted for clinical care may be utilized if conducted within the study window. BSER and/or visual reinforcement audiometry (VRA) (to assess neuro-otologic status) and OAEs (DPOAE or TEOAE) will be obtained. If the BSER and/or VRA is abnormal, then bone conduction will be obtained to distinguish between sensorineural hearing loss, conductive loss, or mixed loss. If the OAEs are abnormal, then acoustic immittance measures (tympanometry and acoustic reflexes) will be obtained to better define the middle or inner ear abnormality (e.g., otitis media).

If a study subject proceeds to cochlear implantation during the course of the study, he/she will not require additional study-related hearing assessments following the implantation procedure. Prior to the implantation, efforts will be made to obtain audiology testing that would have been performed at the Month 6 visit.

8.2. Laboratory Evaluations

Blood for study-specified laboratory evaluations may be obtained by methods such as the following: venipuncture, heel stick, indwelling heparin- or saline-locked intravenous catheter, etc. As detailed below, blood will be obtained for assessment of hematology safety labs, chemistry safety labs, whole blood CMV viral load/resistance testing, and ganciclovir population pharmacokinetics. If an insufficient volume of blood is obtained for all of the tests at any given study visit, the following prioritization as to which tests to send will apply (most important to least important): 1) hematology safety labs (most important); 2) chemistry safety labs (second most important); 3) whole blood CMV viral load/resistance testing (third most important); and 4) ganciclovir population pharmacokinetics (least important). With the exception of the hematology safety labs and the creatinine and ALT assessments, those lab tests which are unable to be obtained due to lack of sufficient blood or parental refusal at a given study visit will not be reported as protocol deviations. If urine is not obtainable, a protocol deviation will not be reported. Saliva will be collected using polyester fiber–tipped swabs. As far as possible safety labs and other research specimens should be taken to coincide with clinical care. If it is not possible to obtain samples for safety labs at a study visit and bloods were obtained for clinical care within 2 days of the study visit, the data may be extracted from the medical records.

8.2.1. Clinical Laboratory Evaluations

Blood will be drawn at each study visit. For all study-related tests, a total of 8.75 mL will be drawn from a given study subject during the period of valganciclovir administration, and an additional 3.0 mL will be drawn for study labs when valganciclovir is not being administered.

The breakdowns of the amount of blood for individual tests are provided in Appendix A, and below. Clinical laboratory results can be used for chemistry and hematology safety labs if collected for clinical care and within the required study window. If labs drawn for the study required assessments are not evaluable, blood draws will not be repeated.

8.2.1.1. Hematology Safety Labs

All hematology safety laboratory assessments will be conducted at the PI's local lab. These assessments will provide information on the safety of administering the study drug. They will be collected at each study visit while the study subject is receiving valganciclovir and at the two week visit thereafter. The following will be tested: white blood cell count, differential, hemoglobin, and platelet count. The total amount of blood required for the hematology safety labs is 2.5 mL over 8 weeks.

8.2.1.2. Chemistry Safety Labs

All chemistry safety laboratory assessments will be conducted at the PI's local lab. These assessments will provide information on the safety of administering the study drug. They will be collected at each study visit while the study subject is receiving valganciclovir and at the two week visit thereafter. The following will be tested: ALT, total bilirubin, and creatinine. The total amount of blood required for the chemistry safety labs is 5.0 mL over 8 weeks.

8.2.2. Special Assays or Procedures

8.2.2.1. CMV Viral Load/Resistance Testing

Assessment of CMV viral load in whole blood will be conducted at the UAB Central Laboratory. In study subjects with increasing whole blood viral loads during the course of treatment, assessment for antiviral resistance may be undertaken on the serially collected samples. Whole blood will be collected at each study visit. The total amount of blood required for the whole blood CMV viral loads is 3.5 mL over 6 months. CMV viral load will be assessed by quantitative PCR.

Urine collection by bagged or clean catch specimen will be attempted at each study visit. If urine is not obtainable, a protocol deviation will not be reported. Saliva will be collected at each study visit. Specimens will be shipped to the UAB Central Laboratory for analysis.

Antiviral resistance will be performed in the UAB Viral Resistance Laboratory.

8.2.2.2. Ganciclovir Population Pharmacokinetics

Assessment of ganciclovir plasma concentrations will be conducted at the UAB Central Pharmacokinetic Laboratory. Ganciclovir concentrations will be obtained with each blood draw obtained while the subject is receiving valganciclovir (Study Day 14, Study Day 28, and Study Day 42). Assessments on each of the Study Days will consist of a single trough specimen. For each subject, one of these three draws will occur 0 to 4 hours after a valganciclovir dose, one will occur 4 to 8 hours after a valganciclovir dose, and one will occur 8 to 12 hours after a valganciclovir dose. The required amount of whole blood for plasma ganciclovir determination at each timepoint is at least 200 μL (0.2 mL). Specimens will be processed to separate the plasma, which will be shipped to the UAB Central Pharmacokinetic Laboratory.

8.2.3. Specimen Preparation, Handling, and Shipping

8.2.3.1. Instructions for Specimen Preparation, Handling, and Storage

Specific instructions on specimen collection, preparation, handling, and storage will be provided in the Manual of Procedures for this study.

8.2.3.2. Specimen Shipment

Specific instructions on specimen shipping will be provided in the Manual of Procedures for this study.

9. DMID SAFETY REPORTING AND SAFETY MONITORING

Regulatory requirements including the Food and Drug Administration (FDA) regulations, International Conference on Harmonisation (ICH) Guidelines for Good Clinical Practice (GCP), and European Union (EU) Clinical Trials Directive set forth safety monitoring and reporting responsibilities of sponsors and investigators to ensure the safety and protection of human subjects participating in clinical trials.

