TITLE

A PHASE II RANDOMIZED AND CONTROLLED INVESTIGATION OF SIX WEEKS OF ORAL VALGANCICLOVIR THERAPY IN INFANTS WITH CONGENITAL CYTOMEGALOVIRUS INFECTION AND HEARING LOSS
DMID PROTOCOL NUMBER 11-0069

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1.0 Introduction

This report documents the activities and contributions of the Collaborative Antiviral Study Group Central Unit (CU) leadership including administrative, data management (DCC), virology laboratory and pharmacology at the University of Alabama at Birmingham (UAB) to complete the protocol development, implementation, site activation and study closeout phases for the protocol conducted under the above named contract. Following is a summary of activities during the reporting period from 28 September 2019 – 15 August 2020.

2.0 Overview of Contract and Administration

2.1 Meeting and Teleconferences

2.1.1 Protocol Status Calls

Following the initial nine months of protocol development, a site-wide teleconference was coordinated on July 23, 2012, to provide all site investigators and research staff with an update on the protocol development and plans for the future. Regular monthly conference calls were initiated following study activation. Other calls were held as needed with DMID, and Central Unit staff throughout the contract period to address issues related to issues such as version 4.0 of the protocol and the ability to support successful enrollment. In addition, monthly calls continued to be held with staff at the University College London and UK sites, and calls with US sites to discuss issues related to enrollment, and study activities. The final study call was completed on February 13, 2020.

2.1.2 Clinical Monitor Status Calls

Bi-monthly calls were held with the DMID-CROMS monitoring group, COR, and CU staff to discuss monitor plans, interim monitor visits, projections for enrollment and study implementation requirements and expectations in the beginning of the study. It was determined by DMID-CROMs that the calls would be moved to an email format moving forward.

2.1.3 Annual Site Visits

The required site visits with the NIH COR, Dr. Walla Dempsey, were held on an annual basis throughout the contract periods beginning with the initial site visit on September 19-20, 2012. As noted in the previously submitted reports, subsequent annual visits for this contract took place on the following dates: May 19-20, 2014, September 23-24, 2015, May 15-16, 2017, June 5-7, 2018, and April 8, 2019. These meetings included a protocol update by the principal investigator and other UAB investigators, clinical and administrative staff in the Central Unit, and Data Management/Biostatistical Office. In addition, for a several of the visits, the CU staff coordinated additional activities to take advantage of the COR visit. During the 2014 site visit, a UAB wide lecture on NIH funding opportunities and processes was provided by Dr. Dempsey to investigators. In 2018, Dr. Dempsey was accompanied by Dr. Emily Erbelding, Director of the NIAID Division of Microbiology and Infectious Diseases (DMID), who listened to project updates and met with investigators and staff to provide advice and insight into ongoing projects. For the most recent visit on April 8, 2019, the site visit was scheduled in conjunction with an international CMV conference in Birmingham that was organized by UAB investigators. Although a final site visit was anticipated in May 2020, the COVID-19 related suspensions and travel restrictions prevented scheduling of this activity.

2.1.4 Study Start-Up

A study start-up call with all sites was held with the UK sites on 23 September 2013, and with US sites on 4 February 2014. A later refresher call was held in February 2015. Additional calls were arranged with individual sites who began participation later in the study including Baylor College of Medicine in May 2018. Since that time, all have been activated for enrollment in both the US and UK. No additional sites were added since the previous report due to study closure to enrollment.

2.2 Subcontracts Development and Completion Activities

During the entire contract period, Central Unit staff worked closely with the UAB Office of Sponsored Programs (OSP) to prepare and execute base subcontracts at the eight US sites (excluding UAB) approved for this protocol. Throughout the contract study implementation and enrollment, amendments to add option funding, reallocate enrollment funding, and provide no cost extensions for the subcontract were also executed for each of the subcontracts. In addition, an amendment to terminate participation with Rhode Island Hospital due to the retirement of the site PI was completed, and a new site, Baylor College of Medicine, was added to the study. CU staff continued to work with US sites and the UCL Administrative office throughout the contract period to encourage invoicing and amendment executions within a timely manner. (See Appendix B, Subcontract Tracking Log)

3.0 Protocol Development

3.1 Final DMID Protocol Approval

Version 4.0 dated 4/28/2016 was the final protocol version. No further revisions were done.

3.2 CRF Development
No new CRFs were developed due to the study enrollment closure

4.0 Manual of Procedures (MOP) Development

In conjunction with the protocol development, a Manual of Procedures (MOP) was prepared by CU and DCC staff and included detailed instructions related to all aspects of protocol activities including screening and enrollment, data collection and entry, and specimen collections and shipments. Version 3.0 dated October 1, 2016 of the MOP is the latest version of the MOP. No changes were made during this final contract period.

5.0 Regulatory Documentation

Enrollment and randomization closed effective 21 July 2019. Close Out Visit (COV) were conducted by the DMID-CROM's monitor group.

5.1 Site IRB Approval and FWA Numbers
See Appendix D for initial IRB approvals and FWA numbers.

5.2 Regulatory Records Retention
The Central Unit regulatory staff has maintained essential documents collected from sites during the course of this study. This SharePoint based system is accessible via our website at https://www.uab.edu/medicine/peds/casg/ under a password protected area.

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

5.3 Facilitated (Central) IRB
Four sites participated in facilitated review process. See Appendix F for current Approval Letter.

5.4 Quality Assurance/Quality Management Program Development
The CU quality manager reviewed each investigator's Clinical Quality Management Plan (CQMP) for completeness based on the Department of Microbiology and Infectious Disease (DMID) template of key indicator, guidelines and appropriate tools to monitor the quality process by each investigational team.

6.0 Data Management

General activities in the Statistical Unit, Data Coordinating Center, and Research Programming Group for the reporting period included the following:

Documentation

- Created and Continuing work on SOPs governing application design, deployment, testing and security
- Creation and Revision of SOP for Software Development Life Cycle methodology
- Development and Revisions to existing versions of user manuals, as and when required,
- Development and Maintenance of the Portal System
- RPG Request Tracking System
- Administrative System
- Automated Testing Framework
- Alert System

Infrastructure

- Development and continued to maintenance of the Test, Certification and Production databases.

Other

- Developers meeting as needed.

Protocol Specific activities conducted throughout the contract period were as follows:

- Evaluation of (re-)certification exercise for end users Generated monthly quality control reports
- Generated weekly enrollment reports
- Generated weekly pre-screen failure reports
- Updated email notifications as requested
- Provided enrollment report as requested
- Updated and tested changes to forms as requested
- Developed SAS program to generate virology reports for DSMB meeting
- Generated reports for both open and closed sessions of DSMB meeting
- Participated in DSMB meeting
- Developed SAS programs to generate reports in response to DSMB requests
- Worked with CU to respond to DSMB requests
- Worked with CU to finalize MEDRA coding for DSMB reports
- Responded to CU questions about the monthly report and incorporated changes as needed
- Responded to CU questions about the database

- Responded to Central Lab questions about the database
- Assisted in preparation of annual report for CDER-IND 63389
- Assisted in preparation of semi-annual, annual and final reports
- Generated enrollment report for DMID site visit
- Participated in DMID site visits

6.1 Central Unit Website
The CU continued to maintain a study website, with a password protection section developed and managed by the Data Coordinating Center (DCC) in the UAB School of Public Health. The website offered a portal into a study-specific site, where coordinators could also access the Regulatory Management SharePoint site. This site allowed access to necessary regulatory documents, as well as allowed for real-time enrollment, access to source documents and forms, and most recently, minutes from monthly teleconferences for review of information and reference. The website, SharePoint site, and all contents were reviewed and updated regularly.

6.2 User Manual and Training
The current version of the eDES User Manual is version 1.0 dated September 9, 2014. Due to the importance of a knowledgeable research team that understands and has the skill to correctly utilize the electronic data entry system (eDES), the certification process continued throughout this period through study enrollment closure.

7.0 Statistical Analysis Plan

The full statistical plan was developed in conjunction with the protocol. No changes have been required for the plan during this final contract period.

8.0 Protocol Implementation and Enrollment Activities

8.1 Site Activation and Maintenance

8.1.1 Site Personnel Training
Site personnel completed all required trainings per DMID and IRB guidelines.

8.1.2 Activate Study Sites
A total of 17 sites including 9 UK and 8 US sites were activated for this study. Study sites are in Appendix A.

8.2 Protocol Modifications
No protocol modifications were made for this study.

8.3 Screening and Enrollment

Tracking of screening activities at the sites continued on a monthly basis during the entire study. The number of potential subjects and reason(s) the subject did not enroll was requested and recorded. Sites reported pre-screen failures that occurred due to a number of factors, including no evidence of disease, the subject's age was outside the protocol criteria, or no Sensory Neural Hearing Loss was found in subjects. Five hundred forty-seven (547) subjects were pre-screen failures for the study. Fifty-four (54) subjects enrolled in the overall study of which 35 subjects were randomized.

9.0 Central Unit Virology Laboratory and Pharmacokinetic studies

9.1 Qualification/validation of PK

During the final reporting period, Pharmacokinetic samples continued to be collected for DMID 11-0069 and were shipped to the pharmacology laboratory for analysis. In order to prepare for a potential request for the pharmacokinetic data from another DMID study (11-0067) to be used for an additional registrational filing, the lab undertook re-validating its ganciclovir assay under Good Clinical Practices (GCP) conditions. The assay method remained identical, but considerable additional paperwork was required in preparation of a potential FDA audit. The validation plan has been written and experiments have been scheduled. All laboratory SOPs were followed during these steps. This assay was utilized for final analysis of 11-0069 specimens.

9.2 Qualification/validation of Virology Laboratory

The input of specimen tracking data into the Freezerworks inventory system continued throughout the report period as final samples were received in the CU laboratory.

9.3 Virology Laboratory and Site Study Supplies

Under this study, the Central Unit Laboratory prepared and continued to ship protocol specific specimen kits to the sites as subjects were enrolled. During this final reporting period, all samples received in the CU laboratory were been analyzed for CMV viral load and data uploaded to the eDES system.

10.0 Other Activities

10.1 DSMB Safety Oversite review

The Data Safety and Monitoring Board (DSMB) were used for this study. The DSMB did not find any safety reason to halt study enrollment.

10.2 E-Brief

Publication of the E-Brief, which contains both general and study specific information and updates to all sites were used to ensure sites were kept abreast of current study information.

10.3 Publications
The UAB CU and DMCC will work together to write up the final study findings for scientific journals/presentations.

10.4 Clinicaltrials.gov
The UAB CU and the SIO at NIH are working together to get the data uploaded to CT.gov by December 2020.

11.0 Final Study Overview and Results

11.1. Overview
This study was a Phase II, international, multi-center, double-blind, placebo-controlled evaluation of six weeks of valganciclovir treatment for children (1 month of age through 3 years of age – up to the 4th birthday) with virologically-confirmed congenital CMV infection and sensorineural hearing loss (SNHL).

The target sample size of 54 (27 in each arm) was based on a 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). The randomization schedule was created by the UAB Data Coordinating Center (DCC) and implemented via a 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 was the responsibility of the UAB Data Coordinating Center. Randomization on the study occurred when the diagnosis of congenital CMV infection was confirmed, and the subject was then assigned to receive either 6 weeks of oral valganciclovir or 6 weeks of placebo. Study subjects were 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 at birth and asymptomatic at birth) as a marker of disease severity. Ganciclovir plasma concentrations were obtained with each blood draw while the subject was receiving valganciclovir (Study Day 14, Study Day 28, and Study Day 42). Each subject was randomly assigned at randomization to one of the following schedule for blood draw: 0 to 4 hours after a valganciclovir dose, 4 to 8 hours after a valganciclovir dose, and 8 to 12 hours after a valganciclovir dose.

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

audiologist who provided the hearing assessment at each ear per time point was masked to study assignment, as were all personnel at the UAB Central Unit (with the exception of the UAB Study Statisticians).

No interim analysis for futility or efficacy was 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 was performed periodically and monitored by an independent Data and Safety Monitoring Board established to oversee the conduct and safety of the trial. Halting rules for this study were constructed to interrupt study enrollment if an excessive number of subjects are experiencing neutropenia. These are detailed in the Statistical Analysis Plan.

The final analyses were performed after all subjects completed study participation, data quality check completed, and the database locked.

Study Objectives

- 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.

Endpoints

Primary Endpoint:

1. 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; 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

11.2. Statistical Methods

Analysis Population:

All enrolled subjects were included in the basic demographic and clinical summaries and analyses. Only subjects who took at least one dose of the blinded treatment and who completed hearing assessment data at baseline and Month 6 were included in the analyses of study outcomes that compare treatment groups based on the intention-to-treat (ITT). Safety analyses were done on all participants enrolled in the study. There was no per-protocol analyses conducted because those who did not take the study drug also did not have a Month 6 visit.

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, t-test was used unless there is evidence of deviation from normality in which case Wilcoxon test was used. The frequency and percentages of observed levels were reported for all categorical measures. Fisher's exact test was used to compare the therapy groups with respect to these categorical variables.

For safety data, incidence of serious and non-serious adverse events were 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 were summarized by treatment group. Incidence of neutropenia and the incidence of adverse events leading to discontinuation of therapy was assessed. Fisher's exact test was used to compare proportions between two groups. For comparing the differences the number of adverse events experienced between therapy groups, exact Wilcoxon test was

used. For comparing the grade of the AEs between therapy groups, a generalized linear mixed model (GLMM) with random intercept for ordinal response was utilized since subjects may have more than one AE. For continuous safety parameters (chemistry, hematology, growth parameters), means and standard errors of critical safety laboratory parameters were displayed over time. Mixed model with random intercept -- time, therapy and time by treatment interaction term in the model -- was fitted to compare the safety parameter at each time point between the treatment groups. When the interaction term was significant, pairwise comparisons were performed at each time point to compare the therapy groups. P-value <0.05 was used to conclude significance for the demographic, baseline characteristics, safety parameters, and laboratory parameters.

The primary efficacy assessment was 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 was normal hearing, mild hearing loss, moderate hearing loss, and severe hearing loss. Baseline and 6 month hearing categories were compared and the change in each ear were categorized into binary outcomes: Improved or no change versus Other (i.e., worsened). The “no change” category was further broken down into “Normal to Normal” as one category and “No Change Abnormal” (i.e., same degree of hearing loss at Baseline and Study Month 6) as another category. Hearing of participants who underwent cochlear implantation after baseline were assigned “severe” for both ears at Month 6.

The primary outcome of change in total ear and all other binary outcomes associated with the total ear were analyzed using generalized linear regression model for binary outcome utilizing the generalized estimating equations (GEE) approach in order to accommodate the correlation between the left and right ears of a subject. For best ear outcomes, Fisher’s exact test was used to examine the treatment effect. We performed subgroup descriptive analyses of hearing outcomes 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.

To examine the detection of viral load over time between the treatment groups, we obtained the proportion of viral load detected in blood, saliva, and urine at each time point separately for each therapy group. P-values at each time point were based on the Fisher’s exact test. Since there are a total of 21 tests (7 for each specimen), p-value <0.0024 (=0.05/21) was used to determine significance by Bonferroni method. 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 log10 units). To compare the trajectory of the viral load over time between placebo and active group, a GLMM with random intercept was fitted. Model was fitted separately for blood, saliva, and urine viral load readings. Each model included treatment group, time (discrete), and time by treatment group interaction. Treatment effect was determined to be significant when the p-value associated with the interaction term is less than 0.0067 (=0.05/3) using Bonferroni adjustment method since there are three types of specimen (blood, saliva, and urine). When there was a significant interaction, we looked at the pairwise comparisons of the treatment group per time point as well as the pair of each time and baseline within the same treatment group. P-value <0.0026 (=0.05/17) was the cutoff used to determine significance.

To investigate the association between viral load and hearing outcomes, a summary measure of the viral load over time was calculated and two approaches were used. The first approach considered all time points available by calculating the average area under the curve (AUC) (using trapezoidal rule) applied to the log base 10 viral load. Average was 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 the average AUC enabled 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 those having complete viral load data. The second approach calculated the difference between Month 6 and baseline log10 viral load. The last visit with available viral load was used for those without Month 6 viral load. A general linear model using GEE approach was again fitted to model change on total ear. Unadjusted model (only contains viral load) and adjusted model (with viral load and therapy group) were both considered. To investigate the correlation between viral load and ganciclovir concentration, we utilized Spearman rank correlation.

11.3. Results

Enrollment and Protocol Deviation

A total of 21 sites (9 in the UK and 12 in the US) participated in this study as listed in Table 1a. Figure 1 and Table 1b summarize enrollment and participant flow. A total of 1012 subjects were pre-screened, with 560 resulting in a screen-failure. There were 54 enrolled subjects of which 35 were randomized to placebo (17) and active (18) therapy. Among the 35 randomized, 3 dropped out soon after randomization and 32 completed the study. Table 2a shows the distribution of the enrolled and randomized patients by site. Children's National Medical Center – Washington DC had the most number of patients with 11 enrolled. A combined total of 27 subjects were enrolled by sites in the UK. Table 2b provides the reported reasons for the 19 eligible subjects who were not enrolled. Table 2c provides further information on the site performance with respect to screening, enrollment, and randomization. Figure 2 displays the rates of enrollment and randomization over the period of the study. Table 3 provides details on the 3 subjects who dropped out after randomization. All 3 withdrew consent – only 2 provided specific reasons (one due to family illness and another stated "severe hearing loss borderline eligible".)

A total of 101 subject specific protocol deviations were reported and summarized in Table 4a and Table 4b. Site 296 had 37 deviations on protocol procedure/assessment -- all of these are related to freezer temperature deviations for the specimen storage (see Table 4c for details). There were also a number of deviations attributed to non-compliance (17 deviations) either by the subject, parent, or guardian. Table 4d shows 3 deviations resulted in interruption in study drug. At the site level, there are 65 total site deviations (see Table 5a). Forty seven (47) of these came from site 285 – mostly attributed to sample storage issues. Actions taken to address these deviations are listed in Table 5b.

Participant Characteristics

Of the 35 randomized, 14 (40%) were less than 12 months of age, 26 (74.3%) had been symptomatic at birth, 32 (91.4%) were not Hispanic or Latino, 27 (77.1%) were white, and 14 (40%) were female (Table 6a). The mean age at enrollment was 18.7 months with a mean gestational age of 38 weeks. For participants with available data at birth, the means of weight, length, and head circumference were 3018.8 grams, 49.2 centimeters, and 32.6 centimeters, respectively. No significant differences between therapy groups were found in these characteristics.

Table 7a summarizes the CMV involvement in general and broken by age of presentation (≤ 30 days vs > 30 days of birth). Thirty three (33) of the 35 exhibited hearing deficit >30 days after birth, 5 participants reported having microcephaly at ≤ 30 days of life, another 5 participants reported petechia, and another 5 participants reported elevated bilirubin. Tables 7b and 7c summarize the results of lumbar puncture and neuroimaging, respectively, for those participants who underwent these procedures. Only 7 participants had lumbar puncture and all of them were in the active group with available results for WBC (3 results within 30 days of birth and 5 results 30 days after birth) and protein (1 result 30 days of birth and 3 results 30 days after of birth). Three subjects had PCR results 30 days after birth – 1 negative and 2 positives. A total of 26 subjects had neuroimaging study – 14 in active and 12 in placebo. Eighteen had MRI tests 30 days after birth and 1 participant had MRI ≤30 days after birth, with 10 reporting abnormal results (4 in active and 6 in placebo). Three had CT test 30 days after birth all showing abnormal results. None of the participants had CT scan within 30 days of birth. Also, 6 had HUS test ≤30 days after birth with 3 abnormal results, and 5 had HUS 30 days after birth with 3 abnormal results. Table 7d provides the frequency of reported baseline abnormal findings. The top 3 abnormalities were: ears, nose and throat most likely attributed to the hearing deficit (30 participants), neurological disorders (9 participants), and musculoskeletal disorders (5 participants).

Figures 3a (overall) and 3b (by therapy group) show the treatment disposition of the participants. Out of the 35 randomized, 2 participants in placebo group dropped out soon after randomization without taking study drug, and another participant in the placebo took the study drug but did not complete the 6-week dose of study drug – this participant stayed in the study through its completion at Month 6. One participant in the active group dropped out before the end of the 6-week therapy. Thus, a total of 16 completed 6-week therapy and completed the study in the active group, while 15 completed 6-week therapy in the placebo group but 16 completed the study.

Safety Analyses

A total of 105 Adverse Events (AE) were reported from 25 subjects and only 1 Serious AE (SAE) (Tables 8a and 8b). Fifty seven (57) of the 105 AEs were from 13 of the active participants while the remaining 48 AEs were from 12 placebo participants. The differences in the number of AEs and number of subjects experiencing at least one AE between the active and placebo group were not found to be significant (Table 9a). The single SAE experienced by a participant in the active group was described as respiratory distress requiring hospitalization with Grade 2 (moderate) severity, found to be unrelated to the study product, and had been resolved (Table 9b). Table 10a and Table 10b provide summary of the AEs by Body System and Grade. Eighty three (83) of the 105 AEs were Grade 1 (mild),

21 Grade 2 (moderate), and 1 Grade 3 (severe). There were no significant differences in the severity levels of the AEs between the therapy groups. Table 10c provides a listing of the AEs reported by therapy group. All AEs were resolved. One participant in the active group died after the safety period but before the Month 6 visit defined in the protocol so it was not reported as an SAE. Three AEs in the active group and 8 in the placebo group were classified as related to the study drug. Three AEs (namely discoloration of lips and throat, agitation and hyperactivity) in the placebo group were classified as possibly resulting in an unanticipated medically attended visits occurring from Study Day 1 through two weeks following the last dose of study drug, addressing one of the secondary outcomes of this study.

Table 11a and Figure 4a- Figure 4h summarize the hematology parameters (WBC, hemoglobin, ANC, and platelet) while Table 11b and Figure 5a- Figure 5h summarize the chemistry parameters (serum creatinine, creatinine clearance, ALT, and total bilirubin). The only significant difference found between therapy groups was in platelet (interaction term p-value=0.0341). In particular, at day 14 (p=0.0054), day 28 (p=0.0015), and day 42 (p=0.0121), the active group showed a higher mean platelet relative to the placebo group. Total bilirubin showed significant increase within the placebo group from day 14 to day 28 (p=0.0086) but did not show significant differences between therapy at any other time point of interest.

Table 12 compares reported Grade 3 or 4 neutropenia using lowest ANC of the current study with previous studies – CASG 102, CASG 109, and CASG 112. The current study reported one out of 18 (5.6%) with Grade 3 neutropenia (lowest ANC=690 at Day 42) in the active group and one out of 17 (5.9%) Grade 4 neutropenia (lowest ANC=250 at Day 70) in the placebo group. In CASG 112, during the open label period (Day 0-Day 42) the observed Grade 3 and Grade 4 neutropenia were 14.7% and 4.6%, respectively. Tables 13-16 show that in this study no Grade 3 or 4 events were reported related to anemia (using lowest hemoglobin or platelet), ALT, or creatinine values.

Table 17 shows summary statistics for the concomitant medications taken by the participants. Seven participants did not report any concomitant medications taken during study participation – 2 in active and 5 in placebo. The overall mean number of concomitant medications is 8.1. The mean number is higher for active (due to a participant with 88 concomitant medications) than placebo, but this difference was not significant (p-value~1). The summary statistics for dose (mg/kg) prescribed at each visit (baseline, day 14 and day 28) is summarized in Table 18a and Figure 6 which shows that the prescribed dose at each visit adjusted by weight is centered around 16 mg/kg except for one participant in the active who had a recorded dose around 8 mg/kg at Day 14 and 28 due to a very low creatinine clearance – this subject died after the safety period but before reaching Month 6 visit. The weight and length at the time of dosing are also summarized in Tables 18b and 18c and Figure 7a and Figure 7b. The mean weight of participants is about 11 kg and mean length is about 78 centimeters across the visits. Dose, weight, and length were not significantly different between therapy groups.

Table 19a summarizes the changes in doses. The 3 subjects who dropped out after randomization (2 without taking the drug and 1 who dropped out after a month) did not complete follow up information on dose after baseline. There were no reported dose held in any of the visits although one subject in the placebo group did not take drug after Day 28 but stayed in the study. Of the 32 who completed this form, 21 participants (9 in the active and 12 in the placebo) at day 14 and 17 participants at day 28 (9 in active and 8 in placebo) had dose adjustments. Table 19b and Table 19c provide the reasons of dose adjustments. Reasons given are mostly due to change in weight. One subject in the active group had dose adjustment due laboratory results indicating renal impairment.

Results of the analyses of the PK specimen are summarized in Table 20 and Figure 7a and Figure 7b. As expected, the ganciclovir concentrations for the placebo group were all below the quantifiable limit. Limiting the summary to the active group, the mean GCV concentration values at day 14, 28, and 42 were 2191.9, 1746.1, and 2291.6, respectively. Figure 7b and 7c display the GCV concentration in the linear and log scale as a function of the time post dose and include the placebo group, which explains the cluster of points near the horizontal axes.

Hearing Outcomes

Table 21a shows the quality of the hearing assessments in each ear at baseline and Month 6 visits. A total of 66 ears at baseline and 54 ears at Month 6 had complete or partial information to enable hearing assessment. Two ears from 1 subject in the Active group were “missing” because the hearing assessment was not done at Month 6. Another pair of ears were missing because the participant dropped out early (labelled as “withdrew”) and therefore missed the Month 6 hearing assessment. Two pairs of ears from 2 subjects in the Placebo group who dropped out soon after randomization and did not take the study drug were excluded both at baseline and Month 6. Hearing assessment for both ears at Month 6 for one subject who had cochlear implant was assigned “severe”. “Not evaluable” in this case means hearing assessment information sent to masked study audiologist did not provide enough information to evaluate hearing.

Table 21b summarizes the hearing assessments for both left and right ears at baseline and Month 6. A total of 18 ears (10 placebo and 8 active) were normal at baseline while 18 ears had either mild or moderate hearing loss. A total of 30 ears had severe hearing loss (a pair of ears was from the participant who had cochlear implant). At Month 6, there were 15 ears that are normal, 9 ears with mild or moderate hearing loss, and 30 ears with severe hearing loss. Table 21c shows the change in hearing assessment at Month 6 relative to baseline. There were no improvement observed; 15 ears (9 placebo and 6 active) had normal at baseline and remained normal at Month 6; 32 ears had no change in the hearing loss at baseline; and 7 ears (1 placebo and 6 active) worsened. Table 21d shows the results of classifying the change into binary outcomes and fitting a generalized linear model based on GEE for binary outcomes to examine treatment effects. The primary outcome of this study is the change in the total ear defined as improved/no change versus worsened. Since there were no ears that improved, this outcome was statistically the same as no change versus worsened. Placebo group (96%) had higher percentage of no change in hearing relative to

active (77%) but this difference did not reach significance (p-value=0.0859). Looking at the binary outcome of normal at baseline and no change and Month 6 versus same degree of hearing loss combined with worsened, there was no significant treatment effect (p-value=0.4823).

We further investigated possible trends based on subgroups defined by: (1) CMV involvement (symptomatic at birth versus asymptomatic at birth), and (2) age (less than 12 months versus 1 year or older). Table 21e summarizes the results. Among the 13 ears from participants that were asymptomatic, 4 ears in the placebo group stayed normal while 4 ears each in placebo and active had the same degree of hearing loss. One ear in the active group worsened. Among the 41 ears from symptomatic participants, about the same proportion remained normal but higher proportion in the placebo group had no change on the level of hearing loss. Ears from active group had higher percentage of worsening 5 out of 21 (23.81%) versus 1 out of 20 (5%) in placebo. For the participants less than a year old, 5 ears from the active group and none in the placebo group worsened. For participants 1 year or older, the treatment groups had similar percentages in each change category.

Tables 22a – 22d show similar information except based on the best ear as outcome at each time point instead of total ear. Best ear is defined as the ear with the better assessment at a particular time. Change in best ear is defined as the change in the hearing of the best ear at baseline compared with the hearing of the best ear at Month 6. In this case, the observation is at the participant level. Table 22a shows the quality of the hearing assessment, and Table 22b shows the hearing assessment of the best ear at each time point. Table 22c shows the change in hearing assessment at Month 6 relative to baseline. Out of a total of 35, 27 subjects had both baseline and Month 6 best ear assessments to determine the change in the best ear. As before, there were not improvement in hearing. Three subjects in the active group had worsened hearing. Nine participants in the placebo and 6 in the active retained the normal hearing when comparing best ear. Table 22d shows the results of classifying the change into binary outcomes. Looking at no change (normal to normal combined with same degree of hearing loss) versus worsened, all 3 subjects that had worsened hearing were in the active and none in the placebo. These differences did not reach significance (p-value=0.0752). The same general patterns observed in the total ear analyses were also observed in the subgroup analyses for age and CMV involvement at birth based on best ear (Table 22e).

Viral Load

Table 23 and Figure 8 show the observed proportion detected in each of the specimen by therapy group. There is no significant treatment difference seen in the detection of viremia and CMV in saliva at each time point based on Fisher's exact test. However, there is evidence of a decrease in the proportion of participants with viruria detected at days 28 and 42 (both p-values<0.0024 cutoff) after which the proportion increases back to the level of the placebo participants. Table 24 provides summary statistics of the quantitative viral load in log10 units at each time point by specimen type for each treatment group. Recall that undetectable viral load was replaced by 10 (hence 1 in log10 units). Looking at the results of fitting a mixed model with random intercept (Table 24a, 24b, and 24c) to test for treatment

effect, results from urine and saliva showed significant difference in the change over time as measured by the significance of the coefficient of the interaction term. For CMV in saliva and urine, the difference noted was mainly attributed to the significant decrease from baseline starting day 14 through Month 6 in the active group while placebo group did not show much change over time. On the other hand, in urine, significant differences were observed between the therapy groups at days 14, 28 and 42 where active has lower quantitative viral load. Note that p-value <0.0026 (=0.05/19 pairwise comparisons using Bonferroni method) was used to determine significance. Table 25 shows the estimated Spearman rank correlation and its associated p-value between log10 viral load and GCV concentration at days 14, 28 and 42. P-value <0.0167 (=0.05/3 using Bonferroni method) was used to determine significance. None of these correlation values were significant.

Viral load and Change in Hearing

The summary statistics of the log10 viral load by change in hearing in the total ear are presented in Table 26a (raw change) and Table 26b and Figure 10 (based on change categorized in to normal to normal versus others). From the p-values in Table 26b, there is no evidence of an association between change in hearing outcome and baseline viral load for both unadjusted (i.e. viral load is the only in the model) and adjusted (viral load plus treatment are terms in the model) analyses. Looking at the change in the best ear instead of total ear, there is also no evidence that baseline viral load predicts change in best ear hearing (see Tables 27a, 27b, and Figure 11).

Using the area under the curve (AUC) of the viral load averaged over time, Table 28a, Table 28b, and Figure 12 present the summary statistics of average AUC by change in total ear categories. Looking at the p-values in Table 28b, there is no evidence that average AUC of the viral load is associated with the change in the total ear. Similar conclusions were reached when the outcome as change in the best ear (see Tables 29a, 29b, and Figure 13). Table 30a, Table 30, Figure 14 show the results for change in total ear while Table 31a, Table 31b, and Figure 15 show the results for change in the best ear. None of these analyses resulted in showing a significant association.

Appendix A Active Study Centers

Active Study Sites for DMID 11-0069

Principal Investigator	Site Name
Ahmed, Amina	The Charlotte-Mecklenburg Hospital Authority Carolinas Medical Center Levine Children's Hospital
Bernatoniene, Jolanta	Bristol Royal Hospital for Children
Caserta, Mary	University of Rochester
DeBiasi, Roberta	Children's Research Institute
Demmler-Harrison, Gail	Baylor College of Medicine - Texas Children's Hospital - Houston
Emonts, Marieke	Royal Victoria Infirmary
Faust, Saul	University Hospital Southampton NHS Foundation Trust (UHS NHS FT)
Hackett, Scott	Birmingham Heartlands Hospital
Kelly, Dominic	Oxford Radcliffe Hospital NHSF Trust
Kimberlin, David	University of Alabama at Birmingham
Klein, Nigel	Great Ormond Street Hospital
McMaster, Paddy	The Pennine Acute Hospitals NHS Trust, Manchester
Sanchez, Pablo	Ohio State University - Nationwide Children's Hospital
Shackley, Fiona	Sheffield Children's NHS Foundation Trust
Sharland, Mike	St. George's NHS Trust
Sood, Sunil	The Feinstein Institute for Medical Research
Storch, Gregory	Washington University St Louis

Appendix B Subcontract Tracking Log

Sponsor Award No.	OSP Assigned Agreement Number	Institution Name	SubAward PI Name	Agreement Type	Agreement From Date	Agreement To Date	Date Signed	Current Agreement Status	Current Agreement Status Recorded	Budget Amount	Budget Start Date	Budget End Date
HHSN272201100035C	SC001-Gri	University College (London)	Griffiths, Paul	Subcontract/Subaward	09/28/2011	09/27/2012	07/15/2014	Approved	07/21/2014	$373,159.00	01/01/2013	09/27/2015
HHSN272201100035C	SC001-Gri-A01	University College of London	,	Subcontract/Subaward Amendment	01/01/2015	09/27/2016	06/18/2015	Approved	06/19/2015	$0.00	01/01/2013	09/27/2016
HHSN272201100035C	SC001-Gri-A02	University College (London)	,	Subcontract/Subaward Amendment	01/01/2013	09/27/2017	06/16/2016	Approved	06/17/2016	$388,553.00	01/01/2013	09/27/2017
HHSN272201100035C	SC001-Gri-A03	University College (London)	,	Subcontract/Subaward Amendment	09/28/2013	09/27/2019	05/15/2017	Approved	05/22/2017	$0.00	09/28/2013	09/27/2019
HHSN272201100035C	SC001-Gri-A04	University College (London)	,	Subcontract/Subaward Amendment	09/28/2013	05/31/2020	08/03/2018	Approved	08/08/2018	$0.00	09/28/2013	05/31/2020
HHSN272201100035C	SC002-Ahm	Carolinas HealthCare System	Ahmed, Amina	Subcontract/Subaward	02/01/2012	09/27/2013	07/09/2013	Approved	07/15/2013	$26,310.00	02/01/2012	09/27/2013
HHSN272201100035C	SC002-Ahm-A01	Carolinas HealthCare System	,	Subcontract/Subaward Amendment	02/01/2012	09/27/2015	03/12/2015	Approved	03/16/2015	$16,571.00	02/01/2012	09/27/2015
HHSN272201100035C	SC002-Ahm-A01	Carolinas HealthCare System	,	Subcontract/Subaward Amendment	02/01/2012	09/27/2015	03/12/2015	Approved	03/16/2015	$16,571.00	02/01/2012	09/27/2015
HHSN272201100035C	SC002-Ahm-A02	Carolinas HealthCare System	,	Subcontract/Subaward Amendment	02/01/2012	09/27/2017	06/07/2016	Approved	06/09/2016	$16,932.00	02/01/2012	09/27/2017
HHSN272201100035C	SC002-Ahm-A03	Carolinas HealthCare System	,	Subcontract/Subaward Amendment	09/28/2013	09/27/2017	01/31/2017	Approved	01/31/2017	$8,575.00	09/28/2013	09/27/2017
HHSN272201100035C	SC002-Ahm-A04	Carolinas HealthCare System	Ahmed, Amina	Subcontract/Subaward Amendment	09/28/2013	05/15/2019	03/06/2018	Approved	03/14/2018	$31,418.00	09/28/2013	05/15/2019
HHSN272201100035C	SC002-Ahm-A05	Carolinas HealthCare System	,	Subcontract/Subaward Amendment	09/27/2016	03/31/2020	01/13/2020	Approved	01/15/2020	$0.00	09/28/2013	03/31/2020
HHSN272201100035C	SC003-Amp	University of Utah	Ampofo, Kwabena Krow	Subcontract/Subaward	02/01/2012	09/27/2012	09/16/2013	Approved	09/18/2013	$13,863.00	02/01/2012	09/27/2012
HHSN272201100035C	SC003-Amp-A01	University of Utah	,	Subcontract/Subaward Amendment	02/01/2012	09/27/2015	12/23/2014	Approved	01/07/2015	$14,926.00	02/01/2012	09/27/2015
HHSN272201100035C	SC003-Amp-A01	University of Utah	,	Subcontract/Subaward Amendment	02/01/2012	09/27/2015	12/23/2014	Approved	01/07/2015	$14,926.00	02/01/2012	09/27/2015
HHSN272201100035C	SC003-Amp-A02	University of Utah	,	Subcontract/Subaward Amendment	02/01/2012	09/27/2017	06/10/2016	Approved	06/16/2016	$15,300.00	02/01/2012	09/27/2017
HHSN272201100035C	SC003-Amp-A03	University of Utah	Ampofo, Kwabena Krow	Subcontract/Subaward Amendment		02/01/2012	03/30/2017	Approved	04/04/2017	($53,038.00)	02/01/2012	02/28/2017
HHSN272201100035C	SC004-Bog	Johns Hopkins University	Boger, Ravit	Subcontract/Subaward	02/01/2012	09/27/2012	08/01/2012	Approved	08/10/2012	$10,622.00	02/01/2012	09/27/2012
HHSN272201100035C	SC004-Bog-A01	Johns Hopkins University	,	Subcontract/Subaward Amendment	02/01/2012	06/30/2013	02/13/2014	Approved	02/14/2014	$0.00	02/01/2012	09/27/2013
HHSN272201100035C	SC004-Bog-A02	Johns Hopkins University	,	Subcontract/Subaward Amendment	02/01/2012	09/27/2015	10/02/2015	Approved	10/05/2015	$20,412.00	02/01/2012	09/27/2015
HHSN272201100035C	SC004-Bog-A03	Johns Hopkins University	,	Subcontract/Subaward Amendment	02/01/2012	09/27/2017	01/07/2016	Approved	01/12/2016	$3,465.00	02/01/2012	09/27/2017
HHSN272201100035C	SC004-Bog-A04	Johns Hopkins University	Boger, Ravit	Subcontract/Subaward Amendment	09/28/2013	05/31/2019	02/22/2018	Approved	03/01/2018	$48,058.00	09/28/2013	05/31/2019
HHSN272201100035C	SC004-Bog-A05	Johns Hopkins University	,	Subcontract/Subaward Amendment	09/28/2014	06/30/2018	06/21/2018	Approved	06/21/2018	($15,309.00)	09/28/2014	06/30/2018
HHSN272201100035C	SC004-Bog-A06	Johns Hopkins University	,	Subcontract/Subaward Amendment	09/28/2013	06/30/2018	08/15/2018	Approved	08/16/2018	$798.00	09/28/2013	06/30/2018
HHSN272201100035C	SC005-Cas	University of Rochester Medical Center	Caserta, Mary	Subcontract/Subaward	02/01/2012	09/27/2013	05/31/2013	Approved	05/31/2013	$12,456.00	02/01/2012	09/27/2013

