Statistical Analysis Plan

TRIAL FULL TITLE	A PHASE II RANDOMIZED AND CONTROLLED INVESTIGATION OF SIX WEEKS OF ORAL VALCANCICLOVIR THERAPY IN INFANTS AND CHILDREN WITH CONGENITAL CYTOMEGALOVIRUS INFECTION AND HEARING LOSS DMID Protocol Number: 11-0069
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1 Abbreviations and Definitions

AE	Adverse Event/Adverse Experience
AIC	Akaike Information Criteria
ANC	Absolute Neutrophil Count
AUC	Area Under the Curve
BSER	Brainstem Evoked Response
CASG	Collaborative Antiviral Study Group
CL/F	Oral Clearance
CMV	Cytomegalovirus
CNS	Central Nervous System
Cobs	Observed Concentration
Cpred	Predicted Concentration
CRF	Case Report Form
CROMS	Clinical Research Operations and Management Support
CSF	Cerebrospinal Fluid
CU	Central Unit
DAIDS	The United States Division of AIDS
DCC	Data Coordinating Center
DMID	Division of Microbiology and Infectious Diseases, NIAID, NIH, DHHS
DSMB	Data and Safety Monitoring Board
eDES	Electronic Data Entry System
FDA	Food and Drug Administration, USA
GCV	Ganciclovir
GEE	Generalized Estimating Equations
HEENT	Head, ears, eyes, nose and throat
HIV	Human Immunodeficiency Virus
IA	Independent Audiologist
IPAM	Integrated Pharmacokinetic Adherence Measure
ITT	Intent to Treat
IV	Intravenous
Ka	Absorption Rate
Ke	Elimination Constant
kg	Kilogram
L	Liter
L/hr	Liter Per Hour
LL	Log Likelihood
MedDRA	Medical Dictionary for Regulatory Activities

mg	Milligram
MLEM	Maximum Likelihood Estimation Maximization
N	Number (typically refers to subjects)
N/A	Not applicable
NIAID	National Institute of Allergy and Infectious Diseases, NIH, DHHS
NIH	National Institutes of Health
OAE	Otoacoustic Emissions
PCR	Polymerase Chain Reaction
PK	Pharmacokinetic
PP	Per-protocol
SAE	Serious Adverse Event//Serious Adverse Experience
SAP	Statistical Analysis Plan
Scr	Serum creatinine
SE	Standard error
SNHL	Sensorineural Hearing Loss
$T_{1/2}$	Time of Half life
UAB	University of Alabama at Birmingham
V/F	Volume of Distribution
VGCV	Valganciclovir
VRA	Visual Reinforcement Audiometry
WBC	White Blood Cell

2 Introduction

2.1 Preface

This study is a Phase II, international, multi-center, double-blind, placebo-controlled evaluation of six weeks of valganciclovir treatment for children (up to 4 years of age) with virologically-confirmed congenital CMV infection and hearing loss. In order for the treatment arms of the trial to remain blinded, a valganciclovir placebo will be utilized, as described below. Patients meeting inclusion/exclusion criteria will be offered enrollment onto the trial.

2.2 Purpose of the analyses

These analyses will evaluate whether six weeks of antiviral therapy can stabilize hearing deterioration in older infants, toddlers, and young children who have developed CMV-associated hearing loss.

3 Study Objectives and Endpoints

3.1 Study Objectives

(ICH E3; 8.)

- To assess whether a six week course of oral valganciclovir can stabilize the hearing of children with congenital CMV infection who present with hearing loss.
- To measure CMV viral load in blood, urine, and saliva as a function of systemic exposure to ganciclovir (active metabolite of valganciclovir).
- To define the safety and tolerability of valganciclovir in enrolled subjects.
- To define the pharmacokinetics of ganciclovir (metabolite) following administration valganciclovir (prodrug) in enrolled subjects.

3.2 Endpoints

(ICH E9; 2.2.2)

Primary Endpoint

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

Secondary Endpoints

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

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

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

4. The quantitative log reduction in viruria detected after 6 weeks of therapy

5. Detection of viremia by PCR six weeks and six months after trial entry

6. The quantitative log reduction in viremia detected after 6 weeks of therapy

7. Detection of CMV in saliva by PCR six weeks and six months after trial entry

8. The quantitative log reduction in CMV viral load in saliva detected after 6 weeks of therapy

9. Correlation of change in viral load with change in total ear and best ear hearing at 6 months

10. Incidence of unanticipated medically attended visits occurring from Study Day 1 through two weeks following the last dose of study drug

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

Tertiary Endpoints

1. Blood concentrations of ganciclovir after administration of valganciclovir

3.3 Derived variables

The primary efficacy assessment will be change in total ear hearing assessment between baseline and 6 months post enrollment. Categories used for hearing assessment of each ear for each time point will be normal hearing, mild hearing loss, moderate hearing loss, and severe hearing loss. Baseline and 6 month hearing categories will be compared and the change in each ear will be categorized into binary outcomes: Improved or no change versus Other (i.e., worsened) Note that the total ear assessment at each time point will be provided by the Independent Audiologist and entered in the database following the rules below and the information provided by the audiology reports.
In the model-based analyses, the “no change” category will be broken down into “Protected: normal to normal” as one category and “No Change: same degree of hearing loss at Baseline and Study Month 6” as another category. The rationale behind this is that if one is interested in the improvement of hearing loss, a subject that has normal hearing at baseline cannot improve further. Hence from an efficacy analysis point of view, the “Protected: normal to normal" can be viewed as protective effect of the drug from hearing deterioration. This analysis approach will be similar to the analysis of the previous CASG study that established the efficacy of 6 weeks of IV GCV in symptomatic congenital CMV disease with CNS involvement.

Analysis of actual viral load will be done using log base 10 transformation. Undetectable viral load value will be replaced by a value of 10. A summary measure of the viral load over time will be calculated two ways. The first approach considers all time points available by calculating the average area under the curve (AUC) (trapezoidal rule) applied to the log base 10 viral load. Average is based on the maximum period of time with viral load data for a given subject. To illustrate, if the calculated AUC for log10 VL for a given subject is 200 from baseline to Day 70, then average AUC is 200/70=2.86. Taking average AUC will enable us to use and compare data from subjects who did not have viral load values at the later time due to dropping out early, for example, with subjects with complete viral load data. The second approach is to take using difference between Month 6 and baseline log10 VL. The last visit with available VL will be used for those without Month 6 VL. Section 11 contains more details on Viral Load analyses.

PK data analyses and computations of PK-related derived variables are detailed in Section 10.

