A PHASE II, SINGLE-STAGE, SINGLE-ARM INVESTIGATION OF ORAL VALGANCICLOVIR THERAPY IN INFANTS WITH ASYMPTOMATIC CONGENITAL CYTOMEGALOVIRUS INFECTION

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Day Month Year
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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 Good Clinical Practice guidelines (GCP), and the applicable regulatory requirements, including:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46; 21 CFR Part 50, 21 CFR Part 54, 21 CFR Part 56, and 21 CFR Part 312);
- International Conference on Harmonization (ICH) E6; 62 Federal Register 25691 (1997);
- National Institutes of Health (NIH), National Institute of Allergy and Infectious Diseases (NIAID) Clinical Terms of Award.

Compliance with these standards provides public assurance that the rights, safety and well-being of study subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki.

All key personnel (all individuals responsible for the design and conduct of this study) have completed Human Subjects Protection Training.

SIGNATURE PAGE

The signature below constitutes the approval of this protocol and the attachments, and provides 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 US federal regulations and ICH guidelines.

Site Investigator:

Signed: _____ Date: _____

Name

_____

Title

_____

Signature

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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
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
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	Personal 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
SDCC	Statistical and Data Coordinating Center
SMA	Secondary Medical Assessor
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, Single-Stage, Single-Arm Investigation of Oral Valganciclovir Therapy in Infants with Asymptomatic Congenital Cytomegalovirus Infection
Phase:	II
Population:	Male and female infants with asymptomatic congenital CMV infection. Approximately 229 neonates with confirmed congenital infection without outward manifestations of congenital CMV infection will be offered enrollment in the study.
Number of Sites:	9
Study Duration:	5 years
Subject Participation Duration:	18 months
Description of Agent or Intervention:	Valganciclovir for oral solution, 16 mg/kg/dose administered twice daily for 4 months.
Objectives:	Primary: • To estimate the proportion of subjects with asymptomatic congenital CMV infection who, following treatment with 4 months of oral valganciclovir, develop sensorineural hearing loss (SNHL) by 6 months of life. Secondary: • To define the safety and tolerability of valganciclovir in enrolled subjects. • To estimate the proportion of subjects with asymptomatic congenital CMV infection who, following treatment with 4 months of oral valganciclovir, develop SNHL over the first 18 months of life. Exploratory:

	• To compare changes in whole blood CMV viral load versus plasma CMV viral load during and following antiviral treatment. • To assess correlation between CMV viral load, by body compartment, and SNHL. • To assess correlation between development of ganciclovir resistance, by body compartment, and SNHL. • To assess development of resistance to ganciclovir in the compartment-specific sites of blood, urine, and saliva over time.
Outcome Measures:	Primary Endpoint: • The number of subjects developing sensorineural hearing loss in at least one ear between Baseline and Study Month 6 [both ears with normal hearing at baseline, then at least one ear with sensorineural hearing loss (SNHL) at the 6 month follow-up] Secondary Endpoints: • Cumulative incidence of Grade 3 or higher unsolicited adverse events, safety laboratory adverse events, or serious adverse events • Cumulative incidence of absolute neutrophil counts below $500/mm^3$ • Cumulative incidence of transaminase elevation during treatment $\geq$ 2-times the baseline value • Cumulative incidence of adverse events leading to permanent discontinuation of valganciclovir therapy, or any adverse event that is not recovered / not resolved • Cumulative incidence of sensorineural hearing loss in at least one ear between Baseline and Study Month 4 [both ears with normal hearing at baseline, then at least one ear with sensorineural hearing loss (SNHL) at the 4 month follow-up] • Cumulative incidence of sensorineural hearing loss in at least one ear between Baseline and Study Month 12 [both ears with normal hearing at baseline, then at least one ear with sensorineural hearing loss (SNHL) at the 12 month follow-up]

	• Cumulative incidence of sensorineural hearing loss in at least one ear between Baseline and Study Month 18 [both ears with normal hearing at baseline, then at least one ear with sensorineural hearing loss (SNHL) at the 18 month follow-up] • Cumulative incidence of each degree of worsened hearing (mild, moderate, severe, profound) at Study Months 4, 6, 12, and 18, represented by the ear that has the larger degree of worsening • Proportion of ears of each degree of worsened hearing (mild, moderate, severe, profound) at Study Months 4, 6, 12, and 18 Exploratory Endpoint: • Change in whole blood and plasma CMV viral load through Study Month 6 • Correlation of change in whole blood and plasma CMV viral load with change in hearing at Study Months 4, 6, 12, and 18. • Correlation of change in urine CMV viral load with change in hearing at Study Months 4, 6, 12, and 18 • Correlation of development of ganciclovir resistance in differing body compartments (blood, urine, saliva) with change in hearing at Study Months 4, 6, 12, and 18 • Emergence and kinetics of ganciclovir resistance in differing body compartments (blood, urine, saliva) during antiviral therapy (Study Month 4), and following cessation of antiviral treatment (Study Months 5 and 6)
Inclusion and Exclusion Criteria:	**Inclusion Criteria** • Parent(s)/legal guardian(s) have signed informed consent documents* • Confirmation of CMV by urine PCR testing • Infant ≤ 30 days of age at initiation of study drug • Weight at study enrollment ≥ 1775 grams • Gestational age ≥ 32 weeks at birth * There is a *screening* informed consent for screening phase of study participation, and a *treatment* informed consent for treatment phase of study participation.

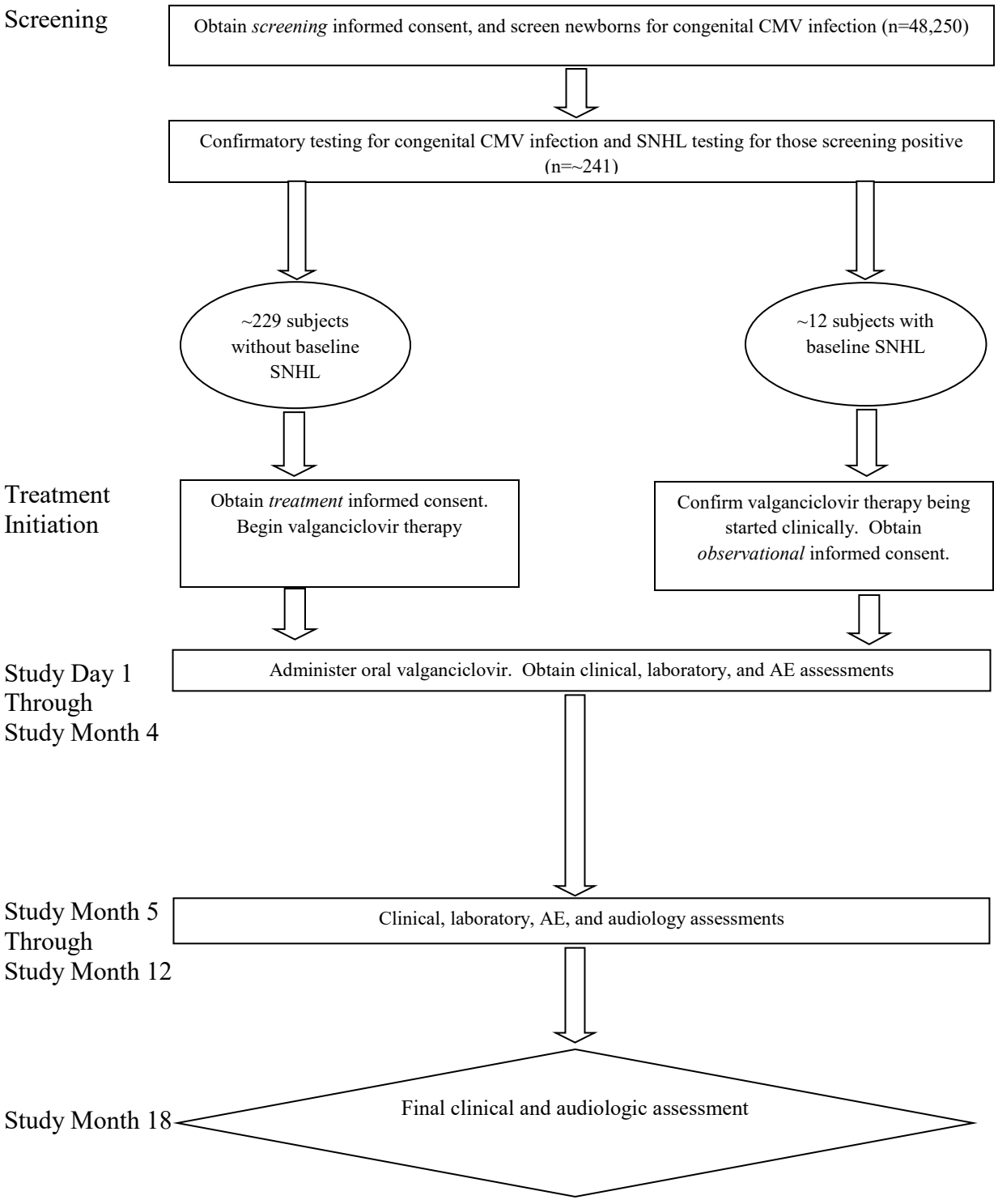
	Exclusion Criteria • Symptomatic congenital CMV disease* • Sensorineural hearing deficits as detected by formal brainstem evoked response (not a screening ABR) of known etiology other than CMV • Prior or current receipt of ganciclovir, valganciclovir, foscarnet, cidofovir, brincidofovir, maribavir, or letermovir • Maternal receipt of CMV hyperimmune globulin during pregnancy • Breastfeeding from mother who is receiving ganciclovir, valganciclovir, foscarnet, cidofovir, brincidofovir, maribavir, or letermovir • Gastrointestinal abnormality which might preclude absorption of an oral medication (e.g., a history of necrotizing enterocolitis) • Infants known to be born to women who are HIV positive (HIV testing is not required for study entry) • Current receipt of other investigational drugs * Symptomatic disease is defined as one or more of the following: 1) thrombocytopenia, if known; 2) petechiae; 3) hepatomegaly; 4) splenomegaly; 5) intrauterine growth restriction; 6) hepatitis (elevated transaminases and/or direct bilirubin), if known; 7) central nervous system involvement of the CMV disease (such as microcephaly; radiographic abnormalities indicative of CMV CNS disease, if known; abnormal CSF indices for age, if known; chorioretinitis, if known; and/or positive CMV PCR from CSF, if known).
Description of Study Design:	This is a phase II, open-label trial to evaluate valganciclovir as a treatment to prevent development of SNHL in infants with asymptomatic congenital CMV infection. The trial will be conducted in two phases (screening of newborns to identify eligible subjects, and treatment of those newborns who have confirmed CMV infection at birth but without outward manifestations of congenital CMV infection).

	Following consent for *screening*, newborns with no outward manifestations of congenital CMV infection who are delivered at one of 9 participating academic medical centers will be screened for CMV infection during their birth hospital stay. A buccal saliva swab will be obtained by swabbing the inside of the newborn's mouth for detection of CMV by PCR. The collected swabs will be transported within 4 days of collection to the Central Laboratory at the University of Alabama at Birmingham for testing. Babies screening positive for congenital CMV infection will have a second saliva sample and a urine sample collected for confirmatory PCR testing. Study drug will not be started until the confirmatory PCR testing is completed; the likelihood of a false-positive screening test is < 0.03%, but performing a confirmatory test ensures that only those babies truly infected with CMV will be exposed to valganciclovir. Approximately 48,250 newborn infants will be screened to detect approximately 241 neonates with asymptomatic congenital CMV infection; these 241 newborns then will have audiology examinations to determine baseline hearing, with approximately 229 having normal hearing in both ears. Those 229 newborns with confirmed CMV infection but without baseline SNHL and who meet all inclusion/exclusion criteria will be offered enrollment into the treatment phase. Through this screening process, approximately 12 neonates congenitally infected with CMV who have SNHL at birth also will be identified. Newborn patients with SNHL and who are being treated clinically with valganciclovir will be offered enrollment into an *observational* substudy as detailed below. After obtaining *treatment* informed consent, enrolled subjects will be treated for four months with oral valganciclovir (16 mg/kg/dose, administered two times per day). **Study Day 1** is the day that the first dose of study medication is administered. Audiologic assessments will be made during the Screening Period and Study Months 4 (end of treatment), 6, 12, and 18. A single, independent study audiologist will assess the audiology test battery for each subject and assign each ear the classifications of normal hearing, mild hearing loss, moderate

	hearing loss, severe hearing loss, or profound hearing loss based upon their hearing thresholds (in decibels). 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 but will continue with all other study-related assessments. Treated infants will be followed for safety throughout the first 6 months of the study (including for 2 months post-treatment). Hematology safety laboratory assessments will be obtained weekly for the first six weeks of study drug administration, then every other week for the next six weeks of study drug administration, and then at months 4 and 5. Chemistry safety laboratory assessments will be obtained every other week for the first 12 weeks (3 months) of treatment, and then at months 4, 5, and 6. Adverse events will be assessed at each study visit during treatment, and at month 5. Whole blood viral load and plasma viral load will be obtained at each study visit during the course of study drug administration, and then at Study Months 5 and 6. Specimens from subjects with increasing viral loads despite antiviral therapy may be evaluated for ganciclovir resistance by molecular methodologies (e.g., deep sequencing, Sanger sequencing, PCR). Urine and saliva will be obtained at Baseline and Study Months 4, 5, and 6 in order to obtain viral isolates to assist in detection of antiviral resistance. Infants with confirmed CMV but who have documented SHNL at baseline and who are being treated clinically with valganciclovir (expected to be about 12 patients) will be offered enrollment into an *observational* substudy. No additional audiologic or safety testing will be done as part of the study. However, available clinical audiologic and safety data will be redacted without alteration from the clinical medical record. Enrolled subjects will be followed for CMV viral load as part of the study. Viral loads would not be routinely followed as part of clinical management (and thus will be study procedures), whereas the valganciclovir treatment and associated safety labs

	as well as the serial hearing testing are part of clinical care for these patients. Blood for CMV viral load will only be obtained at a given study visit if other blood is being obtained by venipuncture for clinical purposes.
Estimated Time to Complete Enrollment:	30 months from enrollment of the first study subject.

Figure 1: Schematic of Study Design:



1 KEY ROLES

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2 BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 Background Information

Congenital cytomegalovirus (CMV) infection is the leading non-genetic cause of sensorineural hearing loss (SNHL)[1-4] and the most frequent known viral cause of mental retardation,[5] affecting 0.5% to 0.7% of live births in industrialized countries.[6-8] With a U.S. birth cohort of 4M annually, between 20,000 and 28,000 babies are estimated to be born each year with congenital CMV infection. Ten percent of congenitally infected neonates have symptomatic disease at delivery, of whom 35% have SNHL, up to 67% have neurologic deficits, and 4% die in the newborn period.[7-11] 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 10 to 15 years.

SNHL occurs at a lower rate among the 90% of congenitally infected neonates who are asymptomatic at delivery, but because there are so many more asymptomatic neonates than symptomatic ones the majority of cases of SNHL caused by CMV occurs in this asymptomatic group (Table 1).[7,12] Overall, congenital CMV is a rare infection but accounts for 21% of hearing loss at birth and 24% of hearing loss by four years of age.[1,13] The overall economic burden of congenital CMV infection exceeds $3 billion annually, adjusted for 2015 dollars.[14-16] For all of these reasons, the Institute of Medicine recently 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 one to two decades away.