HHSN272201100035C	SC005-Cas-A01	University of Rochester Medical Center	,	Subcontract/Subaward Amendment	02/01/2012	09/27/2015	03/17/2015	Approved	03/19/2015	$13,506.00	02/01/2012	09/27/2015
HHSN272201100035C	SC005-Cas-A01	University of Rochester Medical Center	,	Subcontract/Subaward Amendment	02/01/2012	09/27/2015	03/17/2015	Approved	03/19/2015	$13,506.00	02/01/2012	09/27/2015
HHSN272201100035C	SC005-Cas-A02	University of Rochester Medical Center	,	Subcontract/Subaward Amendment	02/01/2012	09/27/2017	01/07/2016	Approved	01/15/2016	$13,840.00	02/01/2012	09/27/2017
HHSN272201100035C	SC005-Cas-A03	University of Rochester Medical Center	Caserta, Mary	Subcontract/Subaward Amendment	09/28/2014	09/27/2017	12/16/2016	Approved	12/21/2016	$28,787.00	09/28/2014	09/27/2017
HHSN272201100035C	SC005-Cas-A04	University of Rochester Medical Center	,	Subcontract/Subaward Amendment	09/28/2013	09/27/2019	04/19/2017	Approved	04/20/2017	$0.00	09/28/2013	09/27/2019
HHSN272201100035C	SC005-Cas-A05	University of Rochester Medical Center	,	Subcontract/Subaward Amendment	01/01/2013	03/31/2020	01/09/2020	Approved	01/10/2020	$0.00	01/01/2013	03/31/2020
HHSN272201100035C	SC006-DeB	Children's Research Institute	DeBiasi, Roberta	Subcontract/Subaward	02/01/2012	09/27/2012	04/09/2012	Approved	04/09/2012	$16,005.00	02/01/2012	09/27/2012
HHSN272201100035C	SC006-DeB-A01	Children's Research Institute	,	Subcontract/Subaward Amendment	02/01/2012	09/27/2013	03/01/2013	Approved	03/04/2013	$0.00	02/01/2012	09/27/2013
HHSN272201100035C	SC006-DeB-A02	Children's Research Institute	,	Subcontract/Subaward Amendment	02/01/2012	09/27/2015	04/01/2015	Approved	04/01/2015	$44,493.00	02/01/2012	09/27/2015
HHSN272201100035C	SC006-DeB-A02	Children's Research Institute	,	Subcontract/Subaward Amendment	02/01/2012	09/27/2015	04/01/2015	Approved	04/01/2015	$44,493.00	02/01/2012	09/27/2015
HHSN272201100035C	SC006-DeB-A03	Children's Research Institute	,	Subcontract/Subaward Amendment	09/28/2013	09/27/2017	05/13/2016	Approved	05/16/2016	$17,887.00	09/28/2013	09/27/2017
HHSN272201100035C	SC006-DeB-A04	Children's Research Institute	,	Subcontract/Subaward Amendment	09/28/2013	09/27/2019	09/08/2017	Approved	09/21/2017	$2,752.00	09/28/2013	09/27/2019
HHSN272201100035C	SC006-DeB-A05	Children's Research Institute	,	Subcontract/Subaward Amendment	09/28/2013	09/27/2019	03/27/2019	Approved	04/01/2019	($6,632.00)	09/28/2013	09/27/2019
HHSN272201100035C	SC006-DeB-A06	Children's Research Institute	,	Subcontract/Subaward Amendment	02/01/2012	04/30/2020	01/15/2020	Approved	01/17/2020	$0.00	02/01/2012	04/30/2020
HHSN272201100035C	SC007-Den	Rhode Island Hospital	Dennehy, Penelope	Subcontract/Subaward	02/01/2012	09/27/2012	05/03/2012	Approved	05/07/2012	$17,398.00	02/01/2012	09/27/2012
HHSN272201100035C	SC007-Den-A01	Rhode Island Hospital	,	Subcontract/Subaward Amendment	02/01/2012	09/27/2013	02/08/2013	Approved	02/11/2013	$0.00	02/01/2012	09/27/2013
HHSN272201100035C	SC007-Den-A02	Rhode Island Hospital	,	Subcontract/Subaward Amendment	02/01/2012	09/27/2015	04/01/2015	Approved	04/01/2015	$49,480.00	02/01/2012	09/27/2015
HHSN272201100035C	SC007-Den-A02	Rhode Island Hospital	,	Subcontract/Subaward Amendment	02/01/2012	09/27/2015	04/01/2015	Approved	04/01/2015	$49,480.00	02/01/2012	09/27/2015
HHSN272201100035C	SC007-Den-A03	Rhode Island Hospital	,	Subcontract/Subaward Amendment	02/01/2012	09/27/2017	05/24/2016	Approved	05/25/2016	$19,936.00	02/01/2012	09/27/2017
HHSN272201100035C	SC007-Den-A04	Rhode Island Hospital	,	Subcontract/Subaward Amendment	09/28/2013	09/27/2019	10/23/2017	Approved	10/30/2017	$26,205.00	09/28/2013	09/27/2019
HHSN272201100035C	SC007-Den-A05	Rhode Island Hospital	,	Subcontract/Subaward Amendment	09/28/2014	09/27/2018	01/04/2019	Approved	01/07/2019	($25,841.00)	09/28/2014	09/27/2018
HHSN272201100035C	SC008-San	University of Texas Southwestern Medical	Sanchez, Pablo	Subcontract/Subaward	02/01/2012	09/27/2012		Withdrawn	01/16/2014	$0.00		
HHSN272201100035C	SC009-Soo	Feinstein Institute for Medical Research	Sood, Sunil	Subcontract/Subaward	02/01/2012	09/27/2012	07/31/2012	Approved	08/09/2012	$19,037.00	02/01/2012	09/27/2012
HHSN272201100035C	SC009-Soo-A01	Feinstein Institute for Medical Research	,	Subcontract/Subaward Amendment	02/01/2012	09/27/2013	02/20/2013	Approved	02/21/2013	$0.00	02/01/2012	09/27/2013
HHSN272201100035C	SC009-Soo-A02	Feinstein Institute for medical Research	,	Subcontract/Subaward Amendment	02/01/2012	09/27/2015	02/27/2015	Approved	03/04/2015	$22,123.00	02/01/2012	09/27/2015
HHSN272201100035C	SC009-Soo-A02	Feinstein Institute for medical Research	,	Subcontract/Subaward Amendment	02/01/2012	09/27/2015	02/27/2015	Approved	03/04/2015	$22,123.00	02/01/2012	09/27/2015
HHSN272201100035C	SC009-Soo-A03	Feinstein Institute for medical Research	,	Subcontract/Subaward Amendment	02/01/2012	09/27/2017	01/26/2016	Approved	02/03/2016	$22,870.00	02/01/2012	09/27/2017

HHSN272201100035C	SC009-Soo-A04	Feinstein Institute for Medical Research	Sood, Sunil	Subcontract/Subaward Amendment	09/28/2013	09/27/2017	05/01/2018	Approved	05/02/2018	$28,291.00	09/28/2013	09/27/2019
HHSN272201100035C	SC009-Soo-A05	Feinstein Institute for Medical Research	,	Subcontract/Subaward Amendment	02/01/2012	03/31/2020		withdrawn	01/08/2020			
HHSN272201100035C	SC010-Sto	Washington University School of Medicine in St.	Storch, Gregory	Subcontract/Subaward	02/01/2012	09/27/2013	12/11/2013	Approved	12/11/2013	$14,037.00	02/01/2012	09/27/2013
HHSN272201100035C	SC010-Sto-A01	Washington University School of Medicine - St	,	Subcontract/Subaward Amendment	02/01/2012	09/27/2015	12/23/2014	Approved	01/06/2015	$15,557.00	02/01/2012	09/27/2015
HHSN272201100035C	SC010-Sto-A01	Washington University School of Medicine - St	,	Subcontract/Subaward Amendment	02/01/2012	09/27/2015	12/23/2014	Approved	01/06/2015	$15,557.00	02/01/2012	09/27/2015
HHSN272201100035C	SC010-Sto-A02	Washington University School of Medicine - St	,	Subcontract/Subaward Amendment	09/28/2014	09/27/2017	12/21/2015	Approved	12/28/2015	$40,702.00	09/28/2014	09/27/2017
HHSN272201100035C	SC010-Sto-A03	Washington University School of Medicine in St.	Storch, Gregory	Subcontract/Subaward Amendment	09/28/2014	09/27/2017	12/22/2016	Approved	12/22/2016	$21,972.00	09/28/2014	09/27/2017
HHSN272201100035C	SC010-Sto-A04	Washington University School of Medicine in St.	,	Subcontract/Subaward Amendment	09/28/2013	09/27/2019	08/18/2017	Approved	08/21/2017	$0.00	09/28/2013	09/27/2019
HHSN272201100035C	SC010-Sto-A05	Washington University	,	Subcontract/Subaward Amendment	02/01/2012	03/31/2020	01/09/2020	Approved	01/10/2020	$0.00	02/01/2012	03/31/2020
HHSN272201100035C	SC011-San	The Research Institute at Nationwide	Sanchez, Pablo	Subcontract/Subaward	08/01/2014	09/27/2015	01/21/2016	Approved	01/25/2016	$45,052.00	08/01/2014	09/27/2015
HHSN272201100035C	SC011-San-A01	The Research Institute at Nationwide	,	Subcontract/Subaward Amendment	09/28/2014	09/27/2017	03/08/2016	Approved	03/14/2016	$14,272.00	09/28/2014	09/27/2017
HHSN272201100035C	SC011-San-A02	Research Institute at Nationwide	,	Subcontract/Subaward Amendment	09/28/2013	09/27/2019	09/22/2017	Approved	10/03/2017	$20,831.00	09/28/2013	09/27/2019
HHSN272201100035C	SC011-San-A03	The Research Institute at Nationwide Children's	,	Subcontract/Subaward Amendment	09/28/2013	05/15/2019	11/09/2018	Approved	11/26/2018	$260.00	09/28/2013	05/15/2019
HHSN272201100035C	SC011-San-A04	The Research Institute at Nationwide Children's	Sanchez, Pablo	Subcontract/Subaward Amendment	02/01/2012	03/31/2020	01/21/2020	Approved	01/24/2020	$0.00	02/01/2012	03/31/2020
HHSN272201100035C	SC012-Har	Baylor College of Medicine	Harrison, Gail Demmler	Subcontract/Subaward	07/01/2017	09/27/2019	03/07/2018	Approved	03/14/2018	$52,529.00	06/01/2017	05/15/2018
HHSN272201100035C	SC012-Har-A01	Baylor College of Medicine	,	Subcontract/Subaward Amendment	06/01/2017	01/31/2020	12/18/2018	Approved	12/19/2018	($10,477.00)	06/01/2017	01/31/2020
HHSN272201100035C	SC012-Har-A02	Baylor College of Medicine	,	Subcontract/Subaward Amendment	06/01/2017	03/31/2020	02/21/2020	Approved	02/26/2020	$0.00	06/01/2017	03/31/2020

Appendix C DSMB Summary of Recommendations and Minutes

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

National Institutes of Health
Bethesda, MD 20892

Division of Microbiology and Infectious Diseases
National Institute of Allergy and Infectious Diseases
5601 Fishers Lane
Bethesda MD 20892

Protocol 11-0069, A Phase II Randomized And Controlled Investigation Of Six Weeks Of Oral Valganciclovir Therapy In Infants And Children With Congenital Cytomegalovirus Infection And Hearing Loss

The **Data and Safety Monitoring Board (DSMB)** met on: 12-Apr-19 for a Data Review Meeting that included: review current Study Status and Safety Summary Report and determine the timeline for future DSMB meetings.

Materials provided for review:

- Agenda: 11-0069 DSMB DRM Agenda Final v1.0 12Apr19.docx
- Contact List: 11-0069 DSMB Contact List v6.0 04Apr19.docx
- Safety Summary Report: 11-0069 DSMB Closed Safety Summary Report 08Nov18-PW.pdf
- Safety Summary Report: 11-0069 DSMB Open Safety Summary Report 08Nov18.pdf
- Line Listing: 11-0069 SAE Line Listing from 28Nov17 to 04Apr19.pdf
- SAE Narratives: 11-0069 SAE Narratives from 28Nov17 to 04Apr19.pdf

Recommendations from the DSMB:

- No safety concerns were identified.
- The study may continue as it is currently being conducted; no changes are recommended at this time.
- For the next DSMB meeting please provide the following:
  - In the Open Safety Summary Report:
    - The date(s) magnetic resonance imaging (MRI) scans were done relative to subject enrollment, and the age of the subject at the time of the scan.
  - In the Closed Safety Summary Report:
    - Provide all data available in the case report form (CRF) pertaining to the presenting symptom of seizures.
    - Provide all data available from the CRF pertaining to the presenting symptom of microcephaly.
- The sites should make at least one additional attempt to obtain a head circumference measurement at birth for all subjects where it is unknown or missing on the 08-Nov-18 Safety Summary Reports.
- All available blood, urine and saliva samples available as of 20-Apr-19 should be batched and sent for polymerase chain reaction (PCR) analysis without waiting for the final samples that will be collected in the next three months, and the results provided to the DSMB when available, for electronic review.
- All available blood samples available as of 20-Apr-19 should be batched and sent for valganciclovir drug levels without waiting for the final samples that will be collected in the next three months, and the results provided to the DSMB when available, for electronic review.

Charles Grose
Charles Grose, MD
DSMB Chair

April 16, 2019
Date

CONFIDENTIAL

Protocol 11-0069, Version 1.0, 12-Apr-19
Page 1 of 2

Division of Microbiology and Infectious Diseases (DMID) has reviewed and agrees with the recommendations.

Walla L. Dempsey -S

Digitally signed by Walla L. Dempsey -S
Date: 2019.04.17 12:08:20 -04'00'

Walla Dempsey, PhD
Clinical Project Manager, DMID

Date

Appendix D IRB Approvals and FWA Numbers

DMID 11-0069 Valgan Toddler

PI	Site Name	Initial IRB Approval	FWA Number	FWA Expiration
Ahmed, Amina	The Charlotte-Mecklenburg Hospital Authority Carolinas Medical Center Levine Children's Hospital	2/18/2015	00000387	12/19/2023
Bernatoniene, Jola	Bristol Royal Hospital for Children	7/21/2015	00000523	7/3/2024
Caserta, Mary	University of Rochester	9/26/2014	00009386	8/28/2023
DeBiasi, Roberta	Children's Research Institute	9/24/2014	00004487	10/10/2023
Demmler-Harrison,	Baylor College of Medicine - Texas Children's Hospital - Houston	2/6/2018	00000286	8/18/2022
Dennehy, Penelop	Rhode Island Hospital	11/18/2014	00000056	1/4/2021
Emonts, Marieke	Royal Victoria Infirmary	5/15/2015	00000487	8/22/2022
Faust, Saul	University Hospital Southampton NHS Foundation Trust (UHS NHS FT)	11/25/2015	00001753	8/26/2022
Hackett, Scott	Birmingham Heartlands Hospital - (University Hospitals NHS Foundation Trust)	7/10/2015	00005179	4/1/2024
Kelly, Dominic	Oxford Radcliffe Hospital NHSF Trust	6/26/2015	00006200	6/6/2023
Kimberlin, David	University of Alabama at Birmingham	9/26/2014	00005960	11/8/2021
Klein, Nigel	Great Ormond Street Hospital	3/3/2015	00007324	7/22/2024
McMaster, Paddy	The Pennine Acute Hospitals NHS Trust, Manchester	12/5/2016	00017304	9/14/2021
Sanchez, Pablo	Ohio State University - Nationwide Children's Hospital	10/21/2014	00002860	6/15/2021
Shackley, Fiona	Sheffield Children's NHS Foundation Trust		00024955	12/5/2021
Sharland, Mike	St. George's NHS Trust	4/16/2015	00024381	7/31/2020
Sood, Sunil	The Feinstein Institute for Medical Research	9/26/2014	00002505	4/25/2022
Storch, Gregory	Washington University St Louis	5/6/2014	00002281	3/27/2023

Appendix E Enrollment

Program Director/Principal Investigator (Last, First, Middle): Kimberlin, David, W.

Inclusion Enrollment Report

This report format should NOT be used for data collection from study participants.

Study Title: A Phase II, Randomized, Placebo-Controlled, Blinded Investigation of Six Weeks of Oral Valganciclovir Therapy Versus Placebo in Infants with Congenital Cytomegalovirus

Total Enrollment: 35 **Protocol Number:** 11-0069

Grant Number: HHSN272201100035C

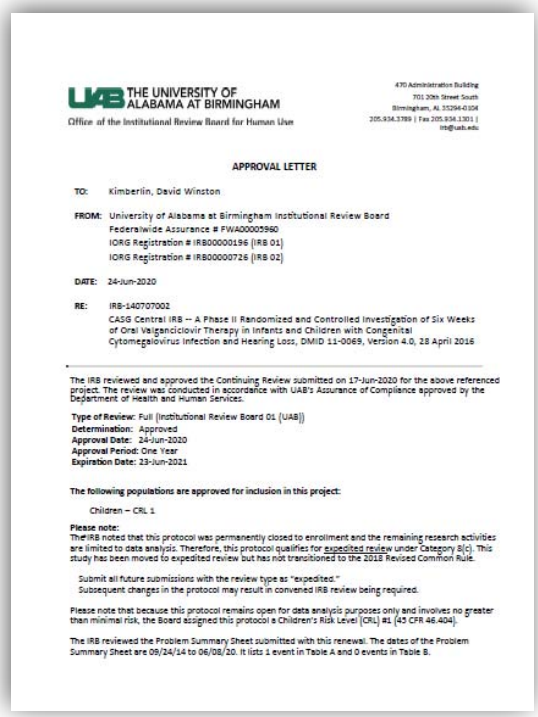
PART A. TOTAL ENROLLMENT REPORT: Number of Subjects Enrolled to Date (Cumulative) by Ethnicity and Race				
Ethnic Category	**Females**	**Males**	**Sex/Gender Unknown or Not Reported**	**Total**
Hispanic or Latino	0	0	0	0 **
Not Hispanic or Latino	12	20	0	32
Unknown (individuals not reporting ethnicity)	2	1	0	3
Ethnic Category: Total of All Subjects*	14	21	0	35 *
Racial Categories				
American Indian/Alaska Native	0	0	0	0
Asian	2	1	0	3
Native Hawaiian or Other Pacific Islander	0	0	0	0
Black or African American	2	2	0	4
White	9	18	0	27
More Than One Race	1	0	0	1
Unknown or Not Reported	0	0	0	0
Racial Categories: Total of All Subjects*	14	21	0	35 *

PART B. HISPANIC ENROLLMENT REPORT: Number of Hispanics or Latinos Enrolled to Date (Cumulative)				
Racial Categories	**Females**	**Males**	**Sex/Gender Unknown or Not Reported**	**Total**
American Indian or Alaska Native	0	0	0	0
Asian	0	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0	0
Black or African American	0	0	0	0
White	0	0	0	0
More Than One Race	0	0	0	0
Unknown or Not Reported	0	0	0	0
Racial Categories: Total of Hispanics or Latinos**	0	0	0	0 **

* These totals must agree.
** These totals must agree.

0925-0001/0002 (Rev. 08/12) Page 1 Inclusion Enrollment Report Format Page

Appendix F IRB Approval Letter



THE UNIVERSITY OF ALABAMA AT BIRMINGHAM
Office of the Institutional Review Board for Human Use

470 Administration Building
701 20th Street South
Birmingham, AL 35294-0104
205.934.3789 | Fax 205.934.1301 |
irb@uab.edu

APPROVAL LETTER

TO: Kimberlin, David Winston

FROM: University of Alabama at Birmingham Institutional Review Board
Federalwide Assurance # FWA00005960
IORG Registration # IRB00000196 (IRB 01)
IORG Registration # IRB00000726 (IRB 02)

DATE: 24-Jun-2020

RE: IRB-140707002
CASG Central IRB -- A Phase II Randomized and Controlled Investigation of Six Weeks of Oral Valganciclovir Therapy in Infants and Children with Congenital Cytomegalovirus Infection and Hearing Loss, DMID 11-0069, Version 4.0, 28 April 2016

The IRB reviewed and approved the Continuing Review submitted on 17-Jun-2020 for the above referenced project. The review was conducted in accordance with UAB's Assurance of Compliance approved by the Department of Health and Human Services.

Type of Review: Full (Institutional Review Board 01 (UAB))
Determination: Approved
Approval Date: 24-Jun-2020
Approval Period: One Year
Expiration Date: 23-Jun-2021

The following populations are approved for inclusion in this project:

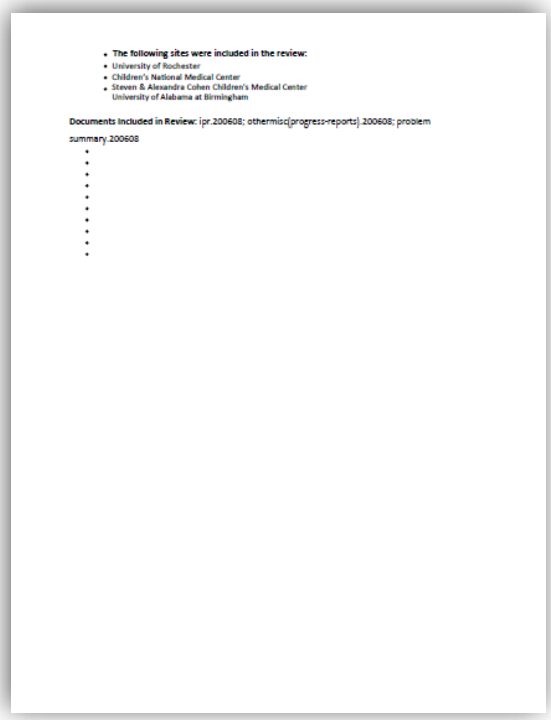
Children – CRL 1

Please note:
The IRB noted that this protocol was permanently closed to enrollment and the remaining research activities are limited to data analysis. Therefore, this protocol qualifies for expedited review under Category 8(c). This study has been moved to expedited review but has not transitioned to the 2018 Revised Common Rule.

Submit all future submissions with the review type as "expedited."
Subsequent changes in the protocol may result in convened IRB review being required.

Please note that because this protocol remains open for data analysis purposes only and involves no greater than minimal risk, the Board assigned this protocol a Children's Risk Level (CRL) #1 (45 CFR 46.404).

The IRB reviewed the Problem Summary Sheet submitted with this renewal. The dates of the Problem Summary Sheet are 09/24/14 to 06/08/20. It lists 1 event in Table A and 0 events in Table B.



- **The following sites were included in the review:**
- University of Rochester
- Children's National Medical Center
- Steven & Alexandra Cohen Children's Medical Center
  University of Alabama at Birmingham

Documents included in Review: ipr.200608; othermisc[progress-reports].200608; problem summary.200608

Appendix G: List of Tables and Figures

Table 1a: Investigators / Centers

Site	Site Name	Country	PI
001	UAB	US	Kimberlin, David
002	Baylor College of Medicine, Houston, TX	US	Demmler-Harrison, Gail
003	Univ of Utah	US	Amphofo, Krow
019	Univ of Rochester	US	Caserta, Mary
048	Washington Univ St. Louis	US	Storch, Gregory
050	Johns Hopkins SOM	US	Boger, Ravit
086	Carolinas Med Ctr- Charlotte	US	Ahmed, Amina
157	Steven and Alexandra Cohen Children's Med Ctr	US	Sood, Sunil
163	Rhode Island Hospital	US	Dennehy, Penelope
185	North Shore-Manhasset Health System	US	Sood, Sunil
273	Children's Nat Med Ctr-Wash DC	US	DeBiasi, Roberta
280	UK-Newcastle	UK	Emonts, Marieke
281	UK-St. George	UK	Sharland, Mike
282	UK-Oxford	UK	Kelly, Dominic
283	UK-Bristol	UK	Bernatoniene, Jolanta
285	UK-Birmingham	UK	Hackett, Scott
286	UK-Southampton	UK	Faust, Saul
292	UK-Great Ormond Street Hospital	UK	Klein, Nigel
294	Nationwide Children's Hospital	US	Sanchez, Pablo
296	UK-North Manchester General Hospital	UK	McMaster, Paddy
297	UK-Sheffield Children's Hospital	UK	Shackley, Fiona

Figure 1: Participant Flow Diagram

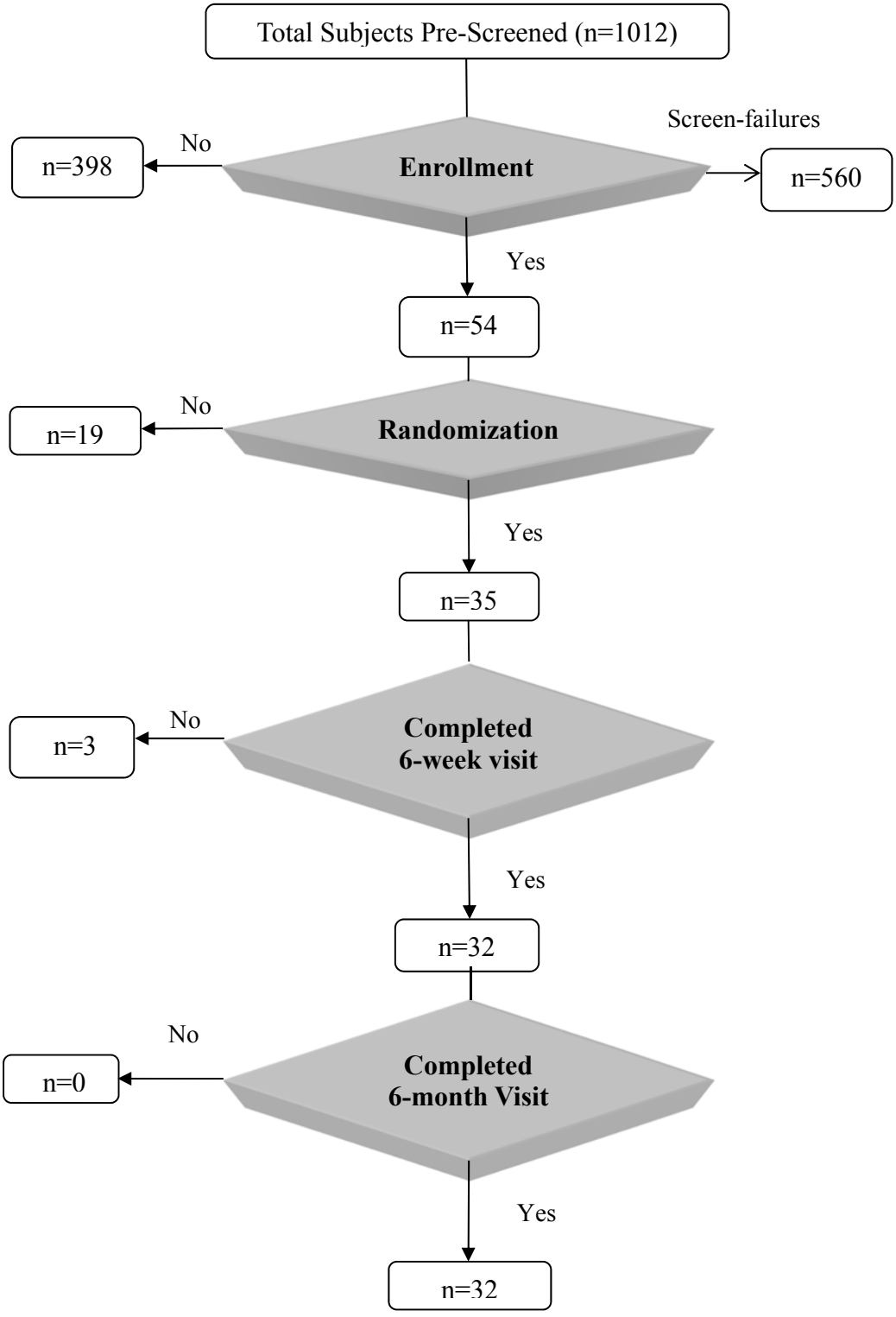


Table 1b: Randomization to Blinded Therapy Groups

Therapy Group	N	%
Active	17	48.57
Placebo	18	51.43
Total Randomized	35	100.0

Table 2a: Distribution of Subjects by Study Site and Therapy Group, and Overall*

							Therapy Group			
		Enrolled	Withdrawn Before Randomization**		Randomized		Active		Placebo	
Site ID Number	Site Location	N	N	%	N	%	N	%	N	%
001	UAB	4	2	10.5	2	5.7	0	0	2	11.1
002	Baylor College of Medicine, Houston, TX	2	1	5.3	1	2.9	1	5.9	0	0
003	Univ of Utah	0	0	0	0	0	0	0	0	0
019	Univ of Rochester	5	3	15.8	2	5.7	0	0	2	11.1
048	Washington Univ St. Louis	1	1	5.3	0	0	0	0	0	0
050	Johns Hopkins SOM	0	0	0	0	0	0	0	0	0
086	Carolinas Med Ctr- Charlotte	2	0	0	2	5.7	1	5.9	1	5.6
157	Steven and Alexandra Cohen Children's Med Ctr	0	0	0	0	0	0	0	0	0
163	Rhode Island Hospital	1	1	5.3	0	0	0	0	0	0
185	North Shore-Manhasset Health System	0	0	0	0	0	0	0	0	0
273	Children's Nat Med Ctr-Wash DC	11	8	42.1	3	8.6	1	5.9	2	11.1
280	UK-Royal Victoria Infirmary at Newcastle	5	0	0	5	14.3	3	17.6	2	11.1
281	UK-St. George	2	0	0	2	5.7	1	5.9	1	5.6
282	UK-Oxford	2	2	10.5	0	0	0	0	0	0
283	UK-Bristol	5	0	0	5	14.3	3	17.6	2	11.1
285	UK-Birmingham	1	0	0	1	2.9	0	0	1	5.6
286	UK-Southampton	4	1	5.3	3	8.6	2	11.8	1	5.6
292	UK-Great Ormond Street Hospital	4	0	0	4	11.4	1	5.9	3	16.7
294	Nationwide Children's Hospital	1	0	0	1	2.9	1	5.9	0	0
296	North Manchester General Hospital	3	0	0	3	8.6	2	11.8	1	5.6
297	Sheffield Children's Hospital	1	0	0	1	2.9	1	5.9	0	0
Total		**54**	**19**	**100**	**35**	**100**	**17**	**100**	**18**	**100**

* %: uses Column total as the denominator.
** 19 subjects were enrolled but were not eligible for randomization

Table 2b: Reasons for withdrawal before randomization

Reason	N (%)
Subject Guthrie card/CMV negative	11 (57.9%)
Parents declined participation	2 (10.5%)
Subject unable to participate within required window	3 (15.8%)
Subject otherwise ineligible for participation *	3 (15.8%)
TOTAL	19 (100%)

*** Subject otherwise ineligible for participation**

Screening ID	Site	Ineligible Reason
1EWW	273	Family did not obtain bloodspot for testing
1JDL	273	Cochlear implant procedure scheduled within two weeks of when subject would start study drug.
5ZX7	163	Subject was ineligible to participate in the protocol

Table 2c: Site Performance in Enrollment

Table 2c.i Enrollment Rate by Site

Site ID Number	Failed Screening	Enrolled	Randomized	Months Recruiting	Number of Screened Subjects per Month[1]	Number of Enrolled Subjects per Month[2]	Number of Randomized Subjects per Month[3]
001	9 (1.6%)	4 (7.4%)	2 (5.7%)	52	0.25	0.08	0.04
002	115(20.5%)	2 (3.7%)	1 (2.9%)	14	8.36	0.14	0.07
003 *	0 (0%)	0 (0%)	0	25	0.00	0.00	0.00
019	4 (0.7%)	5 (9.3%)	2 (5.7%)	51	0.18	0.10	0.04
048	1 (0.2%)	1 (1.9%)	0	53	0.04	0.02	0.00
050 *	11 (2%)	0 (0%)	0	34	0.32	0.00	0.00
086	25 (4.5%)	2 (3.7%)	2 (5.7%)	52	0.52	0.04	0.04
157	4 (0.7%)	0 (0%)	0	52	0.08	0.00	0.00
163 *	7 (1.3%)	1 (1.9%)	0	25	0.32	0.04	0.00
185	0 (0%)	0 (0%)	0	52	0.00	0.00	0.00
273	38 (6.8%)	11 (20.4%)	3 (8.6%)	47	1.04	0.23	0.06
280	106(18.9%)	5 (9.3%)	5 (14.3%)	49	2.27	0.10	0.10
281	37 (6.6%)	2 (3.7%)	2 (5.7%)	47	0.83	0.04	0.04
282	19 (3.4%)	2 (3.7%)	0	46	0.46	0.04	0.00
283	29 (5.2%)	5 (9.3%)	5 (14.3%)	46	0.74	0.11	0.11
285	57 (10.2%)	1 (1.9%)	1 (2.9%)	46	1.26	0.02	0.02
286	5 (0.9%)	4 (7.4%)	3 (8.6%)	43	0.21	0.09	0.07
292	32 (5.7%)	4 (7.4%)	4 (11.4%)	49	0.73	0.08	0.08
294	25 (4.5%)	1 (1.9%)	1 (2.9%)	42	0.62	0.02	0.02
296	31 (5.5%)	3 (5.6%)	3 (8.6%)	31	1.10	0.10	0.10
297	5 (0.9%)	1 (1.9%)	1 (2.9%)	27	0.22	0.04	0.04
Total	560(100%)	54 (100%)	35 (100%)	883	0.70	0.06	0.04

[1]Number of Screened Subjects per Month is the total number of screened patients (those that have failed screening plus those enrolled) divided by the number of months the site has been recruiting.
[2]Number of Enrolled Subjects per Month is the total number of enrolled subjects divided by the number of months the site has been recruiting.
[3]Number of Randomized Subjects per Month is the total number of randomized subjects divided by the number of months the site has been recruiting.

* Site closed to enrollment. See Table 2c.ii. for details.

Table 2c.ii Sites Closed to Enrollment before study closure

Site ID Number	Date Closed	Reason for Site Closure
003	9/11/2016	Closed due to inactivity
050	5/9/2018	PI relocated and the study was not allowed to be transferred by the UAB CU due to the time required to activate a site and the current BAA contract end date.
163	8/3/2018	PI has personal issues and had to re-evaluate her commitment to research

Figure 2: Rate of Enrollment

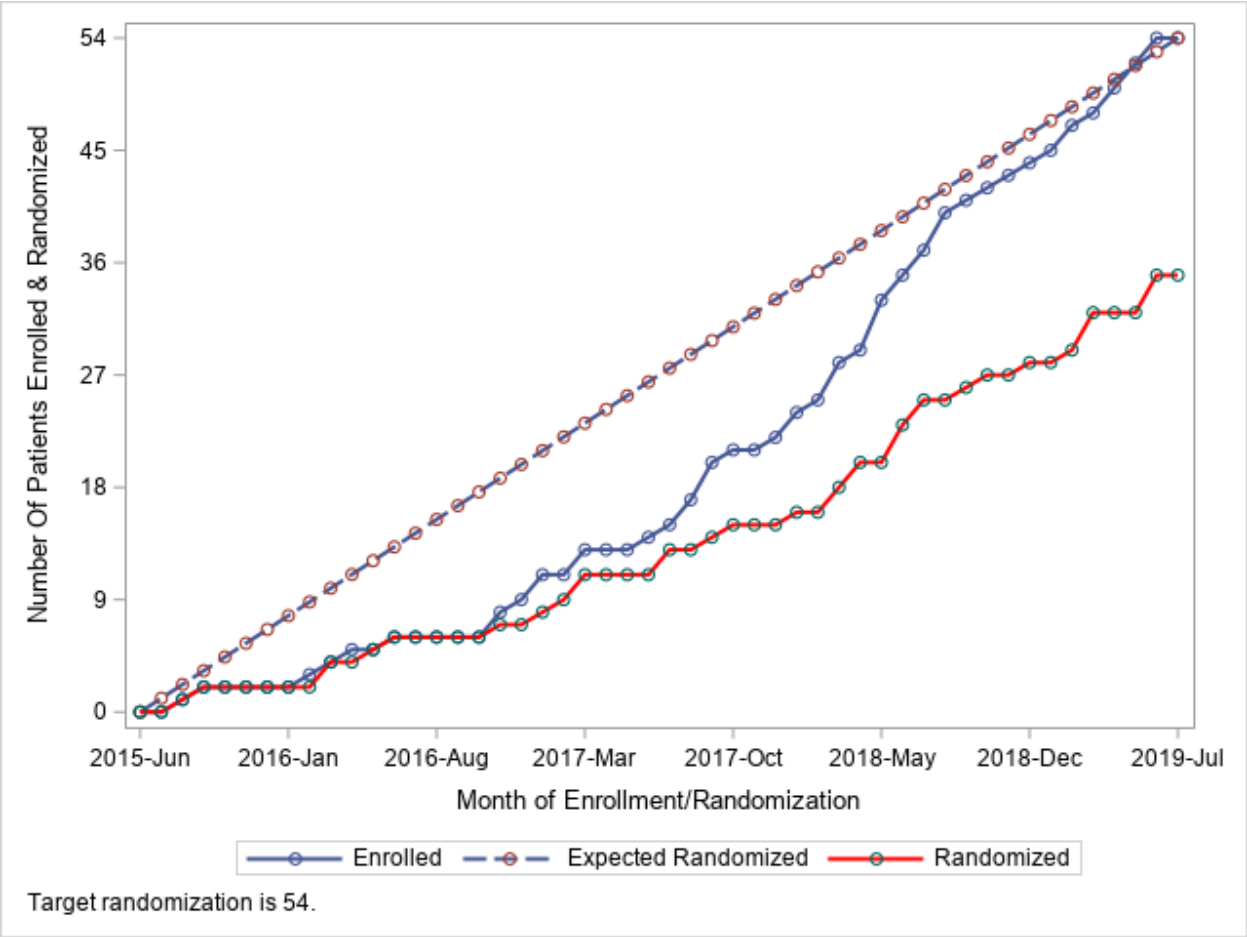


Table 3: Subjects Withdrawn after Randomization from Study

	Randomized	Termination Status			Termination Reason			
All Sites	# Enrolled	# Continuing Participation	# Completed Participation	# Not Completed Participation/ Dropout	# Withdrawal of consent	# Due to Protocol Deviation	# Required treatment outside protocol	Other Reason*
All Sites	35 (100%)	0 (0%)	32 (100%)	3 (100%)	3 (100%)	0 (0%)	1 (100%)	2 (100%)
001	2 (5.7%)	0 (0%)	2 (6.3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
002	1 (2.9%)	0 (0%)	0 (0%)	1 (33.3%)	1 (33.3%)	0 (0%)	0 (0%)	1 (50%)
019	2 (5.7%)	0 (0%)	2 (6.3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
086	2 (5.7%)	0 (0%)	2 (6.3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
273	3 (8.6%)	0 (0%)	3 (9.4%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
280	5 (14.3%)	0 (0%)	5 (15.6%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
281	2 (5.7%)	0 (0%)	2 (6.3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
283	5 (14.3%)	0 (0%)	4 (12.5%)	1 (33.3%)	1 (33.3%)	0 (0%)	1 (100%)	1 (50%)
285	1 (2.9%)	0 (0%)	1 (3.1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
286	3 (8.6%)	0 (0%)	3 (9.4%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
292	4 (11.4%)	0 (0%)	4 (12.5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
294	1 (2.9%)	0 (0%)	1 (3.1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
296	3 (8.6%)	0 (0%)	2 (6.3%)	1 (33.3%)	1 (33.3%)	0 (0%)	0 (0%)	0 (0%)
297	1 (2.9%)	0 (0%)	1 (3.1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

***Listing of Other Reasons**

obs	Site #	PID #1	PID #2	Other Reason specify
1	002	17EH	97699	Family Member illness
2	283	1K5D	72398	severe hearing loss boarderline eligible

Table 4a: Subject-specific Protocol Deviations by Category[#]

	Enroll-ment	Protocol Deviations	Protocol Deviation Results	Protocol Deviation Categories *						
All Sites	# Enrolled	# of Protocol Deviations	# Resulting in Terminations	Eligibility/ enrollment	Vaccination schedule	Follow-up visit schedule	Protocol procedure/ assessment	Vaccination /dosing administration	Blinding policy/ procedure	Other*
All Sites	35 (100%)	101 (100%)	0 (0%)	7 (6.9%)	0 (0%)	7 (6.9%)	81 (80.2%)	3 (3%)	0 (0%)	3 (3%)
001	2 (5.7%)	4 (4%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)	3 (3%)	0 (0%)	0 (0%)	0 (0%)
002	1 (2.9%)	2 (2%)	0 (0%)	0 (0%)	0 (0%)	2 (2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
019	2 (5.7%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)
086	2 (5.7%)	3 (3%)	0 (0%)	2 (2%)	0 (0%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
273	3 (8.6%)	4 (4%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)	3 (3%)	0 (0%)	0 (0%)	0 (0%)
280	5 (14.3%)	9 (8.9%)	0 (0%)	2 (2%)	0 (0%)	1 (1%)	6 (5.9%)	0 (0%)	0 (0%)	0 (0%)
281	2 (5.7%)	5 (5%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)	3 (3%)	0 (0%)	0 (0%)	1 (1%)
283	5 (14.3%)	6 (5.9%)	0 (0%)	1 (1%)	0 (0%)	0 (0%)	3 (3%)	1 (1%)	0 (0%)	1 (1%)
285	1 (2.9%)	2 (2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)	1 (1%)	0 (0%)	0 (0%)
286	3 (8.6%)	13 (12.9%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	11 (10.9%)	1 (1%)	0 (0%)	1 (1%)
292	4 (11.4%)	14 (13.9%)	0 (0%)	2 (2%)	0 (0%)	0 (0%)	12 (11.9%)	0 (0%)	0 (0%)	0 (0%)
294	1 (2.9%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)
296	3 (8.6%)	37 (36.6%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	37 (36.6%)	0 (0%)	0 (0%)	0 (0%)
297	1 (2.9%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Deviation Categories indicate <u>what portion of the protocol has been violated.</u>

***Listing of Other Categories:**

obs	Site #	PID #1	PID #2	Date of Deviation	Other Category Specify
1	283	13TX	23501	01/19/2018	laboratory sample storage
2	286	2ZGU	37898	04/08/2019	sample collection
3	281	7HG6	72893	11/15/2018	Dosing equipment

Table 4b Subject-specific Protocol Deviations by Reason

	Enroll-ment	Protocol Deviations	Protocol Deviation Results	Protocol Deviation Reasons ¥							
All Sites	# Enrolled	# of Protocol Deviations	# Resulting in Terminations	Subject/ Parent/ Guardian Illness	Subject/ Parent/ Guardian Unable to Comply	Subject/ Parent/ Guardian Refusal	Pharmacy error	Laboratory error	Investigator / study decision	Clinic error	Other*
All Sites	35 (100%)	101 (100%)	0 (0%)	4 (4%)	17 (16.8%)	6 (5.9%)	23 (22.8%)	18 (17.8%)	6 (5.9%)	15 (14.9%)	12 (11.9%)
001	2 (5.7%)	4 (4%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	4 (4%)	0 (0%)
002	1 (2.9%)	2 (2%)	0 (0%)	2 (2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
019	2 (5.7%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)	0 (0%)
086	2 (5.7%)	3 (3%)	0 (0%)	0 (0%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (2%)	0 (0%)
273	3 (8.6%)	4 (4%)	0 (0%)	0 (0%)	1 (1%)	0 (0%)	0 (0%)	2 (2%)	1 (1%)	0 (0%)	0 (0%)
280	5 (14.3%)	9 (8.9%)	0 (0%)	0 (0%)	4 (4%)	0 (0%)	0 (0%)	0 (0%)	2 (2%)	0 (0%)	3 (3%)
281	2 (5.7%)	5 (5%)	0 (0%)	1 (1%)	0 (0%)	0 (0%)	1 (1%)	1 (1%)	0 (0%)	1 (1%)	1 (1%)
283	5 (14.3%)	6 (5.9%)	0 (0%)	0 (0%)	1 (1%)	0 (0%)	0 (0%)	1 (1%)	0 (0%)	0 (0%)	4 (4%)
285	1 (2.9%)	2 (2%)	0 (0%)	0 (0%)	2 (2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
286	3 (8.6%)	13 (12.9%)	0 (0%)	1 (1%)	7 (6.9%)	0 (0%)	0 (0%)	1 (1%)	1 (1%)	2 (2%)	1 (1%)
292	4 (11.4%)	14 (13.9%)	0 (0%)	0 (0%)	0 (0%)	5 (5%)	0 (0%)	1 (1%)	2 (2%)	3 (3%)	3 (3%)
294	1 (2.9%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)
296	3 (8.6%)	37 (36.6%)	0 (0%)	0 (0%)	1 (1%)	1 (1%)	22 (21.8%)	11 (10.9%)	0 (0%)	2 (2%)	0 (0%)
297	1 (2.9%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

***Listing of Other Reasons:**

obs	Site #	PID #1	PID #2	Date of Deviation	Other Reason specify
1	283	13TX	23501	01/19/2018	power cut
2	283	1K5D	72398	03/05/2018	This was due to the date the parents could attend the appointment at short notice.
3	292	2674	49683	07/30/2018	Patient difficut to bleed - unable to obtain enough blood for all samples required, so safety bloods prioritised. Unethical to continue attempting to bleed the patient.
4	292	2674	49683	07/08/2018	Not explicitly requested in the protocol.
5	292	2674	49683	06/28/2018	Site labs do not complete Bands % as part of FBC analysis.
6	283	2AH3	83011	03/25/2019	Participants parent did not initial to indicate whether they will permit their child's specimens to be used in future research.
7	286	2ZGU	37898	06/24/2019	no urine sample collected at study month visit 4
8	283	5NTX	59440	05/25/2018	blood sample clotted in the bottle.
9	280	64X3	95929	05/01/2019	4th audiology assessment completed out of window due to 3 previous assessments prior.
10	281	7HG6	72893	12/28/2018	Unable to collect enough blood, two attempts made
11	280	7QCJ	14908	09/06/2017	Admin consent form.
12	280	7QCJ	14908	09/20/2017	Admin.