9.1. Responsibilities

Investigators participating in this clinical trial are responsible for and will:

- Evaluate subject safety including assessment of adverse events (AEs) for seriousness, severity, and causality;
- Notify the Central Unit (the Central Unit notifies the sponsor, DMID), of protocol-defined serious adverse events (SAEs) within 24 hours; (details provided in the MOP)
- Provide detailed written reports, including necessary documentation requested by the sponsor or institutional review board (IRB)/independent ethics committee (IEC), promptly following immediate initial reports; and
- Inform the IRB/IEC of AEs as required by applicable regulatory requirements.

9.2. Adverse Event (AE)

9.2.1. Definition of an Adverse Event

Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of medicinal (investigational) product whether or not considered drug related. The occurrence of an AE may come to the attention of study personnel during study visits and interviews of a study recipient presenting for medical care, or upon review by a study monitor.

9.2.2. Documentation of Reportable Adverse Events

Information to be collected on reportable AEs includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis, which would include MD or DO), and time of

resolution/stabilization of the event. All AEs occurring from Study Day 1 through four weeks following the last dose of study drug must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution. SAE reporting is described in section 9.5.

Any medical condition that is present at the time that the patient is randomized should be considered as a baseline condition and not reported as an AE. However, if the event meets the criteria in Section 9.2.1 and the grade of the event worsens at any time during the study, it should be recorded as an AE.

9.3. Investigator's Assessment of Adverse Event

The determination of seriousness, severity, and causality will be made by an on-site investigator who is qualified (licensed) to diagnose AE information, provide a medical evaluation of AEs, and classify AEs based upon medical judgment. This includes MD or DO. Events will be identified by assessing the subject at each visit. If a subject is hospitalized, the medical record should be reviewed to identify AEs. The PI is responsible for identifying and reporting AEs according to protocol guidelines.

9.3.1. Assessment of Seriousness

Event seriousness will be determined according to the protocol definition of an SAE (see Section 9.5).

9.3.2. Assessment of Severity

All reportable AEs will be graded according to the DIADS Toxicity Table (Appendix B).

9.3.3. Assessment of Relationship to Study Product

Relationship to Study Products: The clinician's assessment of an AE's relationship to valganciclovir study drug is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event should be reported. All AEs must have their relationship to study product assessed using the terms: related or not related. In a clinical trial, the study product must always be suspect.

The investigator must provide an assessment of relationship of AEs to the study product based on:

- Temporal relationship of the event to the administration of study product;

- Whether an alternative etiology has been identified;
- Biological plausibility; and
- Existing therapy, and/or concomitant medications.

To help assess, the following guidelines are used:

- Related– There is a reasonable possibility that the study product caused the adverse event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study product and the adverse event.

- Not Related– There is **not** a reasonable possibility that the administration of the study product caused the event.

9.4. Study Related Adverse Events

In earlier investigations of ganciclovir and valganciclovir in infants, the side effect that was seen commonly was neutropenia. Therefore, neutropenia occurring during the course of the treatment period of the study will be assumed to be associated with study medication.

- The study drug related and expected adverse events as documented from prior studies consist of:
    - anemia
    - neutropenia
    - diarrhea, and
    - elevated alanine aminotransferase (ALT).

9.5. Serious Adverse Event (SAE)

9.5.1. Definition of a Serious Adverse Event

An adverse event or suspected adverse reaction is considered “serious” if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death,
- a life-threatening adverse event*,

- inpatient hospitalization or prolongation of existing hospitalization,
- a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or
- a congenital anomaly/birth defect.
- Important medical events that may not result in death, be life-threatening, or require hospitalizations may be considered serious when, based upon appropriate medical judgment they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

* Life-threatening adverse event. An adverse event is considered “life-threatening” if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event that, had it occurred in a more severe form, might have caused death.

Events related to cochlear implantation will be recorded on the CRF, but will not be considered an AE or SAE unless meeting one or more of the above outcomes:

All SAEs will be:

- recorded on the appropriate SAE eCRF
- followed through resolution or stabilization by a study clinician
- reviewed and evaluated by a study clinician

9.5.2. Reporting Interval

Document all AEs and SAEs from Study Day 1 through four weeks following the last dose of study drug.

All AEs and SAEs will be followed until resolution, even if this extends beyond the study-reporting period. Resolution of an AE is defined as the return to pretreatment status or stabilization of the condition with the expectation that it will remain chronic.

At any time after completion of the study, if the investigator becomes aware of an SAE that is suspected to be related to study product, the investigator will report the event.

9.5.3. Notification of the Sponsor of Serious Adverse Events

When a site identifies any SAE that meets the protocol-defined serious criterion, a call will first be made to the Clinical Studies Administrator at the Central Unit. Within 24 hours of identification, the SAE will be entered into the eCRF and the original signed SAE document will be faxed to the Central Unit. If a signature from the PI is not obtained within 24 hours, it will be faxed without the signature.

Fax: 205-935-8559 to the attention of Central Unit Safety Coordinator.

The Central Unit will report all serious adverse events to DMID pharmacovigilance contractor, at the following email address: SAE Email address - PVG@dmidcroms.com.

Should it be necessary for the Central Unit to contact the DMID Pharmacovigilance Group the following is contact information:

DMID Pharmacovigilance Group
Clinical Research Operations and Management Support (CROMS)
6500 Rock Spring Dr., Suite 650
Bethesda, MD 20814, USA
SAE Hot Line: 1-800-537-9979 (US) or 1-301-897-1709 (outside US)
SAE FAX Phone Number: 1-800-275-7619 (US) or 1-301-897-1710 (outside US)

Other supporting documentation of the event may be requested by the DMID pharmacovigilance contractor and should be provided as soon as possible. The DMID pharmacovigilance contractor will notify the DMID medical monitor and clinical protocol manager. The DMID medical monitor will review and assess the SAE for regulatory reporting and potential impact on study subject safety and protocol conduct. At any time after completion of the study, if the investigator becomes aware of an SAE that is suspected to be related to study product, the investigator will report the event to the DMID Pharmacovigilance Group.

