Oral valganciclovir initiated beyond one month of age as treatment of sensorineural hearing loss caused by congenital cytomegalovirus infection:

A Randomized Clinical Trial

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Abstract

Objective

When initiated within the first month of age, oral valganciclovir therapy improves audiologic outcomes of children with symptomatic congenital cytomegalovirus (cCMV) disease. We sought to determine if valganciclovir initiated after 1 month of age improves cCMV-associated sensorineural hearing loss (SNHL).

Study Design

We conducted a randomized, double-blind, placebo-controlled Phase 2 trial of 6 weeks of oral valganciclovir at United States (n=12) and United Kingdom (n=9) sites. Patients 1 month through 3 years of age with baseline SNHL were enrolled. The primary outcome was change in total ear hearing between baseline and Study Month 6. Secondary outcome measures included change in best ear hearing and reduction in CMV viral load in blood, saliva, and urine.

Results

Of 54 participants enrolled, 35 were documented to have cCMV infection and were randomized (active group: 17; placebo group: 18). Mean age at enrollment was 17.8 ± 15.8 months (valganciclovir) versus 19.5 ± 13.1 months (placebo). Twenty (76.9%) of the 26 ears from subjects in the active treatment group did not have worsening of hearing, compared with 27 (96.4%) of 28 ears from subjects in the placebo group (p= 0.09). All other comparisons of total ear or best ear hearing outcomes also were not statistically significant. Saliva and urine viral

loads decreased significantly in the valganciclovir group but did not correlate with change in hearing outcome.

Conclusions

In this randomized controlled trial, initiation of antiviral therapy beyond the first month of age did not improve hearing outcomes in children with cCMV-associated SNHL.

Trial Registration

ClinicalTrials.gov identifier NCT01649869

Introduction

Congenital infection with cytomegalovirus (cCMV) is the most common non-genetic cause of sensorineural hearing loss (SNHL) in children[1-4] and is the most common known viral cause of intellectual disability.[5] In industrialized countries, 0.5% to 0.7% of newborns are congenitally infected with CMV.[6-8] Ten percent of neonates with cCMV infection have symptomatic (clinically apparent) disease at birth, with at least 35% of these having SNHL.[7-11] Hearing loss occurs at a lower rate (5-10%) among the 90% of neonates with congenital infection who are asymptomatic (clinically inapparent) at birth, but because there are so many more asymptomatic than symptomatic neonates the majority of cases of SNHL caused by cCMV occurs in children who are asymptomatic at birth.[7, 12] SNHL caused by cCMV can progress or fluctuate over time, and many infected children who develop SNHL have had normal hearing at birth.[10]

The Collaborative Antiviral Study Group (CASG) has evaluated antiviral treatment of infants with symptomatic cCMV over the past three decades, initially using intravenous ganciclovir[13-16] and then oral valganciclovir.[17, 18] When begun within the first month following birth, oral valganciclovir therapy improves to at least two years of age the audiologic and developmental outcomes of children who are symptomatic at birth.[18] It is not known whether initiating antiviral therapy beyond one month of age can favorably impact hearing outcomes in infants with cCMV.

Methods

Hypothesis

Initiation of 6 weeks of antiviral therapy beyond the first month of life will result in improved audiologic outcomes 6 months following treatment initiation. At the time of study design, 6 weeks of valganciclovir therapy started within the first month of life was standard of care for the treatment of symtomatic cCMV.[16, 17, 19]

Study Design

The Valgan Toddler study was a randomized, double-blind, placebo-controlled Phase 2 trial of oral valganciclovir conducted at 21 CASG study centers in the United States (n=12) and the United Kingdom (n=9). Ethics board approvals were received at each study site before activation, either through a central institutional review board (IRB) at the University of Alabama at Birmingham (UAB) for U.S. sites, the UK National Health Service Ethics Service for UK sites, or through local IRB review.

Participants

Infants and toddlers from 1 month of age through 3 years of age (up to their 4th birthday) were eligible for study enrollment if they had SNHL of ≥21dB in one or both ears, documented within 12 weeks before study entry. Patients were excluded if they had profound SNHL (>90dB) in both ears, had previously received antiviral therapy for cCMV disease, or had another known cause of SNHL detected on clinical assessment. Following the signing of informed consent, the participant's Newborn Screening card (Guthrie card; dried blood spot, or DBS) was retrieved and tested for CMV DNA by polymerase chain reaction (PCR) unless a virologically confirmed diagnosis of cCMV infection from saliva, urine, or blood had been made within the first 30 days following birth. The assay utilized in the UK followed the same procedures as that in the U.S.