Table 4c: Listing of Action/Steps: Subject-specific PDs

PID	Site	Date of Deviation	Deviation	Steps Taken
974K	296	4/13/2018	Study drug stored in ward's fridge as patient is an inpatient on NICU. Temperature recorded daily plus maximum and minimum reached in a 24 hour period. Maximum temperature recorded 8.5 degree centigrade.	UK study coordinator informed. Advised that the temperature deviation would not affect the stability of the study drug.
974K	296	4/14/2018	Study drug stored in ward's fridge as patient is an inpatient on NICU. Temperature recorded daily plus maximum and minimum reached in a 24 hour period. Maximum temperature recorded 9.3 degree centigrade.	UK study coordinator informed. Advised that the temperature deviation would not affect the stability of the study drug.
974K	296	4/17/2018	Study drug stored in ward's fridge as patient is an inpatient on NICU. Temperature recorded daily plus maximum and minimum reached in a 24 hour period. Maximum temperature recorded 8.1 degree centigrade.	UK study coordinator informed. Advised that the temperature deviation would not affect the stability of the study drug.
974K	296	4/30/2018	Study drug stored in ward's fridge as patient is an inpatient on NICU. Temperature recorded daily plus maximum and minimum reached in a 24 hour period. Maximum temperature reached 8.4 degree centigrade.	Previous communication with UK study coordinator advised that temperature deviation would not affect the stability of the study drug. Pharmacy and UK study coordinator aware of ongoing issue due to the ambient temperature of the neonatal unit affecting fridge temperature briefly when fridge is opened to obtain study drug.
974K	296	5/7/2018	IMP – fridge temp deviation 11.8 degree centigrade	As previously stated.
974K	296	4/23/2018	Study drug stored in ward's fridge as patient is an inpatient on NICU. Temperature recorded daily plus maximum and minimum reached in a 24 hour period. Maximum temperature recorded 8.4 degree centigrade.	UK study coordinator informed. Advised that the temperature deviation would not affect the stability of the study drug.
974K	296	4/24/2018	Study drug stored in ward's fridge as patient is an inpatient on NICU. Temperature recorded daily plus maximum and minimum reached in a 24 hour period. Maximum temperature recorded 8.7 degree centigrade.	UK study coordinator informed. Advised that the temperature deviation would not affect the stability of the study drug.

Table 4c: Listing of Action/Steps: Subject-specific PDs (continued)

PID	Site	Date of Deviation	Deviation	Steps Taken
974K	296	4/26/2018	Study drug stored in ward's fridge as patient is an inpatient on NICU. Temperature recorded daily plus maximum and minimum reached in a 24 hour period. Maximum temperature recorded 9.1 degree centigrade.	UK study coordinator informed. Advised that the temperature deviation would not affect the stability of the study drug.
974K	296	5/2/2018	Study drug stored in ward's fridge as patient is an inpatient on NICU. Temperature recorded daily plus maximum and minimum reached in a 24 hour period. Maximum temperature reached 8.1 degree centigrade.	Previous communication with UK study coordinator advised that temperature deviation would not affect the stability of the study drug. Pharmacy and UK study coordinator aware of ongoing issue due to the ambient temperature of the neonatal unit affecting fridge temperature briefly when fridge is opened to obtain study drug.
974K	296	5/8/2018	IMP – fridge temp deviation 8.5 degree centigrade	As previously stated.
974K	296	5/9/2018	IMP – fridge temp deviation 10.2 degree centigrade	As previously stated.
974K	296	5/15/2018	IMP – fridge temp deviation 9.0 degree centigrade	As previously stated.
974K	296	5/17/2018	IMP – fridge temp deviation 9.1 degree centigrade	As previously stated.
974K	296	4/27/2018	Study drug stored in ward's fridge as patient is an inpatient on NICU. Temperature recorded daily plus maximum and minimum reached in a 24 hour period. Maximum temperature reached 9.1 degree centigrade.	Previous communication with UK study coordinator advised that temperature deviation would not affect the stability of the study drug. Pharmacy and UK study coordinator aware of ongoing issue due to the ambient temperature of the neonatal unit affecting fridge temperature briefly when fridge is opened to obtain study drug.

Table 4c: Listing of Action/Steps: Subject-specific PDs (continued)

PID	Site	Date of Deviation	Deviation	Steps Taken
974K	296	5/5/2018	Study drug stored in ward's fridge as patient is an inpatient on NICU. Temperature recorded daily plus maximum and minimum reached in a 24 hour period. Maximum temperature reached 11.8 degree centigrade.	As previously stated.
974K	296	5/20/2018	IMP - fridge temp deviation 8.6 degree centigrade	As previously stated
974K	296	4/19/2018	Freezer temperature, location for stored research specimens increased to approx. -50 degree centigrade.	Lab staff are aware of increase in freezer temperature - alarm controlled.
974K	296	4/24/2018	Freezer temperature, location for stored research samples increased to approx. -52 degree centigrade.	Lab staff are aware of increased freezer temperature - alarm controlled.
974K	296	6/19/2018	Freezer temperature, location for stored research samples increased to - 57 degree centigrade.	Lab staff are aware of increase in freezer temperature - alarm controlled. Lab staff feel that the increases are probably due to opening freezer door to access other specimens.
974K	296	6/26/2018	Freezer temperature, location for stored research samples increased to - 57 degree centigrade.	Lab staff are aware of increase in freezer temperature - alarm controlled. Lab staff feel that the increases are probably due to opening freezer door to access other specimens.
974K	296	7/16/2018	Freezer temperature, location for stored research samples increased to - 35 degree centigrade.	Lab staff are aware of increase in freezer temperature - alarm controlled. Lab staff feel that the increases are probably due to opening freezer door to access other specimens.
974K	296	10/10/2018	Unable to obtain month 6 hearing assessments. Audiology appointment booked for 9th Oct 2018. Patient unable to attend as was admitted to hospital acutely. Not able to perform hearing assement while in hospital. Appointment rebooked for 5th Nov 2018 (within study schedule window). Patient unable to attend as still an inpatient.	Not applicable. Protocol deviation occurred due to exceptional circumstances.

Table 4c: Listing of Action/Steps: Subject-specific PDs (continued)

PID	Site	Date of Deviation	Deviation	Steps Taken
974K	296	9/10/2018	Freezer temperature where study samples are stored increased to - 49 degree centigrade.	The increase in temperature appears to be brief and it is thought that this happened when freezer door is opened to access samples. Freezer does alarm when temperature increases to - 60 degree centigrade alarmed.
974K	296	4/12/2018	Creatinine clearance not done on day 1. It was discovered as a protocol deviation on 04/17/2018. No length taken on visit 1.	CrCl calculated on 04/17/2018 using available information i.e. length on 04/17/2018, Scr on 04/12/2018. Unable to obtain information re. lab method of Scr determination therefore calculated with 'non-traceable method - CrCl estimated as 43ml/min/1.73m2. Next scheduled dose of IMP reduced to 8mg/kg. CrCl repeated the following day 04/18/2018 when information re. method of Scr determination was available as 'IDMS traceable'. Repeat Scr and length unchanged - CrCl calculated using 'IDMS traceable' method - 32.64 ml/min/1.73m2 - study drug prescribed at 8mg/kg once a day. Site PI has discussed the situation with the UK CI. For preventive Action, all staff have revisited and discussed the protocol procedures again.
974K	296	4/25/2018	No temperature controlled centrifuge available at site. PK samples centrifuged at room temperature.	Advice sought from US & UK coordinating centre. Advised by the PK specialist to process the sample in a non-refrigerated centrifuge.
1YEM	296	6/12/2019	Parent omitted to initial storage of specimens for Future use on the consent form on the day of consent in error. Not noticed by research staff until parent had gone home.	Parent initialled the omitted section on the next clinic visit 5th July 2019.
974K	296	4/25/2018	Study drug stored in ward's fridge as patient is an inpatient on NICU. Temperature recorded daily plus maximum and minimum reached in a 24 hour period. Maximum temperature recorded 8.7 degree centigrade.	UK study coordinator informed. Advised that the temperature deviation would not affect the stability of the study drug.

Table 4c: Listing of Action/Steps: Subject-specific PDs (continued)

PID	Site	Date of Deviation	Deviation	Steps Taken
974K	296	5/8/2018	No temperature controlled centrifuge available at site. PK sample centrifuged at room temperature.	Advice sought from US & UK coordinating centre. Advised by the PK specialist to process the sample in a non-refrigerated centrifuge.
974K	296	5/10/2018	IMP – fridge temp deviation 8.6 degree centigrade	As previously stated.
974K	296	5/16/2018	IMP – fridge temp deviation 9.0 degree centigrade	As previously stated.
974K	296	5/13/2018	IMP – fridge temp deviation 9.0 degree centigrade	As previously stated.
974K	296	5/21/2018	IMP - fridge temp deviation 10.4 degree centigrade	As previously stated
974K	296	5/19/2018	IMP - fridge temp deviation 8.5 degree centigrade	As previously stated
974K	296	7/13/2018	Freezer temperature, location for stored research samples increased to - 44 degree centigrade.	Lab staff are aware of increase in freezer temperature - alarm controlled. Lab staff feel that the increases are probably due to opening freezer door to access other specimens.
974K	296	7/13/2018	Freezer temperature, location for stored research samples increased to - 53 degree centigrade.	Lab staff are aware of increase in freezer temperature - alarm controlled. Lab staff feel that the increases are probably due to opening freezer door to access other specimens.
974K	296	9/7/2018	freezer temperature where study samples were stored increased to - 32 degree centigrade.	The increase in temperature appears to be brief and it is thought that this happened when freezer door is opened to access samples. Freezer does alarm when temperature increases to - 60 degree centigrade alarmed.
3RJM	296	7/25/2018	No data was collected on this visit as the parent withdrew her child from the study.	No steps required. Parents have a right to withdraw their child from the study. Data would not be collected from that moment on.

Table 4d Subject-Specific Protocol Deviations resulting in AEs, SAEs, termination or drug interruption in study drug

Result in:	N	% of Total Deviations=100
Adverse Event	0	0
Serious Adverse Event	0	0
Interruption in study drug	3	3
Termination from Study	0	0

Listing of Details on Protocol Deviations Resulting in Interruption in Study Drug

PID #1	PID #2	Site	Date of Randomization	Deviation	Deviation Category	Action Taken	Deviation Date
3UEF	11935	286	10/10/2017	Participant diagnosed with bronchiolitis on 15/11/17. 2x doses missed of study drug on this date due to not feeding well.	Vaccination /dosing administration	N/A	11/15/2017
1KUH	64010	285	06/11/2019	Parent forgot to administer morning dose of medication on 31 July 2019. Only noticed at 15:00 hours; Advised by sponsor to omit dose and continue dosing as per protocol from evening dose	Vaccination /dosing administration	Parents aware of need to dose twice daily; parents using reminders	07/31/2019
17EH	97699	002	06/01/2018	Mother is unable to schedule a follow-up visit. She will be out of town July 2-6th and will have knee surgery the following week. She will be unable to come in and there are no other family members that can bring in the patient	Follow-up visit schedule	Call schedule on July 18th to see how she is recovering and to see if she is willing to come in for a follow up visit.	07/05/2018

Table 5a: Site-specific Protocol Deviations by Category and Reasons

	Enroll-ment	Site-specific Protocol Deviations	Protocol Deviation Categories				Protocol Deviation Reasons ¥				
All Sites	# Enrolled	# of Protocol Deviations	Eligibility/ enrollment	Follow-up visit schedule	Protocol procedure/ assessment	Other	Subject/ Parent/ Guardian Unable to Comply	Pharmacy error	Laboratory error	Clinic error	Other
All Sites	35 (100%)	65 (100%)	0 (0%)	0 (0%)	12 (18.5%)	53 (81.5%)	0 (0%)	0 (0%)	9 (13.8%)	0 (0%)	56 (86.2%)
001	2 (5.7%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
002	1 (2.9%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
019	2 (5.7%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
086	2 (5.7%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
273	3 (8.6%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
280	5 (14.3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
281	2 (5.7%)	4 (6.2%)	0 (0%)	0 (0%)	0 (0%)	4 (6.2%)	0 (0%)	0 (0%)	3 (4.6%)	0 (0%)	1 (1.5%)
283	5 (14.3%)	3 (4.6%)	0 (0%)	0 (0%)	3 (4.6%)	0 (0%)	0 (0%)	0 (0%)	3 (4.6%)	0 (0%)	0 (0%)
285	1 (2.9%)	47 (72.3%)	0 (0%)	0 (0%)	0 (0%)	47 (72.3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	47 (72.3%)
286	3 (8.6%)	2 (3.1%)	0 (0%)	0 (0%)	0 (0%)	2 (3.1%)	0 (0%)	0 (0%)	2 (3.1%)	0 (0%)	0 (0%)
292	4 (11.4%)	9 (13.8%)	0 (0%)	0 (0%)	9 (13.8%)	0 (0%)	0 (0%)	0 (0%)	1 (1.5%)	0 (0%)	8 (12.3%)
294	1 (2.9%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
296	3 (8.6%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
297	1 (2.9%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Table 5b: Listing of Action/Steps: site-specific PDs

Site #	Date of Deviation	Deviation	Action/Step Taken
292	03/30/2016	Samples moved to freezer with no temperature monitoring. Decanted all samples due to expected power outage	Samples decanted in preparation for power outage
292	04/19/2016	Samples being prepared for shipping therefore door repeatedly opened causing temperature deviations	Temperature monitored to pick up any excursion
286	07/05/2016	Freezer temperature excursion warmer than -59 degrees C on 1/21/16, 2/17/16, 4/14/16 ,5/12/16, 5/20/15, and 6/22/16, related to when freezer door was opened to transfer other samples, study samples remained frozen	Freezer will very briefly go out of range when door opened to add other samples, door not open long enough to defrost samples. Also, temperature may appear to go out of range due to the sensors being re-calibrated.
292	01/25/2016	Samples moved to alternative freezer with no temperature monitoring to enable defrosting / cleaning of freezer. Decanted from 22 Jan 2016 to 25 Jan 2016	Freezer temperatures monitored to avoid any excursion affecting samples
292	03/05/2016	Power outage, samples were transferred to another freezer with no temperature monitoring	Freezer temperatures monitored to ensure any deviation is noted
292	03/08/2016	Samples returned to freezer after power outage on 5th march. therefore door opening repeatedly causing temperature deviations	Samples had been decanted from separate freezer so samples remained frozen.
292	03/21/2016	Freezer opened repeatedly to store samples - temperature deviation of max -59.58 c	Temperature of freezer monitored continuously to ensure any deviation is noted straight away
292	06/29/2016	Temperature deviation to -57.99 c	Temperature monitored to ensure any excursion is noted as soon as possible
286	12/07/2017	Door left open and freezer 20 out of range	We cannot assess the impact of the temperature deviation on samples until they are analysed by downstream laboratories. Upon a visual inspection however they were still frozen.
281	02/23/2018	Rooba Kaupayamootoo, Joanne Benne, Nia Al'sammarai, has left the study and therefore we are unable to document their protocol training date	All new staff are keeping a record of their protocol training on the 'Protocol/ Other training Log'

Table 5b: Listing of Action/Steps: site-specific PDs

Site #	Date of Deviation	Deviation	Action/Step Taken
292	11/21/2015	Freezer Max temp -9.92 c - major power outage, samples decanted to alternative freezer with no temperature monitoring	Samples decanted
292	03/04/2016	Samples decanted to alternative freezer with no temperature monitoring to allow for freezer to be defrosted / cleaned	Samples decanted to alternative freezer to allow for defrosting
281	07/10/2019	Freezer deviated out of temperature range for 12 hours. Highest Temperature recorded was -50.8 degrees celsius.	Specimens were moved eventually to a different freezer due to freezers needing defrosting
281	07/11/2019	Freezer deviated out of temperature range for 4 hours and 40 minutes. Highest Temperature recorded was -45 degrees celsius.	Samples eventually moved due to freezer needing defrosting.
285	07/10/2019	Samples stored in a -80C multiuser freezer in the MIDRU Research facility. Temperature monitoring identified a temperature excursion above -59C. Maximum temp -53C Duration of time above -59C = 15 mins from 16:05 to 16:20.	Laboratory staff informed; Research Management informed; Incident report submitted to NHS Trust; Freezer service scheduled
285	07/15/2019	Samples stored in a -80C Multiuser freezer in the MIDRU Research facility. Temperature monitoring identified a temperature excursion above -59C. Maximum temp -55.5C Duration of time above -59C = 10 mins from 12:00 to 12:10	Laboratory staff informed; Research Management informed; Incident report submitted to NHS Trust; Freezer service scheduled
285	07/24/2019	Samples stored in a -80C Multiuser freezer in the MIDRU Research facility. Temperature monitoring identified a temperature excursion above -59C. Maximum temp -48.4C Duration of time above -59C = 5 mins from 13:35 to 13:40	Laboratory staff informed; Research Management informed; Incident submitted to NHS Trust; Freezer service scheduled
285	07/25/2019	Samples stored in a -80C Multiuser freezer in the MIDRU Research facility. Temperature monitoring identified a temperature excursion above -59C. Maximum temp -46.3C Duration of time above -59C = 5 mins from 15:05 to 15:10	Laboratory staff informed; Research Management informed; Incident submitted to NHS Trust; Freezer service scheduled

Table 5b: Listing of Action/Steps: site-specific PDs

Site #	Date of Deviation	Deviation	Action/Step Taken
285	07/26/2019	Samples stored in a -80C Multiuser freezer in the MIDRU Research facility. Temperature monitoring identified a temperature excursion above -59C. Maximum temp -55.1C Duration of time above -59C = 5 mins from 12:25 to 12:30	Laboratory staff informed; Research Management informed; Incident submitted to NHS Trust; Freezer service scheduled
285	07/30/2019	Samples stored in a -80C Multiuser freezer in the MIDRU Research facility. Temperature monitoring identified a temperature excursion above -59C. Maximum temp -43.5C Duration of time above -59C = 10 mins from 10:20 to 10:30	Laboratory staff informed; Research Management informed; Incident submitted to NHS Trust; Freezer service scheduled
285	08/01/2019	Samples stored in a -80C Multiuser freezer in the MIDRU Research facility. Temperature monitoring identified a temperature excursion above -59C. Maximum temp -45.7C Duration of time above -59C = 15 mins from 13:45 to 14:00	Laboratory staff informed; Research management informed; Incident submitted to NHS Trust; Freezer service scheduled.
281	03/20/2018	Freezer temperature deviated above - 59 degrees celsius for 1 hour 25minutes. Highest temperature was -51.9 degrees celsius.	Freezer being arranged and temoerater deviated and freezer alarmed as programmed too. Freezer not faulty. Human error. Re-training taken place for all staff with access to freezer.
285	07/11/2019	Samples stored in a -80C Multiuser freezer in the MIDRU Research facility. Temperature monitoring identified a temperature excursion above -59C Maximum temp -52.4C Duration of time above -59C = momentary < 5 mins from 14:40 to 14:40	Laboratory staff informed; Research Management informed; Incident report submitted to NHS Trust; Freezer service scheduled
285	08/07/2019	Samples stored in a -80C Multiuser freezer in the MIDRU Research facility. Temperature monitoring identified a temperature excursion above -59C Maximum temp -50.4C Duration of time above -59C = 10 mins from 14:35 to 14:45	Laboratory staff informed; Research Management informed; Incident submitted to NHS Trust; Freezer service scheduled
285	08/12/2019	Samples stored in a -80C Multiuser freezer in the MIDRU Research facility. Temperature monitoring identified a temperature excursion above -59C Maximum temp -58.7C Duration of time above -59C = momentary <5mins from 14:55 to 14:55	Laboratory staff informed; Research Management informed; Incident submitted to NHS Trust; Freezer service scheduled

Table 5b: Listing of Action/Steps: site-specific PDs

Site #	Date of Deviation	Deviation	Action/Step Taken
285	08/15/2019	Samples stored in a -80C Multiuser freezer in the MIDRU Research facility. Temperature monitoring identified a temperature excursion above -59C Maximum temp -58.7C Duration of time above -59C = momentary < 5 mins from 13:20 to 13:20	Laboratory staff informed; Research Management informed; Incident submitted to NHS Trust; Freezer service scheduled
285	08/19/2019	Samples stored in a -80C Multiuser freezer in the MIDRU Research facility. Temperature monitoring identified a temperature excursion above -59C Maximum temp -58.7C Duration above -59C = momentary < 5mins from 15:45 to 15:45	Laboratory staff informed; Research Management informed; Incident submitted to NHS Trust; Freezer service scheduled
285	08/19/2019	Samples stored in a -80C Multiuser freezer in the MIDRU Research facility. Temperature monitoring identified a temperature excursion above -59C maximum temp -28.5C Duration of time above -59C = 3 hr 20 mins from 16:00 to 19:20	Laboratory staff informed; Research Management informed; Incident submitted to NHS Trust; Freezer service scheduled
285	08/20/2019	Samples stored in a -80C Multiuser freezer in the MIDRU Research facility. Temperature monitoring identified a temperature excursion above -59C. Maximum temp -27.6C Duration of time above -59C = 50 mins from 10:00 to 10:50	Laboratory staff informed; Research Management informed; Incident submitted to NHS Trust; Freezer service scheduled
285	08/22/2019	Samples stored in a -80C Multiuser freezer in the MIDRU Research facility. Temperature monitoring identified a temperature excursion above -59C Maximum temp -37.6C Duration of time above -59C = 25 mins from 10:30 - 10:55	Laboratory staff informed; Research Management informed; Incident submitted to NHS Trust; Freezer service scheduled
285	08/27/2019	Samples stored in a -80C Multiuser freezer in the MIDRU Research facility. Temperature monitoring identified a temperature excursion above -59C Maximum temp -48.1C Duration above -59C = 10 mins from 17:15 to 17:25	Laboratory staff informed; Research Management informed; Incident submitted to NHS Trust; Freezer service scheduled
285	08/28/2019	Samples stored in a -80C Multiuser freezer in the MIDRU Research facility. Temperature monitoring identified a temperature excursion above -59C Maximum temp -48C Duration of time above -59C = 20mins from 10:25 to 10:45	Laboratory staff informed; Research Management informed; Incident submitted to NHS Trust; Freezer service scheduled

Table 5b: Listing of Action/Steps: site-specific PDs

Site #	Date of Deviation	Deviation	Action/Step Taken
285	07/16/2019	Samples stored in a -80C Multiuser freezer in the MIDRU Research facility. Temperature monitoring identified a temperature excursion above -59C. Maximum temp -50.8C Duration of time above -59C = 10 mins from 11:50 - 12:00	Laboratory staff informed; Research Management informed; Incident report submitted to NHS Trust; Freezer service scheduled
285	07/16/2019	Samples stored in a -80C Multiuser freezer in the MIDRU Research facility. Temperature monitoring identified a temperature excursion above -59C. Maximum temp -50.5 Duration of time above -59C = 15 mins from 15:55 to 16:10	Laboratory staff informed; Research Management informed; Incident report submitted to NHS Trust; Freezer service scheduled
285	08/20/2019	Samples stored in a -80C Multiuser freezer in the MIDRU Research facility. Temperature monitoring identified a temperature excursion above -59C. Maximum temp -54.5C Duration of time above -59C = 15 mins from 11:40 to 11:55	Laboratory staff informed; Research Management informed; Incident submitted to NHS Trust; Freezer service scheduled
285	08/20/2019	Samples stored in a -80C Multiuser freezer in the MIDRU Research facility. Temperature monitoring identified a temperature excursion above -59C Maximum temp -51C Duration of time above -59C = 5 mins from 14:20 - 14:25	Laboratory staff informed; Research Management informed; Incident submitted to NHS Trust; Freezer service scheduled
285	08/21/2019	Samples stored in a -80C Multiuser freezer in the MIDRU Research facility. Temperature monitoring identified a temperature excursion above -59C Maximum temp -52.5C Duration above -59C = 5 mins from 13:45 to 13:50	Laboratory staff informed; Research Management informed; Incident submitted to NHS Trust; Freezer service scheduled
285	08/21/2019	Samples stored in a -80C Multiuser freezer in the MIDRU Research facility. Temperature monitoring identified a temperature excursion above -59C Maximum temp -43.5C Duration of time above -59C = 15mins from 14:00 to 14:15	Laboratory staff informed; Research Management informed; Incident submitted to NHS Trust; Freezer service scheduled
285	08/22/2019	Samples stored in a -80C Multiuser frezzer in the MIDRU Research facility. Temperature monitoring identified a temperature excursion above -59C Maximum temp -57.4C Duration of time above -59C = 10 mins from 11:05 to 11:15	Laboratory staff informed; Research Management informed; Incident submitted to NHS Trust; Freezer service scheduled

Table 5b: Listing of Action/Steps: site-specific PDs

Site #	Date of Deviation	Deviation	Action/Step Taken
285	09/17/2019	Samples stored in a -80C Multiuser freezer in the MIDRU Research facility. Temperature monitoring identified a temperature excursion above -59C Maximum temp -58.7C Duration of time above -59C = momentary < 5mins from 15:40 to 15:40	Laboratory staff informed; Research Management informed; Incident submitted to NHS Trust; Freezer service scheduled
285	08/07/2019	Samples stored in a -80C Multiuser freezer in the MIDRU Research facility. Temperature monitoring identified a temperature excursion above -59C Maximum temp -58.4C Duration of time above -59C = momentary < 5 mins from 13:50 - 13:50	Laboratory staff informed; Research management informed; Incident submitted to NHS Trust; Freezer service scheduled
285	08/08/2019	Samples stored in a -80C Multiuser freezer in the MIDRU Research facility. Temperature monitoring identified a temperature excursion above -59C Maximum temp -50.5C Duration of time above -59C = 5 mins from 11:10 to 11:15.	Laboratory staff informed; Research Management informed; Incident submitted to NHS Trust; Freezer service scheduled
285	08/09/2019	Samples stored in a -80C Multiuser freezer in the MIDRU Research facility. Temperature monitoring identified a temperature excursion above -59C Maximum temp -57C Duration of time above -59 = momentary < 5mins from 12:55 to 12:55	Laboratory staff informed; Research Management informed; Incident submitted to NHS Trust; Freezer service scheduled
285	09/20/2019	Samples stored in a -80C Multiuser freezer in the MIDRU Research facility. Temperature monitoring recorded a temperature excursion above -59C Maximum temp +0.3C due to freezer monitoring audit. No risk to sample integrity as this was not a reading of internal freezer temp.	Laboratory staff aware and provided details of audit to provide explanation to sponsors
285	09/20/2019	Samples stored in a -80C Multiuser freezer in the MIDRU Research facility. temperature monitoring identified a temperature excursion above -59C Maximum -57.2C Duration of time above -59C = momentary < 5mins from 13:20 to 13:20	Laboratory staff informed; Research Management informed; Incident submitted to NHS Trust; Freezer service scheduled
285	10/03/2019	Samples stored in a -80C Multiuser freezer in the MIDRU Research facility. Temperature monitoring identified a temperature excursion above -59C Maximum temp -56.2C Duration of time above -59C = 60 mins from 15:45 to 16:45	Laboratory staff informed; Research Management informed; Incident submitted to NHS Trust; Freezer service scheduled

Table 5b: Listing of Action/Steps: site-specific PDs

Site #	Date of Deviation	Deviation	Action/Step Taken
285	10/04/2019	Samples stored in a -80C Multiuser freezer in the MIDRU Research facility. Temperature monitoring identified a temperature excursion above -59C Maximum temp -48.1C Duration of time above -59C = 35 mins from 10:35 to 11:10	Laboratory staff informed; Research Management informed; Incident submitted to NHS Trust; Freezer service scheduled
285	10/21/2019	samples stored in a -80C Multiuser freezer in the MIDRU Research facility. Temperature monitoring identified a temperature excursion above -59C Maximum temp -57.8C Duration of time above -59C = 5mins from 13:35 to 13:40.	Laboratory staff informed; Research Management informed; Incident submitted to NHS Trust; Freezer service scheduled
285	10/21/2019	Samples stored in a -80C Multiuser freezer in the MIDRU Research facility. Temperature monitoring identified a temperature excursion above -59C Maximum temp -51.2C Duration of time above -59C = 10 mins from 13:55 to 14:05	Laboratory staff informed; Research Management informed; Incident submitted to NHS Trust; Freezer service scheduled
285	07/12/2019	Samples stored in a -80C Multiuser freezer in the MIDRU Research facility. Temperature monitoring identified a temperature excursion above -59C Maximum temp - 54.5C Duration of time above -59C = momentary < 5mins from 13:25 to 13:25	Laboratory staff informed; Research Management informed; Incident report submitted to NHS Trust; Freezer service scheduled
285	08/05/2019	Samples stored in a -80C Multiuser freezer in the MIDRU Research facility. Temperature monitoring identified a temperature excursion above -59C Maximum temp -57C Duration of time above -59C = 60 mins from 08:40 to 09:40	Laboratory staff informed; Research management informed; Incident submitted to NHS Trust; Freezer service scheduled
283	07/31/2019	Temperature excursion due to defrosting within the department. The freezer was never warmer than -54 degrees for longer than 15 minutes. The samples were never thawed during this time.	Staff informed when defrosting the fridges to keep the fridge door shut wherever possible when moving samples.
283	08/01/2019	Temperature excursion due to defrosting within the department. The freezer was never warmer than -54 degrees for longer than 15 minutes. The samples were never thawed during this time.	Staff informed when defrosting the fridges to keep the fridge door shut wherever possible when moving samples.

Table 5b: Listing of Action/Steps: site-specific PDs

Site #	Date of Deviation	Deviation	Action/Step Taken
285	07/15/2019	Samples stored in a -80C Multiuser freezer in the MIDRU Research facility. Temperature monitoring identified a temperature excursion above -59C. Maximum temp -57.1C Duration of time above -59C = momentary <5 mins from 10:45 to 10:45	Laboratory staff informed; Research Management informed; Incident report submitted to NHS Trust; Freezer service scheduled
285	07/17/2019	Samples stored in a -80C Multiuser freezer in the MIDRU Research facility. Temperature monitoring identified a temperature excursion above -59C. Maximum temp -40.4C Duration of time above -59C = 15mins from 14:15 to 14:30	Laboratory staff informed; Research Management informed; Incident report submitted to NHS Trust; Freezer service scheduled
285	08/28/2019	Samples stored in a -80C Multiuser freezer in the MIDRU Research facility. Temperature monitoring identified a temperature excursion above -59C maximum temp -40.1C Duration of time above -59C = 5mins from 09:30 to 09:35	Laboratory staff informed; Research Management informed; Incident submitted to NHS Trust; Freezer service scheduled
285	08/28/2019	Samples stored in a -80C Multiuser freezer in the MIDRU Research facility. Temperature monitoring identified a temperature excursion above -59C Maximum temp -52.6C Duration of time above -59C = 15 mins from 14:35 to 14:50.	Laboratory staff informed; Research Management informed; Incident submitted to NHS Trust; Freezer service scheduled
285	07/30/2019	Samples stored in a -80C Multiuser freezer in the MIDRU Research facility. Temperature monitoring identified a temperature excursion above -59C Maximum temp -31.1C Duration of time above -59C = 25 mins from 10:35 to 11:00	Laboratory staff informed; Research Management informed; Incident submitted to NHS Trust; Freezer service scheduled
285	07/31/2019	Samples stored in a -80C Multiuser freezer in the MIDRU Research facility. Temperature monitoring identified a temperature excursion above -59C. Maximum temp -55C Duration of time above -59C = 5 mins from 13:45 to 13:50	Laboratory staff informed; Research Management informed; Incident submitted to NHS Trust; Freezer service scheduled
285	09/17/2019	Samples stored in a -80C Multiuser freezer in the MIDRU Research facility. Temperature monitoring identified a temperature excursion above -59C Maximum temp -58C Duration of time above -59C = momentary < 5 mins from 15:50 to 15:50	Laboratory staff informed; Research Management informed; Incident submitted to NHS Trust; Freezer service scheduled

Table 5b: Listing of Action/Steps: site-specific PDs

Site #	Date of Deviation	Deviation	Action/Step Taken
285	01/08/2020	Samples stored in a -80C Multiuser freezer in the MIDRU Research facility. Temperature monitoring identified a temperature excursion above -59C Maximum temp -56.2C Duration of time above -59C = 25 mins from 14:15 to 14:40	Laboratory staff informed and aware
285	08/20/2019	Samples stored in a -80C Multiuser freezer in the MIDRU Research facility. Temperature monitoring identified a temperature excursion above -59C Maximum temp -30C Duration of time above -59C = 30 mins from 14:25 - 14:55	Laboratory staff informed; Research Management informed; Incident submitted to NHS Trust; Freezer service scheduled
285	09/16/2019	Samples stored in a -80C Multiuser freezer in the MIDRU Research facility. Temperature monitoring identified a temperature excursion above -59C Maximum temp -56.7C Duration of time above -59C = 5 mins from 11:50 - 11:55.	Laboratory staff informed; Research Management informed; Incident submitted to NHS Trust; Freezer service scheduled
285	10/17/2019	Samples stored in a -80C Multiuser freezer in the MIDRU Research facility. Temperature monitoring identified a temperature excursion above -59C Maximum temp -55.8C Duration of time above -59C = 5 mins from 14:50 to 14:55	Laboratory staff informed; Research Management informed; Incident submitted to NHS Trust; Freezer service scheduled
283	07/30/2019	Temperature excursion due to defrosting within the department. The freezer was never warmer than -54 degrees for longer than 15 minutes. The samples were never thawed during this time.	Staff informed when defrosting the fridges to keep the fridge door shut wherever possible when moving samples.

Table 6a: Frequency Counts of Baseline Demographics

		Therapy Group		
	Randomized[a]	Active[1]	Placebo[a]	
	N (%)	N (%)	N (%)	p-value[c]
Age[c]				0.6743
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%)	
TOTAL	**35 (100%)**	**17 (100%)**	**18 (100%)**	
CMV Involvement[c]				0.6906
Symptomatic[b] at birth	26 (74.3%)	14 (82.4%)	12 (66.7%)	
Asymptomatic at birth	9 (25.7%)	3 (17.6%)	6 (33.3%)	
TOTAL	**35 (100%)**	**17 (100%)**	**18 (100%)**	
Ethnicity				0.6026
Hispanic/Latino	0	0	0	
Not Hispanic/Latino	32 (91.4%)	15 (88.2%)	17 (94.4%)	
Unknown	3 (8.6%)	2 (11.8%)	1 (5.6%)	
TOTAL	**35 (100%)**	**17 (100%)**	**18 (100%)**	
Sex				0.7332
Female	14 (40.0%)	6 (35.3%)	8 (44.4%)	
Male	21 (60.0%)	11 (64.7%)	10 (55.6%)	
TOTAL	**35 (100%)**	**17 (100%)**	**18 (100%)**	
Race				0.7613
American Indian / Alaska Native African American	0	0	0	
Asian	3 (8.6%)	2 (11.8%)	1 (5.6%)	
Native Hawaiian or Other Pacific Islander	0	0	0	
Black or African American	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	
Unknown or not reported	0	0	0	
TOTAL	**35 (100%)**	**17 (100%)**	**18 (100%)**	

[a] % uses Column total as the denominator. * p-values obtained using Fisher's exact test.
[b] Of the 26 symptomatic, 14 are from Placebo and 12 are from Active group. Among the 14 from Active, only 13 completed wk6 and Month6. Among the 12 from Placebo, only 10 completed wk6 and Month6. All three dropouts are from the Symptomatic group. All asymtptomatic subjects completed Wk6 and Month6 follow-ups.
[c] Randomization is stratified by age group and CMV involvement.

Table 6b: Summary Statistics of Baseline Age, Gestational Age and Birth Weight

			Therapy Group		
		Randomized	Active	Placebo	p-value
Gestational Age at Delivery (weeks)	**N**	**35**	**17**	**18**	0.1959[a]
	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 (in months)	**N**	**35**	**17**	**18**	0.3994[a]
	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	
Birth-weight (grams)	**N**	**35**	**17**	**18**	0.2550[b]
	Mean ± SE	3018.8 ± 674.5	2880.0 ± 864.9	3149.8 ± 410.4	
	Median (min-max)	3118.0 (508-4000)	3033.0 (508-4000)	3180 (1975-3960)	
	Unknown or missing	0	0	0	
Length at Birth (cm)	**N**	**14**	**6**	**8**	0.8976 [b]
	Mean ± SE	49.2± 3.4	49.4 ± 4.9	49.1 ± 1.9	
	Median (min-max)	49.5 (44-58)	48.9 (44-58)	49.5 (45.5-50.8)	
	Unknown or missing	21	11	10	
Head Circumference at Birth (cm)	N	**25**	**13**	**12**	0.4939 [a]
	Mean ± SE	32.6 ± 3.0	32.4 ± 4.1	32.9 ± 1.1	
	Median (min-max)	33.3 (20- 36)	33.7 (20- 36)	32.8 (31-34.8)	
	Unknown or missing	10	4	6	

[a]p-values to compare Active and Placebo were obtained using Wilcoxon exact test.
[b]p-values to compare Active and Placebo were obtained using two sample t-test.

Table 7a: Summary of frequency count of CMV disease involvement

i. Frequency Counts of Presenting Symptoms of CMV Overall				
		Therapy Group		
	Randomized[1]	Active[2]	Placebo[2]	p-value*
CMV Disease	N (%)	N (%)	N (%)	
a. Microcephaly ≤ 30 days of birth	5 (14.71%)	1 (5.9%)	4 (22.2%)	0.3601
b. Chorioretinitis	0 (0.0%)	0 (0%)	0 (0%)	N/A
c. Hearing deficit > 30 days of birth	33 (94.29%)	16 (100%)	17 (88.9%)	~1
d. Intrauterine growth retardation at birth	3 (8.57%)	1 (5.9%)	2 (11.1%)	0.4018
e. Petechia	5 (14.29%)	2 (11.8%)	3 (16.7%)	0.4843
f. Seizures ≤ 30 days of birth	3 (8.%)	2 (11.8%)	1 (5.6%)	0.6026
g. Thrombocytopenia	5 (14.29%)	2 (11.8%)	3 (16.7%)	~1
h. Splenomegaly	1 (2.86%)	1 (5.9%)	0 (0%)	0.4857
Hepatomegaly	2 (5.71%)	0 (0%)	2 (11.1%)	0.4857
j. Elevated transaminases	3 (8.57%)	2 (11.8%)	1 (5.6%)	0.6026
k. Elevated bilirubin	5 (14.29%)	3 (17.6%)	2 (11.1%)	0.6581
Unknown	1 (2.9%)	1 (5.9%)	0 (0%)	N/A

[1]Out of all Randomized subjects (n= 35)
[2]Percentae is out of column total, N/17 for active group and N/18 for placebo group.
*p-value obtained using Fisher's exact test

ii. Symptoms present at <=30 days of birth:

CMV Disease	Total Patients with Symptom (% of 34*)	Total Patients without Symptom (% of 34)	Total Patients with unknown Symptom (% of 34)
a. Microcephaly	5 (14.7)	26 (76.5)	3 (8.8)
b. Chorioretinitis	0 (0.0)	22 (64.7)	12 (35.3)
c. Hearing deficit	22 (64.7)	10 (29.4)	2 (5.9)
d. Intrauterine growth retardation at birth	3 (8.8)	29 (85.3)	2 (5.9)
e. Petechia	5 (14.7)	27 (79.4)	2 (5.9)
f. Seizures	1 (2.9)	32 (94.1)	1 (2.9)
g. Thrombocytopenia	5 (14.7)	18 (52.9)	11 (32.4)
h. Splenomegaly	0 (0.0)	29 (85.3)	5 (14.7)
i. Hepatomegaly	1 (2.9)	28 (82.4)	5 (14.7)
j. Elevated transaminases	2 (5.9)	17 (50.0)	15 (44.1)
k. Elevated bilirubin	5 (14.7)	15 (44.1)	14 (41.2)

iii. Symptoms present at >30 days of birth:

CMV Disease	Total Patients with Symptom (% of 34)	Total Patients without Symptom (% of 34)	Total Patients with unknown Symptom (% of 34)
a. Microcephaly	N/A	N/A	N/A
b. Chorioretinitis	0 (0.0)	20 (58.8)	14 (41.2)
c. Hearing deficit	33 (97.1)	1 (2.9)	0 (0.0)
d. Intrauterine growth retardation at birth	N/A	N/A	N/A
e. Petechia	N/A	N/A	N/A
f. Seizures	2 (5.9)	29 (85.3)	3 (8.8)
g. Thrombocytopenia	1 (2.9)	23 (67.7)	10 (29.4)
h. Splenomegaly	1 (2.9)	27 (79.4)	6 (17.7)
i. Hepatomegaly	1 (2.9)	26 (76.5)	7 (20.6)
j. Elevated transaminases	3 (8.8)	20 (58.8)	11 (32.4)
k. Elevated bilirubin	1 (2.9)	22 (66.7)	11 (32.4)

* There are 34 subjects showing at least one of the CMV disease symptoms, and 1 subject with unknown symptom status.