4 Study Methods

4.1 General Study Design and Plan

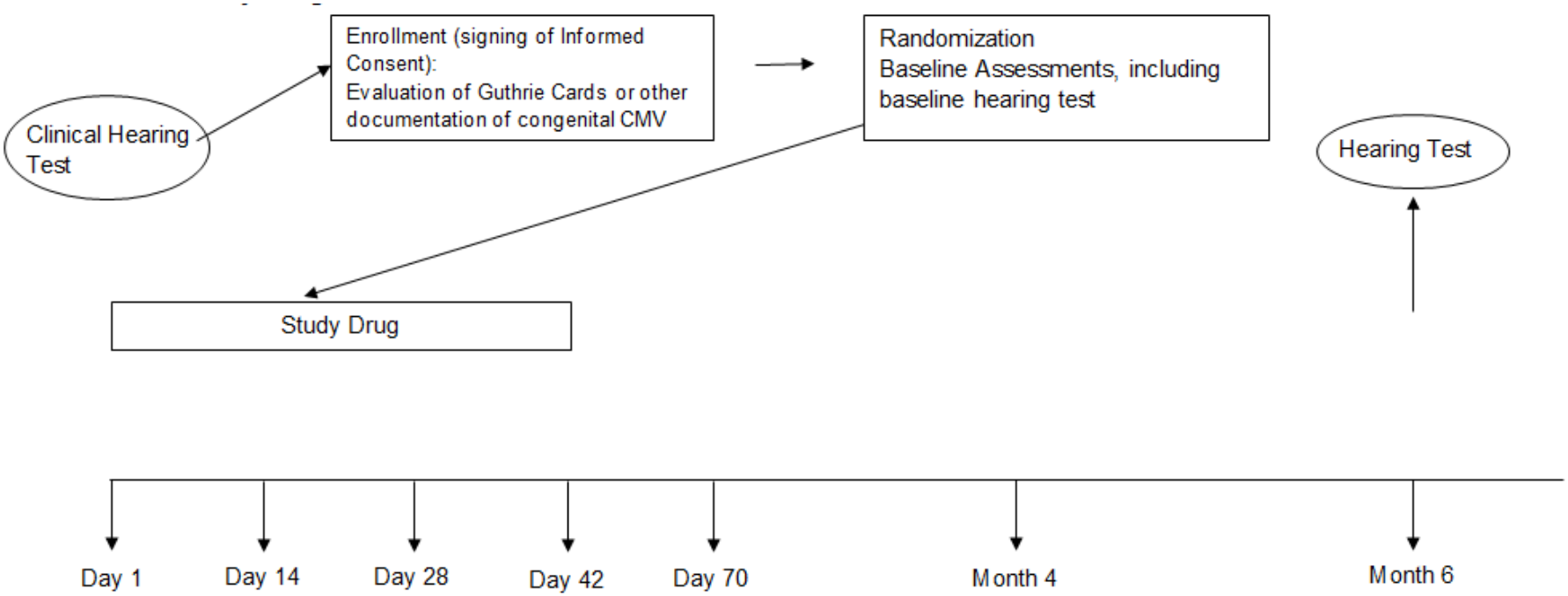
(ICH E3;9)

The current study evaluates whether six weeks of antiviral therapy can stabilize hearing deterioration in older infants, toddlers, and young children who have developed CMV-associated hearing loss. This study is a Phase II, international, multi-center, double-blind, placebo-controlled evaluation of six weeks of valganciclovir treatment for children (up to 4 years of age) with virologically-confirmed congenital CMV infection and hearing loss.

Patients meeting inclusion/exclusion criteria will be offered enrollment into the trial. Randomization on the study occurs when the diagnosis of congenital CMV infection is confirmed, and the subject is then assigned to receive either 6 weeks of oral valganciclovir or 6 weeks of placebo. Study subjects will be stratified according to age at randomization (1 through 11 months, 12 through 23 months, 24 through 35 months, and ≥ 36 months) and CMV involvements (symptomatic and asymptomatic at birth) as a marker of disease severity. An independent Data and Safety Monitoring Board (DSMB) will oversee the conduct of the trial. During the course of their oversight, they may request to have access to unblinded data.

The target sample size is 54 subjects (27 in each arm). Up to 20% over-enrollment will be allowed to replace subjects who drop-out or who have inadequate audiology assessments. The primary endpoint will be change in total ear hearing assessments (improved + no change versus other) between baseline and 6 months. Secondary and tertiary endpoints will be assessments of other measures of hearing outcomes; detection of viruria, viremia, and CMV in saliva by PCR six weeks and six months after trial entry; the quantitative log reduction in viruria, viremia, and CMV viral load in saliva detected after six weeks of therapy; correlation of change in viral load with change in total ear and best ear hearing at six months; incidences of unanticipated medically attended visits and adverse events which lead to permanent discontinuation of valganciclovir therapy or have an unresolved outcome; and assessments of blood concentration of ganciclovir after administration of valganciclovir. Stopping rules will be employed in order to limit exposure of study subjects to a potentially unacceptable treatment.

Figure 1: Schematic of Study Design



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

During the 6 week treatment period and for 4 week thereafter, study subjects will be followed every two weeks for 6 weeks. Subjects will then be seen a month after the end of the treatment period, then at 4 and 6 months after randomization. During the 6 week treatment period and at the 1 month post treatment period, safety labs will be checked and adverse events will be assessed. The dose of study medication will be adjusted for weight change at each of these study treatment visits, hence collection of growth parameters at each of the treatment visits. Whole blood will be obtained for CMV viral load at each of these visits as well. Hearing outcomes will be assessed at baseline and 6 months. Changes in whole blood viral load measurements will be correlated with hearing outcome.

Safety Reviews and Halting Rules

Halting rules for this study therefore have been constructed to interrupt study enrollment if an excessive number of subjects are experiencing neutropenia. Assuming that 75% of subjects receiving ganciclovir developed Grade 3 or 4 neutropenia and given that randomization is expected to be balanced between those in study drug and those in placebo, the stopping rule will be based on assuming that the overall event rate for all study participants (i.e., placebo and active subjects combined) is 37.5%. Therefore, study enrollment will be stopped and an ad hoc review will be performed if a significantly higher proportion (37.5%) of subjects in this study experience Grade 3 or Grade 4 neutropenia, as detailed in the following table:

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

Number enrolled (Y)	Stop/Investigate when number with events equals this number (X)	Probability of observing X or more events assuming p=0.375		Number enrolled (Y)	Stop/Investigate when number with events equals this number (X)	Probability of observing X or more events assuming p=0.375
4	4	0.020		30	17	0.025
5	5	0.007		31	17	0.037

6	5	0.031	32	18	0.024
7	6	0.013	33	18	0.034
8	6	0.036	34	18	0.048
9	7	0.017	35	19	0.032
10	7	0.038	36	19	0.044
11	8	0.019	37	20	0.030
12	8	0.039	38	20	0.041
13	9	0.021	39	21	0.028
14	9	0.039	40	21	0.038
15	10	0.021	41	22	0.026
16	10	0.037	42	22	0.035
17	11	0.021	43	22	0.047
18	11	0.036	44	23	0.032
19	12	0.021	45	23	0.043
20	12	0.034	46	24	0.030
21	13	0.020	47	24	0.040
22	13	0.033	48	25	0.028
23	13	0.050	49	25	0.037
24	14	0.031	50	25	0.048
25	14	0.046	51	26	0.034
26	15	0.029	52	26	0.044
27	15	0.043	53	27	0.032
28	16	0.027	54	27	0.041
29	16	0.040			

In addition to the continual assessment of serious adverse events leading to permanent discontinuation from protocol, the DSMB may request for unblinded safety profile listings.

4.2 Equivalence or Non-Inferiority Studies

(ICH E3; 9.2, 9.7.1, 11.4.2.7. ICH E9; 3.3.2)

Not applicable

4.3 Inclusion-Exclusion Criteria and General Study Population

(ICH E3;9.3. ICH E9;2.2.1)

Male and female infants from 1 month through 3 years of age (up to 4th birthday) with sensorineural hearing loss will be eligible for enrollment. Following confirmation of inclusion/exclusion criteria and the signing of informed consent, the subject's Guthrie card will be retrieved and tested for CMV DNA by PCR unless there is a virologically confirmed diagnosis of congenital CMV infection made within the first 30 days of life. Inclusion criteria were selected to ensure the inclusion of those subjects with congenital CMV disease. Exclusion criteria were selected to limit confounders for safety and efficacy. Renal insufficiency was an exclusion criterion because the active moiety, GCV, is renally cleared and a neonate's renal system is not fully developed. The study population is consistent with those patients seen in clinical practice and who receive IV GCV as standard of care to treat symptomatic congenital CMV.

Inclusion Criteria

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

Exclusion Criteria

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

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

4.4 Randomization and Blinding

(ICH E3; 9.4.3, 9.4.6. ICH E9; 2.3.1, 2.3.2)

The randomization schedule will be created by the UAB Data Coordinating Center (DCC).