9.5.4. Regulatory Reporting for Studies Conducted Under DMID-Sponsored IND

Following notification from the Central Unit DMID, the IND sponsor, will report to FDA any suspected adverse reaction that is both serious and unexpected. DMID will report an adverse event as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the drug and the adverse event. DMID will notify FDA and all participating investigators (i.e., all investigators to whom the sponsor is providing drug under its INDs or under any investigator's IND) and the Central Unit in an IND safety report of potential serious risks from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the sponsor determines that the information qualifies for reporting as specified in 21 CFR Part 312.32. DMID will also notify FDA of any unexpected fatal or life-

threatening suspected adverse reaction as soon as possible but in no case later than 7 calendar days after the sponsor's initial receipt of the information. Relevant follow-up information to an IND safety report will be submitted as soon as the information is available. Upon request from FDA, DMID will submit to FDA any additional data or information that the agency deems necessary, as soon as possible, but in no case later than 15 calendar days after receiving the request.

All serious events designated as "not related" to study product(s), will be reported by DMID to the FDA at least annually in a summary format.

The Site Investigator is responsible for informing the Ethics Committee and/or IRB of the SAE as per local requirements. For non-US sites, the site investigator is responsible for also informing their Regulatory Authority as required by their local regulations.

9.6. Halting Rules

9.6.1. Discontinuation of Study participation for individual subject

Subjects with neutropenia, thrombocytopenia, renal impairment, or hepatotoxicity will be discontinued from study treatment if the criteria outlined in Section 6.3 are met. Since the primary endpoint requires comparison of baseline and 6 month audiology assessments, dropouts and subjects with audiology assessments that are inadequate for study comparison will be replaced in order to reach the target of sample size.

9.6.2. Discontinuation of Study Enrollment Pending Sponsor Review

In prior CASG studies of ganciclovir and valganciclovir that have enrolled 233 subjects, the only laboratory toxicity statistically associated with antiviral treatment has been neutropenia. Halting rules for this study therefore have been constructed to interrupt study enrollment if an excessive number of subjects are experiencing neutropenia. In the CASG 102 study, 63% of subjects receiving parenteral ganciclovir developed Grade 3 or Grade 4 neutropenia.[20] In the CASG 109 study, 38% of subjects receiving oral valganciclovir developed Grade 3 or Grade 4 neutropenia.[24] Whether this lower rate of neutropenia relates to the mode of drug delivery is not known at this time. Assuming that 75% of subjects receiving ganciclovir developed Grade 3 or 4 neutropenia and given that randomization is expected to be balanced between those in study drug and those in placebo, the stopping rule will be based on assuming that the overall event rate for all study participants (i.e., placebo and active subjects combined) is 37.5%. Therefore, study enrollment will be stopped and an ad hoc review will be performed if a significantly higher proportion (37.5%) of subjects in this study experience Grade 3 or Grade 4 neutropenia, as detailed in the following table:

X of the first Y subjects enrolled have Grade 3 or Grade 4 neutropenia, according to the table below. The stopping rules are based on the upper tail probabilities of the cumulative binomial with probability of an event set at 0.375. The cut-off numbers were determined by obtaining the largest value such that the tail probability is less than but closest to 0.05.

Number enrolled (Y)	Stop/Investigate when number with events equals this number (X)	Probability of observing X or more events assuming p=0.375	Number enrolled (Y)	Stop/Investigate when number with events equals this number (X)	Probability of observing X or more events assuming p=0.375
4	4	0.020	30	17	0.025
5	5	0.007	31	17	0.037
6	5	0.031	32	18	0.024
7	6	0.013	33	18	0.034
8	6	0.036	34	18	0.048
9	7	0.017	35	19	0.032
10	7	0.038	36	19	0.044
11	8	0.019	37	20	0.030
12	8	0.039	38	20	0.041
13	9	0.021	39	21	0.028
14	9	0.039	40	21	0.038
15	10	0.021	41	22	0.026
16	10	0.037	42	22	0.035
17	11	0.021	43	22	0.047
18	11	0.036	44	23	0.032
19	12	0.021	45	23	0.043
20	12	0.034	46	24	0.030
21	13	0.020	47	24	0.040
22	13	0.033	48	25	0.028
23	13	0.050	49	25	0.037
24	14	0.031	50	25	0.048
25	14	0.046	51	26	0.034
26	15	0.029	52	26	0.044
27	15	0.043	53	27	0.032
28	16	0.027	54	27	0.041
29	16	0.040			

Additionally, DMID and the Central Unit may interrupt study dosing and/or study entry at any time if medically indicated. To minimize risk, the medical monitor and the DSMB will review cumulative safety data. If enrollment is halted based upon the table above or the review of the safety data, upon completion of the review and receipt of advice of the DSMB, DMID and the Central Unit Administration will determine if study entry or study dosing may continue according to the protocol.

9.7. Safety Monitoring by the DMID Safety Oversight Mechanism

9.7.1. Data and Safety Monitoring Board

A Data and Safety Monitoring Board will be established by the DMID. The DSMB members will consist of persons independent of the investigators or study team with no financial, scientific or other conflict of interest with the study and will be selected by the NIH. The initial responsibility of the DSMB will be to review and make recommendations regarding the initiation of the study. A simple majority will be considered a DSMB quorum for voting and meeting purposes. Members will be able to submit data review comments electronically if they are not able to participate in a data review meeting teleconference. After the initiation of the study and during the course of the study at intervals determined by the DMID, the DSMB will:

1. Review the research protocol, template informed consent document and plans for data and safety monitoring.
2. Evaluate the progress of the study, including periodic assessments of data quality and timeliness, participant recruitment, accrual and retention, participant risk versus benefit, performance of the trial sites, and other factors that can affect study outcome.
3. Review study endpoints for differences between groups and to assess if SAEs are occurring at a rate greater than expected.
4. Consider factors external to the study when relevant information becomes available,
5. Monitor the confidentiality of the study data and the results of monitoring.