Table 7b: Summary CMV disease involvement: Lumbar Puncture

		Therapy Group		
	Randomized	Active	Placebo	p-value
	N (%)	N (%)	N (%)	
Was a lumbar puncture obtained?[1]				0.0073[2]
Yes	7 (20%)	7 (41.2%)	0 (0%)	
No	23 (65.7%)	9 (52.9%)	14 (77.8%)	
Unknown	5 (14.3%)	1 (5.9%)	4 (22.2%)	
Total	**35 (100%)**	**17 (100%)**	**18 (100%)**	
WBC (1000/mm^3) ≤ 30 Days of birth[3]				**N/A**
N	3 (42.9%)	3 (42.9%)	0	
Mean ± SE	12.20 ± 2.61	12.20 ± 2.61	0	
Median (min-max)	14.50 (7.0 – 15.11)	14.50 (7.0 – 15.11)	0	
Not Done/Unknown	4 (57.1%)	4 (57.1%)	0	
Total	**7 (100%)**	**7 (100%)**	**0**	
WBC (1000/mm^3) > 30 Days of birth[3]				**N/A**
N	5 (71.4%)	5 (71.4%)	0	
Mean ± SE	20.13 ± 6.06	20.13 ± 6.06	0	
Median (min-max)	18.00 (9.0 – 43.10)	18.00 (9.0 – 43.10)	0	
Not Done/Unknown	2 (28.6%)	2 (28.6%)	0	
Total	**7 (100%)**	**7 (100%)**	**0**	

[1]Percentage for Lumbar Puncture is out of column total, N/17 for active group, N/18 for placebo group and N/35 for randomized.
[2]p-values to compare Active and Placebo were obtained using Fisher exact test, excluding the 5 subjects with unknown status of a lumbar puncture.
[3]Percentage was based on column total of 7.
[4]There is no data for PCR ≤ 30 days of birth, i.e no subject obtained CMV PCR for ≤ 30 days of birth.

Table 7b: Summary CMV disease involvement: Lumbar Puncture (continued)

Protein (mg/dl) ≤ 30 Days of birth[3]				**N/A**
N	1 (14.3%)	1 (14.3%)	0	
Mean ± SE	1.90	1.90	0	
Median (min-max)	1.90	1.90	0	
Not Done/Unknown	6 (85.7%)	6 (85.7%)	0	
Total	**7 (100%)**	**7 (100%)**	**0**	
Protein (mg/dl) > 30 Days of birth[3]				**N/A**
N	3 (42.9%)	3 (42.9%)	0	
Mean ± SE	246.4 ± 227.1	246.4 ± 227.1	0	
Median (min-max)	38 (1.1-700)	38 (1.1-700)	0	
Not Done/Unknown	4 (57.1%)	4 (57.1%)	0	
Total	**7 (100%)**	**7 (100%)**	**0**	
PCR> 30 Days of birth[3,4]				**N/A**
Positive	2 (28.6%)	2 (28.6%)	0	
Negative	1 (14.3%)	1 (14.3%)	0	
Not Done/Unknown	4 (57.1%)	4 (57.1%)	0	
Total	**7 (100%)**	**7 (100%)**	**0**	

[1]Percentage for Lumbar Puncture is out of column total, N/17 for active group, N/18 for placebo group and N/35 for randomized.
[2]p-values to compare Active and Placebo were obtained using Fisher exact test, excluding the 5 subjects with unknown status of a lumbar puncture.
[3]Percentage was based on column total of 7.
[4]There is no data for PCR ≤ 30 days of birth, i.e no subject obtained CMV PCR for ≤ 30 days of birth.

Table 7c: Summary of CMV disease involvement: Neuroimaging Results

		Therapy Group		
	Randomized	Active	Placebo	p-value
	N (%)	N (%)	N (%)	
Were any neuroimaging studies conducted?[1]				0.6880[1]
Yes	26 (74.3%)	14 (82.4%)	12 (66.7%)	
No	8 (22.9%)	3 (17.6%)	5 (27.8%)	
Unknown	1 (2.9%)	0	1 (5.6%)	
TOTAL	**35 (100%)**	**17 (100%)**	**18 (100%)**	
Specific Tests Results				
CT Test (>30 days)[2,3]				N/A
Normal	0	0	0	
Abnormal	3 (11.5%)	2 (14.3%)	1 (8.3%)	
Unknown / Not Done	23 (88.5%)	12 (85.7%)	11 (91.7%)	
TOTAL	**26 (100%)**	**14 (100%)**	**12 (100%)**	
MRI Test (≤30 days of birth)[3]				N/A
Normal	1 (3.8%)	0	1 (8.3%)	
Abnormal	0	0	0	
Unknown / Not Done	25 (96.2%)	14 (100%)	11 (91.7%)	
TOTAL	**26 (100%)**	**14 (100%)**	**12 (100%)**	
MRI Test (>30 days of birth) [3]				0.6372
Normal	8 (30.8%)	5 (35.7%)	3 (25%)	
Abnormal	10 (38.5%)	4 (28.6%)	6 (50%)	
Unknown / Not Done	8 (30.8%)	5 (35.7%)	3 (25%)	
TOTAL	**26 (100%)**	**14 (100%)**	**12 (100%)**	

[1] Percentage is out of column total (N/35 for randomized, N/17 for Active and N/18 for Placebo.); p-values to compare Active and Placebo were obtained using Fisher exact test, excluding subjects with unknown test/study status.

Table 7c: Summary of CMV disease involvement: Neuroimaging Results (continued)

HUS Test (≤ 30 days of birth) [3]				~1
Normal	3 (11.5%)	1 (7.1%)	2 (16.7%)	
Abnormal	3 (11.5%)	2 (14.3%)	1 (8.3%)	
Unknown / Not Done	20 (76.9%)	11 (78.6%)	9 (75%)	
TOTAL	**26 (100%)**	**14 (100%)**	**12 (100%)**	
HUS Test (> 30 days of birth) [3]				N/A
Normal	2 (7.7%)	2 (14.3%)	0 (0%)	
Abnormal	3 (11.5%)	3 (21.4%)	0 (0%)	
Unknown / Not Done	21 (80.8%)	9 (64.3%)	12 (100%)	
TOTAL	**26 (100%)**	**14 (100%)**	**12 (100%)**	

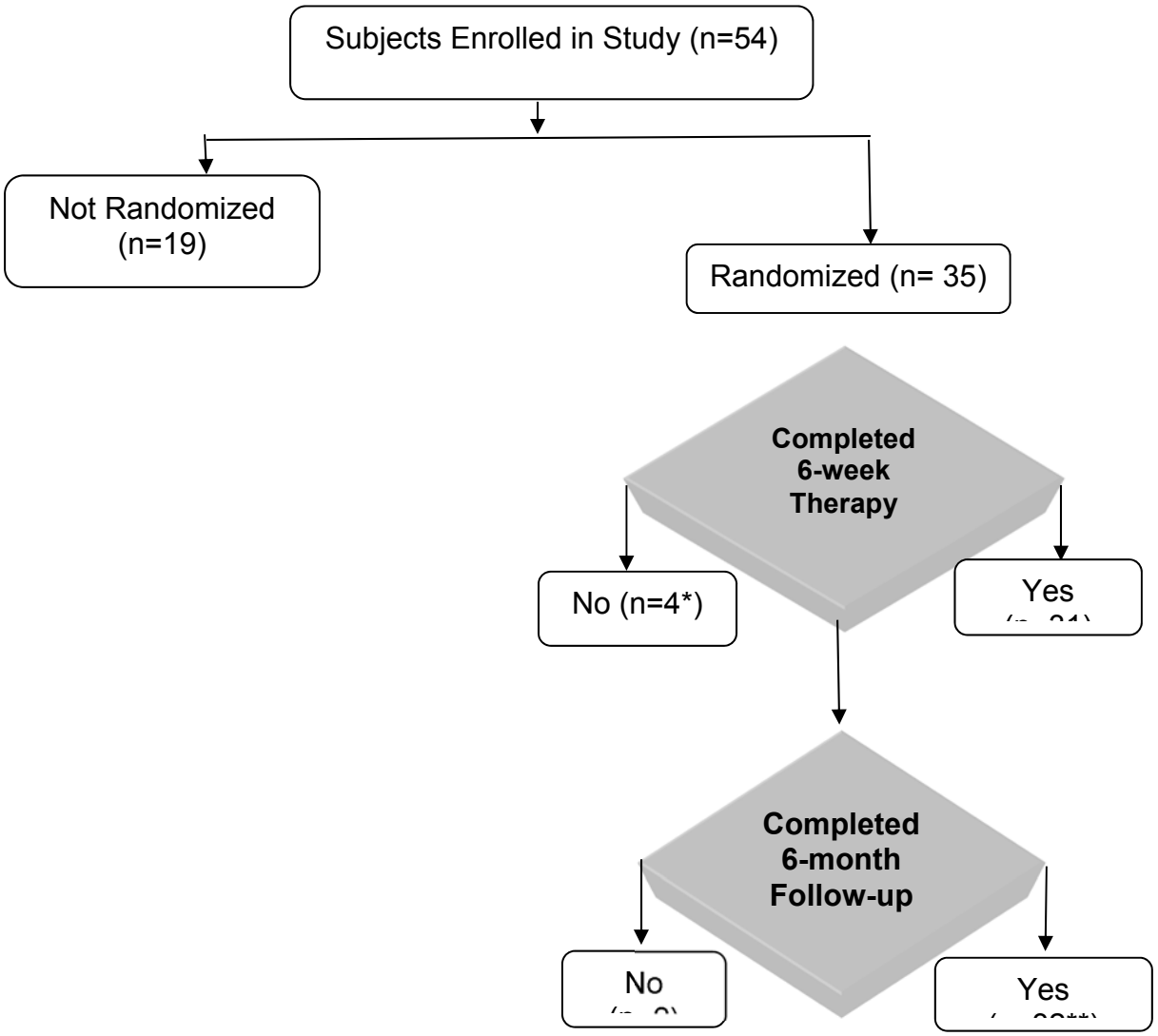
[1] Percentage is out of column total (N/35 for randomized, N/17 for Active and N/18 for Placebo.); p-values to compare Active and Placebo were obtained using Fisher exact test, excluding subjects with unknown test/study status.
[2] There is no CT test done for ≤ 30 days.
[3] Percentage is out of column total who had neuroimaging test (N/26 for randomized, N/14 for Active and N/12 for Placebo.).

Table 7d: Summary of Baseline Abnormal Findings

Baseline	Randomized[1]		Active[2]		Placebo[2]		p-value[3]
Physical Examination	N	%	N	%	N	%	
Cardiovascular	1	2.9	1	5.9	0	0	N/A
Respiratory	2	5.7	2	11.8	0	0	N/A
Cutaneous/Skin	2	5.7	1	5.9	1	5.6	~1
Gastrointestinal	3	8.6	1	5.9	2	11.1	~1
Neurological	9	25.7	5	29.4	4	22.2	0.7112
Genitourinary	1	2.9	1	5.9	0	0	N/A
Musculoskeletal	5	14.3	1	5.9	4	22.2	0.3377
Endocrine/Metabolic	2	5.7	2	11.8	0	0	N/A
Immune System	1	2.9	1	5.9	0	0	N/A
Ears, Nose, Throat	30	85.7	14	82.4	16	88.9	0.6581

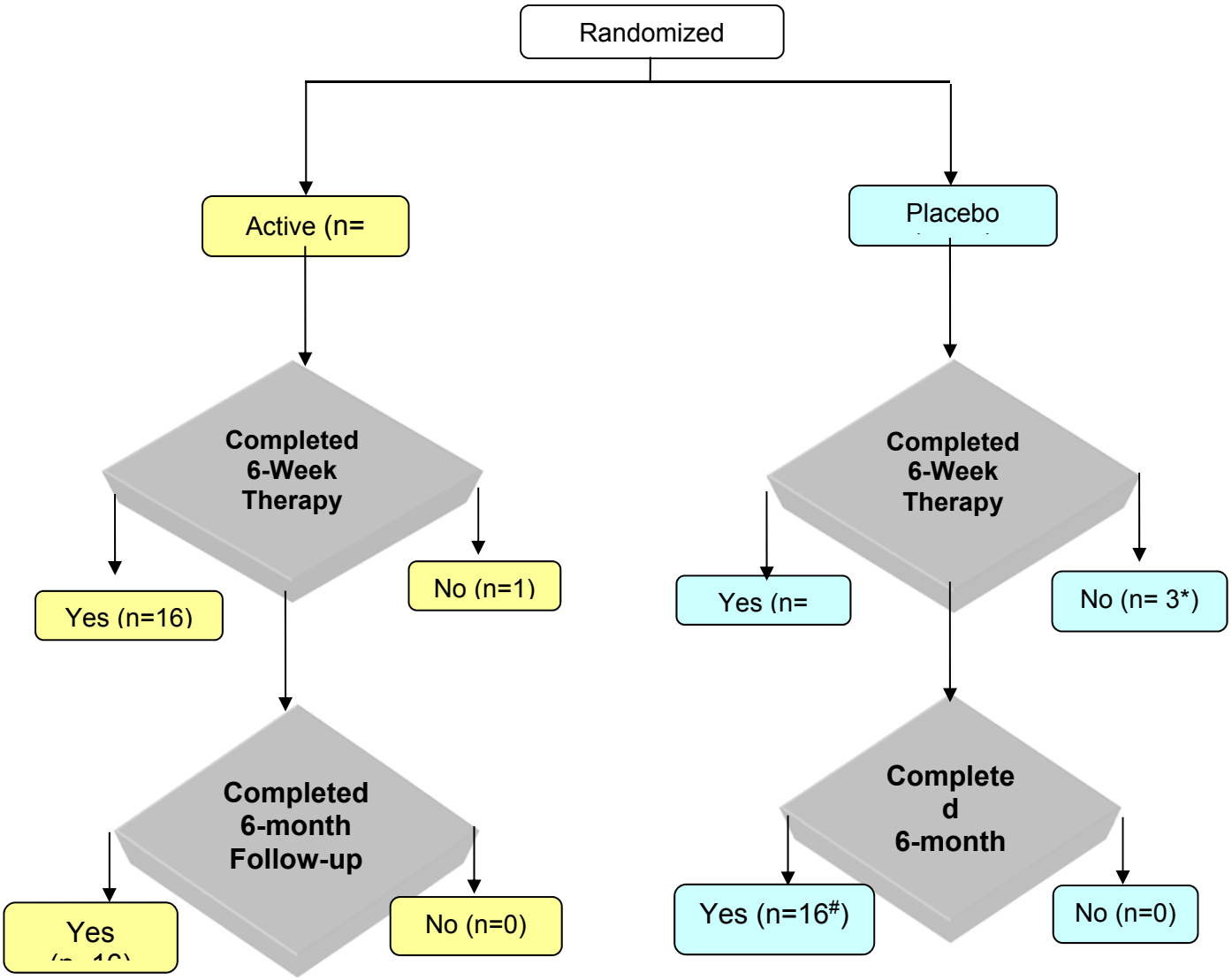
[1]Out of all Randomized subjects (n = 35).
[2]Active and Placebo % uses the column total as the denominator, i.e. N/17 for active and N/18 for placebo.
[3]Fisher's exact test was used to obtain the p-values between active and placebo groups.

Figure 3a: Disposition of Subjects with Study Drug Information



*Two of the four subjects 3RJM & 1K5D dropped out of study without taking study drug after randomization.
Remaining two of the four subjects 17EH & 77VL, are early drug termination and did not complete the 6 weeks/42 days of the drug.
**77VL was early drug terminated subject but stayed in the study till month-6

Figure 3b: Disposition of Randomized Subjects with Study Drug Information



*Two subjects in Placebo group 1K5D & 3RJM, dropped out of study without taking study drug after randomization.
#One subject from Placebo, 77VL did not complete the 6-week dose of study drug but stayed in the study through month-6 visit.

Table 8a: Summary of Adverse Events

	Total of Randomized Subjects N= 35		
	Number of Events (NE)	Number of Subjects with Events (NPE)	Percent of Subjects with Events (NPE/N)[1]
Adverse Events	105	25	71.4
Serious Adverse Events	1	1	2.9
Deaths	0	0	0

Table 8b: Summary of Adverse Events

	Active N=17			**Placebo** N=18		
	Number of Events (NE)[3]	Number of Subjects with Events (NPE)[4]	Percent of Subjects with Events (NPE/N)[2]	Number of Events (NE)[3]	Number of Subjects with Events (NPE)[4]	Percent of Subjects with Events (NPE/N)[2]
Adverse Events	57	13	76.5	48[3]	12	66.7
Serious Adverse Events	1	1	5.9	0	0	0
Deaths	0	0	0.0	0	0	0.0

[1] Percent = NPE/ N
Denominator, N=35, is total number of subjects randomized who have begun treatment with the randomization treatment arm.
[2] Percent = NPE/N
Denominator, N, is total number of subjects randomized (N= 17 for Active; N=18 for Placebo) who have begun treatment with the randomization treatment arm.
[3]p-value to compare the number of AEs between Activ and Placebo was obtained using exact Wilcoxon test. P=0.6166
[4]p-value to compare number of subjects with at least one adverse events in Active and Placebo was obtained using Fisher exact test. P=0.7112.

Table 9a: Listing of Each Subject's Serious Adverse Events

PID #	Site No	SAE Event	Date of Enrollment	Study Days	Onset Date	Severity	Relationship to Study Product	Subject Outcome	Resolution Date	Study Product Status	SAE Category
9PGH/64974	294	Respiratory Distress	07/12/17	147	09/23/17	Grade 2--Moderate	Not Related	Recovered/Resolved	09/24/17	Not applicable	Primary: Hospitalization or prolonged hospitalization Secondary: Not applicable

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

		Therapy Group														
		Randomized					Active					Placebo				
Body System	**Grade**	1	2	3	4	5	1	2	3	4	5	1	2	3	4	5
Respiratory, Thoracic, mediastinal disorders		0	1	0	0	0	0	1	0	0	0	0	0	0	0	0

* Grade 1-5 represents 1=mild, 2=moderate, 3=severe, 4=life-threatening, and 5=death.

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

						Therapy Group									
	Randomized					Active					Placebo				
Grade	1	2	3	4	5	1	2	3	4	5	1	2	3	4	5
Body System															
Blood and Lymphatic System Disorders	4	1	1	0	0	1	1	0	0	0	3	0	1	0	0
Ear and Labyrinth Disorders	5	2	0	0	0	5	0	0	0	0	0	2	0	0	0
Gastrointestinal Disorders	21	5	0	0	0	12	2	0	0	0	9	3	0	0	0
General Disorders and administration site conditions	8	2	0	0	0	3	1	0	0	0	5	1	0	0	0
Infections and infestations	10	1	0	0	0	4	0	0	0	0	6	1	0	0	0
Injury, poisoning and procedural complications	2	0	0	0	0	2	0	0	0	0	0	0	0	0	0
Musculoskeletal and Connective Tissue Disorders	1	1	0	0	0	1	1	0	0	0	0	0	0	0	0
Psychiatric disorders	5	3	0	0	0	3	0	0	0	0	2	3	0	0	0
Renal and Urinary Disorders	3	0	0	0	0	2	0	0	0	0	1	0	0	0	0
Respiratory, Thoracic, Mediastinal disorders	17	5	0	0	0	8	4	0	0	0	9	1	0	0	0
Skin and subcutaneous tissue disorders	7	1	0	0	0	7	0	0	0	0	0	1	0	0	0
Total	83	21	1	0	0	48	9	0	0	0	35	12	1	0	0

* Grade 1-5 represents 1=mild, 2=moderate, 3=severe, 4=life-threatening, and 5=death.

Table 10b: AE Grade by Therapy Group

Frequency (%N)	**Therapy Group**		
	Randomized N=105	**Active N=57**	**Placebo N=48**
Mild (1)	83 (79.05)	48 (84.21)	35 (72.92)
Moderate (2)	21 (20.00)	9 (15.79)	12 (25.00)
Severe (3)	1 (0.95)	0 (0.00)	1 (2.08)

p-value=0.3758 using generalized linear mixed model for ordinal response with random intercept.

Table 10c: Listing of Adverse Events (Active Group)

Obs	Body System	site	PID1	PID2	Visit	Preferred Event Term	Event onset date	Intensity (Grade)	Action taken	Relation	Outcome	Date of resolution
1	Blood and Lymphatic System Disorders	283	19DC	67742	Day 70	Neutropenia	16AUG2019	Moderate (2)	Not applicable	Related	Recovered / Resolved	08/23/2019
2	Blood and Lymphatic System Disorders	280	7QCJ	14908	Day 70	Monocytopenia	04OCT2017	Mild (1)	Dose/procedure not changed	Related	Recovered / Resolved	11/29/2017
3	Psychiatric Disorders	280	573N	98816	Day 14	Screaming / unsettled	17SEP2015	Mild (1)	Dose/procedure not changed	Related	Recovered / Resolved	09/30/2015
4	Ear and Labyrinth Disorders	283	19DC	67742	Day 28	Ear Infection	16JUL2019	Mild (1)	Dose/procedure not changed	Not Related	Recovered / Resolved	07/24/2019
5	Ear and Labyrinth Disorders	280	573N	98816	Unscheduled	Otitis	07NOV2015	Mild (1)	Dose/procedure not changed	Not Related	Recovered / Resolved	11/13/2015
6	Ear and Labyrinth Disorders	292	9HVF	98744	Day 14	Audiological Disturbance	06SEP2015	Mild (1)	Dose/procedure not changed	Not Related	Recovered / Resolved	09/06/2015
7	Ear and Labyrinth Disorders	292	9HVF	98744	Day 28	Audiologicol Disturbance	15SEP2015	Mild (1)	Dose/procedure not changed	Not Related	Recovered / Resolved	09/15/2015
8	Ear and Labyrinth Disorders	292	9HVF	98744	Day 28	Audiological disturbance	17SEP2015	Mild (1)	Dose/procedure not changed	Not Related	Recovered / Resolved	09/17/2015
9	GI Disorders	283	13TX	23501	Day 70	Constipation	25APR2017	Mild (1)	Dose/procedure not changed	Not Related	Recovered / Resolved	12/19/2017
10	GI Disorders	283	13TX	23501	Day 70	One episode of vomiting overnight. Otherwise well.	07JUN2017	Mild (1)	Not applicable	Not Related	Recovered / Resolved	06/07/2017
11	GI Disorders	283	19DC	67742	Day 42	Reduced Appetite	06JUL2019	Mild (1)	Dose/procedure not changed	Not Related	Recovered / Resolved	08/10/2019
12	GI Disorders	283	19DC	67742	Unscheduled	Weight Loss	12JUL2019	Mild (1)	Dose/procedure not changed	Not Related	Recovered / Resolved	08/16/2019
13	GI Disorders	296	1YEM	45590	Day 42	viral gastroenteritis	15AUG2019	Mild (1)	Dose/procedure not changed	Not Related	Recovered / Resolved	08/16/2019

Table 10c: Listing of Adverse Events (Active Group)

Obs	Body System	site	PID1	PID2	Visit	Preferred Event Term	Event onset date	Intensity (Grade)	Action taken	Relation	Outcome	Date of resolution
14	GI Disorders	283	2AH3	83011	Day 42	Teething	22APR2019	Moderate (2)	Dose/procedure not changed	Not Related	Recovered / Resolved	05/16/2019
15	GI Disorders	280	32RK	98819	Day 14	Diarrhoea	01JUL2016	Mild (1)	Dose/procedure not changed	Not Related	Recovered / Resolved	07/02/2016
16	GI Disorders	280	32RK	98819	Day 14	Vomiting	01JUL2016	Mild (1)	Dose/procedure not changed	Not Related	Recovered / Resolved	07/02/2016
17	GI Disorders	286	3UEF	11935	Unscheduled	Teething issues	17JAN2018	Moderate (2)	Dose/procedure not changed	Not Related	Recovered / Resolved	01/18/2018
18	GI Disorders	280	573N	98816	Unscheduled	Vomited in car	13JAN2016	Mild (1)	Dose/procedure not changed	Not Related	Recovered / Resolved	01/13/2016
19	GI Disorders	273	6LEL	52737	Unscheduled	emesis	30MAR2019	Mild (1)	Dose/procedure not changed	Not Related	Recovered / Resolved	03/31/2019
20	GI Disorders	280	7QCJ	14908	Day 42	Gastroenteritis	18OCT2017	Mild (1)	Dose/procedure not changed	Not Related	Recovered / Resolved	10/20/2017
21	GI Disorders	296	974K	87929	Unscheduled	Reflux	03MAY2018	Mild (1)	Dose/procedure not changed	Not Related	Death	10/03/2018
22	GI Disorders	292	9HVF	98744	Day 70	Vomiting	16OCT2015	Mild (1)	Dose/procedure not changed	Not Related	Recovered / Resolved	10/17/2015
23	General Disorders and Administration Site Conditions	283	2AH3	83011	Day 70	long sighted	03JUN2019	Moderate (2)	Not applicable	Not Related	Recovered / Resolved with sequelae	09/30/2019
24	General Disorders and Administration Site Conditions	281	2TA3	72740	Day 70	Fever	27FEB2018	Mild (1)	Not applicable	Not Related	Recovered / Resolved	02/28/2018

Table 10c: Listing of Adverse Events (Active Group)

Obs	Body System	site	PID1	PID2	Visit	Preferred Event Term	Event onset date	Intensity (Grade)	Action taken	Relation	Outcome	Date of resolution
25	General Disorders and Administration Site Conditions	280	573N	98816	Day 14	Pyrexia	27SEP2015	Mild (1)	Dose/procedure not changed	Not Related	Recovered / Resolved	09/27/2015
26	General Disorders and Administration Site Conditions	280	7QCJ	14908	Day 28	Hyperkalemia	18OCT2017	Mild (1)	Dose/procedure not changed	Not Related	Recovered / Resolved	11/01/2017
27	Infections and Infestations	296	1YEM	45590	Day 28	viral illness	23JUL2019	Mild (1)	Dose/procedure not changed	Not Related	Recovered / Resolved	07/31/2019
28	Infections and Infestations	286	3UEF	11935	Unscheduled	Hand, foot and mouth disease	12FEB2018	Mild (1)	Not applicable	Not Related	Recovered / Resolved	02/19/2018
29	Infections and Infestations	286	3UEF	11935	Unscheduled	Tonsillitis	12FEB2018	Mild (1)	Not applicable	Not Related	Recovered / Resolved	02/19/2018
30	Infections and Infestations	273	6LEL	52737	Unscheduled	infection at surgical incision site	26AUG2019	Mild (1)	Not applicable	Not Related	Recovered / Resolved	08/30/2019
31	Injury, Poisoning and Procedural Complications	283	13TX	23501	Day 14	Head, eye and right arm injury. Suspected trauma to lacrimal sac.	05APR2017	Mild (1)	Dose/procedure not changed	Not Related	Recovered / Resolved	04/05/2017
32	Injury, Poisoning and Procedural Complications	283	19DC	67742	Unscheduled	minor injury - bruise right eye and cheek and left forehead	10SEP2019	Mild (1)	Not applicable	Not Related	Recovered / Resolved	11/08/2019
33	Musculoskeletal and Connective Tissue Disorders	273	6LEL	52737	Day 42	buckle fracture of right tibia and fibula	02APR2019	Moderate (2)	Dose/procedure not changed	Not Related	Recovered / Resolved	04/19/2019
34	Musculoskeletal and Connective Tissue Disorders	296	974K	87929	Day 42	Osteopenia	30APR2018	Mild (1)	Dose/procedure not changed	Not Related	Death	11/07/2018

Table 10c: Listing of Adverse Events (Active Group)

Obs	Body System	site	PID1	PID2	Visit	Preferred Event Term	Event onset date	Intensity (Grade)	Action taken	Relation	Outcome	Date of resolution
35	Psychiatric Disorders	283	19DC	67742	Day 70	Lethargic and sleeping more than usual	06AUG2019	Mild (1)	Not applicable	Not Related	Recovered / Resolved	09/06/2019
36	Psychiatric Disorders	280	573N	98816	Day 14	Hallucination / Nightmare	10OCT2015	Mild (1)	Dose/procedure not changed	Not Related	Recovered / Resolved	10/10/2015
37	Renal and Urinary Disorders	280	573N	98816	Day 14	Blood in urine	28SEP2015	Mild (1)	Dose/procedure not changed	Not Related	Recovered / Resolved	09/28/2015
38	Renal and Urinary Disorders	280	573N	98816	Day 14	Protein in urine	28SEP2015	Mild (1)	Dose/procedure not changed	Not Related	Recovered / Resolved	09/28/2015
39	Respiratory, Thoracic, Mediastinal Disorders	283	19DC	67742	Day 28	cough and runny nose	12JUL2019	Mild (1)	Dose/procedure not changed	Not Related	Recovered / Resolved	07/26/2019
40	Respiratory, Thoracic, Mediastinal Disorders	283	19DC	67742	Unscheduled	Runny nose	09SEP2019	Mild (1)	Not applicable	Not Related	Recovered / Resolved	11/08/2019
41	Respiratory, Thoracic, Mediastinal Disorders	283	2AH3	83011	Baseline	Bronchiolitis	26MAR2019	Mild (1)	Dose/procedure not changed	Not Related	Recovered / Resolved	04/18/2019
42	Respiratory, Thoracic, Mediastinal Disorders	286	3UEF	11935	Day 28	Bronchiolitis	08NOV2017	Moderate (2)	Dose/procedure not changed	Not Related	Recovered / Resolved	11/20/2017
43	Respiratory, Thoracic, Mediastinal Disorders	280	573N	98816	Day 14	Blocked Nose	15SEP2015	Mild (1)	Dose/procedure not changed	Not Related	Recovered / Resolved	09/20/2015

Table 10c: Listing of Adverse Events (Active Group)

Obs	Body System	site	PID1	PID2	Visit	Preferred Event Term	Event onset date	Intensity (Grade)	Action taken	Relation	Outcome	Date of resolution
44	Respiratory, Thoracic, Mediastinal Disorders	280	7QCJ	14908	Day 70	Respiratory Tract Infection	30OCT2017	Mild (1)	Dose/procedure not changed	Not Related	Recovered / Resolved	11/06/2017
45	Respiratory, Thoracic, Mediastinal Disorders	296	974K	87929	Unscheduled	Exacerbation	28MAY2018	Moderate (2)	Not applicable	Not Related	Recovered / Resolved	06/01/2018
46	Respiratory, Thoracic, Mediastinal Disorders	292	9HVF	98744	Day 28	Coryzal symptoms	18SEP2015	Mild (1)	Dose/procedure not changed	Not Related	Recovered / Resolved	09/20/2015
47	Respiratory, Thoracic, Mediastinal Disorders	292	9HVF	98744	Day 28	Cough	18SEP2015	Mild (1)	Dose/procedure not changed	Not Related	Recovered / Resolved	09/22/2015
48	Respiratory, Thoracic, Mediastinal Disorders	292	9HVF	98744	Day 70	Coryzal symptoms	23OCT2015	Mild (1)	Dose/procedure not changed	Not Related	Recovered / Resolved	10/26/2015
49	Respiratory, Thoracic, Mediastinal Disorders	294	9PGH	64974	Day 42	Rhinos Virus Infection.	23AUG2017	Moderate (2)	Dose/procedure not changed	Not Related	Recovered / Resolved	08/30/2017
50	Respiratory, Thoracic, Mediastinal Disorders	294	9PGH	64974	Day 70	Asthma	23SEP2017	Moderate (2)	Dose/procedure not changed	Not Related	Recovered / Resolved	09/24/2017
51	Skin and Subcutaneous Tissue Disorders	283	19DC	67742	Day 28	Rash	18JUL2019	Mild (1)	Dose/procedure not changed	Not Related	Recovered / Resolved	07/20/2019
52	Skin and Subcutaneous Tissue Disorders	281	2TA3	72740	Day 70	Petechial rash, left arm	04MAR2018	Mild (1)	Not applicable	Not Related	Recovered / Resolved	03/08/2018

Table 10c: Listing of Adverse Events (Active Group)

Obs	Body System	site	PID1	PID2	Visit	Preferred Event Term	Event onset date	Intensity (Grade)	Action taken	Relation	Outcome	Date of resolution
53	Skin and Subcutaneous Tissue Disorders	280	32RK	98819	Day 28	Nappy Rash	20JUL2016	Mild (1)	Dose/procedure not changed	Not Related	Recovered / Resolved	08/01/2016
54	Skin and Subcutaneous Tissue Disorders	286	3UEF	11935	Unscheduled	fine, erythematous, raised rash on chest and abdo	21OCT2017	Mild (1)	Dose/procedure interrupted	Not Related	Recovered / Resolved	10/27/2017
55	Skin and Subcutaneous Tissue Disorders	286	3UEF	11935	Unscheduled	Impetigo	13FEB2018	Mild (1)	Not applicable	Not Related	Recovered / Resolved	02/19/2018
56	Skin and Subcutaneous Tissue Disorders	280	573N	98816	Unscheduled	Papular rash	14OCT2015	Mild (1)	Dose/procedure not changed	Not Related	Recovered / Resolved	10/28/2015
57	Skin and Subcutaneous Tissue Disorders	280	573N	98816	Unscheduled	Glass in foot	22DEC2015	Mild (1)	Dose/procedure not changed	Not Related	Recovered / Resolved	12/22/2015

Table 10c: Listing of Adverse Events (Placebo Group)

Obs	Body System	site	PID1	PID2	visit	Preferred Event Term	Event onset date	Intensity (Grade)	Action taken	Relation	Outcome	Date of resolution
1	Blood and Lymphatic System Disorders	019	2Q49	27852	Day 42	decrease in hemoglobin	10AUG2017	Mild (1)	Not applicable	Related	Recovered / Resolved	08/23/2017
2	Blood and Lymphatic System Disorders	280	64X3	95929	Day 14	Neutropenia	03OCT2018	Mild (1)	Dose/procedure not changed	Related	Recovered / Resolved	10/10/2018
3	Blood and Lymphatic System Disorders	280	64X3	95929	Day 28	Mild neutropenia	17OCT2018	Mild (1)	Dose/procedure not changed	Related	Recovered / Resolved	10/31/2018
4	Psychiatric Disorders	285	1KUH	64010	Day 14	Agitation*	05JUL2019	Moderate (2)	Dose/procedure not changed	Related	Recovered / Resolved	07/08/2019
5	Psychiatric Disorders	285	1KUH	64010	Unscheduled (Randomized 11JUN2019)	Intermittent hyperactivity*	18JUL2019	Moderate (2)	Dose/procedure not changed	Related	Recovered / Resolved	01/30/2020
6	Psychiatric Disorders	280	64X3	95929	Day 14	Crying since first dose	19SEP2018	Moderate (2)	Dose/procedure not changed	Related	Recovered / Resolved	10/15/2018
7	Skin and Subcutaneous Tissue Disorders	285	1KUH	64010	Day 28	White discolouration of lips and throat*	05JUL2019	Moderate (2)	Dose/procedure not changed	Related	Recovered / Resolved	07/18/2019
8	psychiatric Disorders	281	7HG6	72893	Day 28	Neutropenia	29NOV2018	Mild (1)	Dose/procedure not changed	Related	Recovered / Resolved	12/12/2018
9	Blood and Lymphatic System Disorders	280	64X3	95929	Day 70	neutropenia	28NOV2018	Severe (3)	Not applicable	Not Related	Recovered / Resolved	12/06/2018
10	Ear and Labyrinth Disorders	292	4JKU	96277	Day 70	Bilateral ear infection	04JUL2016	Moderate (2)	Dose/procedure not changed	Not Related	Recovered / Resolved	07/12/2016
11	Ear and Labyrinth Disorders	280	64X3	95929	Day 70	otitis media	27NOV2018	Moderate (2)	Dose/procedure not changed	Not Related	Recovered / Resolved	12/01/2018
12	GI Disorders	273	337J	54148	Unscheduled	teething	28MAR2016	Mild (1)	Dose/procedure not changed	Not Related	Recovered / Resolved	10/04/2016
13	GI Disorders	273	337J	54148	Unscheduled	constipation	04APR2016	Mild (1)	Dose/procedure not changed	Not Related	Recovered / Resolved	10/04/2016

Table 10c: Listing of Adverse Events (Placebo Group)

Obs	Body System	site	PID1	PID2	visit	Preferred Event Term	Event onset date	Intensity (Grade)	Action taken	Relation	Outcome	Date of resolution
14	GI Disorders	292	4JKU	96277	Day 42	Teething pain	01JUN2016	Mild (1)	Dose/procedure not changed	Not Related	Recovered / Resolved	06/24/2016
15	GI Disorders	283	5NTX	59440	Day 28	loose stools	07APR2018	Moderate (2)	Dose/procedure not changed	Not Related	Recovered / Resolved	04/07/2018
16	GI Disorders	283	5NTX	59440	Day 42	vomiting	07APR2018	Moderate (2)	Dose/procedure not changed	Not Related	Recovered / Resolved	04/25/2018
17	GI Disorders	283	5NTX	59440	Day 70	vomiting due to cough	26APR2018	Mild (1)	Dose/procedure not changed	Not Related	Recovered / Resolved	05/24/2018
18	GI Disorders	283	5NTX	59440	Day 70	loose stools x 1 episode	23MAY2018	Mild (1)	Not applicable	Not Related	Recovered / Resolved	05/24/2018
19	GI Disorders	283	5NTX	59440	Day 70	vomit x 1 episode	23MAY2018	Mild (1)	Not applicable	Not Related	Recovered / Resolved	05/24/2018
20	GI Disorders	280	64X3	95929	Day 14	Vomiting	26SEP2018	Mild (1)	Dose/procedure not changed	Not Related	Recovered / Resolved	09/28/2018
21	GI Disorders	280	64X3	95929	Day 14	Constipation	03OCT2018	Moderate (2)	Dose/procedure not changed	Not Related	Recovered / Resolved	10/12/2018
22	GI Disorders	280	64X3	95929	Day 42	Constipation	18OCT2018	Mild (1)	Dose/procedure not changed	Not Related	Recovered / Resolved	11/26/2018
23	GI Disorders	280	64X3	95929	Day 70	Vomiting	14NOV2018	Mild (1)	Dose/procedure not changed	Not Related	Recovered / Resolved	11/27/2018
24	General Disorders and Administration Site Conditions	285	1KUH	64010	Day 28	Nose Bleed	19JUL2019	Mild (1)	Dose/procedure not changed	Not Related	Recovered / Resolved	07/19/2019
25	General Disorders and Administration Site Conditions	019	2Q49	27852	Day 28	Fever	30JUL2017	Mild (1)	Not applicable	Not Related	Recovered / Resolved	08/07/2017

Table 10c: Listing of Adverse Events (Placebo Group)

Obs	Body System	site	PID1	PID2	visit	Preferred Event Term	Event onset date	Intensity (Grade)	Action taken	Relation	Outcome	Date of resolution
26	General Disorders and Administration Site Conditions	273	337J	54148	Day 42	fever	23APR2016	Moderate (2)	Dose/procedure not changed	Not Related	Recovered / Resolved	05/09/2016
27	General Disorders and Administration Site Conditions	280	46WG	38519	Day 42	Fall on chin	26MAR2019	Mild (1)	Dose/procedure not changed	Not Related	Recovered / Resolved	04/08/2019
28	General Disorders and Administration Site Conditions	292	4JKU	96277	Day 70	Raised temperature	04JUL2016	Mild (1)	Not applicable	Not Related	Recovered / Resolved	07/12/2016
29	General Disorders and Administration Site Conditions	280	64X3	95929	Day 14	Fever	26SEP2018	Mild (1)	Dose/procedure not changed	Not Related	Recovered / Resolved	09/27/2018
30	Infections and Infestations	285	1KUH	64010	Day 14	Rhinitis	05JUL2019	Mild (1)	Dose/procedure not changed	Not Related	Recovered / Resolved	07/05/2019
31	Infections and Infestations	292	2674	49683	Day 28	Viral illness.	24JUL2018	Mild (1)	Dose/procedure not changed	Not Related	Recovered / Resolved	08/04/2018
32	Infections and Infestations	292	3ZGW	99577	Day 28	viral illness	25MAY2018	Mild (1)	Dose/procedure not changed	Not Related	Recovered / Resolved	05/27/2018
33	Infections and Infestations	292	3ZGW	99577	Day 70	viral illness	09JUL2018	Mild (1)	Not applicable	Not Related	Recovered / Resolved	07/11/2018
34	Infections and Infestations	001	5RT2	70622	Day 42	Hand, foot mouth disease	17JUL2018	Moderate (2)	Dose/procedure not changed	Not Related	Recovered / Resolved	07/20/2018
35	Infections and Infestations	281	7HG6	72893	Day 42	Tonsiltis	08DEC2018	Mild (1)	Dose/procedure not changed	Not Related	Recovered / Resolved	12/20/2018
36	Infections and Infestations	286	9AJ7	21115	Day 42	Chicken Pox	09APR2016	Mild (1)	Dose/procedure not changed	Not Related	Recovered / Resolved	04/16/2016
37	Renal and Urinary Disorders	285	1KUH	64010	Day 28	Urinary Incontinence	08JUL2019	Mild (1)	Dose/procedure not changed	Not Related	Recovered / Resolved	07/10/2019

Table 10c: Listing of Adverse Events (Placebo Group)

Obs	Body System	site	PID1	PID2	visit	Preferred Event Term	Event onset date	Intensity (Grade)	Action taken	Relation	Outcome	Date of resolution
38	Respiratory, Thoracic, Mediastinal Disorders	285	1KUH	64010	Day 70	Upper Respiratory Infection	07SEP2019	Mild (1)	Not applicable	Not Related	Recovered / Resolved	10/29/2019
39	Respiratory, Thoracic, Mediastinal Disorders	292	3ZGW	99577	Baseline	Upper respiratory tract infection	30APR2018	Mild (1)	Dose/procedure not changed	Not Related	Recovered / Resolved	05/03/2018
40	Respiratory, Thoracic, Mediastinal Disorders	280	46WG	38519	Day 70	Cough & cold	10APR2019	Mild (1)	Dose/procedure not changed	Not Related	Recovered / Resolved	05/20/2019
41	Respiratory, Thoracic, Mediastinal Disorders	280	46WG	38519	Day 70	Cough at night	10APR2019	Mild (1)	Dose/procedure not changed	Not Related	Recovered / Resolved	05/20/2019
42	Respiratory, Thoracic, Mediastinal Disorders	280	46WG	38519	Day 70	Cough	03SEP2019	Mild (1)	Dose/procedure not changed	Not Related	Recovered / Resolved	09/09/2019
43	Respiratory, Thoracic, Mediastinal Disorders	292	4JKU	96277	Day 28	Coryzal symptoms	21MAY2016	Mild (1)	Dose/procedure not changed	Not Related	Recovered / Resolved	05/26/2016
44	Respiratory, Thoracic, Mediastinal Disorders	292	4JKU	96277	Day 70	Coryzal Symptoms	04JUL2016	Mild (1)	Not applicable	Not Related	Recovered / Resolved	07/19/2016
45	Respiratory, Thoracic, Mediastinal Disorders	283	5NTX	59440	Day 28	cough	13MAR2018	Mild (1)	Not applicable	Not Related	Recovered / Resolved	04/06/2018
46	Respiratory, Thoracic, Mediastinal Disorders	283	5NTX	59440	Day 42	cough	07APR2018	Moderate (2)	Dose/procedure not changed	Not Related	Recovered / Resolved	04/25/2018
47	Respiratory, Thoracic, Mediastinal Disorders	283	5NTX	59440	Day 70	cough	26APR2018	Mild (1)	Dose/procedure not changed	Not Related	Recovered / Resolved	05/24/2018
48	psychiatric Disorders	273	337J	54148	Unscheduled	fussiness	30MAR2016	Mild (1)	Dose/procedure not changed	Not Related	Recovered / Resolved	10/04/2016

*Magenta AEs (i.e., discoloration of lips and throat, agitation and hyperactivity) were classified as possibly resulting in an unanticipated medically attended visits occurring from Study Day 1 through two weeks following the last dose of study drug, addressing one of the secondary outcomes.