Table 1. Majority of sequelae from congenital CMV infection occurs in babies who are asymptomatic at birth.

Parameter	Estimated Figure
Number of live births per year	4,248,000
Rate of congenital CMV infection	0.6%
Number of infected infants	25,488
Number of infants symptomatic at birth (12.8%)	3,262
Symptomatic at birth who have or develop disability (50%)	1,631
Number of infants asymptomatic at birth (87.2%)	22,226
Asymptomatic at birth who have or develop disability (13.5%)	**3,001**
Total with congenital CMV-related disabilities	4,632

From reference [17]

Effective treatment has been established to prevent hearing loss or hearing deterioration in neonates with symptomatic congenital CMV infections. After establishing the appropriate dose of intravenous ganciclovir for use in neonates,[18-20] the Collaborative Antiviral Study Group (CASG) published the results of a Phase III randomized controlled investigation conducted during the 1990s of intravenous ganciclovir for the treatment of symptomatic congenital CMV disease involving the central nervous system (CNS).[21] One hundred neonates (infants less than

30 days of age) with symptomatic congenital CMV disease involving the CNS were enrolled and were randomized to ganciclovir treatment (6 mg/kg/dose administered intravenously every 12 hours for 6 weeks) or to no treatment. Infants randomized to the no treatment arm were managed in an identical fashion to those receiving active drug. 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 subjects 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 the subject's best evaluable ear ("functional" assessment) and on total evaluable ears ("biologic" assessment). Twenty-one of 25 ganciclovir recipients (84%) either had improvement in hearing in their best ear between baseline and 6 months or had normal hearing at both timepoints, compared with 10 of 17 subjects (59%) 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 the two additional subjects who did not meet all entry criteria (above) yielded an adjusted p-value of 0.03. None of 25 ganciclovir recipients (0%) had worsening in hearing in their best ear between baseline and 6 months, compared with 7 of 17 subjects (41%) in the no treatment group (adjusted p-value < 0.001; OR 21.11 [95% CI: 2.84,∞]). Five of 24 ganciclovir recipients (21%) had worsening in hearing in their best ear between baseline and ≥ 1 year, compared with 13 of 19 subjects (68%) 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 6 weeks following study enrollment than did subjects who did not receive antiviral therapy. Twenty-nine of 46 ganciclovir-treated subjects (63%) developed Grade 3 or 4 neutropenia during the 6 weeks of study drug administration, compared with 9 of 43 subjects (21%) in the no treatment group over the same period of time (p < 0.01). Fourteen of the 29 subjects (48%) required dosage adjustments, although only 4 subjects had the drug permanently discontinued. The mean time (± standard deviation) of onset of grade 3 or 4 neutropenia for subjects receiving ganciclovir was 14.2 (± 12.3) days, and for the no treatment group was 14.3 (± 13.1) days. Neutropenia in ganciclovir-treated subjects resolved in 12.8 (± 13.6) days, and in the no treatment group in 14.2 (± 13.5) days. All affected subjects resolved their neutropenia.

The effect of treatment on neurodevelopmental outcomes of enrolled subjects was evaluated in a post hoc analysis. Denver Developmental Evaluations performed at 6 weeks, 6 months, and 12 months served as the basis for this analysis.[22] Developmental milestones which ≥ 90% of normal children would be expected to have achieved were identified at each of these developmental stages. Each randomized study subject was evaluated to determine the number of milestones that had been not met ('delays'). 'Delays' were categorized according to the four Denver-focused categories: Personal/Social, Fine Motor, Gross Motor, and Language. The average 'delay' per subject for each test was calculated and compared for subjects who received ganciclovir versus those who received no treatment. Of the 100 subjects enrolled, Denver assessments were available for 74, 74, and 72 subjects at 6 weeks, 6 months, and 12 months, respectively. At the 6 week assessment, the average 'delays' per subject were 1.5 for ganciclovir recipients and 2.05 for 'no treatment' subjects (p =0.13). At 6 months, the average 'delays' were 4.46 and 7.51, respectively (p =0.06). At 12 months, the average delays were 9.78 delays versus 17.14 delays,

respectively (p =0.007). Multivariate analysis of variances (ANOVA)s were utilized to test independent factors known to be related to poor developmental outcomes in congenital CMV infection. After adjustment for these factors, the effect of ganciclovir therapy remained statistically significant at the 12 month assessment (p = 0.007), and approached statistical significance at 6 weeks (p = 0.08) and 6 months (p = 0.08). Thus, infants with symptomatic congenital CMV disease involving the CNS who received 6 weeks of IV ganciclovir therapy had fewer developmental delays at 12 months of age when compared with infants who did not receive ganciclovir. These data suggested that ganciclovir may improve overall neurodevelopmental outcomes up to at least 1 year of age in patients with symptomatic congenital CMV involving the CNS, but given the post hoc design and the basis of the findings residing with Denver Developmental screening evaluations the overall suggestion of benefit in this study was not completely convincing.

A Phase I/II pharmacokinetic/pharmacodynamic (PK/PD) investigation of oral valganciclovir in babies with symptomatic congenital CMV disease with or without CNS involvement then was conducted by the CASG from 2002 to 2007.[23] This study determined that 16mg/kg/dose BID of oral valganciclovir solution reliably provided comparable ganciclovir blood concentrations as the previously studied ganciclovir dose of 6 mg/kg/dose intravenously every 12 hours. Twenty-four subjects under 1 month of age with symptomatic congenital CMV disease were enrolled in this study. In a previous Phase II study, the CASG determined that intravenous ganciclovir (6 mg/kg/dose every 12 hrs) in neonates with symptomatic congenital CMV disease resulted in a median AUC_{12} of 27 ug*h/mL (mean AUC_{12}=32.3+13.7 ug*h/mL, range 17.2 to 55.9 ug*h/mL, n=13).[24] Data from subjects enrolled in the oral valganciclovir study demonstrated that a dose of 15.62 mg/kg provided an AUC_{12} of 27.35 ug*h/mL, thereby justifying the dose of 16 mg/kg noted above. The Phase II valganciclovir trial also documented 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 ganciclovir clearance during the same period.[23] Thus, oral valganciclovir actually is a more reliable method of delivering ganciclovir to young infants than is 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.

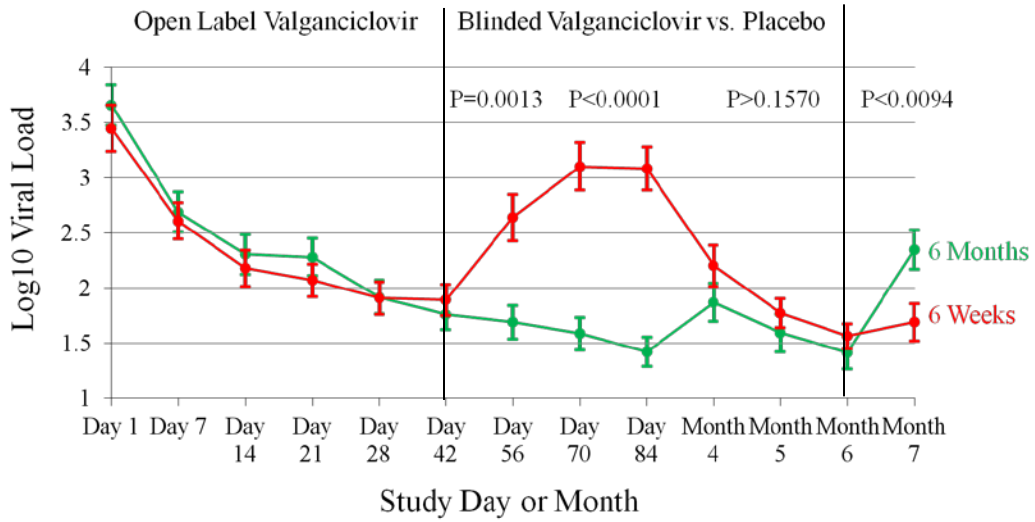
The CASG then undertook a Phase III randomized, placebo controlled trial of six weeks versus six months of oral valganciclovir in neonates with symptomatic congenital CMV disease. Results of this study recently were published in the New England Journal of Medicine.[25] A total of 96 participants were randomly assigned to receive blinded study medication after receiving 6 weeks of valganciclovir; 47 participants were assigned to continue receiving the active drug (the 6-month group), and 49 were assigned to receive placebo (the 6-week group). In the assessment of total-ear hearing, participants who received 6 months of valganciclovir were more likely than those who received 6 weeks of therapy to have improved hearing or to have maintained normal hearing between baseline and 12 months, after adjustment for CNS involvement at baseline (73% vs. 57%; odds ratio, 3.04; 95% confidence interval [CI], 1.26 to 7.35; P = 0.01). Similar results were evident when prematurity and age at the initiation of treatment were added to the model (P = 0.01). The benefit of longer-term therapy in the total ears analysis was maintained at 24

months, with improved outcomes after adjustment for CNS involvement at baseline (77% in the 6-month group vs. 64% in the 6-week group; odds ratio, 2.61; 95% CI, 1.05 to 6.43; P = 0.04). Similar results were evident when prematurity and age at the initiation of treatment were added to the model (P = 0.04). The timing of initiation of valganciclovir within the first month of life (e.g., <3 weeks of age vs. 3 to 4 weeks of age) did not correlate with audiologic outcomes at 12 months or at 24 months (P>0.23 for both comparisons).

In the analysis adjusted for CNS involvement at baseline, participants randomly assigned to receive 6 months of valganciclovir, as compared with those randomly assigned to 6 weeks of treatment, had higher Bayley-III language-composite scores at 24 months (P = 0.005) and higher receptive-communication scale scores at 24 months (P = 0.003). No significant interaction effects were found when outcome and CNS involvement at baseline were incorporated in a single model, indicating that the treatment benefits were similar in the group with CNS involvement and the group without CNS involvement. The differences between the 6-month group and the 6-week group with respect to Bayley-III scores were maintained when age at the initiation of treatment and prematurity were added to the model (P = 0.004 and P = 0.003, respectively). All the other components of the Bayley-III assessments trended toward improved outcomes among participants in the 6-month group, as compared with those in the 6-week group.

Viral loads in whole blood decreased in parallel in the two study groups during the first 6 weeks of open-label valganciclovir therapy and then diverged after randomization (Figure 2). In the analysis that was adjusted for an interaction effect between treatment and the area under the curve (AUC) of the viral load, lower viral loads, as compared with higher viral loads, correlated with better hearing outcomes at 6, 12, and 24 months among participants in the 6-month group (P<0.01 for all comparisons) but not among those in the 6-week group (P>0.68 for all comparisons). There was no correlation between the AUC of the viral load and neurodevelopmental outcomes beyond that provided by treatment.

Figure 2. Whole blood viral load in subjects receiving 6 months (green) and 6 weeks (red) of oral valganciclovir.[25]



Of the 109 participants, 21 (19%) had grade 3 or 4 neutropenia during the first 6 weeks of open label valganciclovir therapy. From week 6 through month 6, a total of 10 of the 47 participants (21%) who received the active drug had grade 3 or 4 neutropenia, as compared with 13 of 49 (27%) who received placebo (P = 0.64). A total of 3 participants had the drug temporarily suspended because of an absolute neutrophil count of less than 500 per cubic millimeter. All treatment interruptions occurred within the first 6 weeks of the study, and treatment was resumed after resolution of the neutropenia. The alanine aminotransferase and aspartate aminotransferase levels increased slightly at months 4 and 5 in the group of participants who received the active drug, although the differences between this group and the group that received placebo were not statistically significant (P>0.59 for both aminotransferase comparisons) or clinically significant (all mean values, <90 U per liter). No deaths occurred. There were no significant differences in the rate of adverse events between the two study groups.

Approximately 10% of asymptomatic children will develop SNHL. This is much higher than the 0.1%–0.4% incidence of hearing loss within the general population.[11] Of CMV-associated SNHL by 4 years of age, almost 75% occurs in children who were asymptomatically infected at birth.[1] Many prospective studies of children with asymptomatic congenital CMV infection showed that approximately half of children with asymptomatic infection who develop hearing loss will have bilateral deficits, which can vary from mild high-frequency loss to profound impairment. Moreover, hearing loss in these children is often progressive and/or delayed onset requiring ongoing audiologic evaluation.[4,26]

The available data on viral load levels between symptomatic and asymptomatic infants congenitally infected with CMV consistently have demonstrated that babies born with symptoms of congenital CMV disease have higher viral loads than do babies born without any symptoms of congenital CMV infection.[27-31] However, while the median values are different between the two groups, there is significant overlap at the individual level such that a baby with a given viral load could be either in the symptomatic group or in the asymptomatic group. Additionally, methodologic differences (assays with different levels of detection in the published studies) make it difficult to compare data across these published results. At the current time, threshold viral load values above which a baby could reliably be categorized as having symptoms and below which they could reliably be considered to be asymptomatic are not clearly delineated.

Several studies that have included infants with both symptomatic and asymptomatic congenital CMV infection have demonstrated that higher viral loads correlate with sensorineural hearing loss (SNHL).[28-30] Studies that have focused primarily[31] or exclusively[32] on asymptomatically infected infants have reported conflicting results. Ross et al.'s 2009 publication[31] found no correlation between a higher viral load and SNHL among asymptomatically infected infants, but found that lower viral loads (< 3,500 ge/mL) are associated with a lower risk of SNHL. However, Forner et al.'s recent publication[32] found that asymptomatic infants with viral loads of ≥ 17,000 copies/mL were more likely to develop SNHL. The Forner paper, though, found no difference in the duration of detectable virus in the blood or urine and SNHL – in other word, subjects who did or did not develop SNHL shed virus in blood or urine for the same duration of time. Given that higher viral loads generally would take a longer period of time to decrease compared with lower viral loads, these data have some intrinsic contradictions. The Forner study

also was limited by a very small sample size – only 33 total infants, with only 10 having SNHL. Even studies by the same research group have reported conflicting results, with an earlier study that reported identifiable thresholds correlating with SNHL[30] yielding to a later study with a larger sample size that did not find such correlation.[31]

As a result of these CASG trials, the U.S. Food and Drug Administration modified the Valganciclovir Package Insert to cite the dose used in CASG studies,[33] and the American Academy of Pediatrics now recommends six months of oral valganciclovir as therapy for infants born with symptomatic congenital CMV disease.[34]

2.2 Rationale

Given the benefit demonstrated from longer-term antiviral treatment of babies with symptomatic congenital CMV disease, and recognizing the fact that most of the disease burden of CMV-associated hearing loss is in the asymptomatically infected population, we hypothesize that infants with asymptomatic congenital CMV infection who are treated with valganciclovir will have protection against hearing deterioration. The primary toxicity of valganciclovir is neutropenia; however, neutropenia rates among infants receiving valganciclovir in CASG studies were modest. Specifically, the rate of neutropenia experienced by infants treated in the recent Phase III CASG study was not higher than that seen in the untreated babies from the earlier CASG study (19% in the valganciclovir group[25] versus 21% in the untreated group[21]). Additionally, no long term complications from ganciclovir therapy have been identified among people who received treatment during the neonatal period on early CASG studies. Specifically, no adolescents who had been treated on a CASG study as young infants in the 1980s developed cancer or pubertal abnormalities when followed up in the 2000s.[35] Given this safety profile, systematic evaluation of the treatment of babies with asymptomatic congenital CMV infection is justified due to the risk of hearing abnormalities that they face.