The S&DCC will provide all data, tables, unique and repeated listings, figures, descriptive statistics, and tests of significance requested by the NIH for all DSMB meetings, interim analysis plan and final analysis.

10. CLINICAL MONITORING

10.1. Site Monitoring Plan

Site Monitoring will be conducted to ensure that human subject protection, study procedures, laboratory procedures, study intervention administration, and data collection processes are of high quality and meet sponsor, GCP/ICH, and regulatory guidelines, and that the study is conducted in accordance with the protocol and study manuals. NIAID/ DMID, the sponsor of this study, or its designee will conduct site monitoring visits as detailed in the monitoring plan.

Site visits will be made at standard intervals in accordance with the monitoring plan. More frequent visits may be made if needed. Monitoring visits will include, but are not limited to, review of regulatory files, case report forms, informed consent forms, medical and laboratory reports, and protocol compliance. Study monitors will meet with investigators to discuss any problems and actions to be taken and document visit findings and discussions.

Every effort will be made to maintain the anonymity and confidentiality of subjects during this study. However, because of the experimental nature of this treatment, the Investigator agrees to allow representatives of the Sponsor (DMID/NIAID) as well as authorized representatives of the Food and Drug Administration or other Regulatory agencies, Genentech/Roche, or the UAB Central Unit, to inspect the facilities used in this study and to inspect, for purposes of verification, the hospital or clinic records of all subjects enrolled into this.

11. STATISTICAL CONSIDERATIONS

11.1. Study Hypotheses

We hypothesize that six weeks of antiviral therapy can stabilize hearing in older infants and toddlers who have developed CMV-associated hearing loss. This study is designed as a proof of principle study.

11.2. Sample Size Considerations

Subjects will be randomized 1:1 to valganciclovir oral solution or valganciclovir placebo. A **sample size of 54 (27 in each arm)** has 90% power to detect a worsening of hearing from 40% to 8.0% in the treatment group based on analyzing two correlated binary outcomes with correlation coefficient of 0.55 at 2.5% level of significance (using PASS 2008 program). Randomization will be stratified by age at randomization (1 through 11 months, 12 through 23 months, 24 through 35 months, and ≥ 36 months) and by CMV involvement (symptomatic and asymptomatic at birth) as a marker of disease severity.

Efficacy and safety analysis will be based on intent-to-treat population (ITT), defined as any child who receives at least one dose of study medication and who has complete hearing assessment data at baseline and Month 6. Children who completed the full six weeks of study medication and have hearing assessment data at baseline and Month 6 will be included in a per protocol (PP) analysis of efficacy, which will be performed as a sensitivity analysis. Since the primary endpoint requires comparison of baseline and 6 month audiology assessments, dropouts and subjects with audiology assessments that are inadequate for study comparison will be replaced.

11.3. Planned Interim Analyses (if applicable)

No interim analysis for futility or efficacy is proposed because this is a small sample study and the penalty for an early look at the outcome data would compromise the study. However, a safety review will be done periodically.

11.3.1. Safety Review

Safety reports will be generated and sent to DMID to be disseminated to the DSMB. This report includes hematology and safety laboratory values and adverse events (serious and non-

serious). In addition, Section 9.7 provides a table of halting rules based on the number of subjects experiencing Grade 3 or 4 neutropenia for consideration by the DSMB.

11.3.2. Immunogenicity or Efficacy Review

None.

11.4. Final Analysis Plan

11.4.1. Primary Outcome

Primary analysis will be based on intent-to-treat population. Categories utilized for hearing assessment of each ear for each time point are normal hearing, mild hearing loss, moderate hearing loss, and severe hearing loss. Based on the hearing assessment of each ear at Month 6 and at Baseline, change in each ear will be categorized into binary outcomes: improved + no change versus other (i.e., worsened). For example, normal in the left ear at baseline and moderate in the same ear at Month 6 will be considered as worsened. The primary outcome will be analyzed using logistic regression based on generalized estimating equations (GEE) in order to accommodate the correlation between the left and right ears of a subject in the modeling. In addition, if there are enough data available we will adjust the analyses by whether or not a subject at birth is asymptomatic or symptomatic from their congenital CMV infection. Additional analyses will be performed to adjust for age and site plus any imbalances in the demographic and clinical characteristics to determine if adding them to the model will impact the results. P-values < 0.05 will be considered significant for the primary outcomes.

A single, independent study audiologist who is masked (blinded) to treatment assignment will assess the audiology test battery for each subject and assign the classifications of normal hearing, mild hearing loss, moderate hearing loss, or severe hearing loss based upon their hearing thresholds (in decibels). The classifications will be assigned by ear (one for the left ear and one for the right ear), giving “total ear” classifications. Following this, the study audiologist will assign the “best ear” classification for the subject at that study visit; for example, if a subject had mild hearing loss in their left ear and severe hearing loss in their right ear, then the “best ear” classification will be mild hearing loss.

Primary analyses will be done on the first 54 subjects recruited. If there were subjects enrolled as replacement for dropouts or missing outcome, these added subjects will be included in the secondary analyses.

For those with missing outcome due to missing baseline and/or Month 6 audiology (including dropouts), we will exclude them from the primary analysis. However, we will perform sensitivity analysis by replacing all missing data with “worsening” outcome.”

11.4.2. Secondary and Tertiary Outcomes

Logistic analyses will be utilized to determine if there is treatment effect based on the best ear outcome. As in the total ear analysis, change in the best ear will be categorized into binary outcomes – namely: 1) improved + no change versus others, which examines positive hearing outcomes defined as improved hearing or protection from hearing impairment in subjects who started with normal hearing at baseline; 2) worsened versus others, which examines deterioration or worsening of hearing; 3) improved versus others; and 4) worse + no change versus others. Similar analyses will be performed for total ears (worsened versus others, improved versus others, and worse + no change versus others.