Table 11a: Changes over Time in Hematology Parameters

		Therapy Group [b]														
		Randomized					Active					Placebo				
		N	Mean	SD	10th pctl	90th pctl	N	Mean	SD	10th pctl	90th pctl	N	Mean	SD	10th pctl	90th pctl
WBC ($1000/mm^3$)	Baseline	34 [a]	11.2	2.54	7.5	14.7	17	11.4	2.48	7.5	15.0	17	11.1	2.67	8.6	14.7
	Day 14	31	10.7	2.52	7.3	13.7	16	10.7	2.23	7.3	13.7	15	10.7	2.89	6.9	15.6
	Day 28	32	10.4	2.89	6.5	14.1	16	10.2	3.24	5.9	14.1	16	10.7	2.59	7.8	15.3
	Day 42	30	10.0	2.52	6.9	13.4	14	9.8	3.23	5.6	14.8	16	10.2	1.78	8.0	12.9
	Day 70	28	10.5	2.91	7.1	14.5	15	11.2	3.40	5.7	15.2	13	9.7	2.08	7.3	12.4
Hemoglobin (g/dl)	Baseline	34 [a]	12.1	0.93	11.2	13.5	17	11.8	0.94	10.6	12.8	17	12.3	0.87	11.2	13.7
	Day 14	31	12.2	1.02	11.3	13.3	16	12.0	1.01	10.8	13.2	15	12.5	1.00	11.3	13.6
	Day 28	32	12.1	0.85	10.8	13.2	16	12.0	0.82	10.5	13.2	16	12.1	0.90	10.8	13.5
	Day 42	30	12.1	0.96	10.8	13.5	14	12.0	0.85	10.7	12.9	16	12.2	1.07	10.9	13.6
	Day 70	28	12.2	0.85	11.0	13.6	15	12.0	0.70	11.0	13.0	13	12.4	1.00	10.9	13.8

[a]Subject 3RJM dropped out of study without taking study drug after randomization and before study visit-1; no baseline labs were collected.

[b] Using general linear mixed model with random intercept was fitted for each parameter. Each model contains therapy, time and therapy by time interaction. A significant (p-value<0.05) nteraction term is an indication of difference in trajectory over time between the therapy groups. No significant interaction was found in WBC.

Table 11a: Changes over Time in Hematology Parameters (continued)

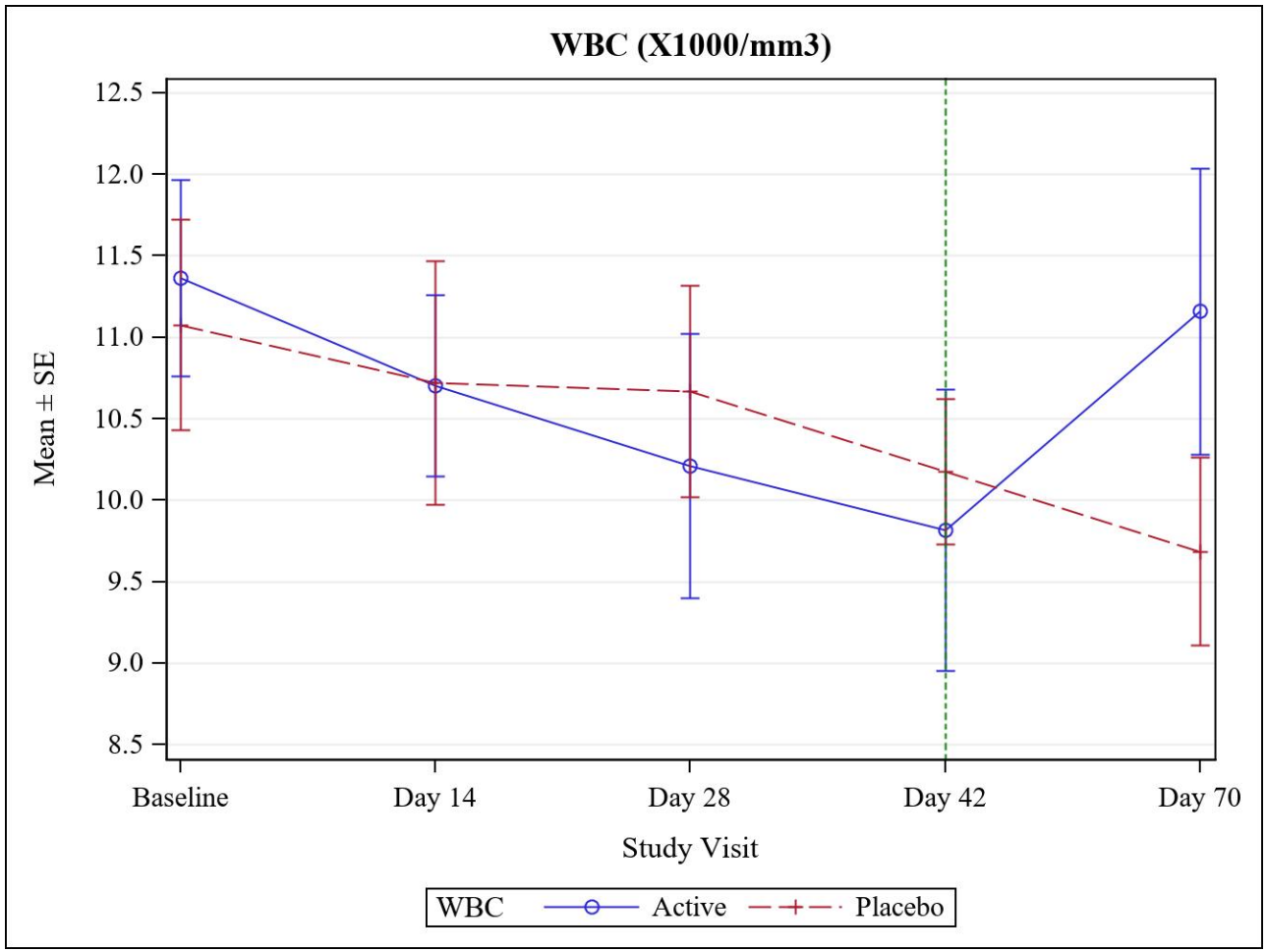
		Therapy Group [b]														
		Randomized					Active					Placebo				
		N	Mean	SD	10th pctl	90th pctl	N	Mean	SD	10th pctl	90th pctl	N	Mean	SD	10th pctl	90th pctl
ANC (cells/10^3µL)	Baseline	34[a]	2864	1164	1570	4661	17	2873	1082	1700	4450	17	2855	1275	1210	4800
	Day 14	31	3005	1381	1700	4899	16	3463	1294	2280	6170	15	2517	1341	1210	4899
	Day 28	32	2863	1385	1300	4537	16	3132	1543	1300	4600	16	2595	1196	1030	3950
	Day 42	30	2766	1077	1295	3969	14	2897	1076	1300	4000	16	2652	1099	1290	3938
	Day 70	28	2935	1175	1360	4692	15	3127	1161	1929	5000	13	2712	1197	1360	4390
Platelet (10^3µL)[#]	Baseline	34 [a]	338	109	215	485	17	367	97	220	503	17	310	117	159	485
	Day 14	31	328	93	228	425	16	371	71	283	432	15	283	93	190	365
	Day 28	32	372	103	251	517	16	419	95	300	545	16	325	89	231	456
	Day 42	30	347	85	245	458	14	390	53	328	470	16	309	92	239	414
	Day 70	28	314	61	239	412	15	316	65	243	417	13	311	58	239	388

[a]Subject 3RJM dropped out of study without taking study drug after randomization and before study visit-1; no baseline labs were collected.

[b] Using general linear mixed model with random intercept was fitted for each parameter. Each model contains therapy, time and therapy by time interaction. A significant (p-value<0.05) nteraction term is an indication of difference in trajectory over time between the therapy groups. No significant interaction was found in ANC. Platelet showed a significant therapy by time interaction (p=0.0341). In particular, significant difference between therapy groups were found at day 14 (p=0.0054), day 28 (p=0.0015) and day 42 (p=0.0121).

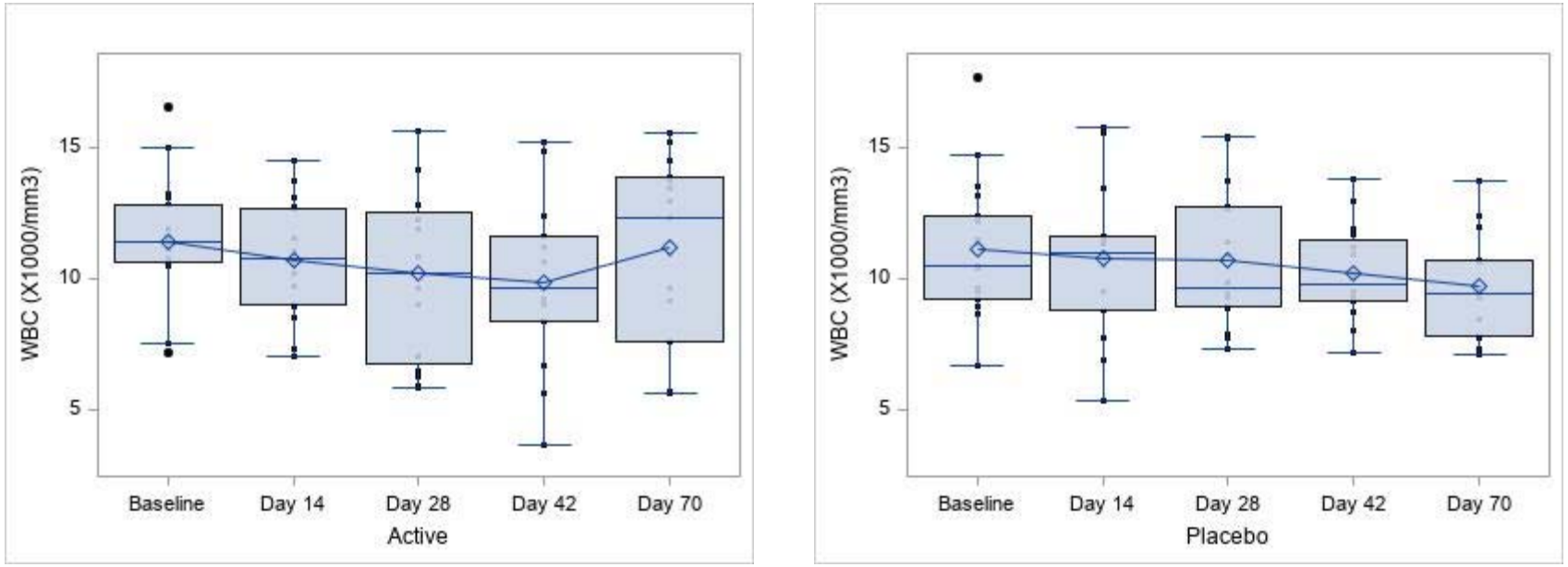
Figure 4: Changes in Hematology Parameters over Time for Enrolled Subjects

Figure 4a: Plot of WBC mean (±SE) over time



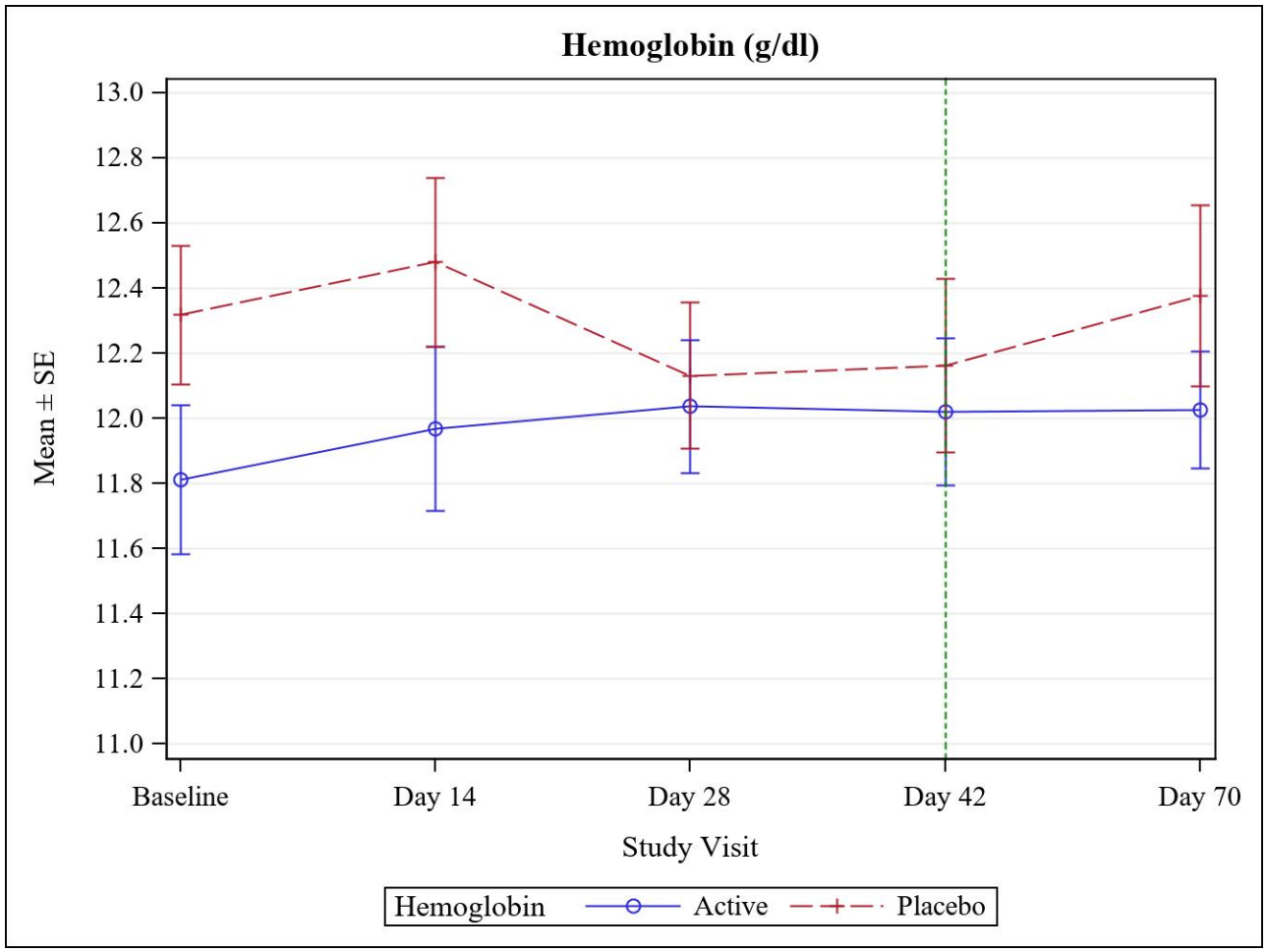
*Green reference line represents end of treatment phase

Figure 4b: Boxplots of WBC over time



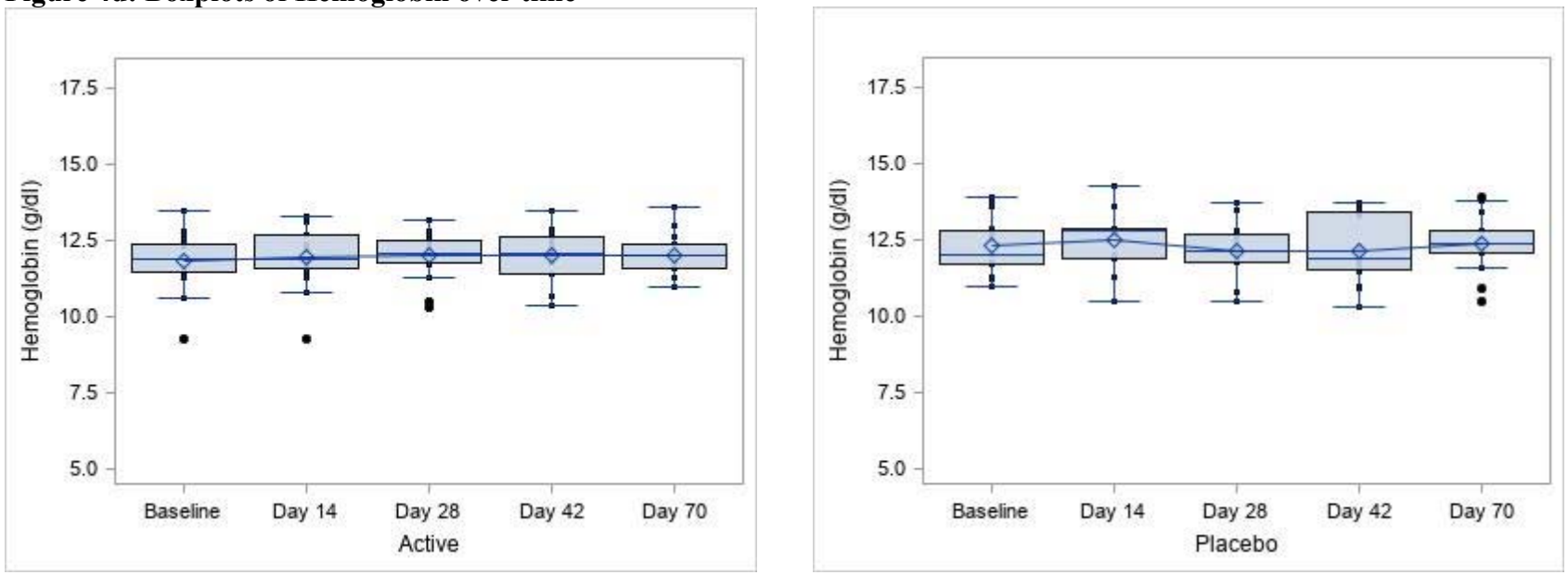
Interpretation: Borders of each box are the 1st (Q1) and 3rd (Q3) quartiles; line inside the box is the median; diamond is the mean; vertical lines outside the box (whiskers) extends through maximum and minimum points that are not outliers; and points beyond the whiskers are outliers greater than or less than 1.5 times IQR(=Q3-Q1). Lines across the boxplots connect the means.

Figure 4c: Plot of Hemoglobin mean (±SE) over time



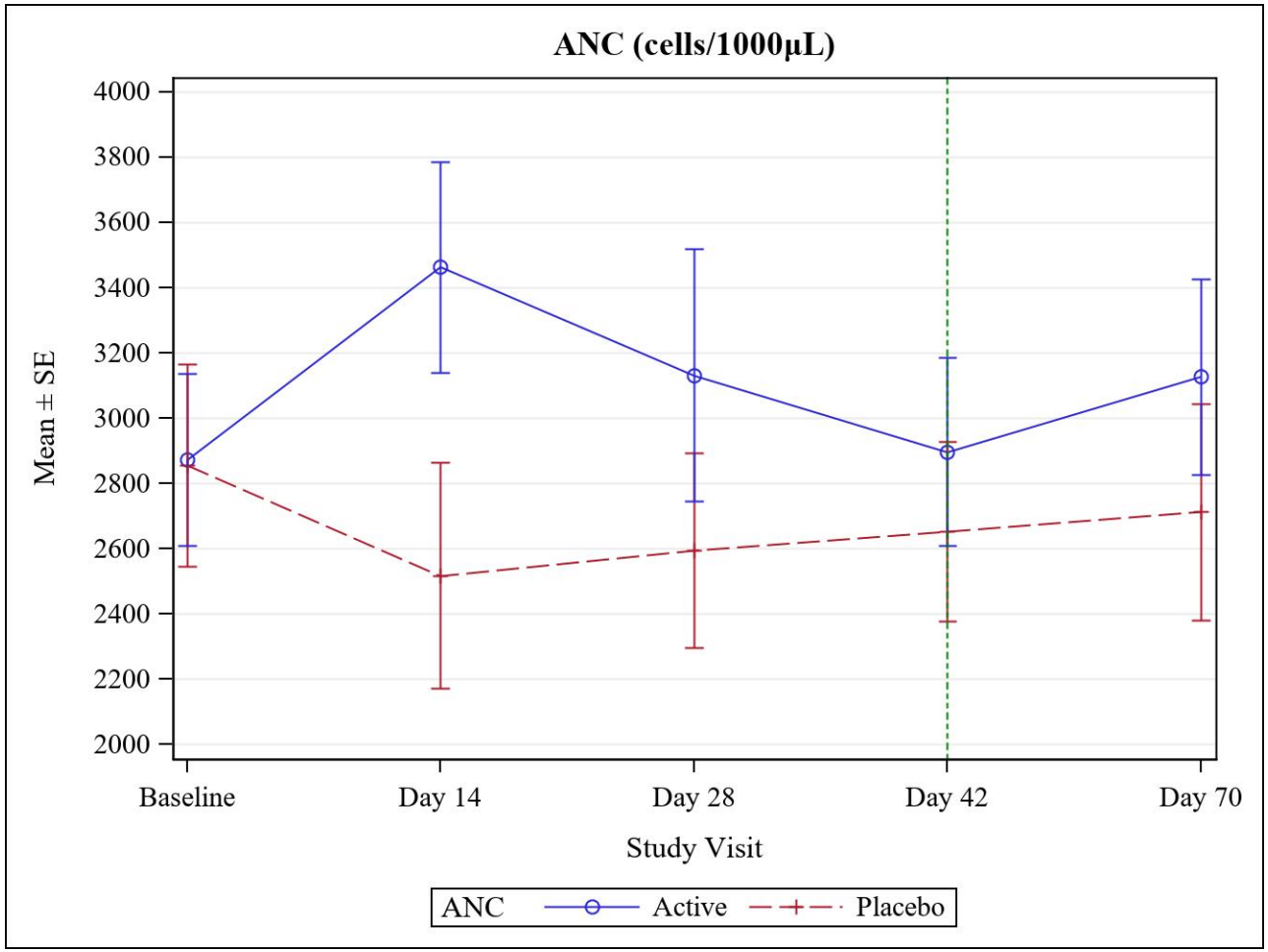
*Green reference line represents end of treatment phase

Figure 4d: Boxplots of Hemoglobin over time



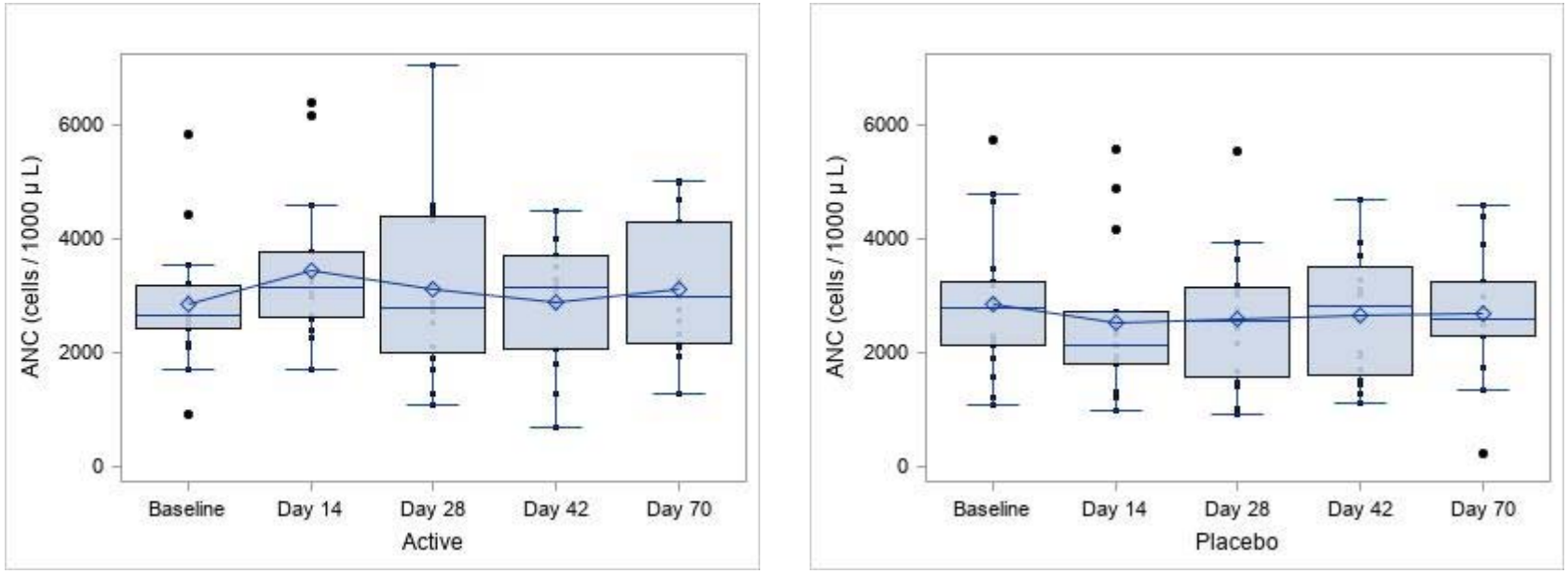
Interpretation: Borders of each box are the 1st (Q1) and 3rd (Q3) quartiles; line inside the box is the median; diamond is the mean; vertical lines outside the box (whiskers) extends through maximum and minimum points that are not outliers; and points beyond the whiskers are outliers greater than or less than 1.5 times IQR(=Q3-Q1). Lines across the boxplots connect the means.

Figure 4e: Plot of ANC mean (±SE) over time



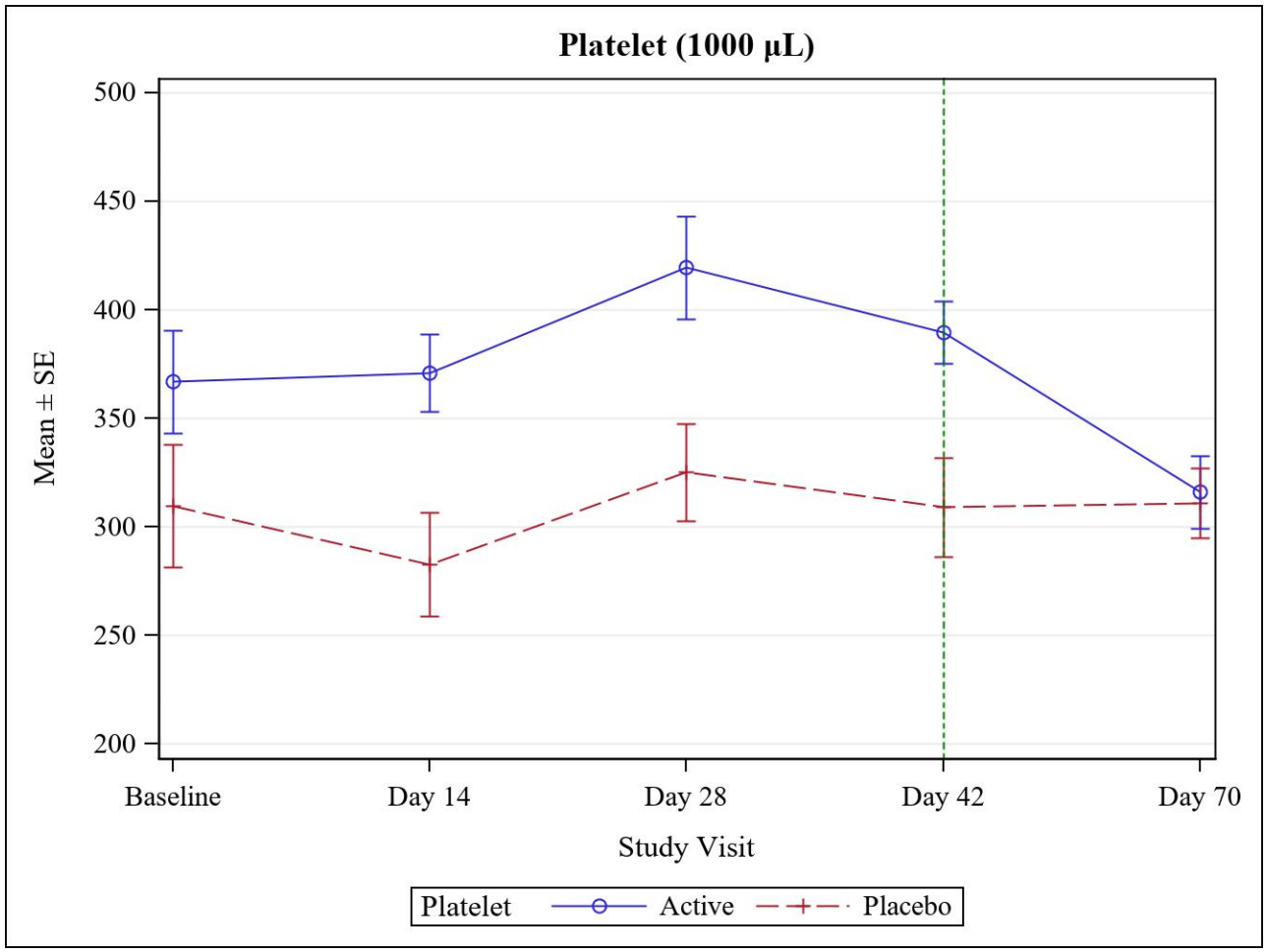
*Green reference line represents end of treatment phase

Figure 4f: Boxplots of ANC over time



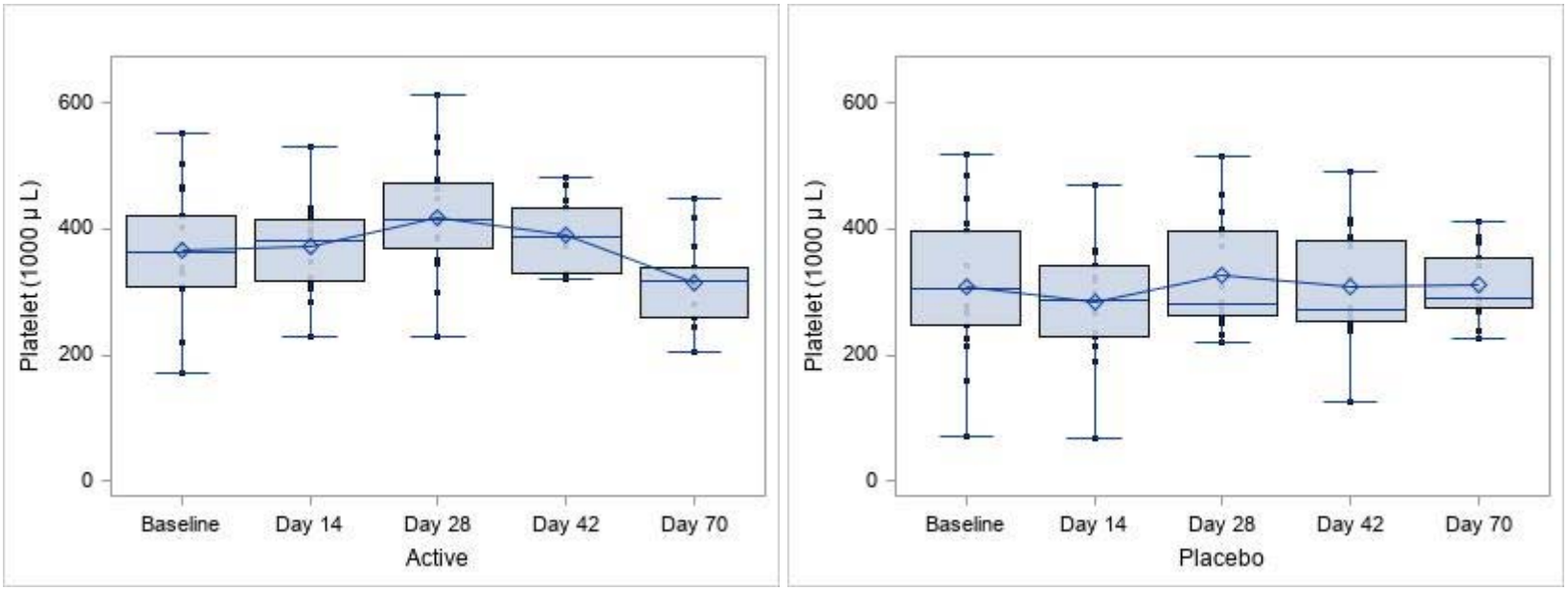
Interpretation: Borders of each box are the 1st (Q1) and 3rd (Q3) quartiles; line inside the box is the median; diamond is the mean; vertical lines outside the box (whiskers) extends through maximum and minimum points that are not outliers; and points beyond the whiskers are outliers greater than or less than 1.5 times IQR(=Q3-Q1). Lines across the boxplots connect the

Figure 4g: Plot of Platelet mean (±SE) over time *



*Green reference line represents end of treatment phase

Figure 4h: Boxplots of Platelet over time



Interpretation: Borders of each box are the 1st (Q1) and 3rd (Q3) quartiles; line inside the box is the median; diamond is the mean; vertical lines outside the box (whiskers) extends through maximum and minimum points that are not outliers; and points beyond the whiskers are outliers greater than or less than 1.5 times IQR(=Q3-Q1). Lines across the boxplots connect the means.

Table 11b: Changes over Time in Chemistry Parameters

		Therapy Group[b]														
		Randomized					Active					Placebo				
		N	Mean	SD	10th pctl	90th pctl	N	Mean	SD	10th pctl	90th pctl	N	Mean	SD	10th pctl	90th pctl
Serum Creatinine (mg/dL)	Baseline	34[a]	0.3	0.07	0.2	0.3	17	0.3	0.09	0.2	0.4	17	0.2	0.06	0.2	0.3
	Day 14	31	0.3	0.07	0.2	0.4	16	0.3	0.08	0.2	0.4	15	0.3	0.07	0.2	0.4
	Day 28	32	0.3	0.07	0.2	0.3	16	0.3	0.09	0.2	0.4	16	0.3	0.06	0.2	0.3
	Day 42	31	0.3	0.07	0.2	0.3	15	0.3	0.08	0.2	0.4	16	0.3	0.05	0.2	0.3
	Day 70	29	0.3	0.06	0.2	0.4	15	0.3	0.07	0.2	0.4	14	0.3	0.06	0.2	0.3
Creatinine Clearance (mL/min/1.73 m^2)	Baseline	33[a]	135.0	46.45	84.4	186.4	16	131.2	53.61	64.1	171.7	17	138.6	39.91	84.4	207.8
	Day 14	31	126.1	58.24	63.0	184.0	16	129.1	70.56	62.9	190.9	15	122.9	43.75	63.0	184.0
	Day 28	32	131.2	47.73	88.0	178.2	16	133.6	52.44	70.8	178.2	16	128.7	44.10	88.0	213.5
	Day 42	30	132.5	46.73	76.2	179.6	15	126.7	51.51	75.4	177.2	15	138.2	42.42	77.1	182.0
	Day 70	25	123.6	32.92	82.3	163.8	13	118.2	35.05	82.3	141.6	12	129.6	30.83	84.7	163.8

[a]Subject 3RJM dropped out of study after randomization and before study visit 1, hence no baseline labs were collected.Subject 974K from site 296 has no Creatinine Clearance collected at baseline.

[b] Using general linear mixed model with random intercept was fitted for each parameter. Each model contains therapy, time and therapy by time interaction. A significant (p-value<0.05) nteraction term is an indication of difference in trajectory over time between the therapy groups. No significant interaction was found in serum creatinine and creatinine clearance.

Table 11b: Changes over Time in Chemistry Parameters (continued)

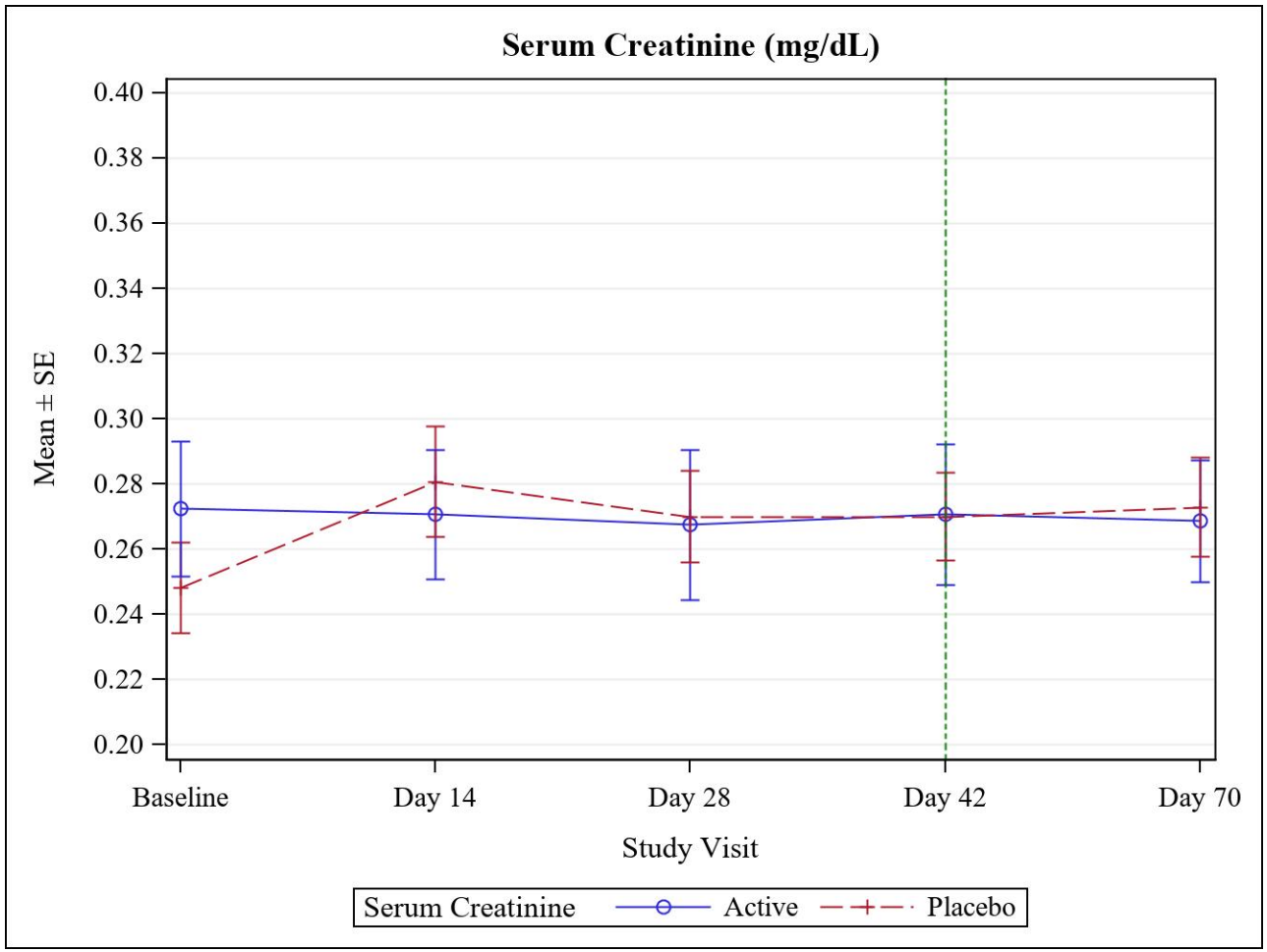
		Therapy Group[b]														
		Randomized					Active					Placebo				
		N	Mean	SD	10th pctl	90th pctl	N	Mean	SD	10th pctl	90th pctl	N	Mean	SD	10th pctl	90th pctl
ALT (U/L)	Baseline	34[a]	24.3	10.24	16.0	35.0	17	22.7	11.15	16.0	32.0	17	25.9	9.30	16.0	38.0
	Day 14	31	24.6	9.72	15.0	40.0	16	22.1	7.19	13.0	34.0	15	27.3	11.49	16.0	43.0
	Day 28	32	24.2	7.92	16.0	36.0	16	21.0	5.15	15.0	28.0	16	27.4	9.02	16.0	42.0
	Day 42	31	24.2	8.25	13.0	35.0	15	22.9	9.62	13.0	39.0	16	25.4	6.81	14.0	35.0
	Day 70	29	23.7	7.26	16.0	36.0	15	22.0	6.00	15.0	32.0	14	25.5	8.23	16.0	37.0
Total Bilirubin (mg/dL)	Baseline	34[a]	0.3	0.13	0.2	0.4	17	0.3	0.12	0.1	0.4	17	0.3	0.13	0.2	0.6
	Day 14	31	0.3	0.17	0.2	0.4	16	0.3	0.12	0.1	0.4	15	0.3	0.20	0.2	0.5
	Day 28	32	0.3	0.13	0.2	0.4	16	0.3	0.14	0.2	0.5	16	0.2	0.11	0.2	0.4
	Day 42	31	0.3	0.11	0.2	0.4	15	0.2	0.07	0.1	0.3	16	0.3	0.12	0.2	0.5
	Day 70	29	0.3	0.10	0.1	0.4	15	0.2	0.10	0.1	0.4	14	0.3	0.11	0.2	0.4

[a]Subject 3RJM dropped out of study after randomization and before study visit 1, hence no baseline labs were collected. Subject 974K from site 296 has no Creatinine Clearance collected at baseline.