The selection of 4 months as the duration of antiviral therapy is based upon two findings in the CASG's previous studies of valganciclovir in infants with symptomatic congenital CMV disease who were treated for either six weeks or six months. First, the viral load data from the 6 week versus 6 month study demonstrated the attainment of virologic control by four months of age in the group that received only 6 weeks of antiviral therapy (decrease of whole blood viral load to the level that was seen in the group still receiving treatment) (Figure 2). Second, potential hepatic toxicity was detected after 4 months of treatment in subjects receiving six months of therapy.[25] There was no increased risk of neutropenia among subjects receiving valganciclovir for longer than 6 weeks. Given that the risk of hearing impairment is lower in the asymptomatic congenital CMV population (that is, most babies with asymptomatic congenital CMV infection will not experience hearing loss), we have selected 4 months of treatment to maximize the likelihood of virologic control and minimize the likelihood of adverse effects of therapy (elevated transaminases).

It is critical that this trial be undertaken now. In 2013, the state of Utah passed a law that requires babies who fail their newborn hearing screen to be tested for CMV infection. Other states (Illinois, Connecticut, Tennessee, Texas, New York, and Florida among them) are

considering similar legislation in their 2015 legislative sessions. This type of "targeted screening" for congenital CMV infection will not identify the overwhelming majority of at-risk neonates, since only 25% of babies with asymptomatic congenital CMV who ultimately develop CMV-associated SNHL have hearing loss present in the first month of life (with the remaining 75% developing hearing loss in later months or the first few years of life).[10] However, targeted screening portends universal screening for congenital CMV infection, as has recently been recommended by a Consensus Conference of leading world experts who gathered before the 5th International Congenital CMV Conference in Brisbane, Australia, on April 19, 2015.[36] A similar staged implementation was seen in the 1990s with hearing screening, whereby testing newborns for hearing abnormalities began in a targeted fashion and only later expanded to universal hearing screening for all babies born in the United States.[37,38] Once asymptomatic babies are identified through targeted or universal screening programs, there will be tremendous pressure on the managing physician to "do something," which inevitably will mean treating with oral valganciclovir. Therefore, the window of time to assess the benefit, if any, versus the risk in the asymptomatically infected congenital CMV population is narrow. Failure to establish the estimates of clinical effectiveness and to define the risks from treatment now could lead to widespread treatment outside of the confines of a clinical trial, thereby putting babies treated in such a manner at risk of harm with no opportunity to assess for evidence of benefit.

2.3 Potential Risks and Benefits

2.3.1 Potential Risks

The dose of oral valganciclovir to be used in this trial will be 16 mg/kg/dose administered twice daily. This is the dose evaluated in previous CASG studies of symptomatic congenital CMV disease for as well as safety,[23,25] pharmacokinetics/pharmacodynamics,[23,39] and efficacy.[25] The primary clinical toxicity of valganciclovir, which is metabolized to ganciclovir, at this dose in this population is neutropenia. In the CASG's Phase III randomized controlled study of 6 weeks of parenteral ganciclovir versus no treatment in babies with symptomatic congenital CMV disease, 63% of treated neonates developed Grade 3 or 4 neutropenia utilizing the Division of AIDS Toxicity Tables[40] during the six week course of treatment, compared with 21% of the subjects randomized to no treatment.[21] In the CASG study of the pharmacokinetics of oral valganciclovir, neonatal subjects received approximately two weeks of parenteral ganciclovir and four weeks of oral valganciclovir, and 38% developed Grade 3 or 4 neutropenia.[23] In the recently published CASG study of six weeks versus six months of oral valganciclovir in babies with symptomatic congenital CMV disease, 19% developed Grade 3 or 4 neutropenia during the first six weeks of treatment during which all babies received active therapy,[25] which is comparable to the 21% of babies in the no treatment arm of the original study.[21] This difference in rates of neutropenia with intravenous ganciclovir and oral valganciclovir likely relates to the higher maximum concentration of the drug associated with intravenous versus oral drug delivery,[25] and suggests that administration of the oral prodrug (valganciclovir) is a safer way to administer ganciclovir into the body than intravenous ganciclovir. Subjects treated with oral valganciclovir from week six to month six were not more likely to have neutropenia compared with those receiving placebo (21% versus 27%, respectively; p=0.64).[25] Thus, neutropenia induced by oral valganciclovir occurs much less frequently than with parenteral ganciclovir, and

appears to be limited to the first six weeks of therapy. Among subjects receiving six months of therapy with oral valganciclovir in the recent CASG study of longer-term treatment in babies with symptomatic congenital CMV disease, there was a suggestion of elevation in transaminases after four months of therapy, although this did not reach statistical significance.[25] All laboratory abnormalities associated with valganciclovir (neutropenia and possibly transaminitis) were fully reversible upon temporary cessation of the drug.

In addition to neutropenia, the clinical hematologic toxicities of valganciclovir include anemia, thrombocytopenia, pancytopenia, and aplastic anemia. In animal studies, ganciclovir was carcinogenic, mutagenic, and caused aspermatogenesis.[33] However, no long-term complications from ganciclovir therapy have been identified among people who received treatment during the neonatal period on early CASG studies. Specifically, no adolescents who had been treated on a CASG study as young infants in the 1980s developed cancer or pubertal abnormalities when followed up in the 2000s.[35] Some additional adverse events reported in the valganciclovir package insert are diarrhea, vomiting, hypertension, upper respiratory tract infection, urinary tract infection, pyrexia, and headache.

Subjects will be asked to provide personal health information (PHI). All attempts will be made to keep this PHI confidential within the limits of the law. However, there is a chance that unauthorized persons will see the subjects' PHI. All records will be kept in a locked file cabinet or maintained in a locked room at the participating CASG sites. Electronic files will be password protected. Only people who are involved in the conduct, oversight, monitoring, or auditing of this study will be allowed access to the PHI that is collected. Any publications from this study will not use information that will identify subjects by name. Organizations that may inspect and/or copy research records maintained at the participating CASG sites for quality assurance and data analysis include groups such as National Institute of Allergy and Infectious Diseases (NIAID) and their authorized representatives, the Food and Drug Administration (FDA), and the study's pharmaceutical collaborator Genentech, Inc. (which would only occur with the consent of NIAID as the holder of the IND for the study).

2.3.2 Known Potential Benefits

There may be no direct benefit from the experimental treatment to the asymptomatically infected subjects enrolled in this study. However, six weeks of intravenous ganciclovir has been proven to protect against hearing deterioration in patients with symptomatic congenital CMV disease when treatment was initiated during the first month of life.[21] Six months of oral valganciclovir has been proven to provide enhanced protection against hearing deterioration in this population when compared with six weeks of treatment, and to improve neurodevelopmental outcomes. This trial will determine whether prolonged oral valganciclovir therapy can protect against hearing deterioration in infants congenitally infected with CMV who are asymptomatic at birth. Subjects who participate will contribute to the knowledge about the safety and effectiveness of valganciclovir in congenitally CMV infected neonates.

3 OBJECTIVES

3.1 Study Objectives

Primary:

- To estimate the proportion of subjects with asymptomatic congenital CMV infection who, following treatment with 4 months of oral valganciclovir, develop sensorineural hearing loss (SNHL) by 6 months of life.

Secondary:

- To define the safety and tolerability of valganciclovir in enrolled subjects.
- To estimate the proportion of subjects with asymptomatic congenital CMV infection who, following treatment with 4 months of oral valganciclovir, develop SNHL over the first 18 months of life.

Exploratory:

- To compare changes in whole blood CMV viral load versus plasma CMV viral load during and following antiviral treatment.
- To assess correlation between CMV viral load, by body compartment, and SNHL.
- To assess correlation between development of ganciclovir resistance, by body compartment, and SNHL.
- To assess development of resistance to ganciclovir in the compartment-specific sites of blood, urine, and saliva over time.

3.2 Study Outcome Measures

3.2.1 Primary Outcome Measures

- The number of subjects developing sensorineural hearing loss in at least one ear between Baseline and Study Month 6 [both ears with normal hearing at baseline, then at least one ear with sensorineural hearing loss (SNHL) at the 6 month follow-up]

3.2.2 Secondary Outcome Measures

- Cumulative incidence of Grade 3 or higher unsolicited adverse events, safety laboratory adverse events, or serious adverse events
- Cumulative incidence of absolute neutrophil counts below 500/mm^3
- Cumulative incidence of transaminase elevation during treatment ≥ 2-times the baseline value
- Cumulative incidence of adverse events leading to permanent discontinuation of valganciclovir therapy, or any adverse event that is not recovered / not resolved

- Cumulative incidence of sensorineural hearing loss in at least one ear between Baseline and Study Month 4 [both ears with normal hearing at baseline, then at least one ear with sensorineural hearing loss (SNHL) at the 4 month follow-up]
- Cumulative incidence of sensorineural hearing loss in at least one ear between Baseline and Study Month 12 [both ears with normal hearing at baseline, then at least one ear with sensorineural hearing loss (SNHL) at the 12 month follow-up]
- Cumulative incidence of sensorineural hearing loss in at least one ear between Baseline and Study Month 18 [both ears with normal hearing at baseline, then at least one ear with sensorineural hearing loss (SNHL) at the 18 month follow-up]
- Cumulative incidence of each degree of worsened hearing (mild, moderate, severe, profound) at Study Months 4, 6, 12, and 18, represented by the ear that has the larger degree of worsening
- Proportion of ears of each degree of worsened hearing (mild, moderate, severe, profound) at Study Months 4, 6, 12, and 18

3.2.3 Exploratory Outcome Measures

- Change in whole blood and plasma CMV viral load through Study Month 6
- Correlation of change in whole blood and plasma CMV viral load with change in hearing at Study Months 4, 6, 12, and 18.
- Correlation of change in urine CMV viral load with change in hearing at Study Months 4, 6, 12, and 18.
- Correlation of development of ganciclovir resistance in differing body compartments (blood, urine, saliva) with change in hearing at Study Months 4, 6, 12, and 18.
- Emergence and kinetics of ganciclovir resistance in differing body compartments (blood, urine, saliva) during antiviral therapy (Study Month 4), and following cessation of antiviral treatment (Study Months 5 and 6)

4 STUDY DESIGN

This is a phase II, open-label trial to evaluate valganciclovir as a treatment to prevent development of SNHL in infants with asymptomatic congenital CMV infection. The trial will be conducted in two phases (screening of newborns to identify eligible subjects, and treatment of those newborns who have confirmed CMV infection at birth but without outward manifestations of congenital CMV infection).

Following consent for *screening*, newborns with no outward manifestations of congenital CMV infection who are delivered at one of 9 participating academic medical centers will be screened for CMV infection during their birth hospital stay. A buccal saliva swab will be obtained by swabbing the inside of the newborn's mouth for detection of CMV by PCR. The collected swabs will be transported within 4 days of collection to the Central Laboratory at the University of Alabama at Birmingham for testing. Babies screening positive for congenital CMV infection will have a second saliva sample and a urine sample collected for confirmatory PCR testing. Study drug will not be started until the confirmatory PCR testing is completed; the likelihood of a false-positive screening test is < 0.03%, but performing a confirmatory test ensures that only those babies truly infected with CMV will be exposed to valganciclovir. Approximately 48,250 newborn infants will be screened to detect approximately 241 neonates with asymptomatic congenital CMV infection; these 241 newborns then will have audiology examinations to determine baseline hearing, with approximately 229 having normal hearing in both ears. Those 229 newborns with confirmed CMV infection but without baseline SNHL and who meet all inclusion/exclusion criteria will be offered enrollment into the treatment phase.

Through this screening process, approximately 12 neonates congenitally infected with CMV who have SNHL at birth also will be identified. Newborn patients with SNHL and who are being treated clinically with valganciclovir will be offered enrollment into an *observational* substudy as detailed below.

After obtaining *treatment* informed consent, enrolled subjects will be treated for four months with oral valganciclovir (16 mg/kg/dose, administered two times per day). **Study Day 1** is the day that the first dose of study medication is administered. Audiologic assessments will be made during the Screening Period and Study Months 4 (end of treatment), 6, 12, and 18. A single, independent study audiologist will assess the audiology test battery for each subject and assign each ear the classifications of normal hearing, mild hearing loss, moderate hearing loss, severe hearing loss, or profound hearing loss based upon their hearing thresholds (in decibels). 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 but will continue with all other study-related assessments.

Treated infants will be followed for safety throughout the first 6 months of the study (including for 2 months post-treatment). Hematology safety laboratory assessments will be obtained weekly for the first six weeks of study drug administration, then every other week for the next six weeks of study drug administration, and then at months 4 and 5. Chemistry safety laboratory

assessments will be obtained every other week for the first 12 weeks (3 months) of treatment, and then at months 4, 5, and 6. Adverse events will be assessed at each study visit during treatment, and at month 5.

Whole blood viral load and plasma viral load will be obtained at each study visit during the course of study drug administration, and then at Study Months 5 and 6. Specimens from subjects with increasing viral loads despite antiviral therapy may be evaluated for ganciclovir resistance by molecular methodologies (e.g., deep sequencing, Sanger sequencing, PCR). Urine and saliva will be obtained at Baseline and Study Months 4, 5, and 6 in order to obtain viral isolates to assist in detection of antiviral resistance.

4.1 Substudies (if applicable)

Infants with confirmed CMV but who have documented SHNL at baseline and who are being treated clinically with valganciclovir (expected to be about 12 patients) will be offered enrollment into an observational substudy. No additional audiologic or safety testing will be done as part of the study. However, available clinical audiologic and safety data will be redacted without alteration from the clinical medical record. Enrolled subjects will be followed for CMV viral load as part of the study. Viral loads would not be routinely followed as part of clinical management (and thus will be study procedures), whereas the valganciclovir treatment and associated safety labs as well as the serial hearing testing are part of clinical care for these patients. Blood for CMV viral load will only be obtained at a given study visit if other blood is being obtained by venipuncture for clinical purposes. Inclusion of these substudy subjects will enhance the understanding of antiviral effects on audiologic outcomes from congenital CMV infection, bridging the gap between the completely asymptomatic population in the main study and the symptomatic populations assessed in prior CASG trials.[18-21,23,25]

5 STUDY ENROLLMENT AND WITHDRAWAL

5.1 Subject Inclusion Criteria

- Parent(s)/legal guardian(s) have signed informed consent documents*
- Confirmation of CMV by urine PCR testing
- Infant ≤ 30 days of age at initiation of study drug
- Weight at study enrollment ≥ 1775 grams
- Gestational age ≥ 32 weeks at birth

* There is a *screening* informed consent for screening phase of study participation, and a *treatment* informed consent for treatment phase of study participation.