The sensitivity of DBS testing is low (34%), but the specificity is high (99%), so a positive result ruled in cCMV infection.[20]

Randomization and Masking

Enrolled participants who had a virologically confirmed diagnosis of cCMV infection within the first 30 days following birth or whose DBS was PCR-positive for CMV DNA were then randomized to either valganciclovir (16 mg/kg/dose administered orally twice daily)[17] or placebo administered for six weeks. Study randomization occurred when the diagnosis of cCMV infection was confirmed. Study participants were stratified according to age at randomization (1 through 11 months, 12 through 23 months, 24 through 35 months, and 36 through 47 months) and CMV disease status [symptomatic (clinically apparent manifestations of CMV at birth) or asymptomatic (clinically asymptomatic at birth)], but without preset goals for the numbers enrolled in each strata.

Study Procedures

During the six-week treatment period, study participants were seen every 2 weeks, then one month following the final dose of study drug, then at months 4 and 6. At each of the visits during the treatment phase and 1 month after finishing study drug, blood was obtained for hematology and chemistry testing, and adverse event assessments were made. At each of these visits and at study months 4 and 6, blood, urine, and saliva were obtained for quantitative CMV PCR (viral load) assessment.[17, 18] Dose adjustments for weight change were made at each study visit during the participant's treatment period.

Hearing was assessed at baseline (window: Study Day -90 to Study Day -1) and at Study Month 6 using age-appropriate brainstem evoked response (BSER, also known as auditory brainstem response or ABR) and/or visual reinforcement audiometry (VRA) testing, as

previously described.[18] If a study participant proceeded to cochlear implantation during the course of the study, he/she did not require additional study-related hearing assessments following the implantation procedure.

Study site staff performing the patient assessments, as well as parents/caregivers, were blinded to the randomization. Only the site research pharmacist was unblinded.

Outcomes

Hearing was assessed as improved, unchanged, or worsened between Baseline and Study Month 6. Unchanged hearing assessments could be normal at both time points or could have the same degree of hearing loss at both time points. The primary outcome measure was improved hearing or the same degree of loss versus worsened hearing in total ear hearing assessments between Baseline and Study Month 6, as previously established.[16, 18] Secondary outcome measures included: 1) improved hearing versus unchanged or worsened hearing in total ear hearing assessments between Baseline and Study Month 6; 2) improved hearing or normal hearing at both Baseline and Study Month 6 versus same degree of abnormal hearing or worsened hearing in total ear hearing assessments; 3) change in best ear hearing assessments between Baseline and Study Month 6; 4) quantitative log reduction in viruria detected after 6 weeks of therapy; 5) quantitative log reduction in viremia detected after 6 weeks of therapy; and 6) quantitative log reduction in CMV viral load in saliva detected after 6 weeks of therapy.

Statistical Methods

The target sample size of 54 randomized subjects (27 in each arm) was based on a 90% power to detect a difference in the proportion of worsening of hearing from 40% in the placebo group to 8.0% in the treatment group, which was similar to the difference seen in outcomes in the prior randomized controlled trial of intravenous ganciclovir,[16] and was based on analyzing two

correlated binary outcomes with correlation coefficient of 0.55 at 2.5% level of significance (using PASS 2008 program). Only participants who took at least one dose of the blinded treatment and completed hearing assessments at baseline and Study Month 6 were included in outcome analyses comparing treatment groups based on an intention-to-treat (ITT) analysis.

All continuous variables were summarized using descriptive statistics: n (non-missing sample size), mean, standard error, median, maximum and minimum (or 10^{th} and 90^{th} percentiles). For comparing therapy groups with respect to these continuous variables, a t-test was used unless there was evidence of deviation from normality in which case a Wilcoxon test was used. The frequency and percentages of observed levels were reported for all categorical measures. Fisher exact test was used to compare the therapy groups with respect to these categorical variables.