For other secondary and tertiary outcomes, Fisher's exact test will be used to compare binary outcomes (such as detection of viruria or subject with at least one AE or SAE), and Wilcoxon Rank test will be used to compare continuous outcomes (such as quantitative log reduction) between the two treatment groups 6 weeks and 6 months after initial treatment.

Logistic model utilizing generalized estimating equations will also be used to determine the association between change in hearing and change in viral load. Change in viral load over time will be measured by the area under the curve computed using the trapezoidal rule. Spearman rank correlation will be utilized to examine the association between viral load and PK parameters. Poisson regression model will be used to compare the number of AEs/SAEs experienced by subjects between the two groups.

As in the primary outcomes, missing change in hearing outcomes will be replaced by worsened outcome as sensitivity analyses for all secondary hearing outcomes..

12. SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

The site will maintain appropriate medical and research records for this trial, in compliance with ICH E6, Section 4.9 and regulatory and institutional requirements for the protection of confidentiality of subjects. As part of participating, the site will permit authorized representatives of the sponsor(s), DMID, the UAB Central Unit and regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits, and evaluation of the study safety and progress.

Documentation of source data is necessary for the reconstruction, evaluation, and validation of clinical findings, observations, and other activities during a clinical trial. Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Examples of these original documents and data records include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, subjects' evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, Source Document Worksheets (SDWs), copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and subject files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical trial. Source documentation serves to substantiate the integrity of trial data, confirms observations that are recorded, and confirm the existence of study participants. This standard also serves to ensure data quality by creating audit trails and enabling verification that data are present, complete, and accurate. Sites that are participating in this trial should consult the MOP, and DMID/NIAID Source Document Standards (most current version) for specific instruction and forms.

Local, state, institution, IRB/independent ethics committee (IEC) policies and procedures may be different from those stated in this standard. The site should refer to local, state, institution, IRB/IEC policies and procedures and follow them if they are more stringent than the DMID Standards.

According to the ICH GCP 4.9: "The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the eCRFs and in all required reports. Data reported on the eCRFs, which are derived from source documents, should be consistent with the source documents or discrepancies should be explained."

SDWs that mirror each data field on the eCRF will be available for use by sites to record and maintain data for each study participant enrolled in the study. Some data on the SDW may be extracted from the medical record or other source documents, and some data may be recorded on the SDW as the source document.

13. QUALITY CONTROL AND QUALITY ASSURANCE

The study site will have a quality management plan. Data will be evaluated for compliance with the protocol and accuracy in relation to source documents. The study will be conducted in accordance with procedures identified in the protocol. Items to be reviewed include, but are not limited to: eligibility (including informed consent), AE reporting, study/clinical endpoints, follow-up contacts, regulatory documents, study discontinuation, and review of clinical records. Data that will be reviewed, who is responsible for implementation, and the schedule for internal reviews will be specified or referenced in the quality management plan.

The investigational sites are responsible for conducting routine quality control (QC) and quality assurance (QA) activities to internally monitor study progress and protocol compliance. The Principal Investigators will provide direct access to all trial-related sites, source data /source documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities. The Principal Investigator will ensure all study personnel are appropriately trained and applicable documentations are maintained on site. DMID clinical site monitors will verify the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, Good Clinical Practice, and the applicable regulatory requirements. Clinical monitoring reports will be submitted to DMID and to the Central Unit.. The Statistical and Data Coordinating Center (SDCC) will implement quality control procedures beginning with the data entry system and generate data quality control checks that will be run on the database. Missing data or data anomalies will be communicated to the site(s) for clarification and resolution by the Central Unit.

The study monitors will verify that the clinical trial is conducted and data are generated, documented, and reported in compliance with the protocol, ICH E6(R1), and the applicable regulatory requirements. Reports will be submitted to DMID on monitoring activities. The study site will provide direct access to all trial-related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor and their designees.

The Statistical and Data Coordinating Center (S&DCC) has extensive experience in data management for over approximately 16 currently active national/international collaborative studies, and systems and approaches employed for this proposal will be based on existing, highly successful platforms. A distributed data management system, where the clinical centers are responsible for the entry and management of data from their own center, is both cost-effective (as it removes a significant number of queries) and results in higher quality data.

14. ETHICS/PROTECTION OF HUMAN SUBJECTS

14.1. Ethical Standard

This trial will be conducted in compliance with the protocol, International Conference on Harmonization Good Clinical Practice E6 (ICH-GCP), and the applicable regulatory requirements, including:

- U.S. Code of Federal Regulations applicable to clinical studies (45 CFR 46 and 21 CFR including parts 50 and 56 concerning informed consent and IRB regulations, if under IND, 21 CFR 312).
- Completion of Human Subjects Protection Training. Refer to http://grants.nih.gov/grants/guide/notice-files/NOT-OD-01-061.html; http://cme.cancer.gov/clinicaltrials/learning/humanparticipant-protections.asp

The investigator will ensure that this study is conducted in full conformity with the principles set forth in The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research of the US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (April 18, 1979) and codified in 45 CFR Part 46 and/or the ICH E6; 62 Federal Regulations 25691 (1997).

14.2. Institutional Review Board

Reviewing IRBs must be registered with the OHRP to conduct FDA-regulated studies. In the United States and in other countries, institutions are required to hold a current US Federalwide Assurance (FWA) issued by OHRP.

This protocol, informed consent documents, relevant supporting information, and all types of volunteer recruitment or advertisement information will be submitted to the Institutional Review Board (IRB) for review and must be approved before the study is initiated. Any amendments to the protocol must also be approved by the IRB prior to implementing changes in the study.

The investigator is responsible for keeping the IRB apprised of the progress of the study and of any changes made to the protocol as deemed appropriate, but in any case at least once per year. The investigator must also keep the IRB informed of any significant AEs.

All IRB approved documents as well as relevant study correspondence should be copied and sent to the UAB Central Unit.