Randomization will be implemented by the web-based randomization system developed and maintained at the UAB Data Coordinating Center at the University of Alabama at Birmingham. The generation and maintenance of study randomization codes will be the responsibility of the UAB Data Coordinating Center. The codes will be kept in a secure location in the Data Coordinating Center.
A site will enter the data via electronic data entry system (eDES). Once an eligible participant is enrolled, the subject's Guthrie card will be retrieved and tested for CMV DNA by PCR, unless there is a virologically confirmed diagnosis of congential CMV infection made within the first 30 days of life. Once a diagnosis of congenital infection is confirmed, the site will complete the Randomization form via eDES and will lock the form to successfully randomize a subject. Once the subject is randomized, an email alert will be sent to the site PI, site staff, and responsible parties containing information, randomization ID, center information and PK schematic for the subject. No information about the treatment assignment will be provided in this email alert. Site pharmacist will receive a separate email that contains the treatment assignment. Study monitors will be responsible for checking if the drug accountability documents shows the correct treatment based on the randomization email for each subject.

Blinding

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

analyzes the audiology data will be masked to study assignment, as will all personnel at the UAB Central Unit (with the exception of the UAB Study Statistician).

Upon completion of the six month follow-up period for all study subjects, or if the study is stopped early for any reason, the study will be unmasked after all enrolled study participants have completed the Month 6 follow-up assessments and the database is frozen. In an emergency situation, in which knowledge of the treatment assignment will be used to reduce/remove an immediate hazard to a volunteer, the study PI and/or a local site PI will have the ability to access the treatment assignment. In this situation (emergency unblinding) the study/local PI must explain and justify the nature of the event that resulted in the decision to immediately unblind to the DMID Medical Monitor and the Protocol Chair as soon as possible. This justification will be documented as a protocol deviation, and the IRBs and regulatory agencies will be informed as is appropriate.

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

The DSMB access to unblinded data is to be determined and will be based on the charter. Two data reports will be generated for each DSMB meeting: Open reports (with blinded information), and Closed reports (with unblinded information). The Closed Report will be prepared by the Protocol Statistician. Open reports will be distributed to and reviewed by the Sponsor (NIAID/DMID) and the CASG CU, and will be distributed to Genetech, Inc. The Closed Reports will be distributed to the Sponsor's pharmacovigilance contractor, DMID Clinical Research Operations and Management System (CROMS), via e-mail as a password protected Adobe Acrobat document. The password will be sent in a separate email. DMID CROMS then will distribute the Closed Reports only to the DSMB and maintain the reports as access restricted files.

4.5 Study Variables

(ICH E3; 9.5.1. ICH E9; 2.2.2)

The following table summarizes the visit, visit windows and the information to be collected and evaluations to be done at each visit.

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

Valganciclovir vs. Placebo Administration[g]			←	—	—	→			
Total volume of blood required			2.0 mL	2.25 mL	2.25 mL	2.25 mL	2.0 mL	0.5 mL	0.5 mL

a) Baseline demographics and birth history consist of date of birth; gender; race; ethnicity; birth weight; length at birth, if available; head circumference at birth, if available; and gestational age at birth. Degree of CMV disease involvement consists of neuroimaging abnormalities if imaging was performed; petechiae at any time from birth through study randomization, if known; thrombocytopenia at any time from birth through study randomization, if obtained; hepatomegaly at any time from birth through study randomization, if noted; splenomegaly at any time from birth through study randomization, if noted; CSF white blood cell count at any time from birth through study randomization, if obtained; CSF protein concentration at any time from birth through study randomization, if obtained; CSF CMV PCR at any time from birth through study randomization, if performed; seizures at any time from birth through study randomization, if noted; elevated transaminases at any time from birth through study randomization, if obtained; elevated bilirubin at any time from birth through study randomization, if obtained; medical history and baseline conditions prior to study randomization, by body system, chorioretinitis, intrauterine growth restriction, urine CMV testing (e.g., viral culture, shell-vial culture, PCR) within 90 days prior to study enrollment, if obtained clinically

b) WBC with differential, hemoglobin, Platelet enumeration (approximate total blood needed for these tests is 0.5 mL)

c) ALT, total bilirubin, creatinine (approximate total blood needed for these tests is 1.0 mL)

d) BSER and/or VRA (to assess neuro-otologic status) and OAEs will be obtained. If the BSER and/or VRA is abnormal, then bone conduction will be obtained to distinguish between sensorineural hearing loss, conductive loss, and mixed loss. If the OAEs are abnormal, then acoustic immittance measures (tympanometry and acoustic reflexes) will be obtained to better define the middle or inner ear abnormality (e.g., otitis media).

e) Required amount of whole blood for quantitative CMV PCR is at least 0.5 mL. Urine collection by bagged or clean catch specimen for quantitative PCR. Saliva collection by polyester fiber-tipped swabs for quantitative PCR.

f) Required amount of whole blood for plasma ganciclovir determination is at least 0.25 mL

g) Valganciclovir or placebo administration begins on Day 1 of the study; study medication dose adjusted for weight change, if needed, at each study visit while on treatment

Hearing assessments at each time point and at each ear as well as the change in the best ear comparing Month 6 with baseline will be provided by a single Independent Audiologist (IA) who will interpret the audiology reports of all patients at all protocol-specified visits requiring hearing assessments. The IA will enter the data directly to the eDES.

Section 3.3 describes the derived variables and the techniques and rules used to obtain the transformed data that will be used in the analyses

5 Sample Size

(ICH E3; 9.7.2. ICH E9; 3.5)

The planned enrollment is 54 subjects. Dropouts and subjects with audiology assessments that are inadequate for study comparison will be replaced (up to 20%, or n=10).

A sample size of 54 (27 in each arm) has 90% power to detect a worsening of hearing from 40% to 8.0% in the treatment group based on analyzing two correlated binary outcomes with correlation coefficient of 0.55 at 2.5% level of significance (using PASS 2008 program).

6 General Considerations

6.1 Timing of Analyses

The final analysis will be performed after all subjects have completed study participation, all subjects have been 100% monitored by an independent monitor, data quality check has been completed and the data base has been locked.

6.2 Analysis Populations

(ICH E3; 9.7.1, 11.4.2.5. ICH E9; 5.2)

All enrolled subjects will be included in the basic demographic and clinical summaries and analyses. Only subjects who took at least one dose of the blinded treatment and who have completed hearing assessment data at baseline and Month 6 will be included in the analyses of study outcomes that compare treatment groups based on the intention-to-treat (ITT). Safety analyses will be done on all participants enrolled in the study. Children who have completed the full six weeks

of study medication and have hearing assessment data at baseline and Month 6 will be included in a per-protocol (PP) analysis of efficacy, which will be performed as a sensitivity analysis.

6.3 Covariates and Subgroups

(ICH E3; 9.7.1, 11.4.2.1. ICH E9; 5.7)

The primary outcome will be analyzed using logistic regression based on generalized estimating equations (GEE) in order to accommodate the correlation between the left and right ears of a subject in the modeling. In addition, if there are enough data available we will adjust the analyses by whether or not a subject at birth is asymptomatic or symptomatic from their congenital CMV infection. Additional analyses will be performed to adjust for age and site plus any imbalances in the demographic and clinical characteristics to determine if adding them to the model will impact the results.

6.4 Missing Data

(ICH E3; 9.7.1, 11.4.2.2. ICH E9;5.3. EMA Guideline on Missing Data in Confirmatory Clinical Trials)

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

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

6.5 Interim Analyses and Data Monitoring

(ICH E3; 9.7.1, 11.4.2.3. ICH E9; 4.1, FDA Feb 2010 "Guidance for Industry Adaptive Design Clinical Trials for Drugs and Biologics")

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

6.5.1 Safety Review

Safety reports will be generated and sent to DMID to be disseminated to the DSMB. This report includes hematology and safety laboratory values and adverse events (serious and non-serious). In addition, Section 9.7 provides a table of halting rules based on the number of subjects experiencing Grade 3 or 4 neutropenia for consideration by the DSMB.