Categories used for hearing assessment of each ear for each time point were normal hearing (0 to 20 dB), mild hearing loss (21 to 45 dB), moderate hearing loss (46 to 70 dB), and severe hearing loss (71 dB or higher).[3, 10, 16, 18] Baseline and six month hearing categories were compared and the change in each ear was categorized into binary outcomes, as detailed above. Hearing of participants who underwent cochlear implantation after baseline were assigned "severe" for both ears at Study Month 6. The primary outcome of change in total ear hearing and all other binary outcomes associated with total ear evaluations were analyzed by a generalized linear regression model for binary outcome and utilizing the generalized estimating equations (GEE) approach to accommodate the correlation between the left and right ears of a participant. For best ear outcomes, Fisher exact test was used to examine the treatment effect. Subgroup descriptive analyses of hearing outcomes were performed by (1) asymptomatic or

symptomatic at birth and (2) age (11 months or younger vs greater than 1 year old). P-value <0.05 was used to conclude significance.

In a post-hoc analysis, hearing was converted to a single decibel value by averaging the 1000, 2000, and 4000 Hz responses. Baseline dB hearing values were subtracted from Study Month 6 hearing values to determine change in acuity. Differences in hearing were analyzed using the GEE approach.

To compare the trajectory of the viral load over time between the placebo and active therapy groups, a generalized linear mixed model with random intercept was fitted. Analysis of quantitative viral load as an outcome was performed based on log base 10 transformation of the viral load, with undetectable viral load assigned a value of 10 (value of 1 in $\log_{10}$ units). The model was fitted separately for blood, saliva, and urine viral load measures. Treatment effect was determined to be significant when the p-value associated with the interaction term was less than 0.0067 (=0.05/3) using Bonferroni adjustment method, thus accounting for the three types of specimens assayed (blood, saliva, and urine). P-value <0.0026 (=0.05/17) was the cutoff used to determine significance.

Results

Study Population

Participants enrolled at 17 of the 21 study sites (8 U.S. sites, 9 UK sites) from February 24, 2015, to July 21, 2019 (Figure 1). Of 54 participants enrolled in the study, 35 had virologic confirmation of cCMV and were randomized (active group: 17; placebo group: 18). Of the 19 subjects that were not randomized, 11 had negative DBS PCR results; the reasons for the remaining 8 subjects not randomizing are provided in Figure 1. All 35 randomized subjects had either a virologic diagnosis of cCMV made during the neonatal period or a positive DBS PCR result following enrollment on the study. Thirty-two of the 35 randomized participants completed follow-up through their 6-month study visit. The mean age at enrollment was 18.7 months. No imbalances were observed between the groups across baseline demographic characteristics (Table 1). The majority (82.4% of active drug recipients and 66.7% of placebo recipients) had symptomatic cCMV disease at birth, as previously defined,[18] although none had antiviral therapy initiated within the first month of age.

The distribution of hearing categorization at baseline and at 6 months by ear and randomization group is presented in Table 1 and Table 2 (available at www.jpeds.com), respectively; change in total ear hearing at 6 months relative to baseline is presented in Table 3, and change in best hear hearing at 6 months relative to baseline is presented in Table 4 (available at www.jpeds.com). Of the 54 ears in the total ear hearing analysis, 36 were from participants enrolled in the United Kingdom and 18 were from those enrolled in the United States. One subject, in the active group, underwent cochlear implantation following randomization on the trial.

Primary Outcome

Twenty (76.9%) of the 26 ears from subjects in the active group did not have worsening of hearing between baseline and Study Month 6, compared with 27 (96.4%) of 28 ears from subjects in the placebo group (OR 7.22, 95% CI 0.76-68.94; p=0.09), indicating that there was no benefit of 6 weeks of treatment in these participants.

Secondary Outcomes

Likewise, no significant differences were detected in the secondary total ear hearing outcome measure of improved versus unchanged or worsened (0 ears in both groups; p-value not applicable since no participants had improved hearing); or of improved or unchanged (normal at both timepoints) (6 ears in active group, 9 ears in placebo group) versus unchanged (same degree of abnormal at both timepoints) or worsened (20 ears in active group, 19 years in placebo group) (OR 1.45, 95% CI 0.51-4.12; p=0.48). Of the 7 ears that worsened, six were from participants enrolled in the United Kingdom (5 in the valganciclovir group, 1 in the placebo group) and 1 was from a participant enrolled in the United States (in the valganciclovir group). For the 6 UK participants who had worsened hearing between Baseline and Study Month 6, all had been symptomatic at birth, 4 were in participants under 12 months of age (3.6 to 4.5 months of age, all in the valganciclovir group) and 2 were in participants 12 months or older (one in the valganciclovir group and one in the placebo group). The 1 U.S. ear that worsened was from a participant who was asymptomatic at birth and < 12 months of age at enrollment and was in the valganciclovir group. Secondary best ear hearing outcome analyses similarly were not statistically significantly different (Table 4, (available at www.jpeds.com).