[b] Using general linear mixed model with random intercept was fitted for each parameter. Each model contains therapy, time and therapy by time interaction. A significant (p-value<0.05) nteraction term is an indication of difference in trajectory over time between the therapy groups. No significant interaction was found in ALT. There is a significant difference in change of total bilirubin over time between active and placebo group. However, none of the pairwise comparison between placebo and active groups at each time point was found to be significantly different. The main driver of this significant interaction is that in the placebo group, there was a significant increase in total bilirubin from Day 14 to day 28 (p=0.0086).

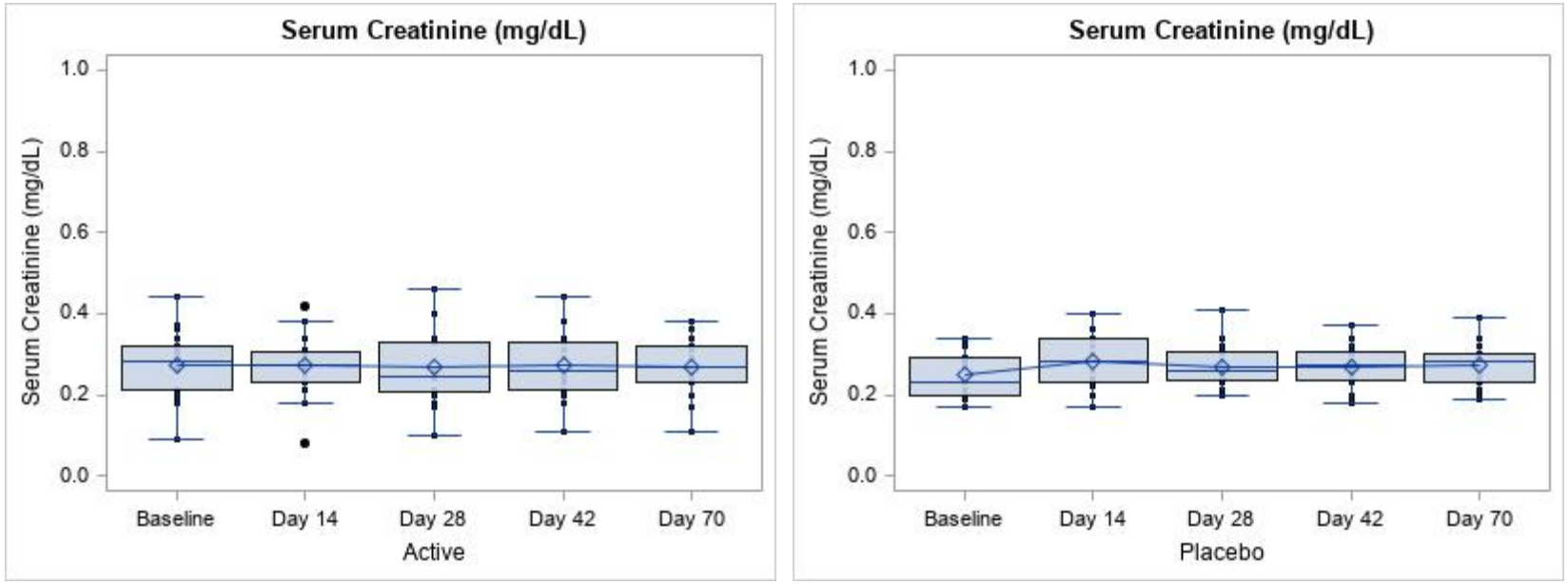
Figure 5: Changes in Chemistry Parameters over Time for Enrolled Subjects

Figure 5a: Plot of Serum Creatinine mean (±SE) over time



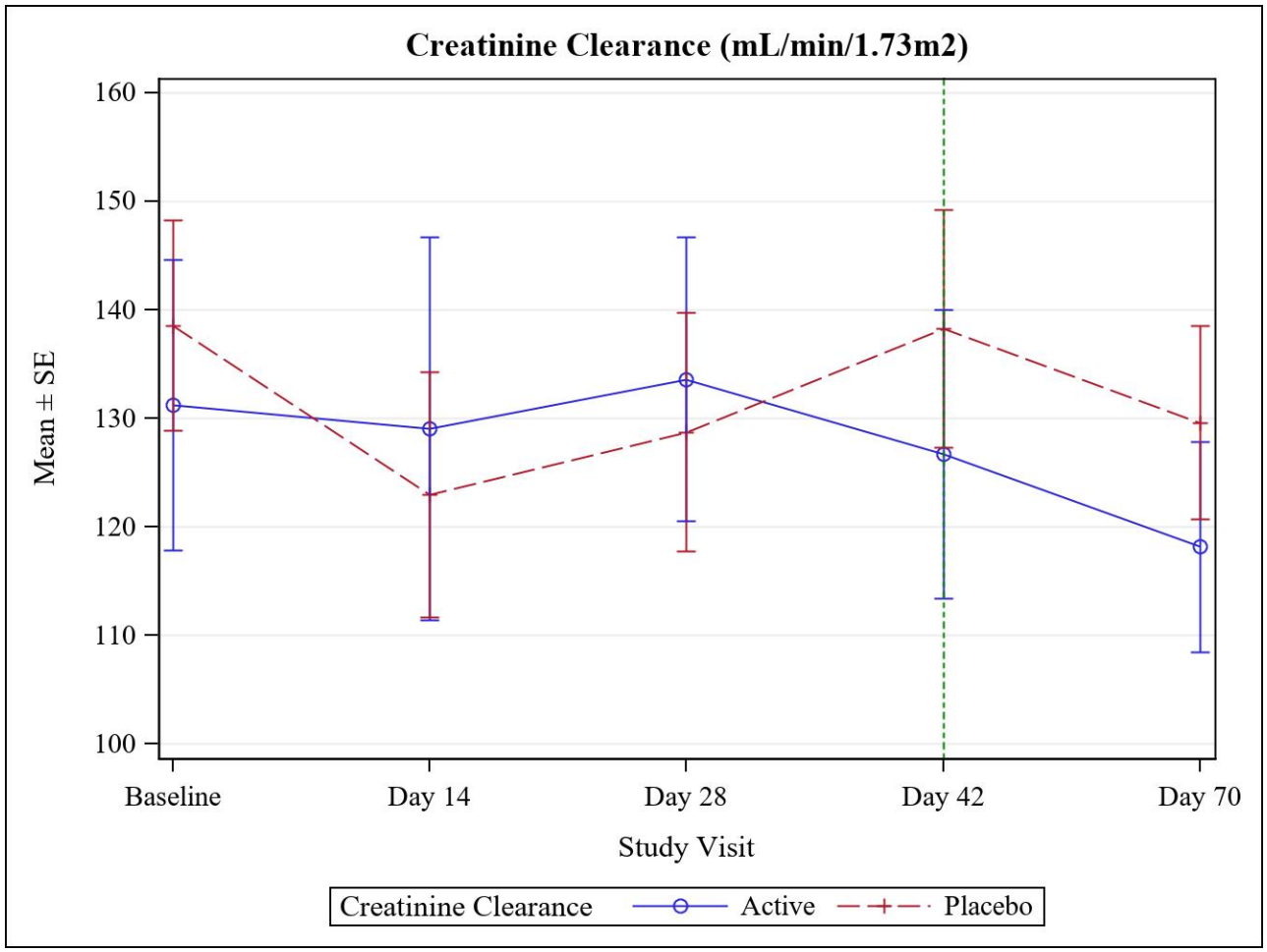
* Green reference line represents end of treatment phase

Figure 5b: Boxplots of Serum Creatinine over time



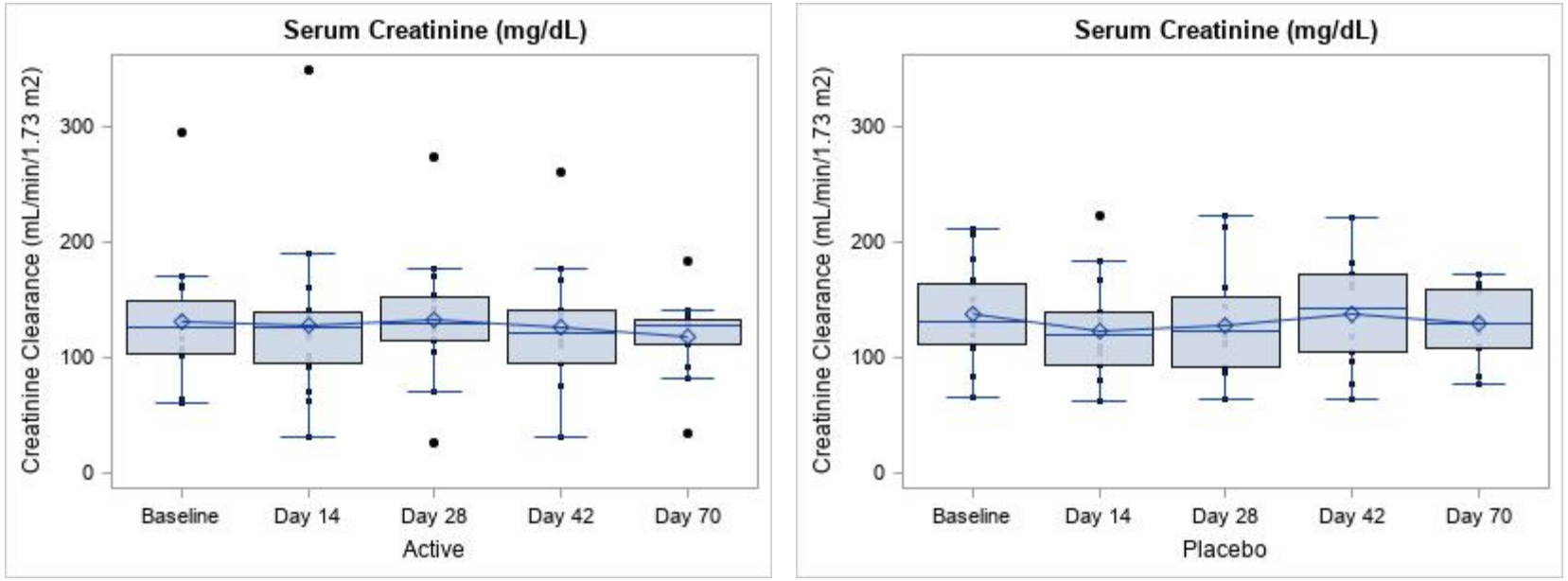
Interpretation: Borders of each box are the 1st (Q1) and 3rd (Q3) quartiles; line inside the box is the median; diamond is the mean; vertical lines outside the box (whiskers) extends through maximum and minimum points that are not outliers; and points beyond the whiskers are outliers greater than or less than 1.5 times IQR(=Q3-Q1). Lines across the boxplots connect the means.

Figure 5c: Plot of Creatinine Clearance mean (±SE) over time



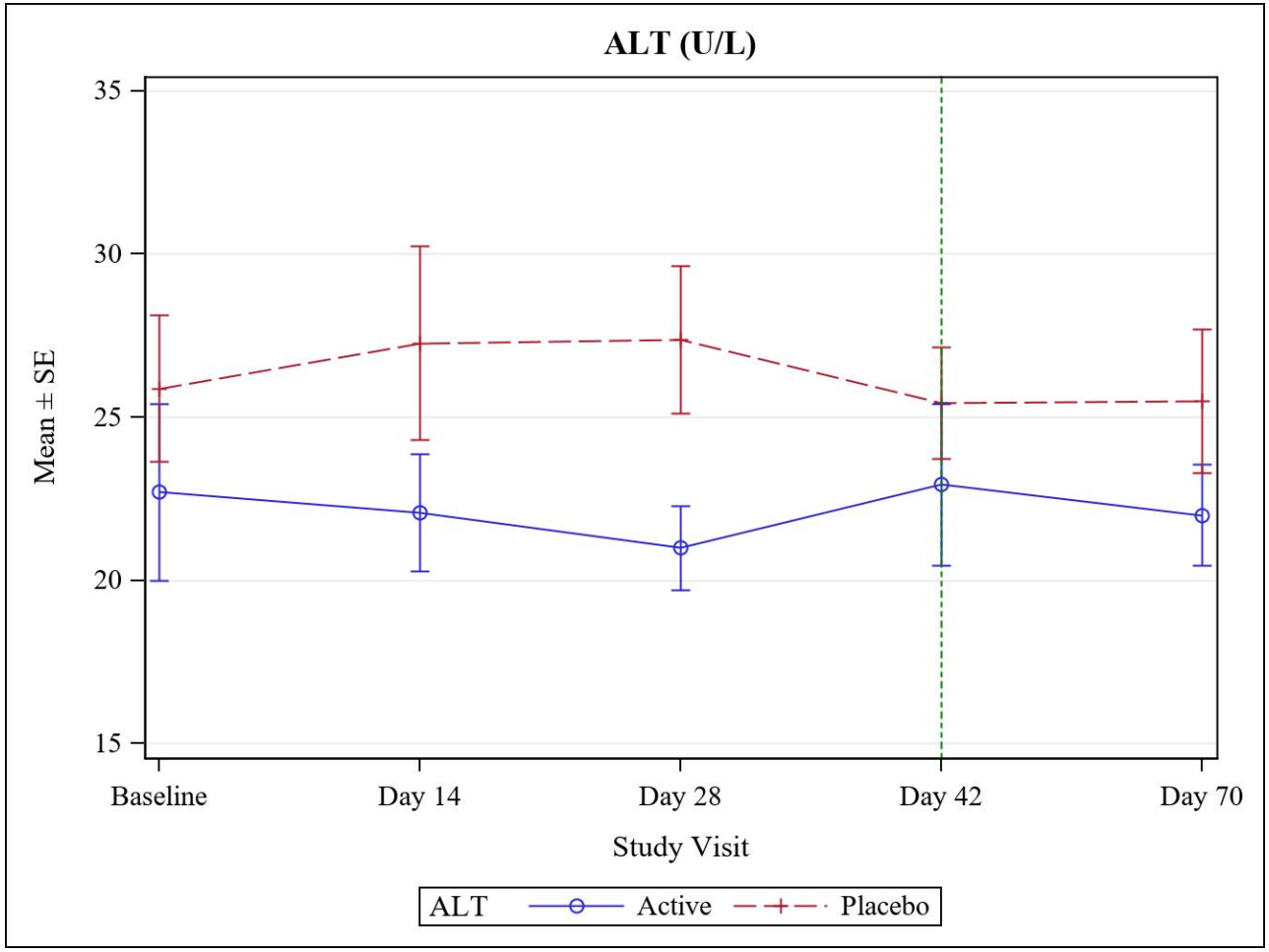
* Green reference line represents end of treatment phase

Figure 5d: Boxplots of Creatinine Clearance over time



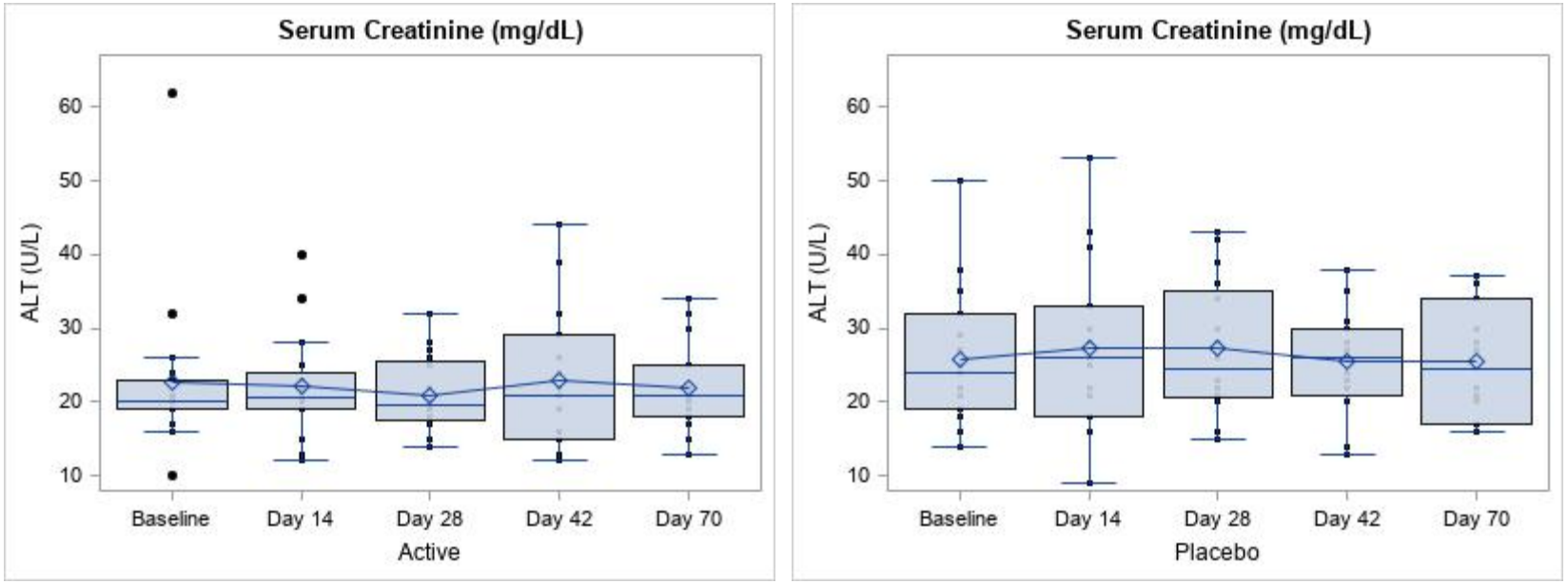
Interpretation: Borders of each box are the 1st (Q1) and 3rd (Q3) quartiles; line inside the box is the median; diamond is the mean; vertical lines outside the box (whiskers) extends through maximum and minimum points that are not outliers; and points beyond the whiskers are outliers greater than or less than 1.5 times IQR(=Q3-Q1). Lines across the boxplots connect the

Figure 5e: Plot of ALT mean (±SE) over time



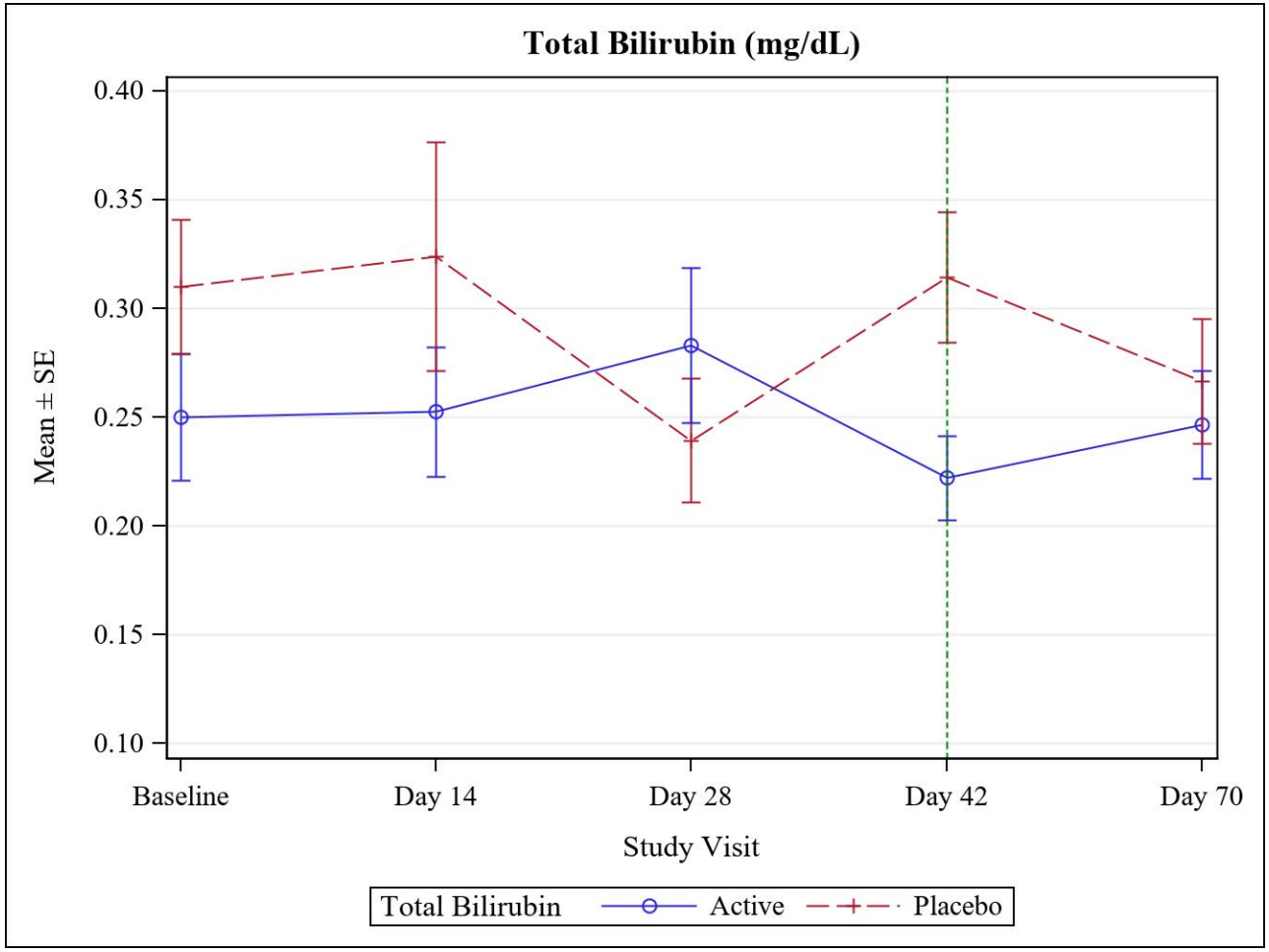
* Green reference line represents end of treatment phase

Figure 5f: Boxplots of ALT over time



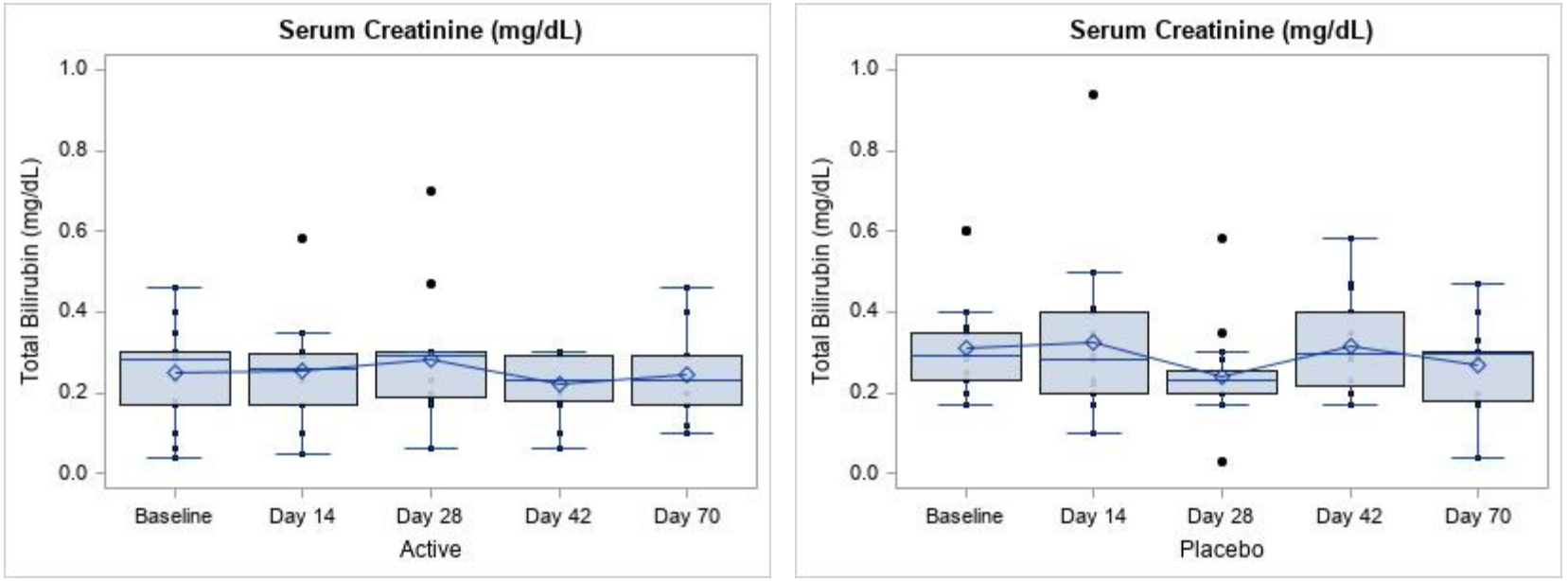
Interpretation: Borders of each box are the 1st (Q1) and 3rd (Q3) quartiles; line inside the box is the median; diamond is the mean; vertical lines outside the box (whiskers) extends through maximum and minimum points that are not outliers; and points beyond the whiskers are outliers greater than or less than 1.5 times IQR(=Q3-Q1). Lines across the boxplots connect the means.

Figure 5g: Plot of Total Bilirubin mean (±SE) over time



* Green reference line represents end of treatment phase

Figure 5h: Boxplots of Total Bilirubin over time



Interpretation: Borders of each box are the 1st (Q1) and 3rd (Q3) quartiles; line inside the box is the median; diamond is the mean; vertical lines outside the box (whiskers) extends through maximum and minimum points that are not outliers; and points beyond the whiskers are outliers greater than or less than 1.5 times IQR(=Q3-Q1). Lines across the boxplots connect the means.

Table 12: Maximum Degree of Neutropenia (Lowest ANC) During Day 1-42 Period

Grade	Number of Subjects/N (%)					
	CASG 102 No Treatment Group[a]	CASG 102 Ganciclovir Group[a]	CASG 109 Valganciclovir[b]	CASG 112 [c]		11-0069 Day 0-Day 70
				Day 0-Day 42	Day 42-Month 7	
Grade 3 (ANC 500-749 cells/10^3 μL)	8/43 (18.6%)	18/46 (39.1%)	7/24 (29.2%)	Valganciclovir 16/109 (14.7%)	Placebo: 8/49 (16.3%)	Placebo 0/18 (0%)
					Valganciclovir: 7/47 (14.9%)	Valganciclovir 1/17 (5.9%)
Grade 4 (ANC < 500 cells/10^3 μL)	1/43 (2.3%)	11/46 (23.9%)	2/24 (8.3%)	Valganciclovir 5 /109 (4.6%)	Placebo: 5/49 (10.2%)	Placebo 1/18 (5.6%)
					Valganciclovir: 3/47 (6.4%)	Valganciclovir 0/17 (0%)
Total with Grade 3 or Grade 4 Neutropenia	9/43 (20.9%)	29/46 (63.0%)	9/24 (37.5%)	Valganciclovir 21/109 (19.3%)	Placebo: 13/49 (26.5%)	Placebo 1/18 (5.6%)
					Valganciclovir: 10/47 (21.3%)	Valganciclovir 1/17 (5.9%)

[a] J Pediatr 2003;143:16-25
[b] J Infect Dis 2008;197:836-845
[c] N Engl J Med 2015; 372: 933-43

Table 13: Maximum Degree of Anemia (Lowest HGB) for 11-0069 Valganciclovir

Grade	Number of Subjects (%) During Day 1-42	Number of Subjects (%) During Day 1-70
Grade 3 (Hemoglobin 6.0-6.9 g/dl)	0 (0%)	0 (0%)
Grade 4 (Hemoglobin < 6.0 g/dl)	0 (0%)	0 (0%)
Total with Grade 3 or Grade 4 Anemia	0 (0%)	0 (0%)

Table 14: Maximum Degree of Anemia (Lowest PLT) for 11-0069 Valganciclovir

Grade	Number of Subjects (%) During Day 1-42	Number of Subjects (%) During Day 1-70
Grade 3 (Platelet 25-50 10^3µL)	0 (0%)	0 (0%)
Grade 4 (Platelet < 25 10^3µL)	0 (0%)	0 (0%)
Total with Grade 3 or Grade 4 Anemia	0 (0%)	0 (0%)

Table 15: Maximum Degree of ALT (Highest ALT) for 11-0069 Valganciclovir

Grade	Number of Subjects (%) During Day 1-42	Number of Subjects (%) During Day 1-70
Grade 3 (ALT 5.1-10.0 ULN†)	0 (0%)	0 (0%)
Grade 4 (ALT >10.0 ULN†)	0 (0%)	0 (0%)
Total with Grade 3 or Grade 4 ALT	0 (0%)	0 (0%)

†Upper Limit Normal Range

Table 16: Maximum Degree of Creatinine (Highest creatinine) for 11-0069 Valganciclovir

Grade	Number of Subjects (%) During Day 1-42	Number of Subjects (%) During Day 1-70
Grade 3 (Creatinine 1.9-3.4 ULN†)	0 (0%)	0 (0%)
Grade 4 (Creatinine >3.4 ULN†)	0 (0%)	0 (0%)
Total with Grade 3 or Grade 4 Creatinine	0 (0%)	0 (0%)

†Upper Limit Normal Range

Table 17: Summary of Concomitant Medications by Treatment Group (Blinded Treatment Phase)

	Randomized (N=35)	Active (N=17)	Placebo (N=18)	P-Value
Number of Subjects with versus without Concomitant Medications				
# of Subjects at least one Concomitant Medication	28 (80.0)	15 (88.2)	13 (72.2)	0.1993*
# of Subjects without any Concomitant Medication	7 (20.0)	2 (11.8)	5 (27.8)	
# of Concomitant Medications				
N	35	15	13	~1 **
Mean ± SE	8.1 ± 2.7	12.3 ± 5.8	7.5 ± 2.3	
Median	3	5	4	
(Min-Max)	1 - 88	1 - 88	1 - 30	

* p-value calculated using Fisher's Exact test

** p-value calculated using Wilcoxon test

Table 18a: Dose (mg/kg) of Valganciclovir or Placebo
[a]

		Therapy Group			
Study Day		**Randomized**	**Active**	**Placebo**	**p-value[d]**
Baseline/ Day 1	N	33[b]	17	16	0.9791
	Mean ± SD	16.0±0.1	16.0±0.1	16.0±0.1	
	Median (Min, Max)	16.0 (15.5, 16.2)	16.0 (15.7, 16.2)	16.0 (15.5, 16.1)	
Day 14	N	32[c]	16	16	0.3674
	Mean ± SD	15.7±1.5	15.5±2.1	15.9±0.3	
	Median (Min, Max)	16.0 (7.7, 16.4)	16.0 (7.7, 16.4)	16.0 (14.9, 16.1)	
Day 28	N	32 [c]	16	16	0.2241
	Mean ± SD	15.8±1.4	15.5±2.0	16.0±0.1	
	Median (Min, Max)	16.0 (8.2, 16.4)	16.0 (8.2, 16.4)	16.0 (15.7, 16.3)	

[a]Dosage level for Placebo subjects reflects the dosage of simple syrup as 60-90% sucrose.
[b] Subject 3RJM dropped out of study after randomization and before study visit-1; hence no study drug was ever administered. Subject 1K5D had study drug held due to a need to repeat labs on day 1 for a low platelet count at baseline. This subject had drug dose calculated at baseline but drug was never administered.
[c]Subject 17EH only had dose information at enrollment. Subject dropped out of study about a month after randomization due to mother withdrawing consent.
[d]p-values to compare Active and Placebo were obtained using general linear mixed model.

Figure 6a: Dose (mg/kg) over Time

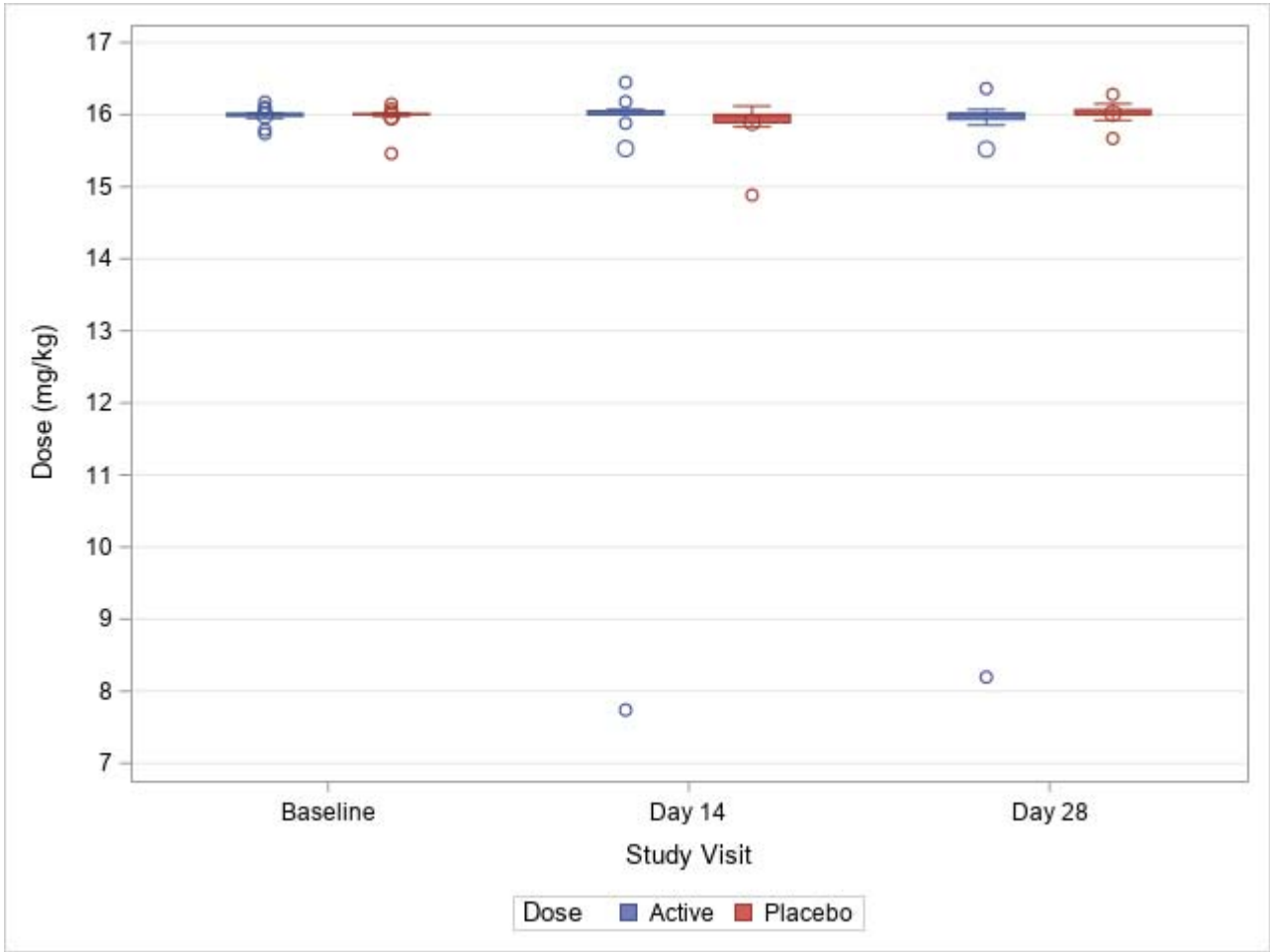


Table 18b: Weight (kg) at the Time of Dosing of Valganciclovir or Placebo

		Therapy Group			
Study Day		**Randomized**	**Active**	**Placebo**	**p-value[c]**
Baseline/ Day 1	N	34[a]	17	17	0.7073
	Mean ± SD	10.5 ± 4.0	10.2 ± 4.9	10.7 ± 3.0	
	Median (Min, Max)	9.9 (2.9, 19.9)	8.1 (2.9, 19.9)	10.4 (7.0, 16.8)	
Day 14	N	32[b]	16	16	0.6069
	Mean ± SD	10.8 ± 3.8	10.5 ± 4.6	11.1 ± 3.0	
	Median (Min, Max)	10.7 (3.2, 19.6)	9.5 (3.2, 19.6)	10.7 (7.2, 17.2)	
Day 28	N	32[b]	16	16	0.6227
	Mean ± SD	10.9 ± 3.8	10.7 ± 4.5	11.2 ± 3.1	
	Median (Min, Max)	10.9 (3.7, 19.7)	9.6 (3.7, 19.7)	10.9 (7.4, 18.1)	

[a] Subject 3RJM dropped out of study after randomization and before study visit-1; hence no weight measurement was done.
[b] Subjects 1K5D and 17EH missed dose information for day 14 and day 28. They dropped out of study after about a month since randomization.
[c] p-values to compare Active and Placebo were obtained using general linear mixed model.

Figure 6b: Weight at Dosing

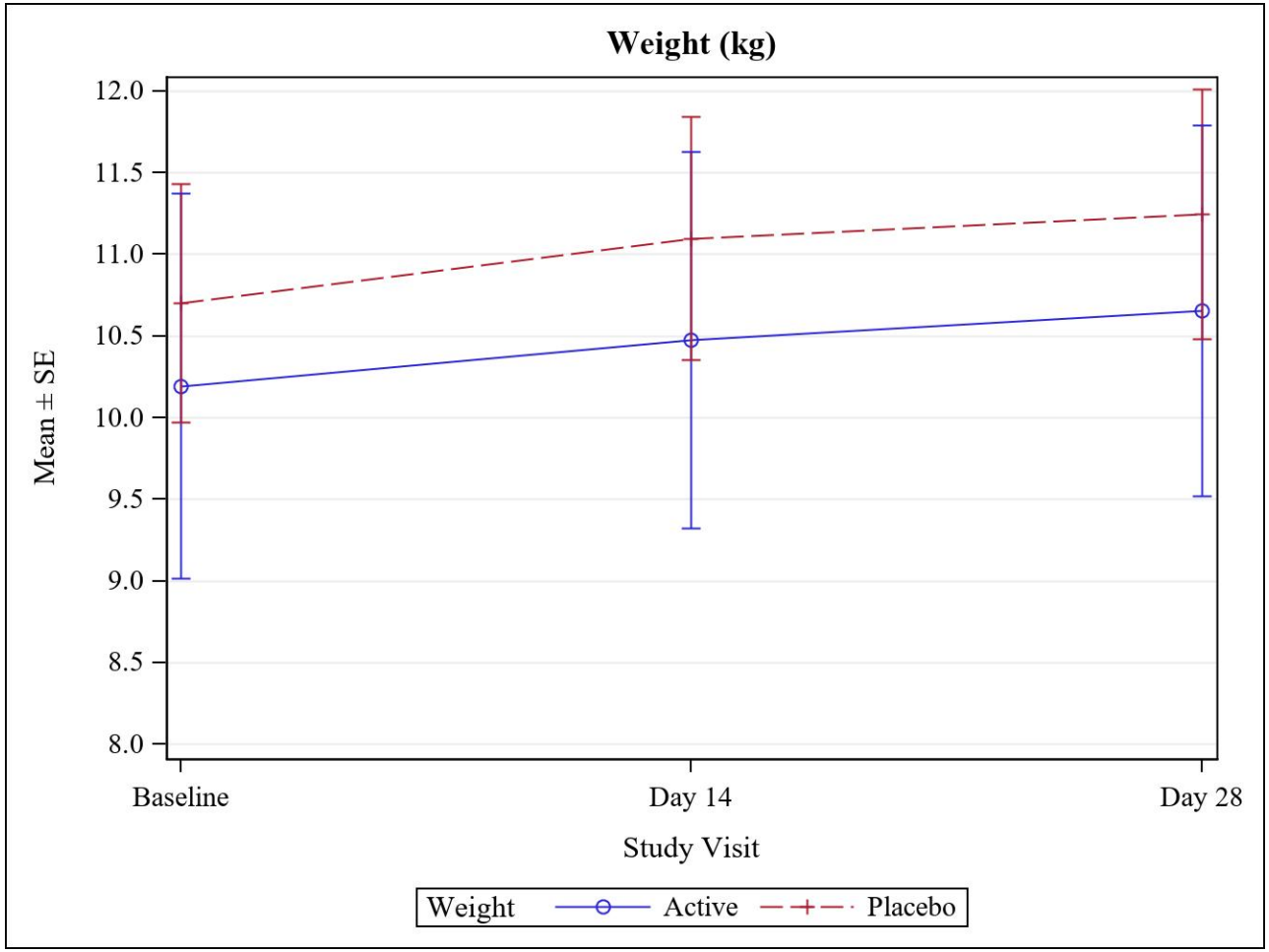


Table 18c: Length (cm) at the Time of Dosing of Valganciclovir or Placebo

		Therapy Group			
Study Day		**Randomized**	**Active**	**Placebo**	**p-value[d]**
Baseline/ Day 1	N	33[a]	16	17	0.4543
	Mean ± SD	78.3 ± 12.6	77.5 ± 15.0	79.1 ± 10.3	
	Median (Min, Max)	77.9 (58.3, 105.8)	74.8 (58.3, 105.8)	78.0 (64.0, 94.0)	
Day 14	N	32[b]	16	16	0.5724
	Mean ± SD	79.1 ± 13.0	77.9± 15.6	80.4 ± 10.1	
	Median (Min, Max)	78.5 (47.0, 106.0)	75.4 (47.0, 106.0)	79.9 (62.5, 94.0)	
Day 28	N	31[c]	16	15	0.4533
	Mean ± SD	79.4 ± 13.5	77.7 ± 16.4	81.2 ± 9.8	
	Median (Min, Max)	78.5 (43.0, 106.3)	75.7 (43.0, 106.3)	80.6 (64.0, 94.0)	

a. Subject 3RJM dropped out of study after randomization and before study visit-1; hence no length measurement taken. Subject 974K has missing length at baseline.
b. In addition to drop-out 3RJM, Subjects 1K5D and 17EH missed length information for day 14. They dropped out of study after about a month since randomization. Subject 974K has length data at Day 14.
c. In addition to drop-out 3RJM, Subjects 1K5D and 17EH missed length information for day 28. They dropped out of study after about a month since randomization. Subject 974K has length data at Day 28. Subject 3ZGW has missing length at day-2.
d. p-values to compare Active and Placebo were obtained using general linear mixed model.