6.5.2 Stopping Rules

In prior CASG studies of ganciclovir and valganciclovir that have enrolled 233 subjects, the only laboratory toxicity statistically associated with antiviral treatment has been neutropenia. Halting rules for this study therefore have been constructed to interrupt study enrollment if an excessive number of subjects are experiencing neutropenia. In the CASG 102 study, 63% of subjects receiving parenteral ganciclovir developed Grade 3 or Grade 4 neutropenia.[1] In the CASG 109 study, 38% of subjects receiving oral valganciclovir developed Grade 3 or Grade 4 neutropenia.[2] Whether this lower rate of neutropenia relates to the mode of drug delivery is not known at this time. Assuming that 75% of subjects receiving ganciclovir developed Grade 3 or 4 neutropenia and given that randomization is expected to be balanced between those in study drug and those in placebo, the stopping rule will be based on assuming that the overall event rate for all study participants (i.e., placebo and active subjects combined) is 37.5%. Therefore, study enrollment will be stopped and an ad hoc review will be performed if a significantly higher proportion (37.5%) of subjects in this study experience Grade 3 or Grade 4 neutropenia, as detailed in the following table:

The stopping rules are based on the tail probabilities of the cumulative binomial. If the number of subjects “X” who experience Grade 3 or 4 neutropenia is greater than or equal to “m” out of “n” subjects, enrollment into the protocol will be held as described above while the DSMB decides whether study closure should occur. The stopping rules are based on the upper tail probabilities of the cumulative binomial with probability of an event set at 0.375. The cut-off numbers were determined by obtaining the largest value such that the tail probability is less than but closest to

0.05. More specifically, the following values of (m/n) apply for this Phase II protocol:

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

6.5.3 Adjustment of Confidence Intervals and p-values

There will be no planned adjustments on the confidence intervals since there is no proposed interim analysis.

6.5.4 Practical Measures to Minimize Bias

Not applicable as there is no interim analysis for this study.

6.5.5 Documentation of Interim Analyses

Not applicable as there is no interim analysis for this study

6.6 Multi-center Studies

(ICH E3;9.7.1, 11.4.2.4. ICH E9; 3.2)

This study is a multi-center study. The primary outcome of hearing was analyzed by a single independent audiologist. Data will be analyzed by combining data from all study centers.

6.7 Multiple Testing

(ICH E3; 9.7.1, 11.4.2.5. ICH E9; 2.2.5)

Based on the hearing assessment of each ear at Month 6 and at Baseline, change in each ear will be categorized into binary outcome: improved + no change versus other (i.e. worsened). For example, normal in the left ear at baseline and moderate in the same ear at Month 6 will be considered as worsened. P-values < 0.05 will be considered significant for the primary outcomes. There are no planned adjustments for multiple testing for secondary outcomes.

7 Summary of Study Data

All continuous variables will be summarized using the following descriptive statistics: n (non-missing sample size), mean, standard error, median, maximum and minimum. The frequency and percentages (based on the non-missing sample size) of observed levels will be reported for all categorical measures. In general, all data will be listed, sorted by site, treatment and subject, and when appropriate by visit number within subject. All summary tables will be structured with a column for 1. Randomized/not randomized/total and 2. Active, placebo and total, and will be annotated with the total population size relevant to that table/treatment, including any missing observations.

7.1 Subject Disposition

The following flowchart will be used to summarize the subject disposition in the study and treatment. Numbers will be obtained based on the following CRFs: Inclusion/Exclusion, Randomization, Study Treatment Termination or Completion, and Study Termination or Completion.

Figure 2a: Enrollment Flow

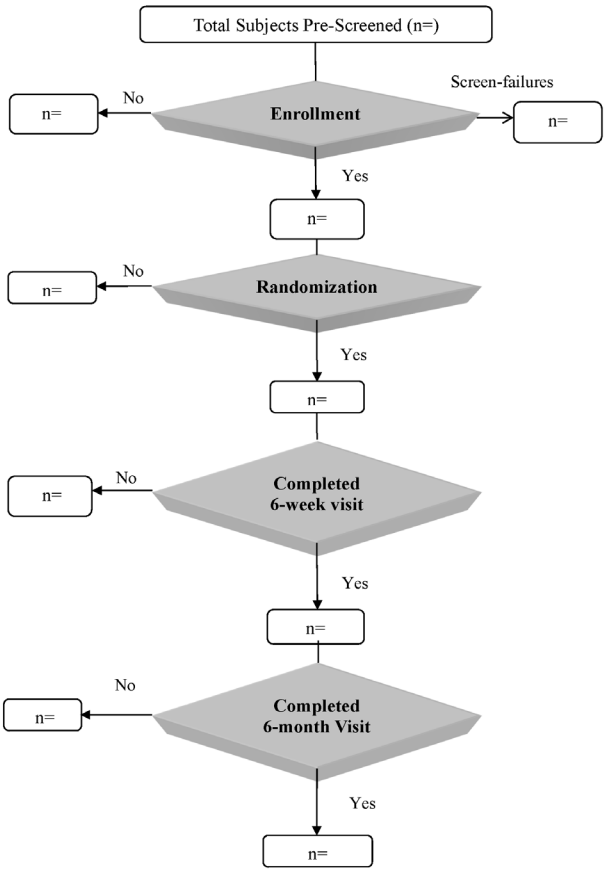
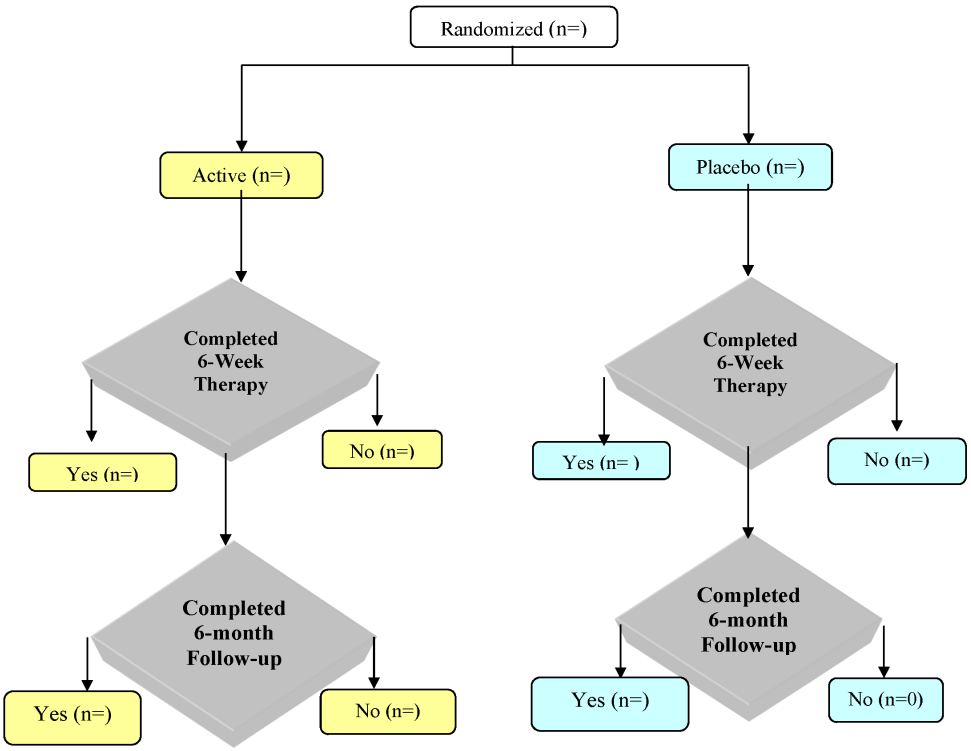


Figure 2b: Treatment Disposition of Subjects



7.2 Protocol Deviations

Protocol deviations will be summarized by site and type of deviation; deviations that resulted in adverse and serious adverse events; and protocol deviations that resulted in termination. The summary statistics will be produced in accordance with Section 7.

A raw listing of all protocol deviations will be provided by site by subject ID, deviation date, resulting in AE, SAE, and termination; deviation description; reason for the deviation; deviation category; effect on product stability; and deviation resolution.

As per protocol, 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. Hence, hearing outcomes from these subjects past implantation will not be included in the analyses.

Finally, any subjects enrolled but not eligible will also be excluded from the analyses.