Viral load in saliva and urine, but not in blood, decreased significantly in the valganciclovir group compared with the placebo group over the course of treatment, before establishing a new post-therapy baseline that was 1.5 (saliva) to 2.0 (urine) logs lower compared

with their pre-therapy initial value (Figure 2, available at www.jpeds.com). Blood, saliva, or urine viral load did not correlate with change in hearing outcome in either the unadjusted (viral load alone) or adjusted (viral load plus treatment category) analyses for total ear or best ear analyses when assessed as baseline viral load or as viral load averaged over time.

Post-Hoc Analyses

Post-hoc assessment of change in hearing by symptomatology category at birth or age at enrollment demonstrated no significant differences between treatment groups (Table 5). Post hoc analysis of change in hearing aggregated into a single dB value similarly demonstrated no significant differences between treatment groups (Mean difference -6.50, 95% CI -25.04-12.03; P=0.49).

Safety Assessments

During the 42-day treatment period, 1 (5.9%) of the 17 valganciclovir recipients experienced Grade 3 neutropenia (absolute neutrophil count 500-749 cells/μL$^{\alpha}$), while 1 (5.6%) of the 18 placebo recipients had Grade 4 neutropenia (absolute neutrophil count < 500 cells/μ). There was no Grade 3 or 4 event related to anemia or thrombocytopenia (using lowest hemoglobin or platelet count), alanine aminotransferase, or creatinine values. No participant had treatment held due to toxicity; however, one participant (randomized to active drug) had the dose decreased by 50% per protocol due to decreased creatinine clearance at Study Day 14.

Discussion

In this randomized, double blind, placebo-controlled study, initiation of antiviral therapy beyond the first month of age to children with cCMV-associated SNHL did not improve or stabilize hearing outcomes when administered for six weeks. Valganciclovir decreased CMV viral loads in saliva and urine, but with no measurable clinical effect on hearing outcomes. The 6-week duration of treatment was well tolerated, and the rate of neutropenia in recipients of active drug (5.9%) was lower than the 19.3% seen in the first 6 weeks of therapy in our earlier study of valganciclovir in younger infants.[21]

In prior randomized controlled studies of participants with symptomatic cCMV disease at birth and with or without SNHL, antiviral therapy was started within the first month of age.[15, 16, 18] Our inability to detect a treatment benefit when therapy is started beyond this time may indicate that there is a "therapeutic window" in which antiviral management is beneficial. This could be because the pathogenesis of SNHL in patients with cCMV infection is driven by viral replication only early in life (and perhaps by immune-mediated or inflammatory processes later), or because it is driven by viral replication throughout but the "brain-inner ear barrier" allows more ganciclovir penetration into the inner ear early in life. It also is possible that our treatment duration of 6 weeks was of insufficient length to produce a therapeutic benefit, especially if the treatment effect is smaller than could be detected with our limited sample size. This possibility is supported by our finding after the Valgan Toddler study was designed that 6 months of treatment started within the first month of age is superior to 6 weeks of treatment in patients with symptomatic cCMV disease.[18] It also is possible that there is a therapeutic benefit, but it is later than the 6 month follow-up time period. At the time of study design, the known benefits of 6

weeks of antiviral treatment of infants with symptomatic cCMV disease were most apparent at 6 months of age, which is why the Valgan Toddler study utilized this follow-up window.

Another significant possibility, however, is that the population enrolled simply was too heterogeneous with respect to degree of cCMV manifestations and age at time of treatment to demonstrate a treatment effect. Overall, three-quarters of our randomized participants were symptomatic with cCMV disease at birth, with much of the symptomatology being quite severe (Table 1). This is a far greater percentage than we anticipated enrolling at the outset of the study. Likewise, the mean age at enrollment was 18.7 months, and the distribution of age through the first three years of life was broad (Table 1)

This study demonstrates the challenges of studying antiviral treatments of cCMV infection and disease. Despite a large number of study sites across two countries, after four years of enrollment we still fell short of our target randomized sample size. We utilized the gold-standard trial design (double-blind, placebo-controlled), but this likely also contributed to our enrollment challenges. Study limitations include the relatively small sample size despite enrollment spanning four years (August 2015 through June 2019), the heterogeneity of subjects enrolled (age and symptomatology), and the lack of systematic genetic testing for other causes of SNHL.