Figure 6c: Length (cm) at the Time of Dosing

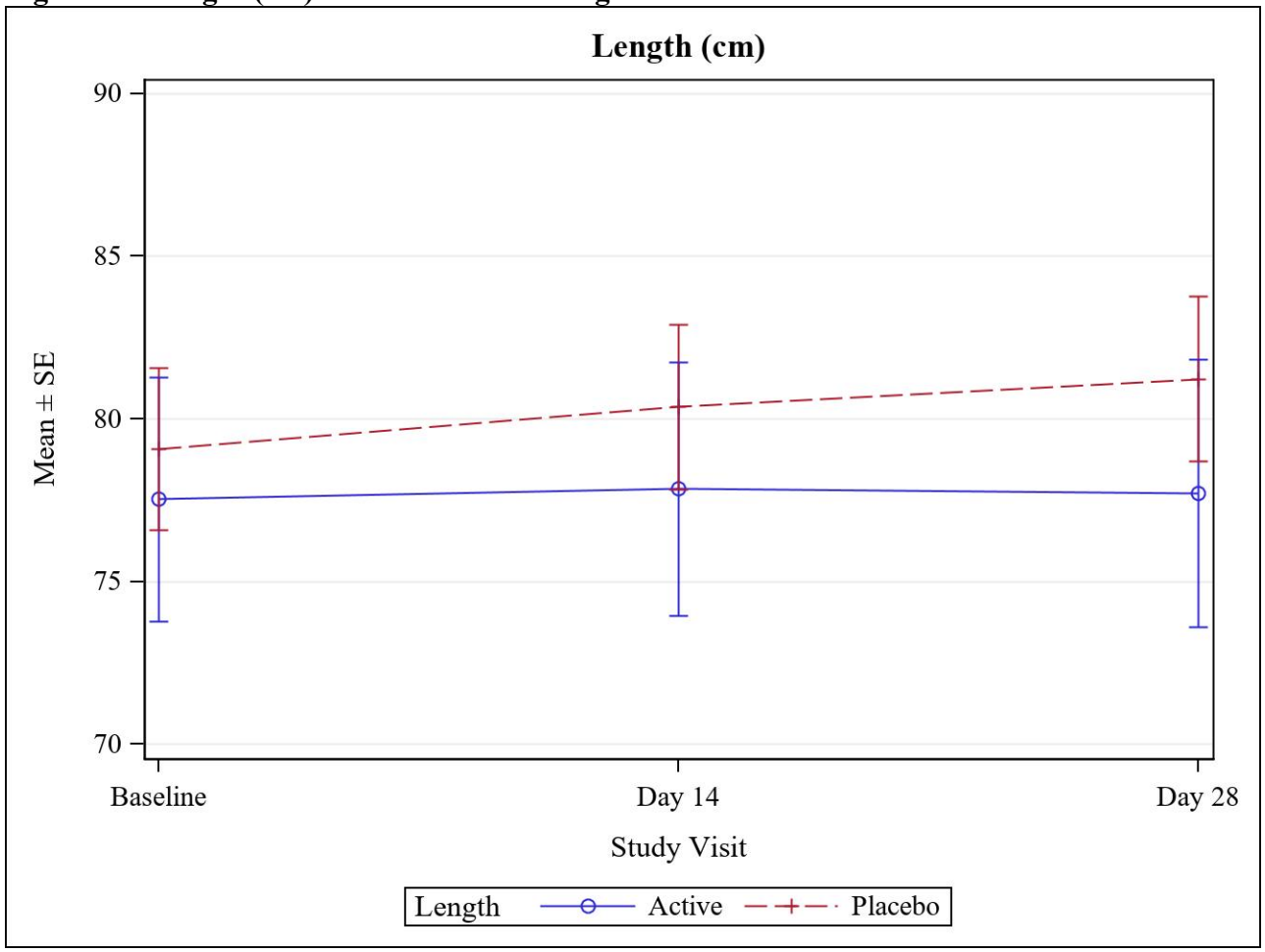


Table 19. Treatment Compliance by Visit and Therapy Group

Table 19a: Dosing Administration by Treatment Group and Visit

		Therapy Group		
	Randomized[1]	**Active[2]**	**Placebo[2]**	**p-value[5]**
Baseline				N/A
Total	34[3] (100.0%)	17 (50%)	17 (50%)	
Day 14 (n=32[4])				0.4578
No Change	11 (34.4%)	7 (43.8%)	4 (25.0%)	
Adjusted	21 (65.6%)	9 (56.3%)	12 (75.0%)	
Held	0 (0%)	0 (0%)	0 (0%)	
Day 28 (n=32[4])				~ 1
No Change	15 (46.9%)	7 (43.8%)	8 (50.0%)	
Adjusted	17 (53.1%)	9 (56.3%)	8 (50.0%)	
Held	0 (0%)	0 (0%)	0 (0%)	

[1]Out of total n = 34 for baseline, 32 for day 14 and day 28.
[2]Active and Placebo % uses the column total as the denominator, i.e. N/17 for active and placebo at baseline, N/16 for active and placebo at day 14 and 28.
[3]Subject 3RJM dropped out of study after randomization without taking study drug.
[4] Subject 17EH dropped out a month after randomization and did not complete dose information for day14 and day28 while subject and 1K5D dropped out soon after randomization without taking the study drug.
[5] P-value between active and placebo group for day 14 and day 28 is calculated using Fisher's exact test.

Table 19b: Reasons for Adjusted or Held Dose and Significant Changes in Laboratory Parameters

Day 14 (n=32)		**Therapy Group**		
Number Subjects with Dose Adjusted or Held: N=21	**Randomized[1] N (%)**	**Active[2] N (%)**	**Placebo[2] N (%)**	**p-value[3]**
Significant Change in Weight	18 (85.7%)	8 (88.9%)	10 (83.3%)	~1
Significant Change in Lab	1 (4.8%)	1 (100%)	0 (0%)	N/A
If there is significant change in lab, below provide significant changes in specific lab parameters:				
2a. Neutropenia	0 (0%)	0 (0%)	0 (0%)	
2b. Thrombocytopenia	0 (0%)	0 (0%)	0 (0%)	
2c. Renal Impairment**	1 (100%)	1 (100%)	0 (0%)	
2d. Hepatomeglia	0 (0%)	0 (0%)	0 (0%)	
2e. Other Lab	0 (0%)	0 (0%)	0 (0%)	
Other***	4 (19.0%)	2 (50%)	2 (50%)	N/A
**One subject had both weight and lab reasons ***One subject had both weight and Other reaons selected from Active group				
Day 28 (n=32)		**Therapy Group**		
Number Subjects with Dose Adjusted or Held: N=17	**Randomized N (%)**	**Active N (%)**	**Placebo N (%)**	
Significant Change in Weight	17 (100%)	9 (100%)	8 (100%)	N/A
Significant Change in Lab	0 (0%)	0 (0%)	0 (0%)	N/A
If there is significant change in lab, below provide significant changes in specific lab parameters:				
2a. Neutropenia	0 (0%)	0 (0%)	0 (0%)	
2b. Thrombocytopenia	0 (0%)	0 (0%)	0 (0%)	
2c. Renal Impairment	0 (0%)	0 (0%)	0 (0%)	
2d. Hepatomeglia	0 (0%)	0 (0%)	0 (0%)	
2e. Other Lab	0 (0%)	0 (0%)	0 (0%)	
Other[4]	1 (5.9%)	1 (100%)	0 (0%)	N/A

[1] Randomized %: uses total N=21 as the denominator for day 14 and N=17 for day 28.
[2] Denominator for active and placebo are the total in active and total in placebo who had withheld dose.
[3] Fisher's exact test was used to obtain the p-value to compared active and placebo group.
[4]One subject had both weight and other reaons selected from active group.

Table 19b: Reasons for Adjusted or Held Dose by Treatment Group and Visit and Significant Changes in Laboratory Parameters (continued)

PID#	Site	Visit	Other Reasons for Adjusted or Held Dose	Group
3UEF/11935	286	Day 14	Small weight gain	Active
2ZGU/37898	286	Day 14	Visit 2 weight lower than visit 1 weight; this is due to age of child and level of development, meaning it's difficult for them to stand completely still. We will try to be more accurate at subsequent visits.	Active
2ZGU/37898	286	Day 28	Visit 2 weight lower than visit 1 weight; this is due to age of child and level of development, meaning it's difficult for them to stand completely still. We will try to be more accurate at subsequent visits- further to this visit three's weight was taken more accurately and will be done in the same way on subsequent visits.	Active
5RT2/70622	001	Day 14	weight change was not significant but dose was slightly adjusted to accommodate weight.	Placebo
9AJ7/21115	286	Day 14	Dose adjusted as the participant had lost a small amount of weight (0.19), but the Dr was happy to adjust the dose to ensure it was as accurate as possible.	Placebo

Table 20: PK Specimen Results: GCV concentration in the Active Group

		Active				
		N	Mean	SD	10th pclt	90th pctl
Drug concentration (PK) (Coc.ng/ml)	Day 14	15	2191.92	2097.22	192.1	5489.6
	Day 28	16	1746.11	1365.37	267.0	3723.5
	Day 42	14	2291.56	1713.15	625.4	5097.0

*all subjects assigned to placebo have BQL (Below Quantifiable Limit) results as expected.

Figure 7a: Change over Time in GCV concentration (linear scale)

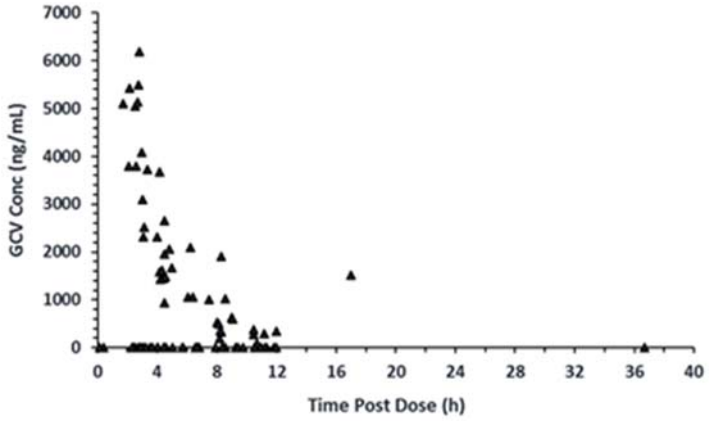


Figure 7b: Change over Time in GCV concentration (Log scale)

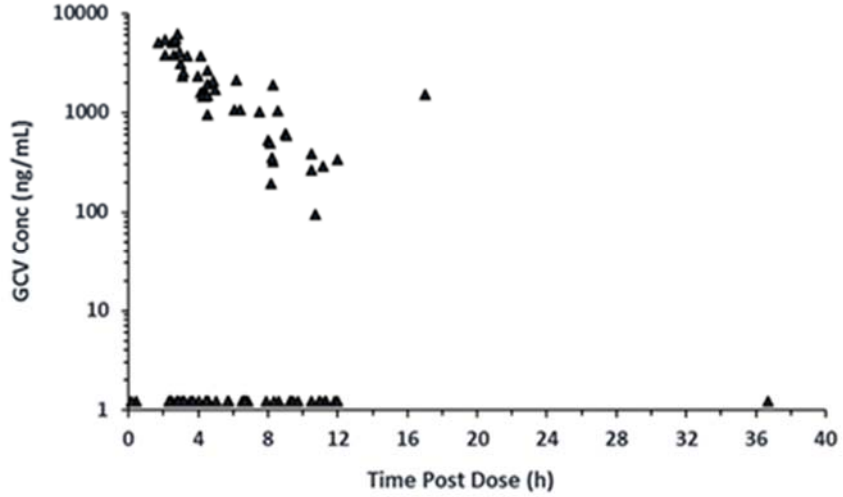


Table 21a: Quality of Hearing Assessment Left and Right (Total Ear)

Count (%N)	Baseline			Month 6		
	Placebo (N=36)	Active (N=34)	Total	Placebo (N=36)	Active (N=34)	Total
Complete	29 80.56	34 100.00	63	22 61.11	24 70.59	46
Emission+SF only	1 2.78	0 0.00	1	4 11.11	0 0.00	4
Emission only	2 5.56	0 0.00	2	2 5.56	0 0.00	2
Cochlear Implant[a]	0 0.00	0 0.00	0	0 0.00	2 5.88	2
Not Evaluable[b]	0 0.00	0 0.00	0	4 11.11	4 11.76	8
Missing/ Withdrew/ Excluded[c]	4 11.11	0 0.00	4	4 11.11	4 11.11	8

[a]Hearing assessment for both ears at Month 6 for one subject who had cochlear implant was assigned "severe". [b]"Not evaluable": hearing assessment information sent to audiologist did not provide enough information to evaluate hearing.
[c]One subject in the Active group was "missing" because hearing assessment was not done at Month 6. One subject (n=2 ears) "withdrew" or dropped out before Month 6 hearing assessment. Two subjects (n=4 ears) in the Placebo group who dropped out soon after randomization and did not take the study drug were excluded both at baseline and Month 6.

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

Count (%N)	Baseline			Month 6		
	Placebo (N=36)	Active (N=34)	Total	Placebo (N=36)	Active (N=34)	Total
Normal	10 27.78	8 23.53	18	9 25.00	6 17.65	15
Mild	3 8.33	6 17.65	9	1 2.78	1 2.94	2
Moderate	5 13.89	4 11.76	9	5 13.89	2 5.88	7
Severe[a]	14 38.89	16 47.06	30	13 36.11	17 50.00	30
Not Evaluable[b]	0 0.00	0 0.00	0	4 11.11	4 11.76	8
Missing/Excluded/ Withdrew [c]	4 11.11	0 0.00	4	4 11.11	4 11.11	8

[a]Hearing assessment for both ears at Month 6 for one subject who had cochlear implant was assigned "severe". Baseline hearing assessment for this subject was severe on left ear and mild on the right ear.
[b]"Not evaluable": hearing assessment information sent to audiologist did not provide enough information to evaluate hearing. Four ears from subjects in the Placebo group had one normal, one mild and two severe baseline assessments while four ears from subjects in the Active group had one normal and three severe baseline assessments.
[c]One subject in the Active group was "missing" because hearing assessment was not done at Month 6 – patient hospitalized and died. One subject (n=2 ears) "withdrew" or dropped out before Month 6 hearing assessment. Two subjects (n=4 ears) in the Placebo group who dropped out soon after randomization and did not take the study drug were excluded both at baseline and Month 6.

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

Count (%N)	Placebo (N=28)	Active (N=26)	Total (N=54)
Improved	0 0.00	0 0.00	0
No Change (Normal to Normal)	9 32.14	6 23.08	15
No Change (Abnormal)	18 64.29	14 53.85	32
Worsened	1 3.57	6 23.08	7

*There are 16 ears with missing change in hearing assessments

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

Outcome		**Placebo (N=28)**	**Active (N=26)**	**Pvalue[b]**
Primary Outcome	Improved or No Change[a]	27 (96.43)	20 (76.92)	0.0859[c]
	Worsened	1 (3.57)	6 (23.08)	
Secondary Outcome	Improved[a]	0 (0.00)	0 (0.00)	NA
	No Change or Worsened	28 (100.00)	26 (100.00)	
Secondary Outcome	Improved or Normal to Normal[a]	9 (32.14)	6 (23.08)	0.4823
	No Change Abnormal or Worsened	19 (67.86)	20 (76.92)	

[a]Outcome being modelled.
[b]Results from fitting generalized linear model based on GEE
[c]Due to the small counts, modeling results from generalized linear model based on GEE may not be reliable.

Table 21e: Subgroup Analysis (Total Ears)

Count %N	Asymptomatic at Birth			Symptomatic at Birth		
	Placebo (N=8)	Active (N=5)	Total[a] (N=13)	Placebo (N=20)	Active (N=21)	Total[b] (N=41)
Normal to Normal	4 50.00	0 0.00	4	5 25.00	6 28.57	11
No Change (Abnormal)	4 50.00	4 80.00	8	14 70.00	10 47.62	24
Worsened	0 0.00	1 20.00	1	1 5.00	5 23.81	6
	[a]3 ears with missing hearing assessment.			[b]13 ears with missing hearing assessment.		
Count %N	**Subjects Aged 1-11 months**			**Subjects Aged >= 12 months**		
	Placebo (N=8)	Active (N=11)	Total[c] (N=19)	Placebo (N=20)	Active (N=15)	Total[d] (N=35)
Normal to Normal	3 37.50	1 9.09	4	6 30.00	5 33.33	11
No Change (Abnormal)	5 62.50	5 45.45	10	13 65.00	9 60.00	22
Worsened	0 0.00	5 45.45	5	1 5.00	1 6.67	2
	[c]11 ears with missing hearing assessment.			[d]5 ears with missing hearing assessment.		

Table 22a: Quality of Hearing Assessment Best Ear

Count (%N)	Baseline			Month 6		
	Placebo (N=18)	Active (N=17)	Total (N=35)	Placebo (N=18)	Active (N=17)	Total (N=35)
Complete	16 88.89	17 100.00	33	11 61.11	11 64.71	22
Emission+SF only	1 5.56	0 0.00	1	3 16.67	0 0.00	3
Emission only	0 0.00	0 0.00	0	1 5.56	0 0.00	1
Cochlear Implant[a]	0 0.00	0 0.00	0	0 0.00	1 5.88	1
Not Evaluable[b]	0 0.00	0 0.00	0	1 5.56	3 17.65	4
Missing/Withdrew/ Excluded[c]	1 5.56	0 0.00	1	2 11.11	2 11.76	4

[a]Hearing assessment for both ears at Month 6 for one subject who had cochlear implant was assigned "severe".
[b]"Not evaluable": hearing assessment information sent to audiologist did not provide enough information to evaluate hearing.
[c]One subject in the Active group was "missing" because hearing assessment was not done at Month 6. One subject (n=2 ears) "withdrew" or dropped out before Month 6 hearing assessment. Two subjects (n=4 ears) in the Placebo group who dropped out soon after randomization and did not take the study drug were excluded both at baseline and Month 6.

Table 22b: Hearing Assessment Best Ear

	Baseline			Month 6		
	Placebo (N=18)	Active (N=17)	Total (N=35)	Placebo (N=16)	Active (N=16)	Total (N=32)
Normal	9 50.00	8 47.06	17	9 56.25	6 37.50	15
Mild	2 11.11	4 23.53	6	1 6.25	1 6.25	2
Moderate	1 5.56	2 11.76	3	1 6.25	0 0.00	1
Severe[a]	5 27.78	3 17.65	8	4 25.00	5 31.25	9
Not Evaluable[b]	0 0.00	0 0.00	0	1 6.25	3 18.75	4
Missing/Withdrew/ Excluded[c]	1 5.56	0 0.00	1	0 0.00	1 6.25	1

[a]Hearing assessment for both ears at Month 6 for one subject who had cochlear implant was assigned "severe". Baseline hearing assessment for this subject was severe on left ear and mild on the right ear so best ear at baseline was mild.
[b]"Not evaluable": hearing assessment information sent to audiologist did not provide enough information to evaluate hearing; one subject in the Placebo group with mild best ear at baseline and 3 subjects in the Active group with normal, mild and severe best ear at baseline.
[c]One subject in the Active group was "missing" because hearing assessment was not done at Month 6. One subject "withdrew" or dropped out before Month 6 hearing assessment. Two subjects in the Placebo group who dropped out soon after randomization and did not take the study drug were excluded both at baseline and Month 6.

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

Count (%N)	Placebo (N=15)	Active (N=12)	Total (N=27)
Improved	0 0.00	0 0.00	0
No Change (Normal to Normal)	9 60.00	6 50.00	15
No Change (Abnormal)	6 40.00	3 25.00	9
Worsened	0 0.00	3 25.00	3

*There are 8 subjects with missing change in best ear hearing assessments.

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

Outcome		Placebo (N=15)	Active (N=12)	Pvalue*
Secondary Outcome	Improved or No Change	15 100.00	9 75.00	0.0752
	Worsened	0 0.00	3 25.00	
Secondary Outcome	Improved	0 0.00	0 0.00	NA
	No Change or Worsened	15 100.00	12 100.00	
Secondary Outcome	Improved or Normal to Normal	9 60.00	6 50.00	0.7068
	No Change Abnormal or Worsened	6 40.00	6 50.00	

*Based on Fisher's exact test

Table 22e: Subgroup Analysis (Best Ears)

Count Column %	Asymptomatic at Birth			Symptomatic at Birth		
	Placebo (N=6)	Active (N=2)	Total[a] (N=8)	Placebo (N=9)	Active (N=10)	Total[b] (N=19)
Normal to Normal	4 66.67	0 0.00	4	5 55.56	6 60.00	11
No Change (Abnormal)	2 33.33	1 50.00	3	4 44.44	2 20.00	6
Worsened	0 0.00	1 50.00	1	0 0.00	2 20.00	2
	[a] 1 subject with missing hearing assessments.			[b]7 subjects with missing hearing assessments.		
Count Column %	**Subjects Aged 1-11 months**			**Subjects Aged > 12 months**		
	Placebo (N=5)	Active (N=5)	Total[c] (N=10)	Placebo (N=10)	Active (N=7)	Total[d] (N=17)
Normal to Normal	3 60.00	1 20.00	4	6 60.00	5 71.43	11
No Change (Abnormal)	2 40.00	1 20.00	3	4 40.00	2 28.57	6
Worsened	0 0.00	3 60.00	3	0 0.00	0 0.00	0
	[c] 5 subjects with missing hearing assessments.			[d] 3 ears with missing hearing assessments.		

Table 23: CMV Detection Over time

Specimen	Visit	Count/N (%N)		p-value*
		Active	Placebo	
Blood	Baseline	7/17 (41.18)	12/17 (70.59)	0.1663
	Day 14	4/15 (26.67)	5/15 (33.33)	1
	Day 28	1/16 (6.25)	4/15 (26.67)	0.1719
	Day 42	2/14 (14.29)	4/15 (26.67)	0.6513
	Day 70	6/15 (40)	3/13 (23.08)	0.4348
	Month 4	4/15 (26.67)	5/15 (33.33)	1
	Month 6	3/15 (20)	4/15 (26.67)	1
Saliva	Baseline	11/17 (64.71)	11/17 (64.71)	1
	Day 14	6/16 (37.5)	10/16 (62.5)	0.289
	Day 28	4/16 (25)	9/16 (56.25)	0.1489
	Day 42	3/16 (18.75)	9/16 (56.25)	0.0659
	Day 70	7/16 (43.75)	8/16 (50)	1
	Month 4	10/16 (62.5)	8/15 (53.33)	0.7224
	Month 6	7/16 (43.75)	8/16 (50)	1
Urine	Baseline	14/15 (93.33)	12/13 (92.31)	1
	Day 14	9/13 (69.23)	9/9 (100)	0.115
	Day 28	4/15 (26.67)	13/13 (100)	<.0001**
	Day 42	1/12 (8.33)	11/12 (91.67)	0.0001**
	Day 70	10/14 (71.43)	11/11 (100)	0.1052
	Month 4	10/13 (76.92)	7/7 (100)	0.5211
	Month 6	11/14 (78.57)	10/11 (90.91)	0.6043

*p-value obtained used Fisher's exact test;
**p-value<0.0024 (=0.05/21) is significant

Figure 8: Percent Detected Over Time

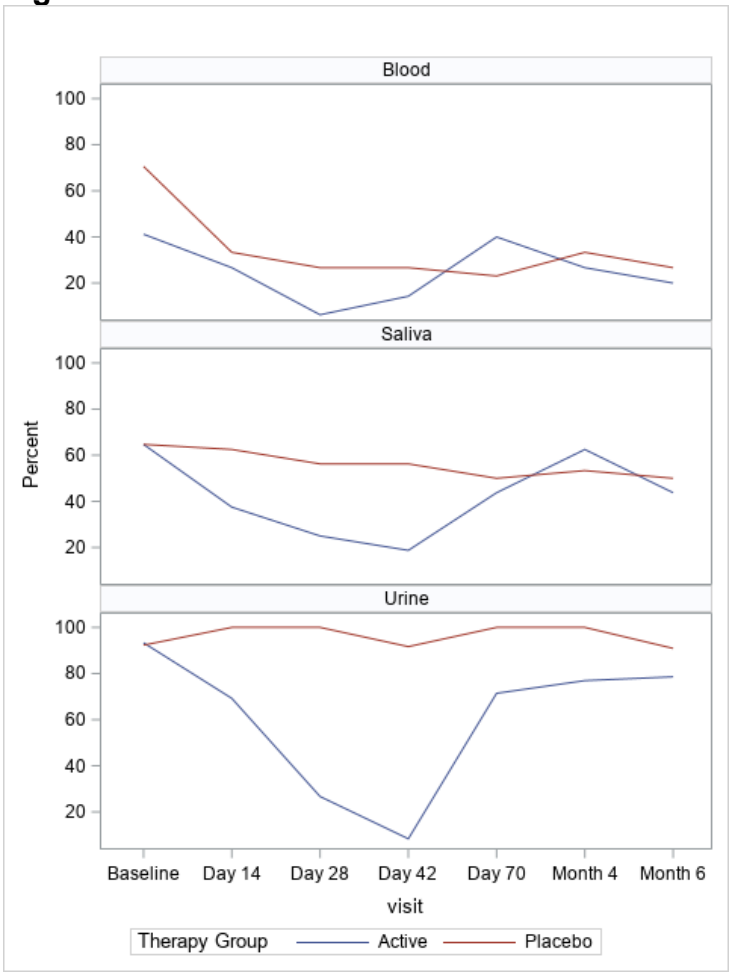


Table 24: Log10 Viral Load Summary Statistics Over Time

		Therapy Group														
		Randomized					Active					Placebo				
		N	Mean	SD	10th Pctl	90th Pctl	N	Mean	SD	10th Pctl	90th Pctl	N	Mean	SD	10th Pctl	90th Pctl
Blood	Baseline	34	2.094	1.024	1.000	3.274	17	1.869	1.110	1.000	3.479	17	2.318	0.907	1.000	3.162
	Day 14	30	1.505	0.816	1.000	2.988	15	1.352	0.607	1.000	2.382	15	1.658	0.980	1.000	3.215
	Day 28	31	1.266	0.623	1.000	2.520	16	1.084	0.335	1.000	1.000	15	1.460	0.796	1.000	2.705
	Day 42	29	1.331	0.673	1.000	2.616	14	1.203	0.522	1.000	2.230	15	1.449	0.789	1.000	2.860
	Day 70	28	1.645	1.005	1.000	3.324	15	1.807	1.103	1.000	3.603	13	1.457	0.885	1.000	3.106
	Month 6	30	1.463	0.740	1.000	2.667	15	1.407	0.730	1.000	2.678	15	1.519	0.772	1.000	2.657
	Month 12	30	1.452	0.891	1.000	3.175	15	1.338	0.750	1.000	2.373	15	1.566	1.027	1.000	3.454
Saliva	Baseline	34	3.409	2.238	1.000	6.550	17	3.539	2.367	1.000	7.227	17	3.280	2.167	1.000	6.550
	Day 14	32	2.762	2.129	1.000	5.816	16	2.309	1.972	1.000	5.486	16	3.215	2.245	1.000	6.932
	Day 28	32	2.226	1.782	1.000	5.308	16	1.410	0.773	1.000	2.938	16	3.042	2.132	1.000	5.746
	Day 42	32	2.094	1.751	1.000	4.678	16	1.290	0.640	1.000	2.616	16	2.898	2.133	1.000	6.514
	Day 70	32	2.182	1.594	1.000	4.173	16	1.740	0.920	1.000	3.123	16	2.624	1.996	1.000	5.840
	Month 6	31	2.508	1.627	1.000	4.394	16	2.347	1.196	1.000	3.828	15	2.681	2.019	1.000	5.483
	Month 12	32	2.299	1.562	1.000	4.698	16	2.045	1.358	1.000	4.437	16	2.553	1.750	1.000	5.247
Urine	Baseline	28	4.672	1.701	2.780	7.040	15	4.633	1.679	2.780	6.251	13	4.717	1.794	3.017	7.454
	Day 14	22	3.651	1.680	1.000	5.857	13	2.795	1.471	1.000	4.597	9	4.889	1.116	2.963	6.076
	Day 28	28	2.910	1.970	1.000	5.579	15	1.470	0.890	1.000	3.408	13	4.571	1.492	2.649	6.346
	Day 42	24	2.501	1.721	1.000	4.996	12	1.116	0.403	1.000	1.000	12	3.886	1.359	2.250	5.311
	Day 70	25	3.485	1.380	1.000	5.237	14	2.863	1.305	1.000	4.161	11	4.277	1.061	2.848	5.357
	Month 6	20	3.677	1.464	1.000	5.220	13	3.059	1.417	1.000	4.559	7	4.825	0.635	3.860	5.589
	Month 12	25	3.662	1.486	1.000	5.016	14	3.235	1.390	1.000	4.699	11	4.205	1.486	2.594	5.750

Viral load values below detection limit were replaced by 10 (i.e. 1 in log10 units)

Table 24a: Summary of Modeling[a] Results (Blood)

	p-value
Visit by treatment interaction	0.0912[b]
Pairwise Comparisons[c]	
Placebo-Active: Baseline	0.1270
Placebo-Active: Day 14	0.2807
Placebo-Active: Day 28	0.1724
Placebo-Active: Day 42	0.3187
Placebo-Active: Day 70	0.1970
Placebo-Active: Month 4	0.8426
Placebo-Active: Month 6	0.3544
Active: Baseline-Day 14	0.0210
Active: Baseline-Day 28	0.0005
Active: Baseline-Day 42	0.0023
Active: Baseline-Day 70	0.9191
Active: Baseline-Month 4	0.0440
Active: Baseline-Month 6	0.0192
Placebo: Baseline-Day 14	0.0041
Placebo: Baseline-Day 28	0.4592
Placebo: Baseline-Day 42	0.8644
Placebo: Baseline-Day 70	0.7257
Placebo: Baseline-Month 4	0.7732
Placebo: Baseline-Month 6	0.4727

[a]Fitted mixed model with random intercept
[b] Not significant using Bonferroni cutoff of 0.0167 (=0.05/3)
[c]Pairwise comparisons should be interpreted with caution because the overall interaction effect was not significant.

Figure 9a: Log 10 VL over time

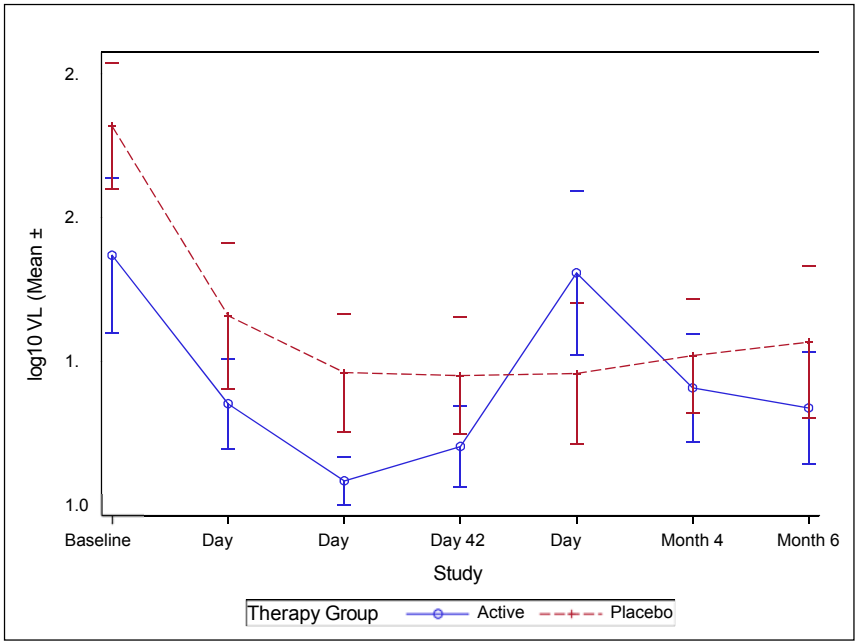


Table 24b: Summary of Modeling[a] Results(Saliva)

	p-value
Visit by treatment interaction	0.0005[b]
Pairwise Comparisons	
Placebo-Active: Baseline	0.6799
Placebo-Active: Day 14	0.2386
Placebo-Active: Day 28	0.0211
Placebo-Active: Day 42	0.0232
Placebo-Active: Day 70	0.2524
Placebo-Active: Month 4	0.9297
Placebo-Active: Month 6	0.5794
Active: Baseline-Day 14	0.0011 [c]
Active: Baseline-Day 28	<.0001 [c]
Active: Baseline-Day 42	<.0001 [c]
Active: Baseline-Day 70	<.0001 [c]
Active: Baseline-Month 4	0.0017 [c]
Active: Baseline-Month 6	<.0001 [c]
Placebo: Baseline-Day 14	0.8818
Placebo: Baseline-Day 28	0.5912
Placebo: Baseline-Day 42	0.6536
Placebo: Baseline-Day 70	0.3955
Placebo: Baseline-Month 4	0.8405
Placebo: Baseline-Month 6	0.9862

[a]Fitted mixed model with random intercept
[b]Significant using Bonferroni cutoff of 0.0167 (=0.05/3)
[c] Significant using Bonferroni cutoff of 0.0026 (=0.05/19)

Figure 9b: Log 10 VL over time (Saliva)

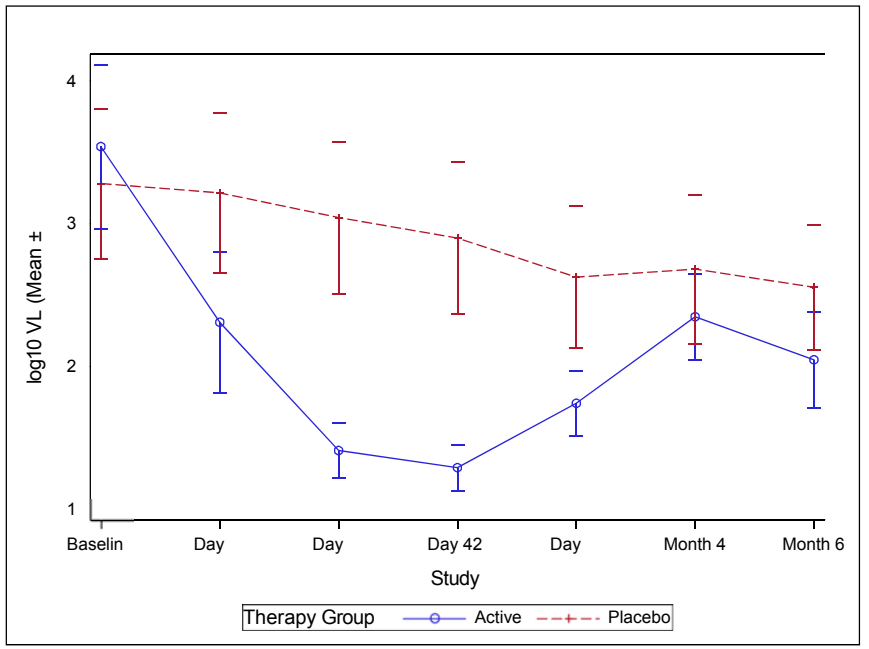


Table 24c: Summary of Modeling[a] Results (Urine)

	p-value
Visit by treatment interaction	<0.0001[b]
Pairwise Comparisons	
Placebo-Active: Baseline	0.9892
Placebo-Active: Day 14	<.0001[b]
Placebo-Active: Day 28	<.0001[b]
Placebo-Active: Day 42	<.0001[b]
Placebo-Active: Day 70	0.0127
Placebo-Active: Month 4	0.0136
Placebo-Active: Month 6	0.4155
Active: Baseline-Day 14	<.0001[c]
Active: Baseline-Day 28	<.0001 [c]
Active: Baseline-Day 42	<.0001 [c]
Active: Baseline-Day 70	<.0001 [c]
Active: Baseline-Month 4	0.0001 [c]
Active: Baseline-Month 6	0.0007 [c]
Placebo: Baseline-Day 14	0.3963
Placebo: Baseline-Day 28	0.1687
Placebo: Baseline-Day 42	0.174
Placebo: Baseline-Day 70	0.3783
Placebo: Baseline-Month 4	0.3369
Placebo: Baseline-Month 6	0.0643

[a]Fitted mixed model with random intercept
[b]Significant using Bonferroni cutoff of 0.0167 (=0.05/3)
[c] Significant using Bonferroni cutoff of 0.0026 (=0.05/19)

Figure 9c.: Log 10 VL over time

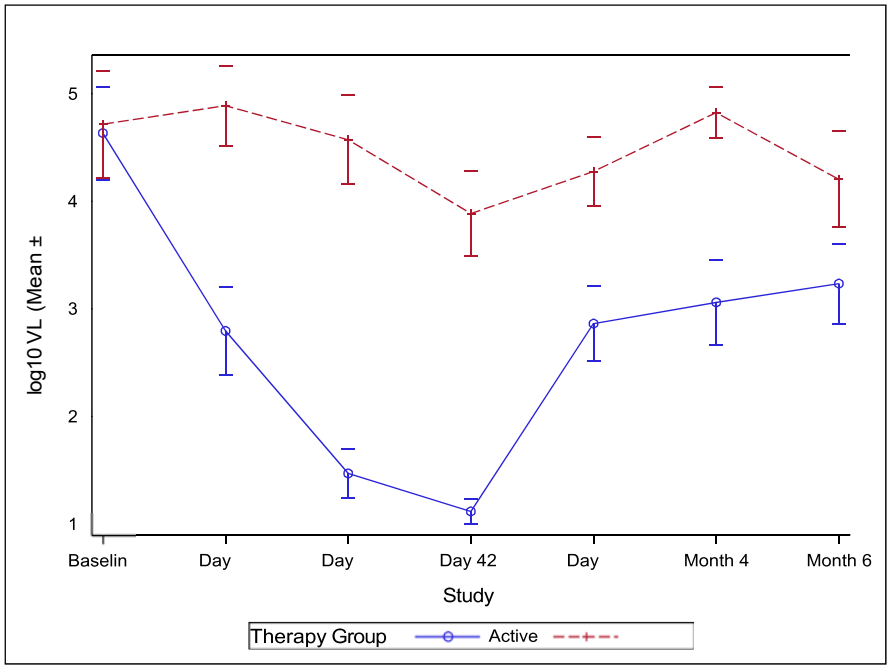


Table 25: Spearman Rank Correlation between GCV concentration and log10 VL

Type	Visit	n	Correlation	p-value
Blood	Day 14	14	0.29732	0.3019
	Day 28	16	0.02801	0.9180
	Day 42	14	0.01082	0.9707
Saliva	Day 14	15	0.39888	0.1408
	Day 28	16	-0.46560	0.0691
	Day 42	14	-0.22325	0.4430
Urine	Day 14	12	0.60864	0.0357
	Day 28	15	-0.49960	0.0579
	Day 42	10	-0.40618	0.2441

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

Change in Total Ear Hearing	Randomized					Active					Placebo				
	N	Mean	SD	10th Pctl	90th Pctl	N	Mean	SD	10th Pctl	90th Pctl	N	Mean	SD	10th Pctl	90th Pctl
BLOOD															
Normal to Normal	15	1.873	0.999	1.000	3.151	6	1.413	1.012	1.000	3.479	9	2.180	0.918	1.000	3.151
No Change Abnormal	32	1.846	0.995	1.000	3.172	14	1.430	0.884	1.000	3.179	18	2.169	0.978	1.000	3.172
Worsened	7	2.532	0.757	1.000	3.274	6	2.481	0.816	1.000	3.274	1	2.836	.	2.836	2.836
SALIVA															
Normal to Normal	15	3.012	2.043	1.000	5.589	6	2.280	1.458	1.000	4.271	9	3.500	2.304	1.000	7.502
No Change Abnormal	32	3.109	2.253	1.000	6.426	14	3.295	2.332	1.000	6.426	18	2.964	2.247	1.000	6.550
Worsened	7	4.527	2.270	1.000	8.036	6	4.831	2.326	1.000	8.036	1	2.707	.	2.707	2.707
URINE															
Normal to Normal	12	4.137	1.420	3.017	5.635	5	4.318	1.278	3.027	6.251	7	4.008	1.600	1.000	5.635
No Change Abnormal	23	4.894	1.903	3.017	7.454	11	4.552	1.562	3.542	6.173	12	5.208	2.191	3.017	8.122
Worsened	7	4.583	2.044	1.000	6.173	6	4.667	2.226	1.000	6.173	1	4.077	.	4.077	4.077

[#]Viral load values below detection limit were replaced by 10 (i.e. 1 in log10 units)

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

BLOOD: p-value*=0.6049 (unadjusted); p-value*=0.4611 (adjusted for therapy)

Change in Total Ear Hearing	Randomized					Active					Placebo				
	N	Mean	SD	10th Pctl	90th Pctl	N	Mean	SD	10th Pctl	90th Pctl	N	Mean	SD	10th Pctl	90th Pctl
Normal to Normal	15	1.873	0.999	1.000	3.151	6	1.413	1.012	1.000	3.479	9	2.180	0.918	1.000	3.151
No Change Abnormal + Worsened	39	1.969	0.985	1.000	3.179	20	1.745	0.977	1.000	3.226	19	2.204	0.963	1.000	3.172

SALIVA: p-value*=0.4532 (unadjusted); p-value*=0.4791 (adjusted for therapy)

Change in Total Ear Hearing	Randomized					Active					Placebo				
	N	Mean	SD	10th Pctl	90th Pctl	N	Mean	SD	10th Pctl	90th Pctl	N	Mean	SD	10th Pctl	90th Pctl
Normal to Normal	15	3.012	2.043	1.000	5.589	6	2.280	1.458	1.000	4.271	9	3.500	2.304	1.000	7.502
No Change Abnormal + Worsened	39	3.364	2.293	1.000	6.550	20	3.756	2.380	1.000	7.231	19	2.950	2.184	1.000	6.550

URINE: p-value*=0.1407 (unadjusted); p-value*=0.1235 (adjusted for therapy)

Change in Total Ear Hearing	Randomized					Active					Placebo				
	N	Mean	SD	10th Pctl	90th Pctl	N	Mean	SD	10th Pctl	90th Pctl	N	Mean	SD	10th Pctl	90th Pctl
Normal to Normal	12	4.137	1.420	3.017	5.635	5	4.318	1.278	3.027	6.251	7	4.008	1.600	1.000	5.635
No Change Abnormal + Worsened	30	4.822	1.905	1.890	7.454	17	4.593	1.754	1.000	6.173	13	5.121	2.121	3.017	8.122

[#]Viral load values below detection limit were replaced by 10 (i.e. 1 in log10 units)

*p-values for association between change in log10 VL and change in hearing based on fitting generalized linear model for binary outcome using generalized estimating equations to address repeated measures.