5.2 Subject Exclusion Criteria

- Symptomatic congenital CMV disease*
- Sensorineural hearing deficits as detected by formal brainstem evoked response (not a screening ABR) of known etiology other than CMV
- Prior or current receipt of ganciclovir, valganciclovir, foscarnet, cidofovir, brincidofovir, maribavir, or letermovir
- Maternal receipt of CMV hyperimmune globulin during pregnancy
- Breastfeeding from mother who is receiving ganciclovir, valganciclovir, foscarnet, cidofovir, brincidofovir, maribavir, or letermovir
- Gastrointestinal abnormality which might preclude absorption of an oral medication (e.g., a history of necrotizing enterocolitis)
- Infants known to be born to women who are HIV positive (HIV testing is not required for study entry)
- Current receipt of other investigational drugs

* Symptomatic disease is defined as one or more of the following: 1) thrombocytopenia, if known; 2) petechiae; 3) hepatomegaly; 4) splenomegaly; 5) intrauterine growth restriction; 6) hepatitis (elevated transaminases and/or direct bilirubin), if known; 7) central nervous system involvement of the CMV disease (such as microcephaly; radiographic abnormalities indicative of CMV CNS disease, if known; abnormal CSF indices for age, if known; chorioretinitis, if known; and/or positive CMV PCR from CSF, if known).

5.3 Treatment Assignment Procedures

5.3.1 Randomization Procedures

This is a single-arm study; subjects will not be randomized to treatment.

5.3.2 Masking Procedures

This is a single-arm open-label study. No masking procedures will be done.

5.3.3 Reasons for Withdrawal

5.3.3.1 Reasons for Withdrawal Prior to Initiation of Study Drug

The criteria for discontinuation of study participation following confirmation of congenital CMV infection in the *screening* process but prior to initiation of study medication in the *treatment* portion of the study:

- Study subject (parent/legal guardian) wishes to withdraw
- The study is terminated
- Any other reason which, in the opinion of the investigator, precludes the study subject's participation in the study. Note: The site principal investigator must call the study Principal Investigator (or designee) prior to discontinuing a study subject for this reason.

5.3.3.2 Reasons for Withdrawal During Treatment

The criteria for discontinuations during the time that study medication is being provided include:

- Discontinuation of Study Product
  - Development of a related serious adverse event warranting withdrawal of therapy
  - Deterioration in general condition for which alternative treatment is indicated and which, in the opinion of the investigator, warrants withdrawal of therapy
  - Development of a medical disease or condition, or any new clinical findings for which continued participation, in the opinion of the site principal investigator or appropriate sub-investigator, would compromise the safety of the subject, would interfere with the subject's successful completion of this study, or would interfere with the evaluation of responses.

- Subject Withdrawal
  - 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
  - The study is terminated
  - Any other reason which, in the opinion of the investigator, precludes the study subject's participation in the study. The site principal investigator must call the study Principal Investigator (or designee) prior to discontinuing a study subject for this reason.

5.3.3.3 Reasons for Withdrawal After Completion of Treatment

Criteria for discontinuing study subjects from the study after study medication is complete 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 site principal investigator must call the study Principal Investigator (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

5.3.4 Handling of Withdrawals

Study subjects may withdraw voluntarily from participation in the study at any time. Up to 20% 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 from the study or discontinues study intervention at any time prior to completion of the study, the reason for this decision will be recorded on the appropriate electronic case report form (eCRF). SAEs and AEs will be followed according to guidelines in Section 9. The study subject should be asked to complete follow-up visits.

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 enrolled study subjects will continue to be followed as long as possible.

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 11.2) 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.

5.3.5 Termination of Study

The ethics committees, FDA, UAB Central Unit, or DMID 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
- Data recording is inaccurate or incomplete
- The Investigator has not been adhering to the protocol or applicable regulatory guidelines in conducting the study

6 STUDY INTERVENTION/INVESTIGATIONAL PRODUCT

6.1 Study Product Description

Valganciclovir is marketed for the treatment of CMV retinitis and the prevention of CMV disease in select transplant patients. In adults, valganciclovir is approved for the treatment of CMV retinitis in patients with acquired immunodeficiency syndrome (AIDS), and for the prevention of CMV disease in kidney, heart, and kidney-pancreas high-risk transplant patients. Valganciclovir is approved for the prevention of CMV disease in kidney transplant patients (4 months to 16 years of age) and heart transplant patients (1 month to 16 years of age) at high risk.[33]

6.1.1 Acquisition

Valganciclovir for Oral Solution will be provided for this study by Genentech Inc. Purified water (USP) for preparation of nonparenteral pharmaceutical products will be obtained at the local investigational pharmacy. Upon request by DMID, the study products will be shipped to the following address:

DMID-Clinical Agents Repository Contract (CAR)
Fisher BioServices
20439 Seneca Meadows Parkway
Germantown, MD 20876
Tel: (240) 477-1350
Fax: (240) 477-1360
Email: DMID.CAR@ThermoFisher.com

Study product (valganciclovir) will be shipped to the investigational site upon request and approval by DMID.

6.1.2 Formulation, Packaging, and Labeling

Valganciclovir for oral solution will be supplied as a white to slightly yellow powder for constitution, forming a colorless to brownish yellow tutti-frutti flavored solution in the following strength: 50 mg per mL. It will be packaged in glass bottles containing approximately 100 mL of solution after constitution. The valganciclovir oral solution formulation does not contain lactose anhydrous.

6.1.2.1 Packaging and Labeling

The study drug will be supplied in its original manufacturer's bottle. Each container will also be labeled in compliance with applicable regulatory requirements, including the FDA-required cautionary statement "Caution- New drug -Limited by Federal (or United States) Law to Investigational Use Only."

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 (77ºF); excursions permitted to 15 ºC to 30 ºC (59 ºF to 86 ºF). Store reconstituted oral solution at 2° to 8°C (36 ºF to 46 ºF) for no longer than 49 days. Do not freeze. Shake bottle well before using.

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

6.2.1 Dosage

Valganciclovir should be dosed at 16 mg/kg body weight, unless specific dosage adjustment conditions (e.g., renal function) have been met, administered orally twice daily for 4 months. Specific dosing volumes will be provided for each subject. Dose modifications for neutropenia, thrombocytopenia, and hepatotoxicity are detailed in Section 6.3.

6.2.2 Preparation

Valganciclovir for Oral Solution will be prepared by the site Research Pharmacist for dispensing to the subject. A new bottle will be reconstituted and dispensed monthly during the 4 month treatment period. Instructions for reconstitution will be provided in the protocol-specific Manual of Procedures (MOP).

6.2.3 Administration

Valganciclovir oral solution has been shown not to adhere to syringes or to nasogastric tubing. Valganciclovir oral solution should be administered into the subject's mouth via an oral dosing syringe. Valganciclovir will be dispensed monthly. Parent/guardians will be provided with specific storage and administration instructions.

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

6.3 Modification or Termination of Study Intervention/Investigational Product for a Participant

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

6.3.1 Neutropenia

If the ANC reproducibly (within one week) decreases to < 500 cells/mm^3, valganciclovir will be held until the ANC recovers to ≥ 750 cells/mm^3, and then administration of drug will resume at the normal dose. If the ANC again reproducibly (within one week) decreases to < 750 cells/mm^3, the valganciclovir 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. 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 valganciclovir may 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, valganciclovir administration at the normal dose may resume. If the platelet count at baseline was < 100,000/mm^3, then valganciclovir may 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, valganciclovir administration at the normal dose may resume. Recurrence of platelet count below these threshholds will lead to study drug discontinuation.

6.3.3 Hepatotoxicity

If the ALT reproducibly (within one week) increases to ≥ 5-times the baseline value, valganciclovir will be held until ALT falls to ≤ 2-times the baseline value, at which time valganciclovir will be restarted. If the ALT again increases ≥ 5-times the baseline value, study drug will be discontinued.

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

After receipt of the study product, the site principal investigator (PI) is responsible for study product distribution and disposition and has ultimate responsibility for study product accountability. The Site PI will delegate to the site Research Pharmacist the responsibility for study product accountability. The site pharmacist will dispense valganciclovir in its original bottle and distribute it to the PI (or designee) or to the patient's parent or legal guardian. Each pharmacist will be responsible for and maintain logs of receipt, accountability, dispensation, storage conditions, and disposal of study drug. All study product, whether administered or not, must be documented on the appropriate study product accountability record or dispensing log. Parents/guardians will be instructed to return used bottles to the PI each month. 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 be retained at the site until monitored and released for disposition as applicable.

- Upon release for disposition, used or partially used study product will be disposed of by the local site pharmacy in accordance with local regulations.
- Upon completion or termination of the study and after the final monitoring visit, final disposition of the unused study product will be determined by DMID and communicated to the UAB central unit by the DMID Clinical Project Manager for the study. Specifically, all

unopened study drug either will be returned to the Clinical Agents Repository (CAR) 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 Assessment of Subject Compliance with Study Intervention/Investigational Product

Assessment of compliance with administration of study medication throughout the 4 month treatment period will be achieved by utilization of a medication diary. The parent(s) or legal guardian(s) will complete this diary on a daily basis, indicating the time of drug administration and whether the subject vomited following the dose. The diary will be collected at each study visit, and a new diary provided at that time.

6.6 Concomitant Medications/Treatments

6.6.1 Concomitant Medication Assessment

All concomitant medications will be recorded at each study visit throughout the 4 month treatment period. Administration of any medications will be documented in the subject's source documentation and reported on the subject's electronic case report form (eCRF). Concomitant medications will include all medications, vitamins, and supplements taken within the 4 month study treatment schedule.

6.6.2 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
- Zidovudine
- Didanosine
- Mycophenolate mofetil
- Other Investigational drugs, including but not limited to brincidofovir, maribavir, or letermovir

6.6.3 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

7.1 Screening

It is anticipated that screening of neonates will occur at most sites within the first 2 days of life, prior to discharge from the birth hospital. A *screening* informed consent form will be utilized for permission to conduct the screening test, which consists of obtaining a swab of the buccal mucosa for saliva PCR for CMV DNA. Babies screening positive for congenital CMV infection will have sensorineural hearing testing performed, as is standard of care for babies identified as being congenitally infected with CMV. A second saliva sample and a urine sample will be collected by study personnel (which will be covered by the *screening* informed consent) for confirmatory PCR testing. The likelihood of a false-positive screening test is < 0.03%, but performing a confirmatory test ensures that only those babies truly infected with CMV will be exposed to valganciclovir.

Sensorineural hearing testing will consist of a BSER (to assess neuro-otologic status) and OAEs (DPOAE or TEOAE). If the BSER 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).

Neonates who screen positive for CMV DNA on their confirmatory PCR testing and who do not have sensorineural hearing loss (SNHL) will be offered enrollment in the treatment portion of the study if they meet all inclusion criteria and do not meet any exclusion criteria.

Neonates who screen positive for CMV DNA on their confirmatory PCR testing and who have SNHL will be offered enrollment into an observational substudy if they are being treated clinically with valganciclovir and meet all inclusion criteria and no exclusion criteria. For this group with SNHL at baseline, all clinical audiologic and safety data will be redacted without alteration from the clinical medical record to the study case report forms. The only research laboratory samples that will be obtained are the whole blood, plasma, urine, and saliva specimens for viral load determination (see Footnote ‘m’ in the Schedule of Events, Appendix B); viral loads would not be routinely followed as part of clinical management (and thus will be study procedures), whereas the valganciclovir treatment and associated safety labs as well as the serial hearing testing are part of clinical care for these patients. Blood for CMV viral load will only be obtained at a given study visit if other blood is being obtained by venipuncture for clinical purposes. Non-study clinical and laboratory assessments that are not performed according to the intervals and listings in Appendix B (Schedule of Events) will not be assessed as protocol deviations, nor will failure to obtain the virology specimen if a venipuncture is not performed as part of clinical care at a given study visit. An *observational* informed consent signed by the neonate’s parent(s) or guardian(s) must be signed prior to enrollment into the observational substudy. The *observational* consent will be signed following the confirmatory PCR testing for CMV DNA and prior to or on Day 1.

7.2 Enrollment/Baseline

7.2.1 Study Day 1 Assessment (Study Day -3 through Study Day 1, unless alternative window is specified)

- After reviewing inclusion/exclusion criteria for treatment portion of the study, confirm that the *treatment* informed consent from parent or legally authorized representative has been signed; *treatment* informed consent will be obtained prior to starting any subject-related assessments or study drug administration.
- Document baseline demographics and clinical assessments
  - Date of birth
  - Gender
  - Race
  - Ethnicity
  - Birth weight
  - Length at birth, if available
  - Head circumference at birth, if available
  - Gestational age at birth
  - Medical history and baseline conditions prior to study enrollment, by body system
- Obtain 0.5 mL of blood for hematology safety labs
  - WBC count with differential
  - Hemoglobin concentration
  - Platelet count
- Obtain 1.0 mL of blood for chemistry safety labs
  - Alanine aminotransferase (ALT)
  - Direct bilirubin
  - Serum creatinine
- Measure growth parameters
  - Length in centimeters
  - Weight in kilograms
  - Head circumference in centimeters
- Review of adverse events and serious adverse events (for Adverse Events that occur following the first dose of study medication)
- Record concomitant medications
- Obtain 0.7 mL of blood for CMV viral load
  - Urine collection by bagged specimen (if obtainable) and saliva collected by buccal swab will be attempted on Study Day 1 (window: Study Day -3 to Study Day 7 for whole blood and urine; and Study Day -30 to Study Day 7 for saliva). If urine is obtainable, it will be frozen and sent to the Central Unit Central Laboratory for processing. If urine is not obtainable, a note will be made on the CRF but a protocol deviation will not be reported.
- Medication diary will be distributed and parent or legal guardian will be instructed on its use.

7.2.2 Study Day 1

- The first dose of study drug will be administered (and this day will be known as **Study Day 1**)

7.2.3 Substudy Assessments

- For the approximately 12 patients identified as being asymptomatically congenitally infected with CMV and with SNHL, the virology specimen for CMV viral load is the only study-related laboratory specimen collected for them; this specimen will be obtained only if the subject is having a venipuncture performed as part of clinical care. All other data will be redacted without alteration from the clinical chart, if available as part of the subject's clinical care. Non-study clinical and laboratory assessments that are not performed according to the intervals and listings in Appendix B (Schedule of Events) will not be assessed as protocol deviations. If a venipuncture is not performed as part of clinical care at a given study visit, then the failure to obtain the virology specimen also will not be reported as a protocol deviation.

7.3 Follow-up

7.3.1 Study Day 7 (± 2 days)

- Obtain 0.5 mL of blood for hematology safety labs
  - WBC count with differential
  - Hemoglobin concentration
  - Platelet count
- Measure growth parameters
  - Length in centimeters
  - Weight in kilograms
  - Head circumference in centimeters
- Review of adverse events and serious adverse events
- Record concomitant medications
- Obtain 0.7 mL of blood for CMV viral load
- Obtain any updated results from etiological investigations for SNHL
- Collect medication diary, and distribute new one
- Adjust dose of study medication for weight change, if needed

7.3.1.1 Substudy Assessments

- For the approximately 12 patients identified as being asymptomatically congenitally infected with CMV and with SNHL, the virology specimen for CMV viral load is the only study-related laboratory specimen collected for them; this specimen will be obtained only if the subject is having a venipuncture performed as part of clinical care. All other data will be redacted without alteration from the clinical chart, if available as part of the subject's clinical care. Non-study clinical and laboratory assessments that are not performed according to the intervals and listings in Appendix B (Schedule of Events) will not be assessed as protocol

deviations. If a venipuncture is not performed as part of clinical care at a given study visit, then the failure to obtain the virology specimen also will not be reported as a protocol deviation.