Our results stand in contrast to those of the open-label, non-randomized CONCERT study from the Netherlands, which identified a therapeutic benefit of oral valganciclovir on SNHL.[22] The CONCERT population was much more homogenous than ours, with participants initiating therapy through the first 12 weeks of age and all subjects being asymptomatically (clinically inapparently) infected with cCMV at birth but having SNHL at the time of enrollment. Given these differences from our currently reported study and our prior findings that antiviral

therapy initiated early in life provides audiologic benefit, it may be that the "therapeutic window" for initiation of antiviral therapy can be extended out to the first three months of life (ie, <13 weeks of age) rather than within the first month, and that it more confidently can be expanded to include very young infants with cCMV infection and isolated SNHL.[23-25] Ideally this should be proven through the conduct of another randomized controlled study to guide evidence-based medical practice, but this is not likely to be possible given the challenges identified above. Identification of biomarker(s) that predicts increased likelihood of developing SNHL could be beneficial for the design of future studies of new antiviral agents or approaches to therapeutic management.[26]

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Figure 1. Enrollment, Randomization, and Follow-up of Children in the Trial

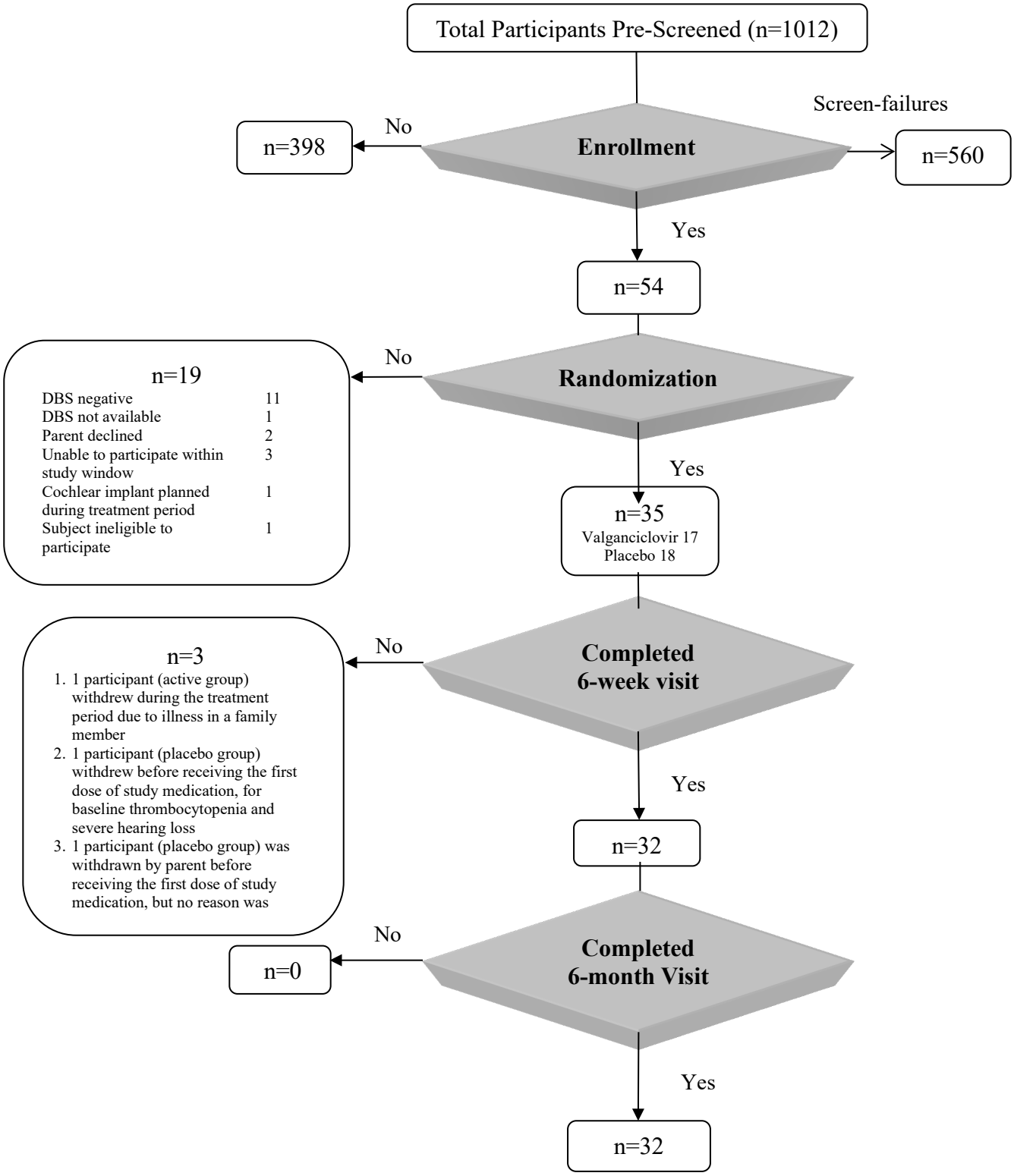
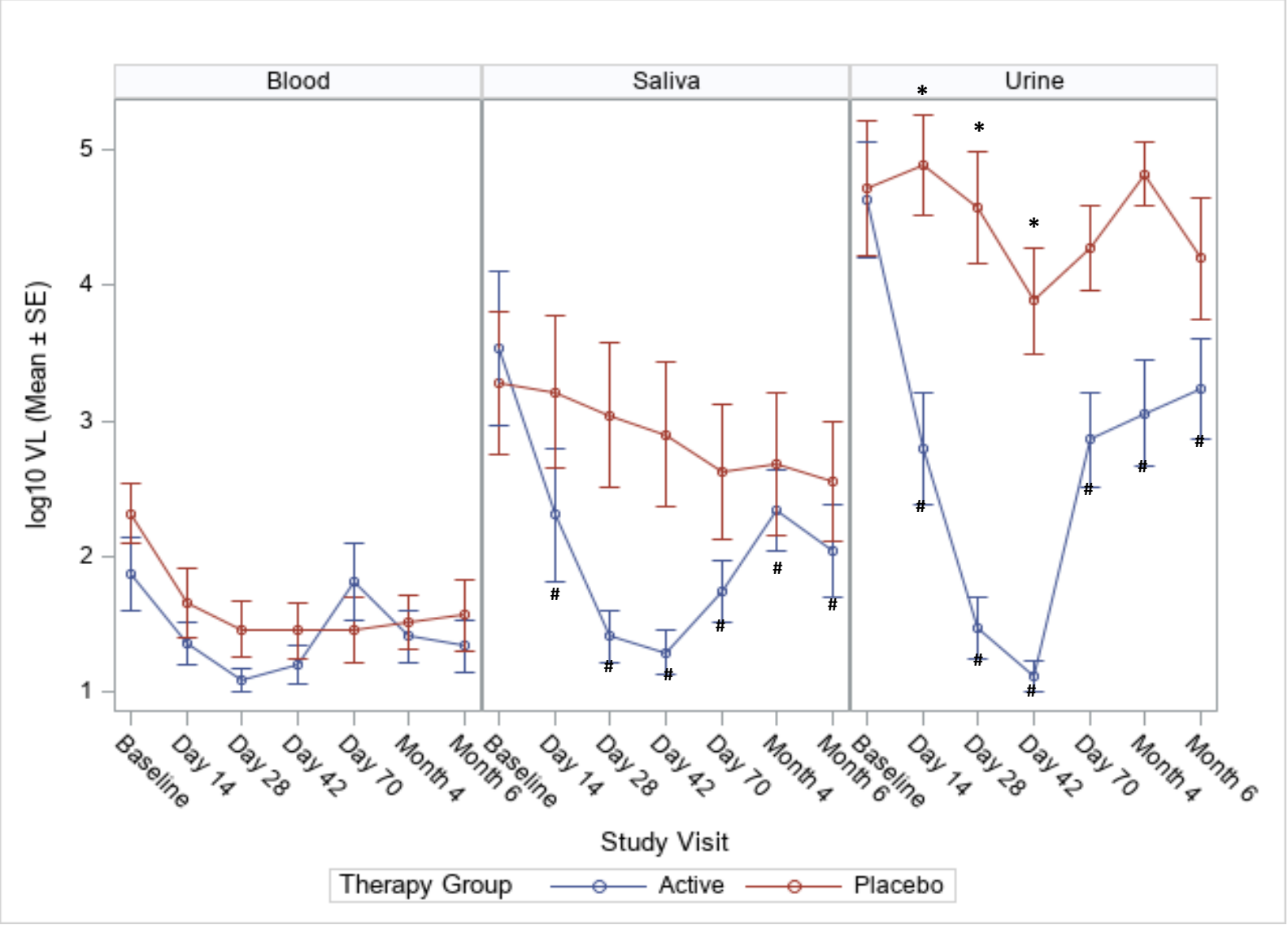