7.3 Demographic and Baseline Variables

- Age at enrollment (actual and categorized as 1-11 months, 12-23 months, 24-35 months, 36 or more months)
- Gender
- Ethnicity
- Gestational Age (actual and categorized as pre-term, i.e., 31-<=37 weeks, and term)
- Race
- Sex
- Birth Weight
- Length at birth
- Head circumference at birth

The summary statistics will be produced in accordance with section 7.

7.4 Degree of CMV Disease Involvement at Birth

The degree of CMV disease involvement at birth will be recorded, if known.

- Neuroimaging abnormalities
- Petechiae

- Thrombocytopenia
- Hepatomegaly
- Splenomegaly
- CSF white blood cell count
- CSF protein concentration
- CSF CMV PCR
- Seizures
- Elevated transaminases
- Elevated bilirubin

7.5 Concurrent Illnesses and Medical Conditions at Baseline

- Symptoms of CMV
- Medical and Surgical Abnormalities (Neurologic, Cardiovascular, Pulmonary, Gastrointestinal, HEENT, Musculoskeletal, Hepatobiliary/pancreatic, Hematologic/lymphatic, Genitourinary, Endocrine/metabolic, Dermatological, Immune system, Body as a whole, Metabolism and nutrition disorders)
- CMV disease involvement

The summary statistics will be produced in accordance with section 7.

7.6 Prior and Concurrent Medications

Questions regarding medications will be asked at each visit. List of medications taken at baseline and at each visit, date medication started and stopped, or if medication being taken is ongoing will be noted. A listing by subject ID, visit, drug, start date, stop date, if ongoing or not, and reason for taking the medication will be provided. Summary of medications that were considered as prohibited medications while in the study will be presented as a separate listing.

7.7 Treatment Compliance

Ganciclovir plasma concentrations will be obtained with each blood draw obtained while the subject is receiving valganciclovir (Study Day 14, Study Day 28, and Study Day 42). For each subject, one of these three draws will occur 0 to 4 hours after a valganciclovir dose, one will occur 4 to 8 hours after a valganciclovir dose, and one will occur 8 to 12 hours after a valganciclovir dose. The summary statistics will be produced in accordance with section 7.

An integrated pharmacokinetic-adherence measure (IPAM) will be applied to determine the degree of regimen adherence. Briefly, this unique approach will compare predicted drug concentrations (Cpred) with measured concentrations (Cobs) to determine the magnitude of variability at each time point. A pharmacokinetic model will be developed for GCV. This model was used to simulate, or predict, the concentration that was measured in the subject at each clinic visit where a sample was obtained. If the log of Cpred/Cobs ratios clustered around zero, then the subject will be relatively adherent. If the log ratios will be consistent but deviated from zero, the subject was regularly non-adherent. Lastly, if the log ratios deviated widely from zero, the subject will exhibit a large degree of nonadherence. When the plausible sources of variability in plasma concentrations (i.e. pharmacokinetic, analytical, draw timing, and dosing history) will be considered, an acceptable range of difference between Cpred and Cobs will be approximately 40%. The number of Cobs that fell within this ±40% range will be simply divided by the total number of observations to derive the IPAM score (e.g., 4 out of 8 samples within the range of variability equals 0.50 (50%) adherence). This will be done for 40%, 50%, and 60% variability. The IPAM score is therefore a continuous scale from 0.0 to 1.0. The average IPAM score for all subjects will be used to determine adherence rates relative to clinical outcomes and toxicities seen throughout the study period.

The summary statistics will be produced in accordance with section 7.

8 Efficacy Analyses

All efficacy variables will be listed by subject. Data will be summarized by treatment group. Continuous efficacy variables will be summarized by n, mean, standard error, minimum and maximum, and categorical efficacy variables will be summarized by number and percent.

8.1 Primary Efficacy Analysis

The primary endpoint is the change in total ear hearing assessments between baseline and 6 months, and will be assessed using the intent-to-treat population. At baseline and at 6 months, hearing thresholds (in decibels) will be determined using age-appropriate and developmentally-appropriate audiologic assessments. The decibel hearing thresholds in each ear classified whether the ear has normal hearing, mild hearing loss, moderate hearing loss, or severe hearing loss. Based on the hearing assessment of each ear at Month 6 and at Baseline, change in each ear

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

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

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

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

For those study subjects proceeding to cochlear implantation during the course of the study, he/she will not require additional study-related hearing assessments following the implantation procedure. Efficacy analyses will utilize "severe" as final hearing assessment at Month 6 for those who underwent cochlear implantation.

The summary statistics will be produced in accordance with section 7.

8.2 Secondary Efficacy Analyses

Logistic analyses will be utilized to determine if there is treatment effect based on the best ear outcome. As in the total ear analysis, change in the best ear will be categorized into binary outcomes – namely: improved + no change versus worse; improved + no change (normal to normal) versus worse + no change (abnormal to

abnormal); and improved versus other between baseline and Study Month 6. In addition to the primary outcome, we will analyze the binary outcome for change in the total ears categorized as: improved+ no change (normal to normal) versus worse and improved vs other.

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

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

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

The summary statistics will be produced in accordance with section 7.

9 Safety Analyses

Analyses of safety data will be based on data from all subjects receiving at least one dose of study drug. As per protocol, safety data will be collected only through Study Day 70, i.e., four weeks after the last study dose.

Incidence of serious and non-serious adverse events will be summarized by body system and system organ class using Medical Dictionary of Regulatory Activities (MedDRA) codes, the United States Division of AIDS (DAIDS) toxicity grade, and relation to drug. Frequencies (numbers and percentages) of subjects with one or more adverse events will be summarized by treatment group. Incidence of neutropenia and the incidence of adverse events leading to discontinuation of therapy will be assessed. Fisher's exact test will be used to compare proportions and Wilcoxon rank sum test will be used to compare continuous safety parameters

between two groups. Poisson regression model will be used to compare the number of AEs experienced by subjects between two groups.

Raw listings of all AEs and SAEs will be provided sorted by treatment group, subject ID and onset date.

When calculating the incidence of AEs by toxicity grade for a given body system, the most severe AE will be counted for subjects with multiple AEs.

9.1 Extent of Exposure

An integrated pharmacokinetic-adherence measure (IPAM) will be applied to determine the degree of regimen adherence (see Section 7.6 Treatment Compliance) for more details. In addition, ganciclovir concentration from PK analysis will be reported.

9.2 Adverse Events

Analyses of AEs will be based on data from all subjects receiving at least one dose of study drug. As per protocol, safety data will be collected only through Study Day 70, i.e., four weeks after the last study dose.

AEs will be reported by treatment based on the relation to study drug, toxicity grade, and body system. When calculating the incidence of adverse events, or any sub-classification thereof by treatment, time period, severity, etc., each subject will only be counted once and any repetitions of adverse events will be ignored; the denominator will be the total number in each treatment group or overall sample size as appropriate.

9.3 Deaths, Serious Adverse Events and other Significant Adverse Events

Analyses of SAEs will be based on data from all subjects receiving at least one dose of study drug. As per protocol, safety data will be collected from Study Day 1 through four weeks following the last dose of study drug.

9.4 Pregnancies

Not applicable to this study.

9.5 Clinical Laboratory Evaluations

Chemistry and hematology laboratory evaluations will be reported. The summary statistics will be produced in accordance with section 7. Flags are defined as values outside of the site- and age-specific normal ranges. The reported upper and lower limits by the site will be used to determine if the reported laboratory value was outside of the reported limits which will translate to a flag for the particular laboratory values. The number and percent (relative to the total laboratory done for that parameter) of flags will be reported in summary tables for each of the laboratory parameters. Means and standard errors of critical safety laboratory parameters (ANC, hemoglobin, WBC, platelet, ALT, bilirubin, and creatinine) over time will be displayed in a figure. Mixed model with random intercept and time, therapy and time by therapy interaction term will be will be used to compare the safety parameter at each time point between the treatment groups.