7.3.2 Study Day 14 (± 2 days)

- Obtain 0.5 mL of blood for hematology safety labs
  - WBC count with differential
  - Hemoglobin concentration
  - Platelet count
- Obtain 1.0 mL of blood for chemistry safety labs
  - Alanine aminotransferase (ALT)
  - Direct bilirubin
  - Serum creatinine
- Measure growth parameters
  - Length in centimeters
  - Weight in kilograms
  - Head circumference in centimeters
- Review of adverse events and serious adverse events
- Record concomitant medications
- Obtain 0.7 mL of blood for CMV viral load
- Obtain any updated results from etiological investigations for SNHL
- Collect medication diary, and distribute new one
- Adjust dose of study medication for weight change, if needed

7.3.2.1 Substudy Assessments

- For the approximately 12 patients identified as being asymptomatically congenitally infected with CMV and with SNHL, the virology specimen for CMV viral load is the only study-related laboratory specimen collected for them; this specimen will be obtained only if the subject is having a venipuncture performed as part of clinical care. All other data will be redacted without alteration from the clinical chart, if available as part of the subject's clinical care. Non-study clinical and laboratory assessments that are not performed according to the intervals and listings in Appendix B (Schedule of Events) will not be assessed as protocol deviations. If a venipuncture is not performed as part of clinical care at a given study visit, then the failure to obtain the virology specimen also will not be reported as a protocol deviation.

7.3.3 Study Day 21 (± 2 days)

- Obtain 0.5 mL of blood for hematology safety labs
  - WBC count with differential
  - Hemoglobin concentration
  - Platelet count
- Measure growth parameters
  - Length in centimeters

- Weight in kilograms
- Head circumference in centimeters

- Review of adverse events and serious adverse events
- Record concomitant medications
- Obtain 0.7 mL of blood for CMV viral load
- Obtain any updated results from etiological investigations for SNHL
- Collect medication diary, and distribute new one
- Adjust dose of study medication for weight change, if needed

7.3.3.1 Substudy Assessments

- For the approximately 12 patients identified as being asymptomatically congenitally infected with CMV and with SNHL, the virology specimen for CMV viral load is the only study-related laboratory specimen collected for them; this specimen will be obtained only if the subject is having a venipuncture performed as part of clinical care. All other data will be redacted without alteration from the clinical chart, if available as part of the subject's clinical care. Non-study clinical and laboratory assessments that are not performed according to the intervals and listings in Appendix B (Schedule of Events) will not be assessed as protocol deviations. If a venipuncture is not performed as part of clinical care at a given study visit, then the failure to obtain the virology specimen also will not be reported as a protocol deviation.

7.3.4 Study Day 28 (± 2 days)

- Obtain 0.5 mL of blood for hematology safety labs
  - WBC count with differential
  - Hemoglobin concentration
  - Platelet count
- Obtain 1.0 mL of blood for chemistry safety labs
  - Alanine aminotransferase (ALT)
  - Direct bilirubin
  - Serum creatinine
- Measure growth parameters
  - Length in centimeters
  - Weight in kilograms
  - Head circumference in centimeters
- Review of adverse events and serious adverse events
- Record concomitant medications
- Obtain 0.7 mL of blood for CMV viral load
- Obtain any updated results from etiological investigations for SNHL
- Collect medication diary, and distribute new one
- Adjust dose of study medication for weight change, if needed

7.3.4.1 Substudy Assessments

- For the approximately 12 patients identified as being asymptomatically congenitally infected with CMV and with SNHL, the virology specimen for CMV viral load is the only study-related laboratory specimen collected for them; this specimen will be obtained only if the subject is having a venipuncture performed as part of clinical care. All other data will be redacted without alteration from the clinical chart, if available as part of the subject's clinical care. Non-study clinical and laboratory assessments that are not performed according to the intervals and listings in Appendix B (Schedule of Events) will not be assessed as protocol deviations. If a venipuncture is not performed as part of clinical care at a given study visit, then the failure to obtain the virology specimen also will not be reported as a protocol deviation.

7.3.5 Study Day 35 (± 2 days)

- Obtain 0.5 mL of blood for hematology safety labs
  - WBC count with differential
  - Hemoglobin concentration
  - Platelet count
- Measure growth parameters
  - Length in centimeters
  - Weight in kilograms
  - Head circumference in centimeters
- Review of adverse events and serious adverse events
- Record concomitant medications
- Obtain 0.7 mL of blood for CMV viral load
- Obtain any updated results from etiological investigations for SNHL
- Collect medication diary, and distribute new one
- Adjust dose of study medication for weight change, if needed

7.3.5.1 Substudy Assessments

- For the approximately 12 patients identified as being asymptomatically congenitally infected with CMV and with SNHL, the virology specimen for CMV viral load is the only study-related laboratory specimen collected for them; this specimen will be obtained only if the subject is having a venipuncture performed as part of clinical care. All other data will be redacted without alteration from the clinical chart, if available as part of the subject's clinical care. Non-study clinical and laboratory assessments that are not performed according to the intervals and listings in Appendix B (Schedule of Events) will not be assessed as protocol deviations. If a venipuncture is not performed as part of clinical care at a given study visit, then the failure to obtain the virology specimen also will not be reported as a protocol deviation.

7.3.6 Study Day 42 (± 3 days)

- Obtain 0.5 mL of blood for hematology safety labs
  - WBC count with differential

  - Hemoglobin concentration
  - Platelet count
- Obtain 1.0 mL of blood for chemistry safety labs
  - Alanine aminotransferase (ALT)
  - Direct bilirubin
  - Serum creatinine
- Measure growth parameters
  - Length in centimeters
  - Weight in kilograms
  - Head circumference in centimeters
- Review of adverse events and serious adverse events
- Record concomitant medications
- Obtain 0.7 mL of blood for CMV viral load
- Obtain any updated results from etiological investigations for SNHL
- Collect medication diary, and distribute new one
- Adjust dose of study medication for weight change, if needed

7.3.6.1 Substudy Assessments

- For the approximately 12 patients identified as being asymptomatically congenitally infected with CMV and with SNHL, the virology specimen for CMV viral load is the only study-related laboratory specimen collected for them; this specimen will be obtained only if the subject is having a venipuncture performed as part of clinical care. All other data will be redacted without alteration from the clinical chart, if available as part of the subject's clinical care. Non-study clinical and laboratory assessments that are not performed according to the intervals and listings in Appendix B (Schedule of Events) will not be assessed as protocol deviations. If a venipuncture is not performed as part of clinical care at a given study visit, then the failure to obtain the virology specimen also will not be reported as a protocol deviation.

7.3.7 Study Day 56 (± 3 days)

- Obtain 0.5 mL of blood for hematology safety labs
  - WBC count with differential
  - Hemoglobin concentration
  - Platelet count
- Obtain 1.0 mL of blood for chemistry safety labs
  - Alanine aminotransferase (ALT)
  - Direct bilirubin
  - Serum creatinine
- Measure growth parameters
  - Length in centimeters
  - Weight in kilograms
  - Head circumference in centimeters
- Review of adverse events and serious adverse events

- Record concomitant medications
- Obtain 0.7 mL of blood for CMV viral load
- Obtain any updated results from etiological investigations for SNHL
- Collect medication diary, and distribute new one
- Adjust dose of study medication for weight change, if needed

7.3.7.1 Substudy Assessments

- For the approximately 12 patients identified as being asymptomatically congenitally infected with CMV and with SNHL, the virology specimen for CMV viral load is the only study-related laboratory specimen collected for them; this specimen will be obtained only if the subject is having a venipuncture performed as part of clinical care. All other data will be redacted without alteration from the clinical chart, if available as part of the subject's clinical care. Non-study clinical and laboratory assessments that are not performed according to the intervals and listings in Appendix B (Schedule of Events) will not be assessed as protocol deviations. If a venipuncture is not performed as part of clinical care at a given study visit, then the failure to obtain the virology specimen also will not be reported as a protocol deviation.

7.3.8 Study Day 70 (± 3 days)

- Obtain 0.5 mL of blood for hematology safety labs
  - WBC count with differential
  - Hemoglobin concentration
  - Platelet count
- Obtain 1.0 mL of blood for chemistry safety labs
  - Alanine aminotransferase (ALT)
  - Direct bilirubin
  - Serum creatinine
- Measure growth parameters
  - Length in centimeters
  - Weight in kilograms
  - Head circumference in centimeters
- Review of adverse events and serious adverse events
- Record concomitant medications
- Obtain 0.7 mL of blood for CMV viral load
- Obtain any updated results from etiological investigations for SNHL
- Collect medication diary, and distribute new one
- Adjust dose of study medication for weight change, if needed

7.3.8.1 Substudy Assessments

- For the approximately 12 patients identified as being asymptomatically congenitally infected with CMV and with SNHL, the virology specimen for CMV viral load is the only study-related laboratory specimen collected for them; this specimen will be obtained only if the subject is having a venipuncture performed as part of clinical care. All other data will be

redacted without alteration from the clinical chart, if available as part of the subject's clinical care. Non-study clinical and laboratory assessments that are not performed according to the intervals and listings in Appendix B (Schedule of Events) will not be assessed as protocol deviations. If a venipuncture is not performed as part of clinical care at a given study visit, then the failure to obtain the virology specimen also will not be reported as a protocol deviation.

7.3.9 Study Day 84 (± 3 days)

- Obtain 0.5 mL of blood for hematology safety labs
  - WBC count with differential
  - Hemoglobin concentration
  - Platelet count
- Obtain 1.0 mL of blood for chemistry safety labs
  - Alanine aminotransferase (ALT)
  - Direct bilirubin
  - Serum creatinine
- Measure growth parameters
  - Length in centimeters
  - Weight in kilograms
  - Head circumference in centimeters
- Review of adverse events and serious adverse events
- Record concomitant medications
- Obtain 0.7 mL of blood for CMV viral load
- Obtain any updated results from etiological investigations for SNHL
- Collect medication diary, and distribute new one
- Adjust dose of study medication for weight change, if needed

7.3.9.1 Substudy Assessments

- For the approximately 12 patients identified as being asymptomatically congenitally infected with CMV and with SNHL, the virology specimen for CMV viral load is the only study-related laboratory specimen collected for them; this specimen will be obtained only if the subject is having a venipuncture performed as part of clinical care. All other data will be redacted without alteration from the clinical chart, if available as part of the subject's clinical care. Non-study clinical and laboratory assessments that are not performed according to the intervals and listings in Appendix B (Schedule of Events) will not be assessed as protocol deviations. If a venipuncture is not performed as part of clinical care at a given study visit, then the failure to obtain the virology specimen also will not be reported as a protocol deviation.

7.3.10 Study Month 4 (± 10 days, unless alternative window is specified)

- Obtain 0.5 mL of blood for hematology safety labs
  - WBC count with differential
  - Hemoglobin concentration

  - Platelet count
- Obtain 1.0 mL of blood for chemistry safety labs
  - Alanine aminotransferase (ALT)
  - Direct bilirubin
  - Serum creatinine
- Measure growth parameters
  - Length in centimeters
  - Weight in kilograms
  - Head circumference in centimeters
- Review of adverse events and serious adverse events
- Record concomitant medications
- Obtain a new hearing assessment or record results from clinically obtained hearing assessment (Window: -10 to +30 days)
  - BSER (to assess neuro-otologic status) and OAEs (DPOAE or TEOAE) will be obtained. If the BSER 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).
- Obtain 0.7 mL of blood for CMV viral load
  - Urine collection by bagged specimen (if obtainable) and saliva collected by buccal swab will be attempted on Study Month 4. If urine is obtainable, it will be frozen and sent to the Central Unit Central Laboratory for processing. If urine is not obtainable, a note will be made on the CRF but a protocol deviation will not be reported.
- Obtain any updated results from etiological investigations for SNHL
- Collect medication diary

7.3.10.1 Substudy Assessments

- For the approximately 12 patients identified as being asymptomatically congenitally infected with CMV and with SNHL, the virology specimen for CMV viral load is the only study-related laboratory specimen collected for them; this specimen will be obtained only if the subject is having a venipuncture performed as part of clinical care. All other data will be redacted without alteration from the clinical chart, if available as part of the subject's clinical care. Non-study clinical and laboratory assessments that are not performed according to the intervals and listings in Appendix B (Schedule of Events) will not be assessed as protocol deviations. If a venipuncture is not performed as part of clinical care at a given study visit, then the failure to obtain the virology specimen also will not be reported as a protocol deviation.

7.3.11 Study Month 5 (± 10 days)

- Obtain 0.5 mL of blood for hematology safety labs
  - WBC count with differential
  - Hemoglobin concentration
  - Platelet count

- Obtain 1.0 mL of blood for chemistry safety labs
  - Alanine aminotransferase (ALT)
  - Direct bilirubin
  - Serum creatinine
- Measure growth parameters
  - Length in centimeters
  - Weight in kilograms
  - Head circumference in centimeters
- Review of adverse events and serious adverse events
- Obtain 0.7 mL of blood for CMV viral load
  - Urine collection by bagged specimen (if obtainable) and saliva collected by buccal swab will be attempted on Study Month 5. If urine is obtainable, it will be frozen and sent to the Central Unit Central Laboratory for processing. If urine is not obtainable, a note will be made on the CRF but a protocol deviation will not be reported.
- Obtain any updated results from etiological investigations for SNHL

7.3.11.1 Substudy Assessments

- For the approximately 12 patients identified as being asymptomatically congenitally infected with CMV and with SNHL, the virology specimen for CMV viral load is the only study-related laboratory specimen collected for them; this specimen will be obtained only if the subject is having a venipuncture performed as part of clinical care. All other data will be redacted without alteration from the clinical chart, if available as part of the subject's clinical care. Non-study clinical and laboratory assessments that are not performed according to the intervals and listings in Appendix B (Schedule of Events) will not be assessed as protocol deviations. If a venipuncture is not performed as part of clinical care at a given study visit, then the failure to obtain the virology specimen also will not be reported as a protocol deviation.

7.3.12 Study Month 6 (± 10 days, unless alternative window is specified)

- Obtain 1.0 mL of blood for chemistry safety labs
  - Alanine aminotransferase (ALT)
  - Direct bilirubin
  - Serum creatinine
- Measure growth parameters
  - Length in centimeters
  - Weight in kilograms
  - Head circumference in centimeters
- Obtain a new hearing assessment or record results from clinically obtained hearing assessment (Window: -10 to +30 days)
  - BSER and/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).

- Obtain 0.7 mL of blood for CMV viral load
  - Urine collection by bagged specimen (if obtainable) and saliva collected by buccal swab will be attempted on Study Month 6. If urine is obtainable, it will be frozen and sent to the Central Unit Central Laboratory for processing. If urine is not obtainable, a note will be made on the CRF but a protocol deviation will not be reported.
- Obtain any updated results from etiological investigations for SNHL

7.3.12.1 Substudy Assessments

- For the approximately 12 patients identified as being asymptomatically congenitally infected with CMV and with SNHL, the virology specimen for CMV viral load is the only study-related laboratory specimen collected for them; this specimen will be obtained only if the subject is having a venipuncture performed as part of clinical care. All other data will be redacted without alteration from the clinical chart, if available as part of the subject's clinical care. Non-study clinical and laboratory assessments that are not performed according to the intervals and listings in Appendix B (Schedule of Events) will not be assessed as protocol deviations. If a venipuncture is not performed as part of clinical care at a given study visit, then the failure to obtain the virology specimen also will not be reported as a protocol deviation.