14.3. Informed Consent Process

The process of obtaining informed consent must be documented in the medical records, clinic chart, and/or research chart. The consent form must be signed and dated by the study participant/study participant's parent/legal guardian before participation in the study. A copy of the signed consent form must be provided to the study participant/study participant's parent/legal guardian. Signed consent forms must remain in each study participants study file and must be available for verification by study monitors at any time.

The investigational nature and research objectives of this trial, the procedure, and its attendant risks and discomforts will be carefully explained to the study participant/study participant's parent/legal guardian. A signed informed consent document will be obtained from each study participant/study participant's parent/legal guardian prior to entry into this study. At any time during participation in the protocol, if new information becomes available relating to risks, AEs, or toxicities, this information will be provided orally or in writing to all enrolled or prospective study participant/study participants' parent/legal guardian. Documentation will be provided to the IRB and, if necessary, the informed consent will be amended to reflect any relevant information.

An investigator shall seek such consent only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence. The information that is given to the subject or the representative shall be in language understandable to the subject or the representative.

Subjects/subject's parent/legal guardian will sign the informed consent document prior to any procedures being done specifically for the study. Subjects/subject's parent/legal guardian should have the opportunity to discuss the study with their family, friends or personal physician, or think about it prior to agreeing to participate. Subjects/subject's parent/legal guardian may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the subjects /subject's parent/legal guardian for their records. The rights and welfare of the subjects will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

14.3.1. Informed Consent/Assent Process (in Case of a Minor)

Not applicable.

14.4. Exclusion of Women, Minorities, and Children (Special Populations)

This pediatric study will not exclude young children, females, or minorities. This study will be inclusive of all children who meet the inclusion/exclusion criteria, regardless of religion, gender, or ethnic background.

14.5. Subject Confidentiality

The information obtained during the conduct of this clinical study is confidential, and disclosure to third parties other than those noted below is prohibited. The results of the research study may be published, but study participant's names or identities will not be revealed. Records will remain confidential. To maintain confidentiality, the principal investigators at each site will keep records in locked cabinets and the results of tests will be coded to prevent association with volunteers' names. Data entered into computerized files will be accessible only by authorized personnel directly involved with the study and will be encoded. Data received by DMID and forwarded to Genentech/Roche will not include subject specific data but only encoded data. However, subject specific information will be available to the clinical monitors, to the FDA and to health authorities where provided by law. The NIAID/DMID, Genentech/Roche, and the UAB Central Unit may use information obtained during the conduct of this study in connection with the development of the study drug.

The study investigator is obliged to provide the Sponsor (DMID/NIAID) and the S&DCC with complete test results and all data developed in this study. The Sponsor may disclose this information to appropriate regulatory authorities as deemed necessary. .

Subject-specific information may be provided to other appropriate medical personnel only with the study participant's permission. To ensure compliance with current ICH guidelines, data generated by this study must be available for inspection upon request by representatives of national and local health authorities, the Sponsor, UAB Central Unit, and/or the IRB/IEC for each study site.

14.6. Study Discontinuation

Please see Section 5.3 for criteria for discontinuing study and / or study subject participation.

14.7. Future Use of Stored Specimens

Some of the specimens obtained from study participants during this study will be stored indefinitely in the Children's Diagnostic Virology Laboratory at the University of Alabama at Birmingham and may be used in future CMV research. These specimens will be labeled with a code number and not with the study participant's name. At the time of consent for study participation, study participant's parent/legal guardian will have the opportunity to either agree to have their specimens used in future CMV research or decline to have their specimens used in future CMV research. The study participant's parent/legal guardian will indicate his/her preference by initialing the appropriate line or checking the appropriate box of the Consent Form in the section entitled, "Future Use of Specimens". Non-protocol designated, future testing of samples will be performed only on samples from study participants who have consented for future testing of samples. These specimens will only be utilized to better understand the natural history of CMV or improve diagnosis.

A repository for residual samples will be established according to OHRP guidelines ensuring that codes or other personally identifying links will not be distributed to future researchers.

If the study participant's parent/legal guardian has indicated in the signed consent form that he/she does not agree to allow the future use of specimens for future CMV research, then his/her child's specimens will be destroyed at the completion of the study.

15. DATA HANDLING AND RECORD KEEPING

The investigator is responsible to ensure the accuracy, completeness, legibility, and timeliness of the data reported.

Electronic case report forms (eCRFs) will be developed by the UAB Statistical and Data Coordinating Center. The eCRFs will be provided electronically by the UAB Central Unit. Original data will be recorded on source documents (e.g., medical records, research progress notes, Source Document Worksheets documenting research related procedures). Source Document Worksheets that contain each data field on the eCRF will be available for use by sites as a tool to record and maintain data for each study participant enrolled in the study when other source documents are not used to collect original data. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. When making a change or correction, cross out the original entry with a single line and initial and date the change. DO NOT ERASE, OVERWRITE, OR USE CORRECTION FLUID OR TAPE ON THE ORIGINAL. Specific guidance to investigators and study staff on making corrections to source documents and eCRFs will be provided in the MOP for this study.

Data recorded on the eCRF that differ from source documents must be explained on the Add Comment eCRF and in the subject's source documents. With the exception of calculation(s)/conversion(s) of data values, all calculation(s)/conversion(s) must be shown in the source documents for verification.

The integrity of the data is ensured by limited access and password protection. Each person (at study sites, the UAB Central Unit, and the DCC) is assigned access to only the portions of the database they need. Each person's access is provided under "hard" password protection (at least 8 characters and including both symbols and numbers) that are changed at 6 month intervals. At UAB, incremental data back-ups are made on a daily basis, and complete data backups are made on a weekly basis and stored at an off-site repository.