9.6 Other Safety Measures

Growth parameters (weight and length) will be captured serially. Fisher's exact test will be used to compare proportions and Wilcoxon rank sum test will be used to compare continuous safety parameters between two groups at each visit. Growth parameters will be presented graphically to monitor trends and compared at each time point for possible differences. The summary statistics will be produced in accordance with section 7.

10 Pharmacokinetics

If the final number of usable PK specimens warrants, a population PK model may be applied to the dataset. The population PK modeling will be conducted using ADAPT 5 version 049.exe (Biomedical Simulations Resource, Los Angeles, CA), installed on a Dell Latitude E6410 laptop running Windows 7.0, 64 bit operating system(Intel Visual Fortran Compiler Professional Edition 11.1.070 Update 8 for Windows and Intel Math Kernel Library 10.2 Update 7 for Windows). For the analysis, all time values will be truncated. Instead of entering 6 weeks of dosing information, the timeline will be reduced to generally within 3-5 days depending upon the number of available concentration-time points for each subject. Thus, all samples will be still at steady-state. Population PK analysis will be conducted via a nonlinear mixed-effect model approach using ADAPT 5. The Maximum Likelihood Estimation Maximization (MLEM) algorithm will be used for all analyses. The PK base model will be identified previously as a one-compartment model with first-order input and

elimination. All inter-individual error terms in the PK parameters will be assumed to have a log-normal distribution. One error variance model will be used:

$$\mathrm{var}\left\{e(t)\right\} = \left(\sigma_{inter} + \sigma_{slope} y(t)\right)^2$$

where the proportional error model is SDslope and the additive error model is (SDinter). This is the most common error variance model used in ADAPT.

Model selection will be driven by the data and will be based on various goodness of fit indicators, including comparisons based on the Akaike information criteria (AIC), visual inspection of diagnostic scatter plots and evaluation of relative standard errors for the parameter and population estimates. Individual covariate assessments and a stepwise forward inclusion procedure (α =0 .01; i.e. the decrease of -2 log likelihood [-2LL] values larger than 6.63) will be performed in ADAPT to build the full model. During the model building process, if the effects of two covariates will be highly correlated (such as weight and age), it may not have been possible to include both covariates into the model. In this case, in general, the variable with the highest significance (i.e., largest decrease in -2LL values from the base model) will be preferred, but when the decrease in -2LL will be very similar, clinical judgment may have been used to select which of the correlated covariates to include in the model. Covariate effects will be assumed to be linear based on visual inspection between each covariate and the PK parameter of interest (either CL/F and/or V/F). This analysis approach is similar to the analyses of the previous CASG 102 and 109 studies.

The summary statistics will be produced in accordance with section 7.

11 Virology

CMV whole blood viral load will be assessed by PCR at each study visit to assess for changes in viral load over time in study subjects with increasing whole blood viral loads during the course of treatment. Association of changes in whole blood viral load with changes in hearing between baseline and Study Month 6 in total ear and best ear will be evaluated as secondary endpoints. Change in the viral load over time will be measured by computing the average area under the curve (using trapezoidal rule) of all available viral load data for each subject, thus providing one

single value per participant. The area under the curve will be computed based on log base 10 viral load.

Hearing outcomes for this correlation analyses will be based on change in total ear from baseline to Study Month 6. The primary outcome will be defined with regard to change in the total ear: improved or no change versus other (i.e., worsened). Logistic regression based on generalized estimating equations will be utilized to assess if change in the viral load will be associated with the change in the total ear hearing outcomes in order to account for the correlation between outcomes attributed to the left and right ear for the same subject.

All the comments from section 7 onwards may be relevant.

12 Figures

Figures will be used to represent the following:

- enrollment status
- rate of enrollment
- trends of growth parameters (weight and length) over time
- critical safety laboratory parameters (ANC, hemoglobin, WBC, platelet, ALT, bilirubin, and creatinine) over time
- display the study visit flow
- study disposition
- extent of exposure to treatment; ganciclovir concentration over time
- dosage over time
- log base 10 viral load over time
- audiology assessment available at baseline and Month 6.

13 Reporting Conventions

P-values will be reported to 4 decimal places. The mean, standard errors, and any other statistics other than quantiles, will be reported to one decimal

place. Quantiles, such as median, or minimum and maximum will use the same number of decimal places as the original data. Estimated parameters, not on the same scale as raw observations (e.g. regression coefficients) will be reported to 3 significant figures.

14 Technical Details

A second review statistician will independently reproduce the primary analyses and summary statistics tables listed below:

Table 9b: Frequency of Serious Adverse Events by Body System, Grade and Therapy Group

Table 10a: Frequency of Adverse Events by Therapy, Body System, and Grade*

Table 10b: AE Grade by Therapy Group

Table 21a: Quality of Hearing Assessment Left and Right (Total Ear)

Table 21b: Hearing Assessment Left and Right (Total Ear)

Table 21c: Change in Total Ear Hearing at Month 6 Relative to Baseline

Table 21d: Results of Modeling Treatment Effect on Total Ear For Each Outcome

Table 21e: Subgroup Analysis (Total Ears)

Table 22a: Quality of Hearing Assessment Best Ear

Table 22b: Hearing Assessment Best Ear

Table 22c: Change in Best Ear Hearing at Month 6 Relative to Baseline

Table 22d: Results of Analyses of Treatment Effect on Best Ear For Each Outcome

Table 22e: Subgroup Analysis (Best Ears)

Table 23: CMV Detection Over time

Table 24: Log10 Viral Load Summary Statistics Over Time

Table 24a: Summary of Modeling Results (Blood)

Table 24b: Summary of Modeling Results (Saliva)

Table 24c: Summary of Modeling Results (Urine)

Table 25: Spearman Rank Correlation between GCV concentration and log10 VL

Table 26a: Summary Statistics: Baseline Log10 VL by Change in Total Ear Hearing

Table 26b: Association between Baseline Log10 VL and Change (Binary) in Total Ear Hearing

Table 27a: Summary Statistics: Baseline Log10 VL by Change in Best Ear Hearing

Table 27b: Association between Baseline Log10 VL and Change (Binary) in Best Ear Hearing

Table 28a: Summary Statistics: Average AUC Log10 VL and Change in Total Ear Hearing
Table 28b: Association between Average AUC Log10 VL and Change (Binary) in Total Ear Hearing
Table 29a: Summary Statistics: Average AUC Log10 VL and Change in Best Ear Hearing
Table 29b: Association between Average AUC Log10 VL and Change (Binary) in Best Ear Hearing
Table 30a: Summary Statistics: Change in Log10 VL and Change in Total Ear Hearing
Table 30b: Association between Change in Log10 VL and Change (Binary) in Total Ear Hearing
Table 31a: Summary Statistics: Change in Log10 VL and Change in Best Ear Hearing
Table 31b: Association between Change in Log10 VL and Change (Binary) in Best Ear Hearing

15 Summary of Changes to the Protocol

The first version of the protocol under which subjects may be enrolled was Version 3.0.

The protocol was revised to Version 4.0, dated April 28, 2016, which was distributed to the study sites on May 5, 2016 for submission to their IRBs. Under this protocol version, study inclusion criteria and study windows have been liberalized based on the specific screen failure data under earlier protocol versions. Specifically, the inclusion criterion, "CMV shedding in urine by PCR or culture (including shell vial) within 12 weeks prior to study enrollment" was removed; the window for the Baseline study visit was changed from "Day -3 to Day 1" to "Day -30 to Day 1"; the window for the baseline hearing assessment was changed from "Study Day -14 to Study Day 7" to "Study Day -90 to Study Day -1"; and the window for the Month 6 hearing assessment was changed from "± 14 days" to "-14 days to +30 days".

16 References

1 Kimberlin DW, Lin CY, Sanchez PJ, et al. Effect of ganciclovir therapy on hearing in symptomatic congenital cytomegalovirus disease involving the central nervous system: a randomized, controlled trial. *J Pediatr*. 2003;143:16-25.