7.3.13 Study Month 12 (± 30 days, unless alternative window is specified)

- Measure growth parameters
  - Length in centimeters
  - Weight in kilograms
  - Head circumference in centimeters
- Obtain a new hearing assessment or record results from clinically obtained hearing assessment (Window: -10 to +30 days)
  - BSER and/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).
- Obtain any updated results from etiological investigations for SNHL

7.3.13.1 Substudy Assessments

- For the approximately 12 patients identified as being asymptomatically congenitally infected with CMV and with SNHL, all data will be redacted without alteration from the clinical chart, if available as part of the subject's clinical care.

7.4 Final Study Visit

7.4.1 Study Month 18 (± 30 days, unless alternative window is specified)

- Measure growth parameters
  - Length in centimeters
  - Weight in kilograms
  - Head circumference in centimeters
- Obtain a new hearing assessment or record results from clinically obtained hearing assessment (Window: -10 to +30 days)
  - BSER and/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).
- Obtain any updated results from etiological investigations for SNHL

7.4.1.1 Substudy Assessments

- For the approximately 12 patients identified as being asymptomatically congenitally infected with CMV and with SNHL, all data will be redacted without alteration from the clinical chart, if available as part of the subject's clinical care.

7.5 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 asked to complete follow-up visits.

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.

7.6 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 of this protocol.

8 STUDY PROCEDURES/EVALUATIONS

The study procedures and evaluations are summarized in Appendix B. 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

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, if available; head circumference at birth, if available; gestational age at birth; medical history and baseline conditions prior to study enrollment, by body system.

8.1.2 Growth Parameters

To adjust study medication for weight gain, weight will be recorded at multiple study visits. To assess additional growth parameters, length and head circumference will be recorded at multiple study visits.

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.

8.1.4 Hearing Assessment

During the Screening Period (window: ≤ 30 days of age) and at Study Month 4 (window: -10 to +30 days), Study Month 6 (window: -10 to +30 days), Study Month 12 (window: -10 to +30 days), and Study Month 18 (window: -10 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 but will continue with all other study-related assessments. 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, heal 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, and whole blood CMV virology studies. 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); and 3) whole blood CMV virology studies (third most important). With the exception of the hematology safety labs 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 be noted but will not be reported as protocol deviations.

If possible, urine collection by bagged or clean catch specimen will be attempted at designated study visits (Study Day 1, and Months 4, 5, and 6). Inability to collect urine will be documented but not reported as a protocol deviation. Saliva will be collected using polyester fiber-tipped swabs at each of these designated study visits as well. Specimens will be shipped to the UAB Central Laboratory for analysis.

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

The breakdowns of the amount of blood for individual tests are provided in Appendix B. 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 obtained weekly for the first six weeks of study drug administration, then every other week for the next six weeks of study drug administration, and then at months 4 and 5. The following will be tested: white blood cell count, differential, hemoglobin, and platelet count.

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 obtained every other week for the first 12 weeks (3 months) of treatment, and then at months 4, 5, and 6. The following will be tested: ALT, direct bilirubin, and creatinine.

8.2.2 Special Assays or Procedures

8.2.2.1 CMV Virologic Testing

Assessment of CMV viral load by quantitative PCR 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.

Antiviral resistance will be performed in the UAB Viral Resistance 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 ASSESSMENT OF SAFETY

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 Specification of Safety Parameters

An Adverse Event is 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.

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, CROMS PVG, and EMMES 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 Methods and Timing for Assessing, Recording, and Analyzing Safety Parameters

9.2.1 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 9.2.2.

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.

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.

Severity of Event: All reportable AEs will be graded by the investigator according to the protocol toxicity tables (Appendix A) using a four-grade system (Table 2). For safety laboratory results with an absolute number in the toxicity tables (e.g., hemoglobin), grading of the AEs will be according to the toxicity tables and not according to the local laboratory reference range. For safety laboratory results with a reference to the Upper Limit Normal (ULN) in the toxicity tables (e.g., AST or SGOT), grading of the AEs will utilize the ULN of the local laboratory reference range in determining grading of the event per the toxicity tables. Grade 4 AEs will be only reported as SAE if the event meets one of the regulatory definitions of SAE described below (9.2.2) based on the study site physician judgment. The functional table below should be used to grade the severity of an AE that is not specifically identified in the grading table. In addition, all deaths related to an AE are to be classified as grade 5.

Table 2. Four-grade system utilized for this trial (see also Appendix A)

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Clinical adverse event **NOT** identified elsewhere in the grading table	Mild symptoms causing no or minimal interference with usual social & functional activities with intervention not indicated	Moderate symptoms causing greater than minimal interference with usual social & functional activities with intervention indicated	Severe symptoms causing inability to perform usual social & functional activities with intervention or hospitalization indicated	Potentially life-threatening symptoms causing inability to perform basic self-care functions with intervention indicated to prevent permanent impairment, persistent disability, or death

The severity of the events will be mapped to a 3 Grade system for reporting events to the FDA, in accordance with CDISC standards. The four-grade system allows direct comparisons to previous studies. The investigators and the data coordinating center will develop the mapping algorithm to collapse the 4 grades that allow for comparison across studies down to the 3 grades needed to meet CDISC standards.

9.2.2 Serious Adverse Events

Event seriousness will be determined according to the protocol definition of an SAE.

An adverse event or suspected adverse reaction is considered "serious" (will be an SAE) 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. It does not necessarily include all grade 4 AEs according to the toxicity tables in Appendix A.

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 physician
- reviewed and evaluated by a study physician

Relationship to Study Products: The physician'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," and should be followed through resolution or stabilization. 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.

9.2.3 Procedures to be Followed in the Event of Abnormal Laboratory Test Values or Abnormal Clinical Findings

If baseline clinical labs performed on Study Day 1 fall within Grade 1 abnormalities, then a laboratory AE is reported only if the value changes such that it falls into Grade 2 or higher at subsequent visits. For laboratory results that are abnormal according to the local laboratory reference range but not considered a Grade 1 abnormality, these will not be recorded as AEs.

Laboratory parameters other than those specified in sections 8.2.1.1 (hematology safety labs) and 8.2.1.2 (chemistry safety labs) as part of the CBC and complete metabolic panel need to be evaluated by the site physician, recorded in the source document, and reported as laboratory AEs if clinically significant.

9.3 Reporting Procedures

9.3.1 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 20817, 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.

9.3.2 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.

9.3.3 Other Adverse Events (if applicable)

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 site will notify the Statistical and Data Coordinating Center within 24 hours of identification of the following safety laboratory AEs:

- Any absolute neutrophil count (ANC) < 500 cells/mm^3
- Any platelet count < 50,000/mm^3
- Any ALT value ≥ 5-times the baseline value

9.4 Type and Duration of Follow-up of Subjects after Adverse Events

Document all AEs, including safety laboratory AEs, from Study Day 1 through four weeks following the last dose of study drug. Document all SAEs from Study Day 1 through one month after completion of study medication.

All AEs and SAEs will be followed until resolution, even if this extends beyond the study-reporting period, which is 4 weeks following the last dose of study product. 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 Halting Rules

9.5.1 Discontinuation of Study Participation for Individual Subject

Subjects with neutropenia, thrombocytopenia, or hepatotoxicity while on study medication will be discontinued from study treatment if the criteria outlined in Section 6.3 (Modification or

Termination of Study Intervention/Investigational Product for a Participant) or in Section 5.3.3 (Reasons for Withdrawal) 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.

9.5.2 Discontinuation of Study Enrollment, and Study Treatment For All Subjects, Pending Sponsor Review

Enrollment and study product administration will be halted for Safety Monitoring Committee (SMC) review/recommendation if any of the following is reported:

- Two or more subjects experience a study product-related SAE.
- 10% or more subjects (with a minimum of 3 subjects) experience the same severe (Grade 3 or higher) study product-related unsolicited AE.
- 20% or more subjects (with a minimum of 3 subjects) experience the same severe (Grade 3 or higher) study product-related non-neutropenia safety laboratory AE.
- 30% or more subjects (with a minumum of 3 subjects) experience severe (Grade 3 or higher) study product-related neutropenia safety laboratory AE.
- 10% or more subjects (with a minimum of 3 subjects) permanently discontinue study treatment according to the criteria outlined in Section 6.3.

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 SMC will review cumulative safety data. If enrollment is halted based upon the study halting criteria above or the review of the safety data, upon completion of the review and receipt of advice of the SMC, DMID and the Central Unit Administration will determine if study entry or study dosing may continue according to the protocol.

9.6 Safety Oversight (SMC)

Safety oversight will be conducted by an SMC that is an independent group of experts that monitors subject safety and advises DMID. The SMC 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 Sponsor (DMID). The SMC will consist of members with appropriate expertise to contribute to the interpretation of the data from this trial. The SMC meetings will include the following: an organizational meeting; scheduled data reviews; ad hoc (for identified safety issues) meetings as needed; and the final meeting at the end of the study when the final clinical study report is available.

The initial responsibility of the SMC will be to review and make recommendations regarding the initiation of the study. A simple majority will be considered a SMC 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, the SMC will convene at as follows: when 20% of enrolled subjects have available safety data through 4 weeks following the last study product administration, and at least once annually thereafter. A final SMC review meeting will take place 6 to 8 months after clinical database lock to review the cumulative unblinded safety and immunogenicity data for this trial. The data will be provided in a standard summary format. The SMC may be asked to provide recommendations in response to questions posed by DMID.

The SMC will operate under the rules of a DMID-approved charter that will be written at the organizational meeting of the SMC. At this time, each data element that the SMC needs to assess will be clearly defined. Procedures for SMC reviews/meetings will be defined in the charter. The SMC will review applicable data to include, but not limited to, study progress and participant, clinical, and safety data. Reports may include enrollment and demographic information, medical history, concomitant medications, physical assessments, clinical laboratory values, dosing compliance, and solicited and unsolicited AE/SAEs. Additional data may be requested by the SMC, and interim statistical reports may be generated as deemed necessary and appropriate by DMID. The SMC will meet and review these data at the intervals determined by the SMC charter, or ad hoc as needed during this trial. As an outcome of each review/meeting, the SMC will make a recommendation as to the advisability of proceeding with study vaccinations (as applicable), and to continue, modify, or terminate this trial.

Additionally, Statistical and Data Coordinating Center (SDCC) web reports using data entered into AdvantageEDC will be monitored to determine if any of the halting rules described in Section 9.5 (Halting Rules) are met.

9.6.1 Independent Safety Monitor (ISM)

For certain clinical trials, DMID will require an Independent Safety Monitor (ISM) to be assigned for each study site and the requirement for an ISM will be specified in the protocol. An ISM is a physician with relevant expertise whose primary responsibility is to provide to DMID an independent safety assessment in a timely fashion. Participation is for the duration of the DMID study and is a voluntary position that does not receive payment. The ISM must meet the requirements of the NIAID conflict of interest policy.

For this clinical trial an ISM is <u>not</u> required. However, at each participating site, **upon DMID Medical Monitor request,** the principal investigator (PI) will identify a physician with

relevant expertise, to act as a Secondary Medical Assessor (SMA). The SMA will examine a subject and/or medical records and provide a medical assessment (or second medical opinion) to the DMID of the safety event in question. The PI will send to the DMID MM, a summary of the event and include the PI and SMA assessments.

Note: In the case that DMID has requested this type of evaluation multiple times, DMID may request the site(s) identify an ISM to assist DMID with safety oversight.

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, ICH/GCP, and regulatory guidelines, and that the study is conducted in accordance with the protocol and study manuals. 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 informed consents, source documentation, hospital records, clinical and office charts, laboratory notes, memoranda, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, 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. Data collection forms used as source documents will be derived from the eCRFs and be provided by the SDCC. Study monitors will meet with investigators to discuss any problems and actions to be taken and document visit findings and discussions.

11 STATISTICAL CONSIDERATIONS

11.1 Study Hypotheses

Given the benefit demonstrated from longer-term antiviral treatment of babies with symptomatic congenital CMV disease, and recognizing the fact that most of the disease burden of CMV-associated hearing loss is in the asymptomatically infected population, we hypothesize that infants with asymptomatic congenital CMV infection who are treated with valganciclovir will have protection against hearing deterioration.

11.2 Sample Size Considerations

This is a Phase II, multi-center, single-stage, single-arm (open label) evaluation of 4 months of valganciclovir treatment for infants with virologically-confirmed congenital CMV infection who are asymptomatic at birth. The study sample size is 176 male and female infants under 1 month of age with asymptomatic congenital CMV infection without baseline sensorineural hearing loss (SNHL) who are evaluable for the primary endpoint. The goal of the study is to investigate the possible efficacy of valganciclovir therapy in asymptomatic infants congenitally infected with CMV for the prevention of SNHL. All infants enrolled will be given valganciclovir per the protocol. Since the hearing assessments will be based on specific measurements from brainstem auditory evoked response (BSER) evaluation of hearing, which yields objective data, there will not be bias in the measurement of hearing outcomes due to the open label design. A 95% estimate of the upper bound for the true proportion of asymptomatic infants who will develop SNHL by the time they are 6 months of age will be calculated using the exact Clopper-Pearson method. Table 3, below, displays the different sample size scenarios and the estimated upper bound if (1) none, (2) exactly 1, and (3) exactly 2 out of the total sample size develop SNHL. Given our sample size of 176 subjects, the 95% upper confidence bound for the true proportion who will develop SNHL within 6 months of birth is 1.69% and 2.67% if none or exactly 1, respectively, develops SNHL. If these scenarios are observed, they will provide preliminary evidence that valganciclovir treatment of infants with asymptomatic congenital CMV infection may decrease the rate of SNHL based on the landmark study by Dahle et al. that estimates 3.18% of asymptomatic CMV infected infants develop SNHL by 6 months of age.[10] Knowledge of these confidence bounds will allow us to estimate whether antiviral therapy in this population is likely to be of benefit. If the 95% upper confidence bound is lower than the 3.18% estimate from Dahle et al., our data would suggest the possibility of treatment benefit. Upon completion of the audiology analyses from the CHIMES study (which screened 100,000 neonates for asymptomatic congenital CMV infection at seven study sites in the United States from March 2007 through November 2009 and then followed them for audiologic outcomes over the first several years of life[41,42]), we will compare our 95% upper confidence bound with the contemporaneous CHIMES estimates as well.