15.1. Data Management Responsibilities

All eCRFS must be reviewed by the investigator's research team, under the supervision of the investigator, who will ensure that they are accurate and complete. All data must be supported by source documents, which will remain available for review by regulatory personnel and monitors. Adverse events must be graded, assessed for intensity and causality, and reviewed by the site investigator or designee. All laboratory values must be assessed for clinical significance and non clinical significance, and reviewed by the site investigator or designee. Sites that are participating in this trial should consult the MOP and DMID/NIAID Source Document Standards (most current version) for specific instruction.

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site PI. During the study, the investigator must maintain complete and accurate documentation for the study.

The UAB Central Unit and Statistical and Data Coordinating will be responsible for data management, quality review, analysis of the study data, and writing of the clinical study report.

15.2. Data Capture Methods

Clinical and laboratory data will be entered into a 21 CRF Part 11 compliant Internet Data Entry System (IDES) provided by the UAB Statistical and Data Coordinating Center. The data system includes password protection and internal quality checks, such as automated range checks, to identify data that appear to be inconsistent, incomplete, or inaccurate.

15.3. Types of Data

Data for this study will include safety, laboratory (e.g., clinical and virologic), and outcome measures (e.g., virology, audiology).

15.4. Timing/Reports

Safety Reports will be generated and sent to DMID at intervals identified in the DSMB Charter, for dissemination to the DSMB.

15.5. Study Records Retention

Records and documents pertaining to the conduct of this study, including source documents, consent forms, laboratory test results, and medication inventory records, must be retained by the investigator for at least 2 years following completion of the study. No study records shall be destroyed without prior authorization from the UAB Central Unit and NIAID/DMID. These documents should be retained for a longer period, however, if required by local regulations. It is the responsibility of the sponsor to notify the UAB Central Unit, which will notify the investigators, when these documents no longer need to be retained.

15.6. Protocol Deviations

Each investigator must adhere to the protocol as detailed in this document and agree that any changes to the protocol must be approved by the UAB Central Unit and the Sponsor prior to

seeking approval from the IRB/IEC. Each investigator will be responsible for enrolling only those study participants who have met protocol eligibility criteria.

A protocol deviation is any noncompliance with the clinical trial protocol, GCP, or Manual of Procedures requirements. The noncompliance may be either on the part of the study participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with GCP:

4.5 Compliance with Protocol, Sections 4.5.1, 4.5.2, and 4.5.3

5.1 Quality Assurance and Quality Control, Section 5.1.1

5.20 Noncompliance, Sections 5.20.1 and 5.20.2.

It is the responsibility of the site to use continuous vigilance to identify and report deviations within 5 working days of identification of the protocol deviation, or within 5 working days of the scheduled protocol-required activity. However, if the deviation increases study subject risk, the reporting timeline is expedited, requiring submission of deviation within 1 working day of identification. All deviations must be promptly reported to the UAB Central Unit.

All deviations from the protocol must be addressed in the source documents. A completed copy of the DMID protocol deviation form must be maintained with the completed eCRFs. A log of protocol deviation will be maintained in the Project Notebook. Protocol deviations must be sent to the local IRB per the IRB's guidelines.

16. PUBLICATION POLICY

Following completion of this study, the investigators are expected to publish the results in a scientific journal. All research reports and other publications resulting from the work completed in this protocol shall:

- Acknowledge the support of the National Institutes of Health whenever publicizing the results from this clinical trial in any media by including an acknowledgement substantially as follows:
    - Be submitted to the Project Director in the form of advance copies for review and comment prior to the publication to ensure appropriate coordination of the research results.
    - Be furnished in a list of publications resulting from the research as part of the annual progress report submitted to the principal investigator.

The International Committee of Medical Journal Editors (ICMJE) member journals have adopted a trials-registration policy as a condition for publication. This policy requires that all clinical trials be registered in a public trials registry such as ClinicalTrials.gov, which is sponsored by the National Library of Medicine. Other biomedical journals are considering adopting similar policies.

Unless exempted, this trial will be registered prior to enrollment of study subjects. It is the responsibility of the study's PI (e.g., Dr. Kimberlin) to register the non-exempted trials and post results in compliance with Public Law 110-85, the Food and Drug Administration Amendments Act of 2007 (FDAAA).

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SUPPLEMENTS/APPENDICES

APPENDIX A: SCHEDULE OF EVENTS

	Enrollment (Window: Day -90 to Day -1)	**Randomization (Window: Day -30 to Day 1)**	**Study Day**					**Study Month**	
			1 (day -3 to day 1)	14 (± 2 days)	28 (± 2 days)	42 (± 2 days)	70 (± 4 days)	4 (± 7 days)	6 (± 7 days)
Following study enrollment, testing of Guthrie card for CMV DNA by PCR (if congenital CMV infection has not already been documented during first month of life)	X								
Confirmation of congenital CMV infection by documentation during first month of life or by PCR-positive Guthrie card		X							
Baseline demographics[a]		X							
Hematology Safety Labs[b]			X	X	X	X	X		
Chemistry Safety Labs[c]			X	X	X	X	X		
Weight and Length			X	X	X				
Adverse Event Assessment			X	X	X	X	X		
Concurrent Medications			X	X	X	X	X		
Updated results of any etiological investigations for SNHL			X	X	X	X	X	X	X
Hearing Assessment		X[d] Day -90 to Day -1							X -14 to +30 days
Virology Specimens for CMV Viral Load[e]			X	X	X	X	X	X	X
Ganciclovir Population Pharmacokinetics[f]				X	X	X			
Valganciclovir vs. Placebo Administration[g]			←	—	—	→			
Total volume of blood required			2.0 mL	2.25	2.25	2.25	2.0	0.5	0.5 mL