Figure 2 (available at www.jpeds.com). Change in viral load over time, by site and treatment group



* Significantly different from active treatment, using Bonferroni cutoff of 0.0026 (0.05 ÷ 19)
# Significantly different from baseline, using Bonferroni cutoff of 0.0026 (0.05 ÷ 19)

Saliva Pairwise Comparison	P-value	Urine Pairwise Comparison	P-value
Active, Baseline:Day 14	0.001	Active, Baseline:Day 14	< 0.001
Active, Baseline:Day 28	< 0.001	Active, Baseline:Day 28	< 0.001
Active, Baseline:Day 42	< 0.001	Active, Baseline:Day 42	< 0.001
Active, Baseline:Day 70	< 0.001	Active, Baseline:Day 70	< 0.001
Active, Baseline:Month 4	0.002	Active, Baseline:Month 4	< 0.001
Active, Baseline:Month 6	< 0.001	Active, Baseline:Month 6	< 0.001

		Placebo:Active, Day 14	< 0.001
		Placebo:Active, Day 28	< 0.001
		Placebo:Active, Day 42	< 0.001

Table 1. Demographics and Clinical Characteristics of Children Randomized on Trial*

		Therapy Group	
	Randomized	Active	Placebo
	N=35 (%)	N=17 (%)	N=18 (%)
Age			
1-11 months	14 (40.0%)	8 (47.1%)	6 (33.3%)
12-23 months	10 (28.6%)	4 (23.5%)	6 (33.3%)
24-35 months	4 (11.4%)	1 (5.9%)	3 (16.7%)
≥ 36 months	7 (20.00 %)	4 (23.5%)	3 (16.7%)
Ethnicity			
Not Hispanic/Latino	32 (91.4%)	15 (88.2%)	17 (94.4%)
Unknown	3 (8.6%)	2 (11.8%)	1 (5.6%)
Sex			
Female	14 (40.0%)	6 (35.3%)	8 (44.4%)
Male	21 (60.0%)	11 (64.7%)	10 (55.6%)
Race			
Asian	3 (8.6%)	2 (11.8%)	1 (5.6%)
Black	4 (11.4%)	2 (11.8%)	2 (11.1%)
White	27 (77.1%)	12 (70.6%)	15 (83.3%)
More than one race	1 (2.9%)	1 (5.9%)	0
Gestational Age at Delivery (weeks)			
Mean ± SE	38.0 ± 3.2	37.1 ± 4.2	38.8 ± 1.7
Median (min-max)	38.0 (23-42)	38.0 (23-40)	39.0 (35-42)
Unknown or missing	0	0	0
Age at Enrollment (months)			
Mean ± SE	18.7 ± 14.3	17.8 ± 15.8	19.5 ± 13.1
Median (min-max)	14.0 (3-46)	13.0 (3-46)	16.0 (5-45)
Unknown or missing	0	0	0
CMV Involvement at Birth			
Symptomatic at birth	26 (74.3%)	14 (82.4%)	12 (66.7%)
Asymptomatic at birth	9 (25.7%)	3 (17.6%)	6 (33.3%)
Extent of CMV Disease[†]			
Microcephaly ≤ 30 days of birth	5 (14.71%)	1 (5.9%)	4 (22.2%)