Table 3. Sample Size and Upper Bound of Estimates of SNHL

Sample Size	95% Upper Bound Assuming No Subjects Develop SNHL	95% Upper Bound Assuming One Subject Develops SNHL	95% Upper Bound Assuming Two Subjects Develop SNHL
80	3.68%	5.79%	7.66%
100	2.95%	4.66%	6.16%
150	1.98%	3.12%	4.14%
176	**1.69%**	**2.67%**	**3.50%**

Approximately 229 subjects with asymptomatic congenital CMV infection without SNHL will be identified and offered enrollment in order to meet the sample size requirements of 176 evaluable subjects. A recent NIDCD study designed to develop screening methodologies for detection of congenital CMV infection (the CHIMES Study, PI: S. Boppana, who is a co-investigator in this trial) determined that 0.5% of neonates born in the United States have congenital CMV infection, although higher rates of 0.6% to 1.0% were seen in southern states.[42] Additionally, CHIMES data also suggest that 4.9% of neonates with asymptomatic congenital CMV infection will have baseline SNHL and 95.1% will have normal hearing at birth (S Boppana, personal communication). Therefore, to detect 229 neonates with asymptomatic congenital CMV infection without baseline SNHL to offer enrollment in this trial, an anticipated 48,250 babies will be screened for congenital CMV infection by buccal saliva swab PCR, the high sensitivity of which (97.4%) was recently reported by the CHIMES investigators.[42] A *screening* informed consent form will be utilized for permission to conduct the screening test. Of these 48,250 infants, we anticipate that 241 (0.5%) will have asymptomatic congenital CMV infection. This is a conservative estimate, since we have selected study sites that are in regions of the country where congenital CMV incidence rates are in the 0.6% to 1.0% range. Babies screening positive for congenital CMV infection will have sensorineural hearing testing performed, as is standard of care for babies identified as being congenitally infected with CMV. A second saliva sample and a urine sample will be collected by study personnel (which will be covered by the *screening* informed consent) for confirmatory PCR testing. The likelihood of a false-positive screening test is < 0.03%, but performing a confirmatory test ensures that only those babies truly infected with CMV will be exposed to valganciclovir. We estimate that 12 patients (4.9% of 241) will have baseline SNHL, and that 229 patients (95.1% of 241) will have normal hearing. These approximately 229 asymptomatically infected neonates without sensorineural hearing loss will be assessed for all inclusion criteria, and offered enrollment on the treatment portion of the trial if they meet all inclusion criteria and no exclusion criteria. The approximately 12 patients identified as being asymptomatically congenitally infected with CMV and with SNHL very likely will be treated clinically with 6 months of oral valganciclovir.[25,34] If

they are treated, they will be offered enrollment into an observational substudy and all clinical audiologic and safety data will be redacted without alteration from the clinical medical record to the study case report forms. For these 12 subjects, the only research laboratory samples that will be obtained are the whole blood and plasma specimens for viral load determination (see Footnote m in the Schedule of Events, Appendix B); viral loads would not be routinely followed as part of clinical management (and thus will be study procedures), whereas the valganciclovir treatment and associated safety labs as well as the serial hearing testing are part of clinical care for these patients. Blood for CMV viral load will only be obtained at a given study visit if other blood is being obtained by venipuncture for clinical purposes. Non-study clinical and laboratory assessments that are not performed according to the intervals and listings in Appendix B (Schedule of Events) will not be assessed as protocol deviations, nor will failure to obtain the virology specimen if a venipuncture is not performed as part of clinical care at a given study visit.

With an expected 5% (11 of 229, leaving 218) identified as being congenitally infected but electing to not enroll in the treatment study, another 10% enrolling but failing to complete the 6 month hearing evaluation (22 of 218, leaving 196), and a final 10% enrolling but with inadequate baseline or 6 month hearing data to adequately assess change over that time (20 of 196, leaving 176), these 229 subjects will be sufficient to result in 176 subjects evaluable for the primary endpoint. These estimates are based on the real-world experiences of the CASG study of longer-term treatment in infants with symptomatic congenital CMV disease,[25] and of the NIDCD CHIMES study (PI: S. Boppana, who is a co-investigator in this trial) that screened 100,000 babies for congenital CMV infection and identified the methodology that will be employed in this study.[42] Up to 20% over-enrollment will be allowed for operational reasons.

11.3 Planned Interim Analyses (if applicable)

There will be no interim analyses for efficacy for this study. The demographics of the screened population may be assessed and presented prior to completion of the study.

11.4 Final Analysis Plan

11.4.1 Analysis Populations

11.4.1.1 Intent to Treat Population

Any child who receives at least one dose of study medication will be included in an intention to treat (ITT) analysis of safety.

11.4.1.2 Per Protocol Population

Children who complete the full four months of study medication will be included in a per protocol (PP) analysis of efficacy.

11.4.1.3 Safety Population

The Safety Population will consist of all subjects who have received at least one dose of study product and for whom any data on safety are available.

11.4.1.4 Screened Population

The Screened Population will consist of all patients who signed the *screening* informed consent and for whom the saliva PCR for CMV DNA is available.

11.4.2 Baseline Characteristics

Baseline characteristics will be summarized. For both continuous and categorical variables, appropriate summary statistics will be applied. For continuous variables, descriptive statistics will include the number of non-missing values, mean, standard deviation, median, minimum, and maximum. For categorical variables, descriptive statistics will include counts and percentages per category.

11.4.3 Safety Analysis Plan

Safety evaluations will be based on the incidence, severity, and type of AEs. Safety variables will be tabulated and presented for all subjects in the safety population. All tests will use a 5% significance level, i.e., p-values<0.05 will be considered significant, and for estimation a 95% confidence level will be used.

11.4.4 Efficacy Analysis Plan

Primary analysis:
The primary analysis is estimating the proportion of subjects with asymptomatic congenital CMV infection who, following treatment with 4 months of oral valganciclovir, develop SNHL by 6 months of life in at least one ear. Due to the small expected number of subjects who will develop SNHL by 6 months, the Clopper-Pearson method will be used to calculate an exact 95% upper confidence bound for the primary outcome.

Secondary analyses:

For the proportion of subjects who develop SNHL at 4, 12, and 18 months post baseline, we will also use the Clopper-Pearson method to obtain an estimate of the 95% upper confidence bounds separately for each period. In each of these hearing outcomes, we will provide a breakdown on the degree of worsening (mild, moderate, severe). This method will also be used to define safety and tolerability of valganciclovir by estimating the incidence of adverse events of interest. If there is enough information in the data collected, we will use a large-sample method for estimating the 95% confidence interval of interest over the more conservative Clopper-Pearson method.

Analysis of actual viral load will be done using log base 10 transformation for both whole blood and plasma CMV viral loads. Undetectable viral load value will be replaced by a value of 10. To investigate the change over time, we will model the log base 10 viral load using mixed model to accommodate repeated measures. The covariance structure (selected among unstructured, exchangeable, autoregressive, exponential, and toeplitz) that best describes the correlation among the repeated measures over time will be selected using the AIC model selection index. Note that there will be 13 time points for which viral load will be measured. Hence, if time will be represented as discrete variables in the model, this will require spending 12 degrees of freedom in the model, which we believe is unnecessary. In our modeling we will represent time as a continuous variable and will consider fitting linear, quadratic, and cubic to approximate non-linear trends. The simplest model with a good fit based on the test of the coefficients, as well as the profile curves, will be selected. Modeling will be done separately for whole blood and plasma viral loads.

The same method of modeling will be employed to compare the whole blood and plasma CMV viral loads. However, the outcome will be the difference between the whole blood and plasma CMV viral load values for each subject at each time point. If the differences over time are found to be modeled by a linear function and there is no evidence to show that the slope of this line is significantly different from zero, then there is no evidence to conclude a difference between the average viral loads based on whole blood and plasma. Otherwise, there is a difference and this difference will be examined and discussed in more details based on the results of the fitted model.

We will investigate the how viral load is related to hearing outcomes using generalized linear model for binary outcome at each time point relative to baseline hearing.

All tests will use a 5% significance level, i.e., p-values<0.05 will be considered significant.

Ganciclovir resistance will be assessed by molecular methodologies (e.g., deep sequencing, Sanger sequencing, PCR). Blood, urine, and saliva specimens will be obtained serially.

11.4.5 Missing Values and Outliers

Missing safety and/or hearing outcome data will not be imputed. No search for outliers will be performed.

12 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

Data reported in the eCRF derived from the data collection forms should be consistent with the source documents or the discrepancies should be explained.

Each site will permit authorized representatives of the DMID, its designees, and appropriate regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits, monitoring, and evaluation of the study safety and progress. These representatives will be permitted access to all source data, which include, but are not limited to, review of informed consents, hospital records, clinical and office charts, laboratory notes, memoranda, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, 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. Data collection forms used as source documents will be derived from the eCRFs and be provided by the SDCC.

13 QUALITY CONTROL AND QUALITY ASSURANCE

Each study site will have a quality management plan. Following a written DMID-accepted site quality management plan, the investigational site is responsible for conducting routine quality assurance and quality control activities to internally monitor study progress and protocol compliance. The PI 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 inspection by local and regulatory authorities. The PI will ensure all study personnel are appropriately trained and applicable documentation is maintained on site.

DMID-designated clinical monitors will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, ICH/GCP guidelines, and the applicable regulatory requirements. Clinical monitoring reports will be submitted to DMID.

The 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. Any missing data or data anomalies will be communicated to the site(s) for clarification and resolution.

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.

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, 21 CFR 50 and 56, 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 site's Institutional Review Board (IRB) for review and must be approved before the study is initiated. The responsible official for the IRB will sign the IRB letter of approval of the protocol prior to the start of this trial and a copy will be provided to DMID. The IRB FWA number will be provided to DMID. Should amendments to the protocol be required, the amendments will be written by the sponsor and provided to the site principal investigator for submission to the IRB.

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

All subjects must sign an informed consent form that complies with the requirements of both 21 CFR 50 and 45 CFR 46. This study will utilize three consent forms: for the ~ 229 subjects without SNHL, one for the screening portion of the study and one for the interventional portion of the study; and for the ~ 12 patients with SNHL, one for the screening portion of the study (identical to that used for the ~ 229 study subjects) and one for the observational portion of the

study. A signed informed consent document will be obtained from each study participant's parent/legal guardian prior to entry into each of the portions of this study, and prior to conducting any study procedures.

Prior to participation in the trial, subjects will receive a comprehensive explanation of the proposed product, including the nature and risks of the trial, alternate therapies, any known AEs, the investigational status of the components, and the other elements that are part of obtaining proper informed consent. Subjects will also receive a detailed explanation of the proposed use and disclosure of their protected health information, including specifically their blood samples.

DMID will provide the investigator, in writing, any new information that significantly affects risk related to a subject's receipt of the investigational product. This new information will be communicated by the investigator to subjects who consent to participate in the trial in accordance with IRB requirements. The informed consent document will be updated and subjects will be re-consented, if necessary.

Site staff may utilize IRB-approved recruitment methods prior to the subject consenting; however, before any protocol-specific procedures are performed to determine protocol eligibility an informed consent form must be signed. Subjects will be given a copy of all consent forms that they sign.

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.

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.

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 signed 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.

14.4 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

This research is covered by a Certificate of Confidentiality from the NIH. Subject confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. This confidentiality includes documentation, investigation data, subject's clinical information, and all other information generated during participation in the study. The investigators and their staff may not disclose or use information documents, or biospecimens that may identify the subjects in any federal, state, or local civil, criminal, administrative, legislative or other action, or be used as evidence unless the subject has consented. This does not apply to requests for information from the NIH or its representatives that are needed to monitor or audit the study, or for information that must be disclosed in order to meet FDA requirements.

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 Inc. 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 Inc., 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 SDCC 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 parent/legal guardian 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.

Every effort will be made to maintain the anonymity and confidentiality of subjects during this study. Only people who are involved in the conduct, oversight, monitoring, or auditing of this study will be allowed access to the PHI that is collected. Any publications from this study will not use information that will identify subjects by name. Organizations that may inspect and/or copy research records maintained at the participating CASG sites for quality assurance and data analysis include groups such as National Institute of Allergy and Infectious Diseases (NIAID) and their authorized representatives, the Food and Drug Administration (FDA), and the study's pharmaceutical collaborator Genentech, Inc. (which would only occur with the consent of NIAID as the holder of the IND for the study).

14.6 Study Discontinuation

If the study is discontinued, enrolled subjects will continue to be followed for safety assessments. No further study product will be administered.

14.7 Future Use of Stored Specimens

Some of the specimens obtained from study participants during this study will be stored indefinitely in the Molecular Diagnostic Laboratory at the University of Alabama at Birmingham and may be used in future infectious disease research. These specimens will be labeled with a code number and not with the study participant's name. Samples will not be used for human genetic testing. Samples may be shared with other investigators at other institutions. The samples will not be sold for production of any commercial product.

There are no benefits to subjects in the collection, storage, and subsequent research use of specimens. Reports about future research done with a subject's samples will not be kept in their health records. At the time of consent for study participation, study participant's parent/legal guardian will have the opportunity either to agree to have their specimens used in future infectious disease research or to have their samples destoyed at the end of the study. 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. A subject's parent/legal guardian's decision can be changed at any time up to the point the specimens are released for research use by notifying the study doctors or nurses in writing. However, if a subject consents to future use and some of their blood has already been used for research purposes, the information from that research may still be used.

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 infectious disease 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. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Blue or black ink is required to ensure clarity of reproduced copies. When making changes or corrections, 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.

Copies of the electronic CRF (eCRF) will be provided for use as source documents and maintained for recording data for each subject enrolled in the study. Data reported in the eCRF derived from source documents should be consistent with the source documents or the discrepancies should be explained. DMID and/or it designee will provide guidance to investigators on making corrections to the source documents and eCRF.

15.1 Data Management Responsibilities

All source documents and laboratory reports must be reviewed by the clinical team and data entry staff, who will ensure that they are accurate and complete. Adverse events must be graded, assessed for severity and causality, and reviewed by the site PI or designee.

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 Emmes Corporation will serve as the Statistical and Data Coordinating Center for this study and will be responsible for data management, quality review, analysis, and reporting of the study data.

15.2 Data Capture Methods

Clinical data (including AEs, concomitant medications, and reactogenicity data) and clinical laboratory data will be entered into a 21 CFR Part 11-compliant Internet Data Entry System (IDES) provided by The Emmes Corporation. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

15.3 Types of Data

Data for this study will include safety, virologic, clinical laboratory, audiologic, and outcome measures.

15.4 Timing/Reports

Safety data will be reviewed by the SMC per the SMC charter for this study. Interim statistical reports may be generated as deemed necessary and appropriate by DMID. Safety data may be shared with Roche/Genentech as needed to permit required regulatory updates.

15.5 Study Records Retention

Each participating 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.

Records and documents pertaining to the conduct of this study, including CRFs, data collection forms, other source documents, consent forms, laboratory test results, and medication inventory records, must be retained by the investigator for at least 2 years after a marketing application is approved for the drug for the indication for which it is being investigated; or if no application is to be filed or if an application is not approved for the drug, until 2 years after the investigation is discontinued and FDA has been notified. These documents should be retained for a longer period, however, if required by local regulations. No study records will be destroyed without prior authorization from the sponsor, DMID. Informed consent forms for future use will be maintained as long as the samples exist. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

15.6 Protocol Deviations

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 via The Emmes Corporation's IDES. All deviations from the protocol must be addressed in study subject source documents. A completed copy of the DMID Protocol Deviation Form (IDES form) must be maintained in the regulatory file, as well as in the subject's source document. Protocol deviations must be sent to

the local IRB/IEC per their guidelines. The site PI/study staff is responsible for knowing and adhering to their IRB/IEC requirements.

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.

It is the responsibility of DMID to register this trial in an acceptable registry. Any clinical trial starting enrollment after 01 July 2005 must be registered on or before patient enrollment. For trials that began enrollment prior to this date, the ICMJE member journals will require registration by 13 September 2005, before considering the results of the trial for publication.

The ICMJE defines a clinical trial as any research project that prospectively assigns human subjects to intervention or comparison groups to study the cause-and-effect relationship between a medical intervention and a health outcome. Studies designed for other purposes, such as to study pharmacokinetics or major toxicity (e.g., Phase I trials), would be exempt from this policy.