				mL	mL	mL	mL	mL	

a. Baseline demographics and birth history consist of date of birth; gender; race; ethnicity; birth weight; length at birth, if available; head circumference at birth, if available; and gestational age at birth. Degree of CMV disease involvement consists of neuroimaging abnormalities if imaging was performed; petechiae at any time from birth through study randomization, if known; thrombocytopenia at any time from birth through study randomization, if obtained; hepatomegaly at any time from birth through study randomization, if noted; splenomegaly at any time from birth through study randomization, if noted; CSF white blood cell count at any time from birth through study randomization, if obtained; CSF protein concentration at any time from birth through study randomization, if obtained; CSF CMV PCR at any time from birth through study randomization, if performed; seizures at any time from birth through study randomization, if noted; elevated transaminases at any time from birth through study randomization, if obtained; elevated bilirubin at any time from birth through study randomization, if obtained; medical history and baseline conditions prior to study randomization, by body system, chorioretinitis, intrauterine growth restriction; urine CMV testing (e.g., viral culture, shell-vial culture, PCR) within 90 days prior to study enrollment, if obtained clinically
b. WBC with differential, hemoglobin, Platelet enumeration (approximate total blood needed for these tests is 0.5 mL)
c. ALT, total bilirubin, creatinine (approximate total blood needed for these tests is 1.0 mL)
d. BSER and/or VRA (to assess neuro-otologic status) and OAEs will be obtained. If the BSER and/or VRA is abnormal, then bone conduction will be obtained to distinguish between sensorineural hearing loss, conductive loss, and mixed loss. If the OAEs are abnormal, then acoustic immittance measures (tympanometry and acoustic reflexes) will be obtained to better define the middle or inner ear abnormality (e.g., otitis media).
e. Required amount of whole blood for quantitative CMV PCR is at least 0.5 mL. Urine collection by bagged or clean catch specimen for quantitative PCR. Saliva collection by polyester fiber–tipped swabs for quantitative PCR.
f. Required amount of whole blood for plasma ganciclovir determination is at least 0.25 mL
g. Valganciclovir or placebo administration begins on Day 1 of the study; study medication dose adjusted for weight change, if needed, at each study visit while on treatment

APPENDIX B: DIVISION OF AIDS TOXICITY TABLES

CLINICAL				
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

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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CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
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
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)				

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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CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
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)
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

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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CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
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
Hemorrhage (significant acute blood loss)	NA	Symptomatic AND No transfusion indicated	Symptomatic AND Transfusion of $\leq$ 2 units packed RBCs (for children $\leq$ 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)
Pediatric ≤ 17 years (with repeat testing at same visit)	NA	91st – 94th percentile adjusted for age, length, and gender (systolic and/or diastolic)	≥ 95th percentile adjusted for age, length, and gender (systolic and/or diastolic)	Life-threatening consequences (e.g., malignant hypertension) OR Hospitalization indicated (other than emergency room visit)

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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CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
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
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)

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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CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
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)]
Ascites	Asymptomatic	Symptomatic AND Intervention indicated (e.g., diuretics or therapeutic paracentesis)	Symptomatic despite intervention	Life-threatening consequences
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)

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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CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
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)
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)

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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CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
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
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

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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CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
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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CLINICAL				
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

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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CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
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
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				

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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CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Adult ≥ 21 years	BMD t-score -2.5 to -1.0	BMD t-score < -2.5	Pathological fracture (including loss of vertebral length)	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 length)	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
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

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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CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
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
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)

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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CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
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)
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)

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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CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Lipoatrophy (e.g., fat loss from the face, extremities, buttocks)	Detectable by study participant (or by caregiver for young children and disabled adults)	Detectable on physical exam by health care provider	Disfiguring OR Obvious on casual visual inspection	NA

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

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

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

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

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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*
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*
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
Hemoglobin (Hgb)				

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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LABORATORY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Adult and Pediatric ≥ 57 days (HIV POSITIVE ONLY)	8.5 – 10.0 g/dL *1.32 – 1.55 mmol/L*	7.5 – 8.4 g/dL *1.16 – 1.31 mmol/L*	6.50 – 7.4 g/dL *1.01 – 1.15 mmol/L*	< 6.5 g/dL *< 1.01 mmol/L*
Adult and Pediatric ≥ 57 days (HIV NEGATIVE ONLY)	10.0 – 10.9 g/dL *1.55 – 1.69 mmol/L* OR Any decrease 2.5 – 3.4 g/dL *0.39 – 0.53 mmol/L*	9.0 – 9.9 g/dL *1.40 – 1.54 mmol/L* OR Any decrease 3.5 – 4.4 g/dL *0.54 – 0.68 mmol/L*	7.0 – 8.9 g/dL *1.09 – 1.39 mmol/L* OR Any decrease ≥ 4.5 g/dL *≥ 0.69 mmol/L*	< 7.0 g/dL *< 1.09 mmol/L*
Infant*†, 36 – 56 days (HIV POSITIVE OR NEGATIVE)	8.5 – 9.4 g/dL *1.32 – 1.46 mmol/L*	7.0 – 8.4 g/dL *1.09 – 1.31 mmol/L*	6.0 – 6.9 g/dL *0.93 – 1.08 mmol/L*	< 6.00 g/dL *< 0.93 mmol/L*
Infant*†, 22 – 35 days (HIV POSITIVE OR NEGATIVE)	9.5 – 10.5 g/dL *1.47 – 1.63 mmol/L*	8.0 – 9.4 g/dL *1.24 – 1.46 mmol/L*	7.0 – 7.9 g/dL *1.09 – 1.23 mmol/L*	< 7.00 g/dL *< 1.09 mmol/L*
Infant*†, 1 – 21 days (HIV POSITIVE OR NEGATIVE)	12.0 – 13.0 g/dL *1.86 – 2.02 mmol/L*	10.0 – 11.9 g/dL *1.55 – 1.85 mmol/L*	9.0 – 9.9 g/dL *1.40 – 1.54 mmol/L*	< 9.0 g/dL *< 1.40 mmol/L*
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*

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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LABORATORY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
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*
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*
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 (corrected for albumin)				
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*

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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LABORATORY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
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 (corrected for albumin)				
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*
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†
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*

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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LABORATORY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
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	< 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
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*

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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LABORATORY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
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*
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*

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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