Intrauterine growth restriction at birth	3 (8.57%)	1 (5.9%)	2 (11.1%)
Petechiae at birth	5 (14.29%)	2 (11.8%)	3 (16.7%)
Thrombocytopenia at birth	5 (14.29%)	2 (11.8%)	3 (16.7%)
Seizures ≤ 30 days of birth	3 (8.57%)	2 (11.8%)	1 (5.6%)
Splenomegaly (at birth or later)	1 (2.86%)	1 (5.9%)	0 (0%)
Hepatomegaly (at birth or later)	2 (5.71%)	0 (0%)	2 (11.1%)
Elevated transaminases (at birth or later)	3 (8.57%)	2 (11.8%)	1 (5.6%)
Elevated bilirubin (at birth or later)	5 (14.29%)	3 (17.6%)	2 (11.1%)
Baseline total ear hearing assessment‡	N=70 (5)	N=34 (%)	N=36 (%)
Normal	18 (25.71%)	8 (23.53%)	10 (27.78%)
Mild	9 (12.86%)	6 (17.65%)	3 (8.33%)
Moderate	9 (12.86%)	4 (11.76%)	5 (13.89%)
Severe	30 (42.86%)	16 (47.06%)	14 (38.89%)
Not evaluable	0 (0.00%)	0 (0.00%)	0 (0.00%)
Missing/excluded/withdrew	4 (5.71%)	0 (0.00%)	4 (11.11%)

* 24 participants were from the UK, 11 participants were from the U.S.
† Participants can have more than one symptom/sign
‡ See Table 2 (available at www.jpeds.com) for Month 6 total ear hearing assessment

Table 2 (available at www.jpeds.com). Month 6 Total Ear Hearing

		Therapy Group	
	Randomized	Active	Placebo
Month 6 total ear hearing assessment	N=70 (%)	N=34 (%)	N=36 (%)
Normal	15 (21.43%)	6 (17.65%)	9 (25.00%)
Mild	2 (2.86%)	1 (2.94%)	1 (2.78%)
Moderate	7 (10.00%)	2 (5.88%)	5 (13.89%)
Severe	30 (42.86%)	17 (50.00%)	13 (36.11%)
Not evaluable	8 (11.43%)	4 (11.76%)	4 (11.11%)
Missing/excluded/withdrew	8 (11.43%)	4 (11.76%)	4 (11.11%)

Table 3. Change in total ear hearing at six months relative to baseline

	Valganciclovir (N=26)*	Placebo (N=28)[#]	Total (N=54)
Improved	0 (0.00%)	0 (0.00%)	0
No Change (Normal at Baseline and Normal at 6 Months)	6 (23.08%)	9 (32.14%)	15
No Change (Abnormal at Baseline and Same Degree of Abnormal at 6 Months)	14 (53.85%)	18 (64.29%)	32
Worsened	6 (23.08%)	1 (3.57%)	7

* 26 ears in Valganciclovir came from 15 participants
[#] 28 ears in Placebo came from 16 participants

Table 4 (available at www.jpeds.com). Change in best ear hearing at six months relative to baseline

	Valganciclovir (N=12)	Placebo (N=15)	Total (N=27)
Improved	0 (0.00%)	0 (0.00%)	0
No Change (Normal at Baseline and Normal at 6 Months)	6 (50.00%)	9 (60.00%)	15
No Change (Abnormal at Baseline and Same Degree of Abnormal at 6 Months)	3 (25.00%)	6 (40.00%%)	9
Worsened	3 (25.00%)	0 (0.00%)	3

Improved + no change versus worsened, p=0.08
Improved versus no change + worsened, p-value not applicable since no participants had improved hearing
Improved + no change (normal to normal) versus no change (abnormal to abnormal) + worsened, p=0.71

Table 5. Change in total ear hearing at six months relative to baseline, by symptomatology at birth and age at enrollment

	Asymptomatic At Birth		Symptomatic At Birth		Participants Age 1-11 Months		Participants Age 12-47 Months	
	Valganciclovir (N=5)	Placebo (N=10)	Valganciclovir (N=21)	Placebo (N=18)	Valganciclovir (N=11)	Placebo (N=8)	Valganciclovir (N=15)	Placebo (N=20)
Improved	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
No Change (Normal at baseline and Normal at 6 Months)	0 (0.00%)	4 (40.00%)	6 (28.57%)	5 (27.78%)	1 (9.09%)	3 (37.50%)	5 (33.33%)	6 (30.00%)
No Change (Abnormal at Baseline and Same Degree of Abnormal at 6 Months)	4 (80.00%)	6 (60.00%)	10 (47.62%)	12 (66.67%)	5 (45.45%)	5 (62.50%)	9 (60.00%)	13 (65.00%)
Worsened	1 (20.00%)	0 (0.00%)	5 (23.81%)	1 (5.56%)	5 (45.45%)	0 (0.00%)	1 (6.67%)	1 (5.00%)

Abbreviations: CASG, Collaborative Antiviral Study Group; cCMV, congenital cytomegalovirus; SNHL, sensorineural hearing loss

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