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18 APPENDIX A: (ADAPTED FROM) DIVISION OF AIDS TOXICITY TABLES

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Petechiae	Localized to one area	Localized to more than one area	Generalized	NA
Diarrhea *≥ 1 year of age*	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 to 6 stools over baseline per 24-hour period	Increase of ≥ 7 stools per 24-hour period OR IV fluid replacement indicated	Life-threatening consequences (e.g., hypotensive shock)
< 1 year of age	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	Life-threatening consequences (e.g., liquid stools resulting in severe dehydration, hypotensive shock)
Vomiting	Transient or intermittent AND No or minimal interference with oral intake	Frequent episodes 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)
Fever (non-axillary temperatures only)	38.0 to < 38.6°C or 100.4 to < 101.5°F	≥ 38.6 to < 39.3°C or ≥ 101.5 to < 102.7°F	≥ 39.3 to < 40.0°C or ≥ 102.7 to < 104.0°F	≥ 40.0°C or ≥ 104.0°F
Seizures ***New Onset Seizure*** *< 18 years of age (includes new or pre-existing febrile seizures)*	Seizure lasting < 5 minutes with < 24 hours postictal state	Seizure lasting 5 to < 20 minutes with < 24 hours postictal state	Seizure lasting ≥ 20 minutes OR > 24 hours postictal state	Prolonged and repetitive seizures (e.g., status epilepticus) OR Difficult to control (e.g., refractory epilepsy)

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
A Pre-existing Seizure	NA	Increased frequency from previous level of control without change in seizure character	Change in seizure character either in duration or quality (e.g., severity or focality)	Prolonged and repetitive seizures (e.g., status epilepticus) OR Difficult to control (e.g., refractory epilepsy)
Acute Allergic Reaction	Localized urticaria (wheals) with no medical intervention indicated	Localized urticaria with intervention indicated OR Mild angioedema with no intervention indicated	Generalized urticaria OR Angioedema with intervention indicated OR Symptoms of mild bronchospasm	Acute anaphylaxis OR Life-threatening bronchospasm OR Laryngeal edema
ALT or SGPT, High *Report only one*	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x ULN
AST or SGOT, High *Report only one*	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x ULN
Bilirubin ***Direct Bilirubin, High*** *> 28 days of age*	NA	NA	> ULN	> ULN with life-threatening consequences (e.g., signs and symptoms of liver failure)
≤ 28 days of age	ULN to ≤ 1 mg/dL	> 1 to ≤ 1.5 mg/dL	> 1.5 to ≤ 2 mg/dL	> 2 mg/dL
Total Bilirubin, High *> 28 days of age*	1.1 to < 1.6 x ULN	1.6 to < 2.6 x ULN	2.6 to < 5.0 x ULN	≥ 5.0 x ULN
≤ 28 days of age	See Appendix A. Total Bilirubin for Term and Preterm Neonates	See Appendix A. Total Bilirubin for Term and Preterm Neonates	See Appendix A. Total Bilirubin for Term and Preterm Neonates	See Appendix A. Total Bilirubin for Term and Preterm Neonates
Creatinine, High	1.1 to 1.3 x ULN	> 1.3 to 1.8 x ULN OR Increase of > 0.3 mg/dL above baseline	> 1.8 to < 3.5 x ULN OR Increase of 1.5 to < 2.0 x above baseline	≥ 3.5 x ULN OR Increase of ≥ 2.0 x above baseline
Absolute Neutrophil Count (ANC), Low (cells/mm^3; *cells/L*) *> 7 days of age*	800 to 1,000 *0.800 x 10^9 to 1.000 x 10^9*	600 to 799 *0.600 x 10^9 to 0.799 x 10^9*	400 to 599 *0.400 x 10^9 to 0.599 x 10^9*	< 400 *< 0.400 x 10^9*

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
2 to 7 days of age	1,250 to 1,500 *1.250 x 10^9 to 1.500 x 10^9*	1,000 to 1,249 *1.000 x 10^9 to 1.249 x 10^9*	750 to 999 *0.750 x 10^9 to 0.999 x 10^9*	< 750 *< 0.750 x 10^9*
≤ 1 day of age	4,000 to 5,000 *4.000 x 10^9 to 5.000 x 10^9*	3,000 to 3,999 *3.000 x 10^9 to 3.999 x 10^9*	1,500 to 2,999 *1.500 x 10^9 to 2.999 x 10^9*	< 1,500 *< 1.500 x 10^9*
Hemoglobin, Low (g/dL; *mmol/L*) *≥ 13 years of age (male only)*	10.0 to 10.9 *6.19 to 6.76*	9.0 to < 10.0 *5.57 to < 6.19*	7.0 to < 9.0 *4.34 to < 5.57*	< 7.0 *< 4.34*
≥ 13 years of age (female only)	9.5 to 10.4 *5.88 to 6.48*	8.5 to < 9.5 *5.25 to < 5.88*	6.5 to < 8.5 *4.03 to < 5.25*	< 6.5 *< 4.03*
57 days of age to < 13 years of age (male and female)	9.5 to 10.4 *5.88 to 6.48*	8.5 to < 9.5 *5.25 to < 5.88*	6.5 to < 8.5 *4.03 to < 5.25*	< 6.5 *< 4.03*
36 to 56 days of age (male and female)	8.5 to 9.6 *5.26 to 5.99*	7.0 to < 8.5 *4.32 to < 5.26*	6.0 to < 7.0 *3.72 to < 4.32*	< 6.0 *< 3.72*
22 to 35 days of age (male and female)	9.5 to 11.0 *5.88 to 6.86*	8.0 to < 9.5 *4.94 to < 5.88*	6.7 to < 8.0 *4.15 to < 4.94*	< 6.7 *< 4.15*
8 to ≤ 21 days of age (male and female)	11.0 to 13.0 *6.81 to 8.10*	9.0 to < 11.0 *5.57 to < 6.81*	8.0 to < 9.0 *4.96 to < 5.57*	< 8.0 *< 4.96*
≤ 7 days of age (male and female)	13.0 to 14.0 *8.05 to 8.72*	10.0 to < 13.0 *6.19 to < 8.05*	9.0 to < 10.0 *5.59 to < 6.19*	< 9.0 *< 5.59*
Platelets, Decreased (cells/mm^3; *cells/L*)	100,000 to < 124,999 *100.000 x 10^9 to < 124.999 x 10^9*	50,000 to < 100,000 *50.000 x 10^9 to < 100.000 x 10^9*	25,000 to < 50,000 *25.000 x 10^9 to < 50.000 x 10^9*	< 25,000 *< 25.000 x 10^9*
WBC, Decreased (cells/mm^3; *cells/L*) *> 7 days of age*	2,000 to 2,499 *2.000 x 10^9 to 2.499 x 10^9*	1,500 to 1,999 *1.500 x 10^9 to 1.999 x 10^9*	1,000 to 1,499 *1.000 x 10^9 to 1.499 x 10^9*	< 1,000 *< 1.000 x 10^9*

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
≤ 7 days of age	5,500 to 6,999 *5.500 x 10^9 to 6.999 x 10^9*	4,000 to 5,499 *4.000 x 10^9 to 5.499 x 10^9*	2,500 to 3,999 *2.500 x 10^9 to 3.999 x 10^9*	< 2,500 *< 2.500 x 10^9*

Total Bilirubin Table for Term and Preterm Neonates

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Total Bilirubin[a], High (mg/dL; *µmol/L*)[b]				
Term Neonate[c] *< 24 hours of age*	4 to < 7 *68.4 to < 119.7*	7 to < 10 *119.7 to < 171*	10 to < 17 *171 to < 290.7*	≥ 17 *≥ 290.7*
24 to < 48 hours of age	5 to < 8 *85.5 to < 136.8*	8 to < 12 *136.8 to < 205.2*	12 to < 19 *205.2 to < 324.9*	≥ 19 *≥ 324.9*
48 to < 72 hours of age	8.5 to < 13 *145.35 to < 222.3*	13 to < 15 *222.3 to < 256.5*	15 to < 22 *256.5 to < 376.2*	≥ 22 *≥ 376.2*
72 hours to < 7 days of age	11 to < 16 *188.1 to < 273.6*	16 to < 18 *273.6 to < 307.8*	18 to < 24 *307.8 to < 410.4*	≥ 24 *≥ 410.4*
7 to 28 days of age (breast feeding)	5 to < 10 *85.5 to < 171*	10 to < 20 *171 to < 342*	20 to < 25 *342 to < 427.5*	≥ 25 *≥ 427.5*
7 to 28 days of age (not breast feeding)	1.1 to < 1.6 x ULN	1.6 to < 2.6 x ULN	2.6 to < 5.0 x ULN	≥ 5.0 x ULN
Preterm Neonate[c] *35 to < 37 weeks gestational age*	Same as for ***Total Bilirubin, High, Term Neonate*** (based on days of age).	Same as for ***Total Bilirubin, High, Term Neonate*** (based on days of age).	Same as for ***Total Bilirubin, High, Term Neonate*** (based on days of age).	Same as for ***Total Bilirubin, High, Term Neonate*** (based on days of age).
32 to < 35 weeks gestational age and < 7 days of age	NA	NA	10 to < 14 *171 to < 239.4*	≥ 14 *≥ 239.4*
28 to < 32 weeks gestational age and < 7 days of age	NA	NA	6 to < 10 *102.6 to < 171*	≥ 10 *≥ 171*
< 28 weeks gestational age and < 7 days of age	NA	NA	5 to < 8 *85.5 to < 136.8*	≥ 8 *≥ 136.8*
7 to 28 days of age (breast feeding)	5 to < 10 *85.5 to < 171*	10 to < 20 *171 to < 342*	20 to < 25 *342 to < 427.5*	≥ 25 *≥ 427.5*
7 to 28 days of age (not breast feeding)	1.1 to < 1.6 x ULN	1.6 to < 2.6 x ULN	2.6 to < 5.0 x ULN	≥ 5.0 x ULN

a Severity grading for total bilirubin in neonates is complex because of rapidly changing total bilirubin normal ranges in the first week of life followed by the benign phenomenon of breast milk jaundice after the first week of life. Severity grading in this appendix corresponds approximately to cut-offs for indications for phototherapy at grade 3 and for exchange transfusion at grade 4.
b A laboratory value of 1 mg/dL is equivalent to 17.1 µmol/L.
c Definitions: Term is defined as ≥ 37 weeks gestational age; near-term, as ≥ 35 weeks gestational age; preterm, as < 35 weeks gestational age; and neonate, as 0 to 28 days of age.

19 APPENDIX B: SCHEDULE OF EVENTS

	Screening	Treatment Study Day										Treatment Study Month				
	(≤ 30 days of age)	1 (day -3 to day 1)	7 (week 1) (± 2 days)	14 (week 2) (± 2 days)	21 (week 3) (± 2 days)	28 (week 4) (± 2 days)	35 (week 5) (± 2 days)	42 (week 6) (± 3 days)	56 (week 8) (± 3 days)	70 (week 10) (± 3 days)	84 (week 12) (± 3 days)	4 (± 10 days)	5 (± 10 days)	6 (± 10 days)	12 (± 30 days)	18 (± 30 days)
Screening Informed Consent	X															
Saliva for screening detection of CMV DNA by PCR	X															
Urine and saliva for confirmatory detection of CMV DNA by PCR[a]	X															
Treatment or Observational Informed Consent	X[b]	X[b]														
Baseline demographics[c]		X														
Hematology Safety Labs[d]		X[e]	X	X	X	X	X	X	X	X	X	X	X			
Chemistry Safety Labs[f]		X		X		X		X	X	X	X	X	X	X		
Growth Parameters[g]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Event Assessment		X[h]	X	X	X	X	X	X	X	X	X	X	X			
Concomitant Medications		X	X	X	X	X	X	X	X	X	X	X				
Hearing Assessment	X[i]											X[j]		X[k]	X[k]	X[k]
Virology Specimen for CMV Viral Load[l,m]		X[n]	X	X	X	X	X	X	X	X	X	X[o]	X[o]	X[o]		
Updated results of any available etiological investigations for SNHL			X	X	X	X	X	X	X	X	X	X	X	X	X	X
Determination of appropriate dose		X	X	X	X	X	X	X	X	X	X					
Valganciclovir Administration[p]		←	—	—	—	—	—	—	—	—	→					
Total volume of blood required for study	0.0 mL	2.2 mL	1.2 mL	2.2 mL	1.2 mL	2.2 mL	1.2 mL	2.2 mL	2.2 mL	2.2 mL	2.2 mL	2.2 mL	2.2 mL	1.7 mL	0.0 mL	0.0 mL

a) Babies screening positive for congenital CMV infection will have a second saliva sample and a urine sample collected for confirmatory PCR testing. Screening will occur most commonly during the birth hospitalization, and with enough time for initial and confirmatory PCR specimens to be obtained and run.
b) The *treatment* consent or *observational* consent will be signed following the confirmatory PCR testing for CMV DNA and prior to or on Day 1.
c) 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; gestational age at birth; medical history and baseline conditions prior to study enrollment, by body system
d) WBC with differential, Hgb, Plt (approximate total blood needed for these tests is 0.5 cc)
e) Absolute neutrophil count will be determined prior to the first dose of study medication
f) ALT, direct bilirubin, and creatinine (approximate total blood needed for these tests is 1.0 cc)
g) Growth parameters consist of length, weight, and head circumference
h) Adverse events that occur following the first dose of study medication
i) Babies screening positive for congenital CMV infection on their first saliva sample will have sensorineural hearing testing performed, as is standard of care for babies identified as being congenitally infected with CMV. BSER (to assess neuro-otologic status) and OAEs (DPOAE or TEOAE) will be obtained. If the BSER 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).
j) BSER (to assess neuro-otologic status) and OAEs (DPOAE or TEOAE) will be obtained. If the BSER 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) (window: -10 to + 30 days).
k) BSER and/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) (window: -10 to +30 days).
l) Required amount of whole blood for plasma and whole blood CMV PCR is at least 0.7 mL.
m) For the approximately 12 patients identified as being asymptomatically congenitally infected with CMV and with SNHL, Virology specimens for CMV viral load will be the only study-related laboratory specimen collected for them; all other data on the valganciclovir treatment and associated safety labs as well as the serial hearing testing are part of clinical care for these patients, and will be redacted without alteration from the clinical chart. Non-study clinical and laboratory assessments that are not performed according to the intervals and listings in Appendix A (Schedule of Events) will not be assessed as protocol deviations.
n) In addition to whole blood for CMV viral load, urine collection by bagged specimen and saliva collected by buccal swab will be attempted on Study Day 1 (Window: Study Day -3 to Study Day 7 for whole blood and urine; and Study Day -30 to Study Day 7 for saliva). If urine is obtainable, it will be frozen and sent to the Central Unit Central Laboratory for processing. If urine is not obtainable, a protocol deviation will not be reported.
o) In addition to whole blood for CMV viral load, urine collection by bagged specimen and saliva collected by buccal swab will be attempted on Study Month 4 (Window: ± 10 days), Study Month 5 (Window: ± 10 days), and Study Month 6 (Window: ± 10 days). If urine is obtainable, it will be frozen and sent to the Central Unit Central Laboratory for processing. If urine is not obtainable, a protocol deviation will not be reported.
p) Valganciclovir administration begins on **Study Day 1**; drug should be administered within 49 days of reconstitution. Study medication diary will be collected and distributed at each study visit throughout the treatment period.