2 Kimberlin DW, Acosta EP, Sanchez PJ, et al. Pharmacokinetic and pharmacodynamic assessment of oral valganciclovir in the treatment of symptomatic congenital cytomegalovirus disease. *J Infect Dis*. 2008;197:836-45.

17 Listing of Tables and Listings Figures

LIST OF TABLES

Table Title	Number	Population	Endpoint	Time Points or how to conglomerate	Covariates or Subgroups	Summary Statistics	Formal Analysis
Table 1a: Investigators / Centers	1a	NA	NA	NA	NA	Listing	NA
Table 1b: Randomization to Blinded Therapy Groups	1b	Randomized	NA	NA	Therapy Group	n, %	NA
Table 2a: Distribution of Subjects by Study Site and Therapy Group, and Overall	2a	NA	NA	NA	NA	Listing	NA
Table 2b: Reasons for withdrawal before randomization	2b	NA	NA	NA	NA	Listing	NA
Table 2c: Site Performance in Enrollment	2c	NA	NA	NA	NA	Listing	NA
Table 3: Subjects Withdrawn after Randomization from Study	3	NA	NA	Randomization-Month 6	NA	Listing	NA
Table 4a: Subject-specific Protocol Deviations by Category	4a	Full Analysis	Deviations	Baseline-Month6	NA	Listing	NA
Table 4b: Subject-specific Protocol Deviations by Reason	4b	Full Analysis	Deviations	Baseline-Month6	NA	Listing	NA
Table 4c: Listing of Action/Steps: Subject-specific PDs	4c	Full Analysis	NA	Baseline-Month6	NA	Listing	NA
Table 4d: Subject-Specific Protocol Deviations resulting in AEs, SAEs, termination or drug interruption in study drug	4d	Full Analysis	Deviations	Baseline-Month6	NA	Listing	NA
Table 5a: Site-specific Protocol Deviations by Category and Reasons	5a	Full Analysis	Deviations	Baseline-Month6	NA	Listing	NA
Table 5b: Listing of Action/Steps: site-specific PDs	5b	Full Analysis	NA	Baseline-Month6	NA	Listing	NA
Table 6a: Frequency Counts of Baseline Demographics	6a	Full Analysis	Demographics	Baseline	Therapy Group	n, %	Fisher's exact

Table 6b: Summary Statistics of Baseline Age, Gestational Age and Birth Weight	6b	Full Analysis	Age, Gestational Age and Birth Weight	Baseline	Therapy Group	N, N Missing, Mean, SE, Median, Min, Max	T-test or Wilcoxon
Table 7a: Summary of frequency count of CMV disease involvement	7a	Full Analysis	CMV disease involvement	Baseline	Therapy Group	n, %	Fisher's exact
Table 7b: Summary CMV disease involvement: Lumbar Puncture	7b	Full Analysis (where available)	CMV disease involvement	Baseline	Therapy Group	n, %	Fisher's exact
Table 7c: Summary of CMV disease involvement: Neuroimaging Results	7c	Full Analysis (where available)	CMV disease involvement	Baseline	Therapy Group	n, %	Fisher's exact
Table 7d: Summary of Baseline Abnormal Findings	7d	Full Analysis (where available)	Abnormality	Baseline	Therapy Group	n, %	Fisher's exact
Table 8a: Summary of Adverse Events	8a	At least one dose of study drug	Adverse Events	Randomization-Day 70	Therapy Group	n, %	NA
Table 9a: Listing of Each Subject's Serious Adverse Event	9a	At least one dose of study drug	Serious Adverse Events	Randomization-Day 70	Therapy Group	Listing	NA
Table 9b: Frequency of Serious Adverse Events by Body System, Grade and Therapy Group	9b	At least one dose of study drug	Serious Adverse Events	Randomization-Day 70	Therapy Group, Body System, Grade	n, %	NA
Table 10a: Frequency of Adverse Events by Therapy, Body System, and Grade*	10a	At least one dose of study drug	Serious Adverse Events	Randomization-Day 70	Therapy Group, Body System, Grade	n, %	NA
Table 10b: AE Grade by Therapy Group	10b	At least one dose of study drug	Adverse Events	Randomization-Day 70	Therapy Group, Grade	n, %	generalized linear mixed model for ordinal response with random intercept.
Table 10c: Listing of Adverse Events (Active Group)	10c	At least one dose of study drug	Adverse Events	Randomization-Day 70	NA	Listing	NA
Table 10c: Listing of Adverse Events (Placebo Group)	10c	At least one dose of study drug	Adverse Events	Randomization-Day 70	NA	Listing	NA

Table 11a: Changes over Time in Hematology Parameters	11a	At least one dose of study drug	Hematology Parameters	Baseline-Month 6	Therapy Group, Visit	N, Mean, SD, 10th pctl, 90th pctl	General linear mixed model with random intercept was fitted for each parameter. Each model contains therapy, time and therapy by time interaction.
Table 11b: Changes over Time in Chemistry Parameters	11b	At least one dose of study drug	Chemistry Parameters	Baseline-Month 6	Therapy Group, Visit	N, Mean, SD, 10th pctl, 90th pctl	General linear mixed model with random intercept was fitted for each parameter. Each model contains therapy, time and therapy by time interaction.
Table 12: Maximum Degree of Neutropenia (Lowest ANC) During Day 1-42 Period	12	At least one dose of study drug	ANC	Randomization-Day 42	Therapy Group	n, %	NA
Table 13: Maximum Degree of Anemia (Lowest HGB) for 11-0069 Valganciclovir	13	At least one dose of study drug	HGB	Randomization-Day 70	NA	n, %	NA
Table 14: Maximum Degree of Anemia (Lowest PLT) for 11-0069 Valganciclovir	14	At least one dose of study drug	PLT	Randomization-Day 70	NA	n, %	NA
Table 15: Maximum Degree of ALT (Highest ALT) for 11-0069 Valganciclovir	15	At least one dose of study drug	ALT	Randomization-Day 70	NA	n, %	NA
Table 16: Maximum Degree of Creatinine (Highest creatinine) for 11-0069 Valganciclovir	16	At least one dose of study drug	creatinine	Randomization-Day 70	NA	n, %	NA
Table 17: Summary of Concomitant Medications by Treatment Group (Blinded Treatment Phase)	17	At least one dose of study drug	Treatment Group (Blinded Treatment Phase	Baseline-Day 48	Therapy Group, Visit	n, %	NA
Table 18a: Dose (mg/kg) of Valganciclovir or Placebo	18a	At least one dose of study drug	Dose	Day 1, 14 28	Therapy Group, Visit	N, Mean, SD, Median, Min, Max	Fisher's exact and Wilcoxon test

Table 18b: Weight (kg) at the Time of Dosing of Valganciclovir or Placebo	18b	At least one dose of study drug	Dose	Day 1, 14 28	Therapy Group, Visit	N, Mean, SD, Median, Min, Max	General linear mixed model with random intercept was fitted for each parameter. Each model contains therapy, time and therapy by time interaction.
Table 18c: Length (cm) at the Time of Dosing of Valganciclovir or Placebo	18c	At least one dose of study drug	Weight	Day 1, 14 28	Therapy Group, Visit	N, Mean, SD, Median, Min, Max	General linear mixed model with random intercept was fitted for each parameter. Each model contains therapy, time and therapy by time interaction.
Table 19a: Dosing Administration by Treatment Group and Visit	19	At least one dose of study drug	Length	Day 1, 14 28	Therapy Group, Visit	n, %	Fisher's exact
Table 19b: Reasons for Adjusted or Held Dose and Significant Changes in Laboratory Parameters	19a	At least one dose of study drug	Dose	Day 1, 14 28	Therapy Group, Visit	n, %	Fisher's exact
Table 20: PK Specimen Results: GCV concentration in the Active Group	19b	At least one dose of study drug	Dose	Day 1, 14 28	NA	N, Mean, SD, Median, Min, Max	NA
Table 21a: Quality of Hearing Assessment Left and Right (Total Ear)	20	At least one dose of study drug	GCV concentration	Day 14, 28, 42	NA	n, %	NA
Table 21b: Hearing Assessment Left and Right (Total Ear)	21a	At least one dose of study drug	Quality of Total Ear Assessment	Baseline and Month 6	Therapy Group, Visit	n, %	NA
Table 21c: Change in Total Ear Hearing at Month 6 Relative to Baseline	21b	At least one dose of study drug	Hearing Assessment Total Ear	Baseline and Month 6	Therapy Group, Visit	n, %	NA

Table 21d: Results of Modeling Treatment Effect on Total Ear For Each Outcome	21c	At least one dose of study drug	Change in Total Ear Hearing Assessment	Baseline and Month 6	Therapy Group	n, %, p-value	Generalized linear model for binary outcome using GEE was fitted for each parameter. Each model contains therapy, time and therapy by time interaction.
Table 21e: Subgroup Analysis (Total Ears)	21d	At least one dose of study drug	Change in Total Ear Hearing Assessment	Baseline and Month 6	Therapy Group	n, %	NA
Table 22a: Quality of Hearing Assessment Best Ear	21e	At least one dose of study drug	Change in Total Ear Hearing Assessment	Baseline and Month 6	Therapy Group	n, %	NA
Table 22b: Hearing Assessment Best Ear	22a	At least one dose of study drug	Quality of Best Ear Assessment	Baseline and Month 6	Therapy Group	n, %	NA
Table 22c: Change in Best Ear Hearing at Month 6 Relative to Baseline	22b	At least one dose of study drug	Hearing Assessment Best Ear	Baseline and Month 6	Therapy Group	n, %	NA
Table 22d: Results of Analyses of Treatment Effect on Best Ear For Each Outcome	22c	At least one dose of study drug	Change in Best Ear Hearing Assessment	Baseline and Month 6	Therapy Group	n, %, p-value	Generalized linear model for binary outcome using GEE was fitted for each parameter. Each model contains therapy, time and therapy by time interaction.
Table 22e: Subgroup Analysis (Best Ears)	22d	At least one dose of study drug	Change in Best Ear Hearing Assessment	Baseline and Month 6	Therapy Group, Visit (age and symptomatic/asymptomatic at birth)	n, %	NA
Table 23: CMV Detection Over time	22e	At least one dose of study drug	Change in Best Ear Hearing Assessment	Baseline and Month 6	Therapy Group, Visit	n, %, p-value	Fisher's exact
Table 24: Log10 Viral Load Summary Statistics Over Time	23	At least one dose of study drug	CMV detection	Baseline-Month6	Therapy Group, Visit	N, Mean, SD, 10th pctl, 90th pctl	NA

Table 24a: Summary of Modeling Results (Blood)	24	At least one dose of study drug	Quantitative Viral Load	Baseline-Month6	Therapy Group, Visit	p-value	General linear mixed model with random intercept was fitted for each parameter. Each model contains therapy, time and therapy by time interaction.
Table 24b: Summary of Modeling Results (Saliva)	24a	At least one dose of study drug	Quantitative Viral Load (Blood)	Baseline-Month6	Therapy Group, Visit	p-value	General linear mixed model with random intercept was fitted for each parameter. Each model contains therapy, time and therapy by time interaction.
Table 24c: Summary of Modeling Results (Urine)	24b	At least one dose of study drug	Quantitative Viral Load (Saliva)	Baseline-Month6	Therapy Group, Visit	p-value	General linear mixed model with random intercept was fitted for each parameter. Each model contains therapy, time and therapy by time interaction.
Table 25: Spearman Rank Correlation between GCV concentration and log10 VL	24c	At least one dose of study drug	Quantitative Viral Load (Urine)	Day 14, 28, 42	NA	Correlation, p-value	Spearman Rank Correlation
Table 26a: Summary Statistics: Baseline Log10 VL by Change in Total Ear Hearing	25	At least one dose of study drug	concentration and log10 VL	Baseline	Baseline Viral Load, Therapy Group	N, Mean, SD, 10th pctl, 90th pctl	NA
Table 26b: Association between Baseline Log10 VL and Change (Binary) in Total Ear Hearing	26a	At least one dose of study drug	VL by Change in Total Ear Hearing	Baseline	Baseline Viral Load, Therapy Group	N, Mean, SD, 10th pctl, 90th pctl with p-values	Generalized linear model for binary outcome using generalized estimating equations with VL as main predictor for unadjusted model; adjusted model includes therapy group

Table 27a: Summary Statistics: Baseline Log10 VL by Change in Best Ear Hearing	26b	At least one dose of study drug	VL and Change (Binary	Baseline	Baseline Viral Load, Therapy Group	N, Mean, SD, 10th pctl, 90th pctl	NA
Table 27b: Association between Baseline Log10 VL and Change (Binary) in Best Ear Hearing	27a	At least one dose of study drug	VL by Change in Best Ear Hearing	Baseline	Baseline Viral Load, Therapy Group	N, Mean, SD, 10th pctl, 90th pctl with p-values	Generalized linear model for binary outcome using generalized estimating equations with VL as main predictor for unadjusted model; adjusted model includes therapy group
Table 28a: Summary Statistics: Average AUC Log10 VL and Change in Total Ear Hearing	27b	At least one dose of study drug	VL and Change (Binary	Baseline-Month6	AUC Viral Load, Therapy Group	N, Mean, SD, 10th pctl, 90th pctl	NA
Table 28b: Association between Average AUC Log10 VL and Change (Binary) in Total Ear Hearing	28a	At least one dose of study drug	Log10 VL and Change in Total Ear Hearing	Baseline-Month6	AUC Viral Load, Therapy Group	N, Mean, SD, 10th pctl, 90th pctl with p-values	Generalized linear model for binary outcome using generalized estimating equations with VL as main predictor for unadjusted model; adjusted model includes therapy group
Table 29a: Summary Statistics: Average AUC Log10 VL and Change in Best Ear Hearing	28b	At least one dose of study drug	Log10 VL and Change (Binary	Baseline-Month6	AUC Viral Load, Therapy Group	N, Mean, SD, 10th pctl, 90th pctl	NA
Table 29b: Association between Average AUC Log10 VL and Change (Binary) in Best Ear Hearing	29a	At least one dose of study drug	Log10 VL and Change in Best Ear Hearing	Baseline-Month6	AUC Viral Load, Therapy Group	N, Mean, SD, 10th pctl, 90th pctl with p-values	Generalized linear model for binary outcome using generalized estimating equations with VL as main predictor for unadjusted model; adjusted model includes therapy group
Table 30a: Summary Statistics: Change in Log10 VL and Change in Total Ear Hearing	29b	At least one dose of study drug	Log10 VL and Change (Binary	Baseline-Month6	Difference in Viral Load, Therapy Group	N, Mean, SD, 10th pctl, 90th pctl	NA

Table 30b: Association between Change in Log10 VL and Change (Binary) in Total Ear Hearing	30a	At least one dose of study drug	Log10 VL and Change in Total Ear Hearing	Baseline-Month6	Difference in Viral Load, Therapy Group	N, Mean, SD, 10th pctl, 90th pctl with p-values	Generalized linear model for binary outcome using generalized estimating equations with VL as main predictor for unadjusted model; adjusted model includes therapy group
Table 31a: Summary Statistics: Change in Log10 VL and Change in Best Ear Hearing	30b	At least one dose of study drug	Log10 VL and Change (Binary	Baseline-Month6	Difference in Viral Load, Therapy Group	N, Mean, SD, 10th pctl, 90th pctl	NA
Table 31b: Association between Change in Log10 VL and Change (Binary) in Best Ear Hearing	31a	At least one dose of study drug	Log10 VL and Change in Best Ear Hearing	Baseline-Month6	Difference in Viral Load, Therapy Group	N, Mean, SD, 10th pctl, 90th pctl with p-values	Generalized linear model for binary outcome using generalized estimating equations with VL as main predictor for unadjusted model; adjusted model includes therapy group

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