Figure 10: Boxplots: Baseline Log10 VL and Change (Binary) in Total Ear Hearing

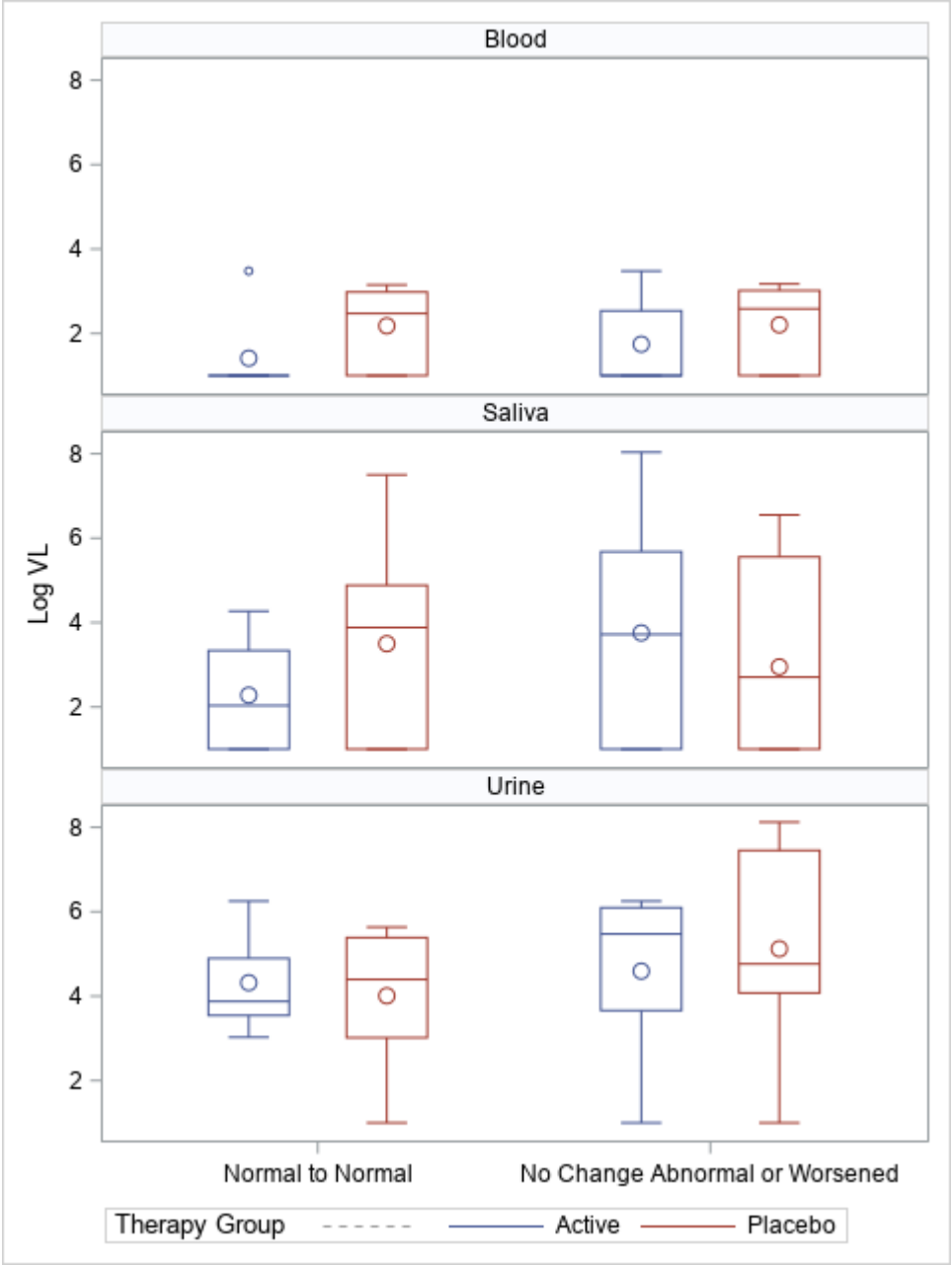


Table 27a: Summary Statistics: Baseline Log10 VL[#] by Change in Best Ear Hearing

BLOOD

Change in Best Ear Hearing	Randomized					Active					Placebo				
	N	Mean	SD	10th Pctl	90th Pctl	N	Mean	SD	10th Pctl	90th Pctl	N	Mean	SD	10th Pctl	90th Pctl
Normal to Normal	15	1.873	0.999	1.000	3.151	6	1.413	1.012	1.000	3.479	9	2.180	0.918	1.000	3.151
No Change Abnormal	9	1.866	1.038	1.000	3.172	3	1.000	0.000	1.000	1.000	6	2.299	1.025	1.000	3.172
Worsened	3	2.692	0.430	2.362	3.179	3	2.692	0.430	2.362	3.179	.	.	.	.	.

SALIVA

Change in Best Ear Hearing	Randomized					Active					Placebo				
	N	Mean	SD	10th Pctl	90th Pctl	N	Mean	SD	10th Pctl	90th Pctl	N	Mean	SD	10th Pctl	90th Pctl
Normal to Normal	15	3.012	2.043	1.000	5.589	6	2.280	1.458	1.000	4.271	9	3.500	2.304	1.000	7.502
No Change Abnormal	9	3.116	2.421	1.000	6.550	3	3.386	2.772	1.000	6.426	6	2.982	2.498	1.000	6.550
Worsened	3	5.940	1.979	4.103	8.036	3	5.940	1.979	4.103	8.036	.	.	.	.	.

URINE

Change in Best Ear Hearing	Randomized					Active					Placebo				
	N	Mean	SD	10th Pctl	90th Pctl	N	Mean	SD	10th Pctl	90th Pctl	N	Mean	SD	10th Pctl	90th Pctl
Normal to Normal	12	4.137	1.420	3.017	5.635	5	4.318	1.278	3.027	6.251	7	4.008	1.600	1.000	5.635
No Change Abnormal	6	5.234	2.526	1.000	8.122	2	3.236	3.162	1.000	5.472	4	6.232	1.819	4.589	8.122
Worsened	3	6.043	0.161	5.863	6.173	3	6.043	0.161	5.863	6.173	.	.	.	.	.

[#]Viral load values below detection limit were replaced by 10 (i.e. 1 in log10 units)

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

BLOOD: p-value*=0.5912 (unadjusted); p-value*=0.4581 (adjusted for therapy)

Change in Best Ear Hearing	Randomized					Active					Placebo				
	N	Mean	SD	10th Pctl	90th Pctl	N	Mean	SD	10th Pctl	90th Pctl	N	Mean	SD	10th Pctl	90th Pctl
Normal to Normal	15	1.873	0.999	1.000	3.151	6	1.413	1.012	1.000	3.479	9	2.180	0.918	1.000	3.151
No Change Abnormal + Worsened	12	2.072	0.978	1.000	3.172	6	1.846	0.966	1.000	3.179	6	2.299	1.025	1.000	3.172

SALIVA: p-value*=0.3491 (unadjusted); p-value*=0.3569 (adjusted for therapy)

Change in Best Ear Hearing	Randomized					Active					Placebo				
	N	Mean	SD	10th Pctl	90th Pctl	N	Mean	SD	10th Pctl	90th Pctl	N	Mean	SD	10th Pctl	90th Pctl
Normal to Normal	15	3.012	2.043	1.000	5.589	6	2.280	1.458	1.000	4.271	9	3.500	2.304	1.000	7.502
No Change Abnormal + Worsened	12	3.822	2.570	1.000	6.550	6	4.663	2.568	1.000	8.036	6	2.982	2.498	1.000	6.550

URINE: p-value*=0.0640 (unadjusted); p-value*=0.0569 (adjusted for therapy)

Change in Best Ear Hearing	Randomized					Active					Placebo				
	N	Mean	SD	10th Pctl	90th Pctl	N	Mean	SD	10th Pctl	90th Pctl	N	Mean	SD	10th Pctl	90th Pctl
Normal to Normal	12	4.137	1.420	3.017	5.635	5	4.318	1.278	3.027	6.251	7	4.008	1.600	1.000	5.635
No Change Abnormal + Worsened	9	5.503	2.039	1.000	8.122	5	4.920	2.208	1.000	6.173	4	6.232	1.819	4.589	8.122

[#]Viral load values below detection limit were replaced by 10 (i.e. 1 in log10 units)

*p-values for association between change in log10 VL and change in hearing based on fitting generalized linear model for binary outcome.

Figure 11: Boxplots: Baseline Log10 VL and Change (Binary) in Best Ear Hearing

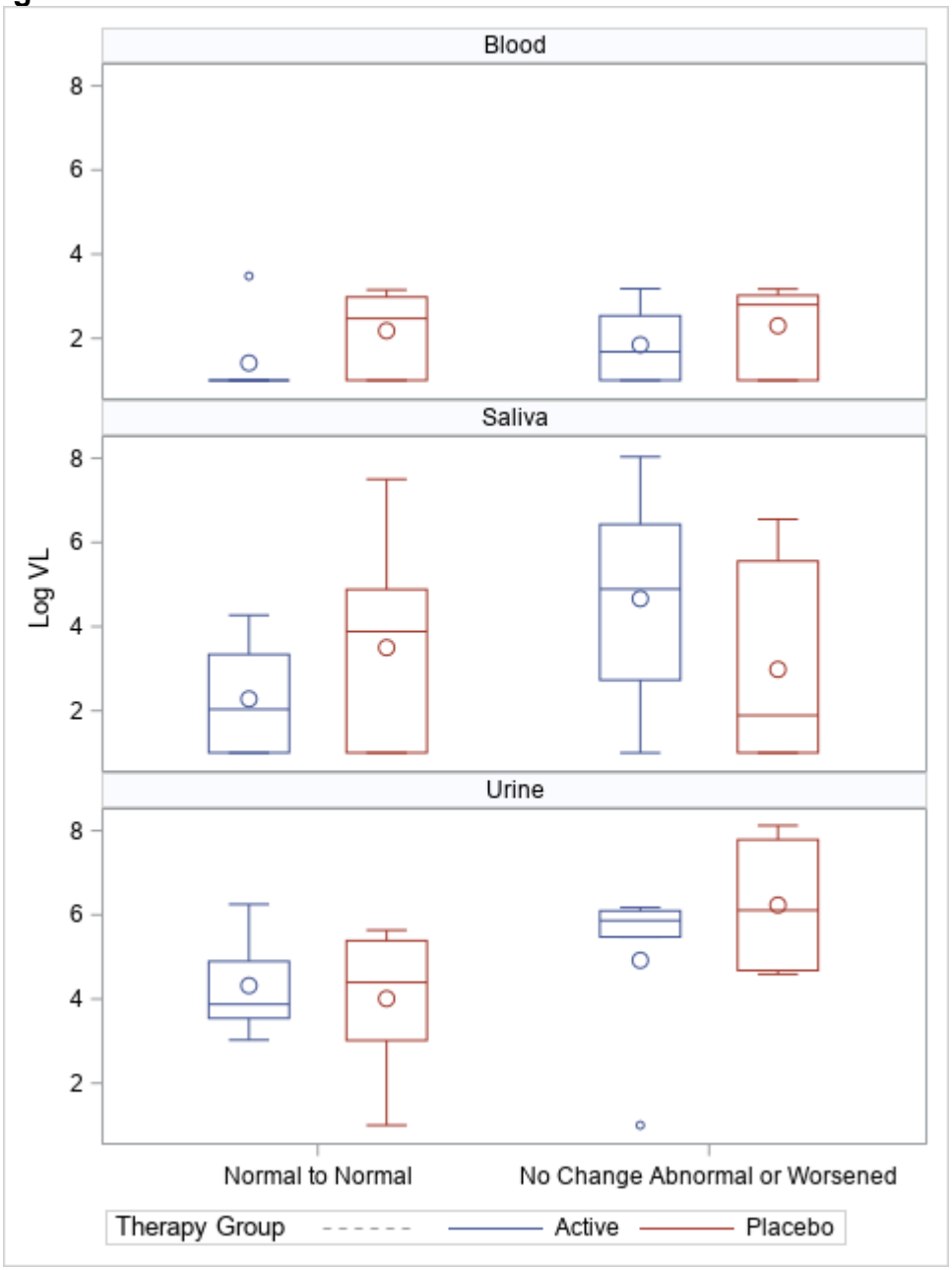


Table 28a: Summary Statistics: Average AUC Log10 VL[#] and Change in Total Ear Hearing

BLOOD															
Change in Total Ear Hearing	Randomized					Active					Placebo				
	N	Mean	SD	10th Pctl	90 th Pctl	N	Mean	SD	10th Pctl	90 th Pctl	N	Mean	SD	10th Pctl	90 th Pctl
Normal to Normal	14	1.427	0.549	0.995	2.300	5	1.139	0.219	0.995	1.489	9	1.587	0.620	0.995	2.722
No Change Abnormal	31	1.258	0.565	0.995	2.012	13	1.214	0.440	0.995	2.012	18	1.289	0.651	0.557	2.847
Worsened	7	1.682	0.486	0.995	2.260	6	1.740	0.506	0.995	2.260	1	1.339	.	1.339	1.339
SALIVA															
Change in Total Ear Hearing	Randomized					Active					Placebo				
	N	Mean	SD	10%	90%	N	Mean	SD	10%	90%	N	Mean	SD	10%	90%
Normal to Normal	15	2.447	1.715	0.995	4.953	6	1.597	0.561	0.995	2.406	9	3.014	2.012	0.995	6.691
No Change Abnormal	32	2.292	1.460	0.995	4.401	14	2.009	0.739	0.995	3.006	18	2.512	1.831	0.995	5.721
Worsened	7	2.279	0.717	0.995	2.949	6	2.393	0.712	0.995	2.949	1	1.593	.	1.593	1.593
URINE															
Change in Total Ear Hearing	Randomized					Active					Placebo				
	N	Mean	SD	10%	90%	N	Mean	SD	10%	90%	N	Mean	SD	10%	90%
Normal to Normal	12	3.411	1.196	1.821	4.516	5	2.241	0.722	1.487	3.331	7	4.246	0.565	3.283	5.153
No Change Abnormal	26	3.641	1.484	1.487	5.447	13	2.645	0.925	1.089	3.376	13	4.637	1.257	3.360	7.028
Worsened	6	3.018	1.034	0.995	3.711	6	3.018	1.034	0.995	3.711	.	.	.	.	.

[#]Viral load values below detection limit were replaced by 10 (i.e. 1 in log10 units)

Table 28b: Association between Average AUC Log10 VL[#] and Change (Binary) in Total Ear Hearing

BLOOD: p-value*=0.7165 (unadjusted); p-value*=0.7412 (adjusted for therapy)

Change in Total Ear Hearing	Randomized					Active					Placebo				
	N	Mean	SD	10th Pctl	90th Pctl	N	Mean	SD	10th Pctl	90th Pctl	N	Mean	SD	10th Pctl	90th Pctl
Normal to Normal	14	1.427	0.549	0.995	2.300	5	1.139	0.219	0.995	1.489	9	1.587	0.620	0.995	2.722
No Change Abnormal + Worsened	38	1.336	0.570	0.995	2.260	19	1.380	0.513	0.995	2.260	19	1.291	0.633	0.557	2.847

SALIVA: p-value*=0.8356 (unadjusted); p-value*=0.9434 (adjusted for therapy)

Change in Total Ear Hearing	Randomized					Active					Placebo				
	N	Mean	SD	10th Pctl	90th Pctl	N	Mean	SD	10th Pctl	90th Pctl	N	Mean	SD	10th Pctl	90th Pctl
Normal to Normal	15	2.447	1.715	0.995	4.953	6	1.597	0.561	0.995	2.406	9	3.014	2.012	0.995	6.691
No Change Abnormal + Worsened	39	2.290	1.349	0.995	4.401	20	2.124	0.734	0.995	2.977	19	2.464	1.792	0.995	5.721

URINE: p-value*=0.6499 (unadjusted); p-value*= 0.1208 (adjusted for therapy)

Change in Total Ear Hearing	Randomized					Active					Placebo				
	N	Mean	SD	10th Pctl	90th Pctl	N	Mean	SD	10th Pctl	90th Pctl	N	Mean	SD	10th Pctl	90th Pctl
Normal to Normal	12	3.411	1.196	1.821	4.516	5	2.241	0.722	1.487	3.331	7	4.246	0.565	3.283	5.153
No Change Abnormal + Worsened	32	3.524	1.417	1.487	5.447	19	2.763	0.948	0.995	3.711	13	4.637	1.257	3.360	7.028

[#]Viral load values below detection limit were replaced by 10 (i.e. 1 in log10 units)

*p-values for association between change in log10 VL and change in hearing based on fitting generalized linear model for binary outcome using generalized estimating equations to address repeated measures.

Figure 12: Boxplots: Average AUC Log10 VL and Change (Binary) in Total Ear Hearing

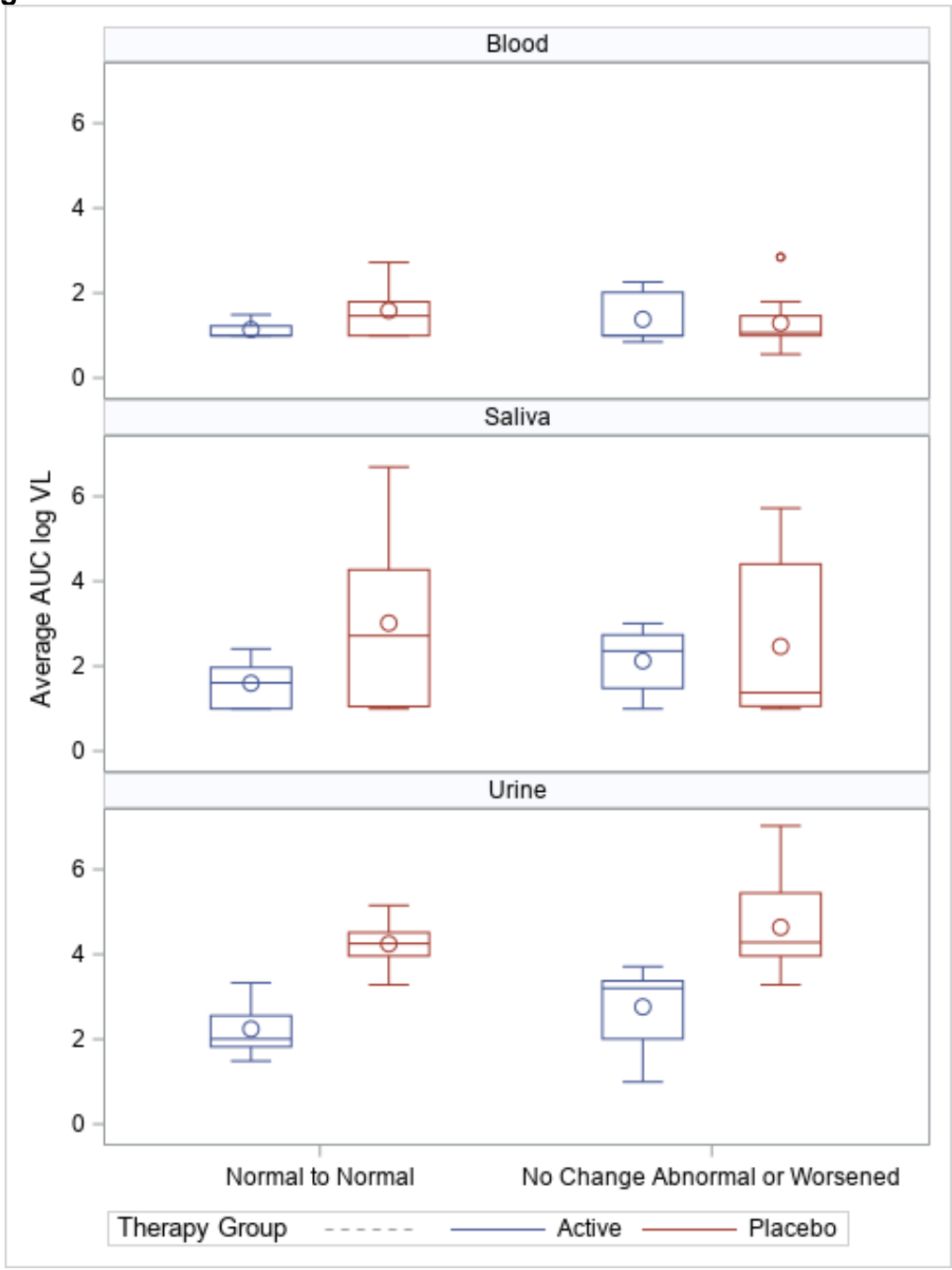


Table 29a: Summary Statistics: Average AUC Log10 VL[#] and Change in Best Ear Hearing

BLOOD															
Change in Best Ear Hearing	Randomized					Active					Placebo				
	N	Mean	SD	10th Pctl	90th Pctl	N	Mean	SD	10th Pctl	90th Pctl	N	Mean	SD	10th Pctl	90th Pctl
Normal to Normal	14	1.427	0.549	0.995	2.300	5	1.139	0.219	0.995	1.489	9	1.587	0.620	0.995	2.722
No Change Abnormal	9	1.174	0.647	0.557	2.847	3	0.995	0.000	0.995	0.995	6	1.264	0.800	0.557	2.847
Worsened	3	1.914	0.403	1.472	2.260	3	1.914	0.403	1.472	2.260	.	.	.	.	.
SALIVA															
Change in Bests Ear Hearing	Randomized					Active					Placebo				
	N	Mean	SD	10th Pctl	90th Pctl	N	Mean	SD	10th Pctl	90th Pctl	N	Mean	SD	10th Pctl	90th Pctl
Normal to Normal	15	2.447	1.715	0.995	4.953	6	1.597	0.561	0.995	2.406	9	3.014	2.012	0.995	6.691
No Change Abnormal	9	2.337	1.724	0.995	5.721	3	2.118	1.026	0.995	3.006	6	2.447	2.072	0.995	5.721
Worsened	3	2.680	0.300	2.357	2.949	3	2.680	0.300	2.357	2.949	.	.	.	.	.
URINE															
Change in Best Ear Hearing	Randomized					Active					Placebo				
	N	Mean	SD	10th Pctl	90th Pctl	N	Mean	SD	10th Pctl	90th Pctl	N	Mean	SD	10th Pctl	90th Pctl
Normal to Normal	12	3.411	1.196	1.821	4.516	5	2.241	0.722	1.487	3.331	7	4.246	0.565	3.283	5.153
No Change Abnormal	7	3.940	1.914	0.995	7.028	3	2.487	1.300	0.995	3.376	4	5.029	1.583	3.360	7.028
Worsened	3	3.497	0.191	3.341	3.711	3	3.497	0.191	3.341	3.711	.	.	.	.	.

[#]Viral load values below detection limit were replaced by 10 (i.e. 1 in log10 units)

Table 29b: Association between Average AUC Log10 VL[#] and Change (Binary) in Best Ear Hearing

Change in Best Ear Hearing	Randomized					Active					Placebo				
	N	Mean	SD	10th Pctl	90th Pctl	N	Mean	SD	10th Pctl	90th Pctl	N	Mean	SD	10th Pctl	90th Pctl
BLOOD: p-value*=0.7658 (unadjusted); p-value*= 0.8331 (adjusted for therapy)															
Normal to Normal	14	1.427	0.549	0.995	2.300	5	1.139	0.219	0.995	1.489	9	1.587	0.620	0.995	2.722
No Change Abnormal Worsened	12	1.359	0.668	0.995	2.260	6	1.454	0.565	0.995	2.260	6	1.264	0.800	0.557	2.847
SALIVA: p-value*=0.9682 (unadjusted); p-value*=0.9242 (adjusted for therapy)															
Normal to Normal	15	2.447	1.715	0.995	4.953	6	1.597	0.561	0.995	2.406	9	3.014	2.012	0.995	6.691
No Change Abnormal + Worsened	12	2.423	1.484	0.995	4.401	6	2.399	0.743	0.995	3.006	6	2.447	2.072	0.995	5.721
URINE: p-value*=0.4847 (unadjusted); p-value*=0.0573 (adjusted for therapy)															
Normal to Normal	12	3.411	1.196	1.821	4.516	5	2.241	0.722	1.487	3.331	7	4.246	0.565	3.283	5.153
No Change Abnormal + Worsened	10	3.807	1.580	2.043	6.238	6	2.992	0.999	0.995	3.711	4	5.029	1.583	3.360	7.028

[#]Viral load values below detection limit were replaced by 10 (i.e. 1 in log10 units)

*p-values for association between change in log10 VL and change in hearing based on fitting generalized linear model for binary outcome.

Figure 13: Boxplots: Average AUC Log10 VL and Change (Binary) in Best Ear Hearing

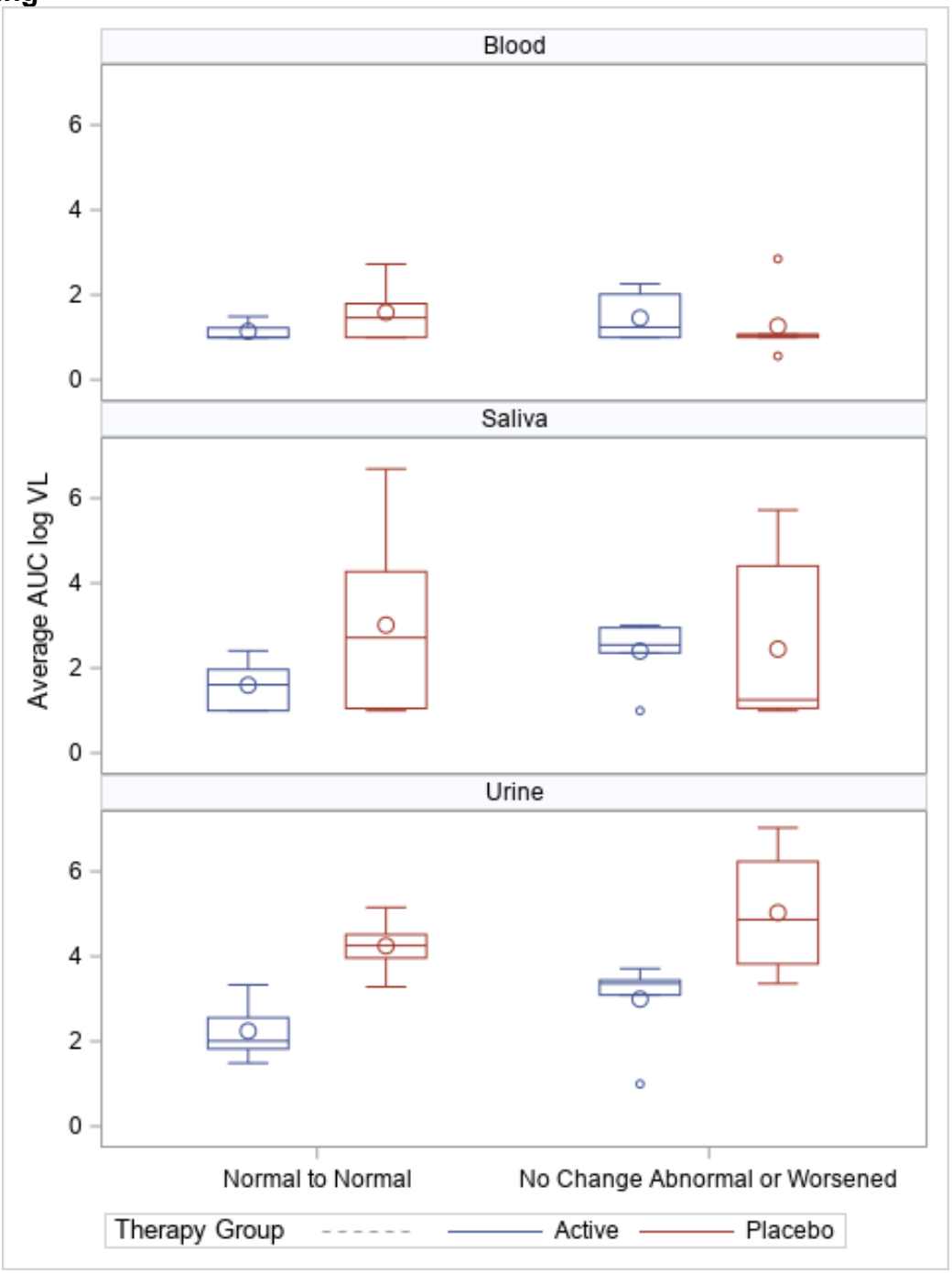


Table 30a: Summary Statistics: Change in Log10 VL[#] and Change in Total Ear Hearing

BLOOD

Change in Total Ear Hearing	Randomized					Active					Placebo				
	N	Mean	SD	10th Pctl	90th Pctl	N	Mean	SD	10th Pctl	90th Pctl	N	Mean	SD	10th Pctl	90th Pctl
Normal to Normal	15	-.038	0.676	-.781	0.322	6	0.310	0.760	0.000	1.861	9	-.271	0.535	-1.36	0.322
No Change Abnormal	32	0.182	0.563	0.000	0.529	14	0.373	0.768	0.000	1.861	18	0.033	0.272	0.000	0.529
Worsened	7	0.966	0.860	0.000	2.179	6	1.127	0.818	0.000	2.179	1	0.000	.	0.000	0.000

SALIVA

Change in Total Ear Hearing	Randomized					Active					Placebo				
	N	Mean	SD	10th Pctl	90th Pctl	N	Mean	SD	10th Pctl	90th Pctl	N	Mean	SD	10th Pctl	90th Pctl
Normal to Normal	15	0.548	1.143	-.885	2.223	6	0.311	1.594	-1.66	2.339	9	0.705	0.792	0.000	2.223
No Change Abnormal	32	0.201	0.947	-.885	1.714	14	0.204	1.050	-.885	2.069	18	0.198	0.891	-1.38	1.714
Worsened	7	0.886	1.333	-.753	3.485	6	0.816	1.446	-.753	3.485	1	1.305	.	1.305	1.305

URINE

Change in Total Ear Hearing	Randomized					Active					Placebo				
	N	Mean	SD	10th Pctl	90th Pctl	N	Mean	SD	10th Pctl	90th Pctl	N	Mean	SD	10th Pctl	90th Pctl
Normal to Normal	15	-.122	1.655	-2.89	1.533	6	-.070	2.297	-3.70	2.875	9	-.157	1.222	-2.89	1.122
No Change Abnormal	28	0.109	1.807	-2.06	2.875	14	-.181	1.766	-2.06	1.533	14	0.399	1.866	-1.43	3.763
Worsened	7	-1.54	1.965	-3.70	1.459	6	-1.69	2.108	-3.70	1.459	1	-.648	.	-.648	-.648

[#]Viral load values below detection limit were replaced by 10 (i.e. 1 in log10 units); Change in viral load = (Month6 log10 VL – Baseline log10 VL); For subjects without the month-6 viral load, the last visit with available viral load was used.

Table 30b: Association between Change in Log10 VL[#] and Change (Binary) in Total Ear Hearing

BLOOD: p-value*=0. 0863 (unadjusted); p-value*=0. 0944 (adjusted for therapy)

Change in Total Ear Hearing	Randomized					Active					Placebo				
	N	Mean	SD	10th Pctl	90th Pctl	N	Mean	SD	10th Pctl	90th Pctl	N	Mean	SD	10th Pctl	90th Pctl
Normal to Normal	15	-.038	0.676	-.781	0.322	6	0.310	0.760	0.000	1.861	9	-.271	0.535	-1.36	0.322
No Change Abnormal + Worsened	39	0.323	0.684	0.000	1.535	20	0.599	0.840	0.000	2.020	19	0.032	0.264	0.000	0.529

SALIVA: p-value*=0.3535 (unadjusted); p-value*=0.3887 (adjusted for therapy)

Change in Total Ear Hearing	Randomized					Active					Placebo				
	N	Mean	SD	10th Pctl	90th Pctl	N	Mean	SD	10th Pctl	90th Pctl	N	Mean	SD	10th Pctl	90th Pctl
Normal to Normal	15	0.548	1.143	-.885	2.223	6	0.311	1.594	-1.66	2.339	9	0.705	0.792	0.000	2.223
No Change Abnormal + Worsened	39	0.324	1.041	-.885	1.714	20	0.388	1.178	-.819	2.204	19	0.256	0.902	-1.38	1.714

URINE: p-value*=0.9510 (unadjusted); p-value*= 0.8826 (adjusted for therapy)

Change in Total Ear Hearing	Randomized					Active					Placebo				
	N	Mean	SD	10th Pctl	90th Pctl	N	Mean	SD	10th Pctl	90th Pctl	N	Mean	SD	10th Pctl	90th Pctl
Normal to Normal	15	-.122	1.655	-2.89	1.533	6	-.070	2.297	-3.70	2.875	9	-.157	1.222	-2.89	1.122
No Change Abnormal + Worsened	35	-.222	1.930	-2.89	1.533	20	-.635	1.951	-3.70	1.496	15	0.329	1.818	-1.43	3.763

[#]Viral load values below detection limit were replaced by 10 (i.e. 1 in log10 units); Change in viral load = (Month6 log10 VL – Baseline log10 VL); For subjects without the month-6 viral load, the last visit with available viral load was used.

*p-values for association between change in log10 VL and change in hearing based on fitting generalized linear model for binary outcome using generalized estimating equations to address repeated measures.

Figure 14: Boxplots: Change in Log10 VL and Change (Binary) in Total Ear Hearing

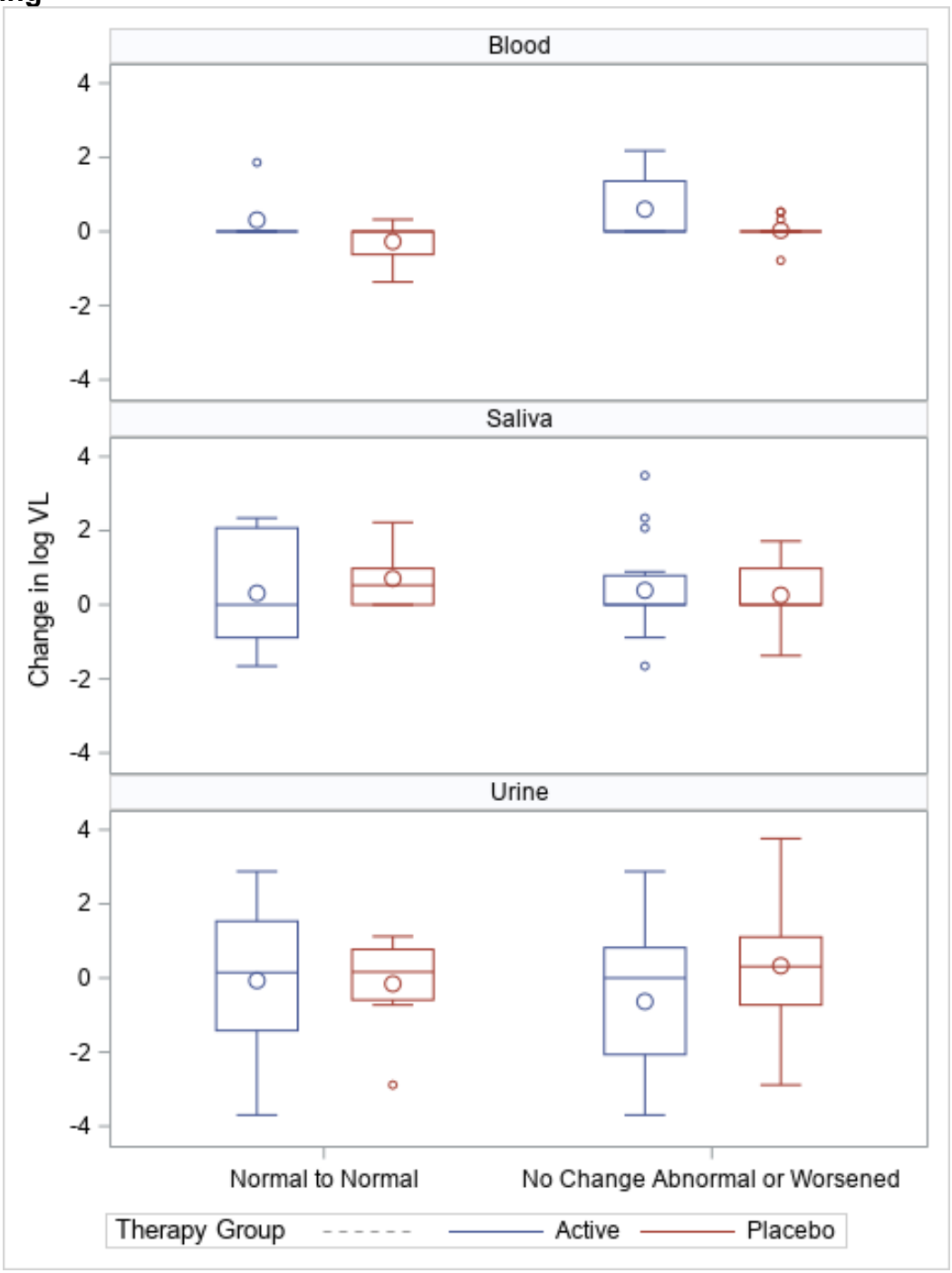


Table 31a: Summary Statistics: Change in Log10 VL[#] and Change in Best Ear Hearing

BLOOD

Change in Best Ear Hearing	Randomized					Active					Placebo				
	N	Mean	SD	10th Pctl	90th Pctl	N	Mean	SD	10th Pctl	90th Pctl	N	Mean	SD	10th Pctl	90th Pctl
Normal to Normal	15	-.038	0.676	-.781	0.322	6	0.310	0.760	0.000	1.861	9	-.271	0.535	-1.36	0.322
No Change Abnormal	9	0.059	0.176	0.000	0.529	3	0.000	0.000	0.000	0.000	6	0.088	0.216	0.000	0.529
Worsened	3	1.632	0.505	1.182	2.179	3	1.632	0.505	1.182	2.179	.	.	.	.	.

SALIVA

Change in Best Ear Hearing	Randomized					Active					Placebo				
	N	Mean	SD	10th Pctl	90th Pctl	N	Mean	SD	10th Pctl	90th Pctl	N	Mean	SD	10th Pctl	90th Pctl
Normal to Normal	15	0.548	1.143	-.885	2.223	6	0.311	1.594	-1.66	2.339	9	0.705	0.792	0.000	2.223
No Change Abnormal	9	0.074	0.819	-1.38	1.714	3	0.227	0.393	0.000	0.680	6	-.003	0.996	-1.38	1.714
Worsened	3	0.173	0.841	-.753	0.891	3	0.173	0.841	-.753	0.891	.	.	.	.	.

URINE

Change in Best Ear Hearing	Randomized					Active					Placebo				
	N	Mean	SD	10th Pctl	90th Pctl	N	Mean	SD	10th Pctl	90th Pctl	N	Mean	SD	10th Pctl	90th Pctl
Normal to Normal	15	-.122	1.655	-2.89	1.533	6	-.070	2.297	-3.70	2.875	9	-.157	1.222	-2.89	1.122
No Change Abnormal	7	0.378	1.902	-2.06	3.763	3	-.587	1.288	-2.06	0.302	4	1.102	2.121	-1.43	3.763
Worsened	3	-1.21	2.582	-3.70	1.459	3	-1.21	2.582	-3.70	1.459	.	.	.	.	.

[#]Viral load values below detection limit were replaced by 10 (i.e. 1 in log10 units); Change in viral load = (Month6 log10 VL – Baseline log10 VL); For subjects without the month-6 viral load, the last visit with available viral load was used.

Table 31b: Association between Change in Log10 VL[#] and Change (Binary) in Best Ear Hearing

BLOOD: p-value*=0.0719 (unadjusted); p-value*= 0.0788 (adjusted for therapy)

Change in Best Ear Hearing	Randomized					Active					Placebo				
	N	Mean	SD	10th Pctl	90th Pctl	N	Mean	SD	10th Pctl	90th Pctl	N	Mean	SD	10th Pctl	90th Pctl
Normal to Normal	15	-.038	0.676	-.781	0.322	6	0.310	0.760	0.000	1.861	9	-.271	0.535	-1.36	0.322
No Change Abnormal Worsened	12	0.452	0.758	0.000	1.535	6	0.816	0.949	0.000	2.179	6	0.088	0.216	0.000	0.529

SALIVA: p-value*=0.2341 (unadjusted); p-value*=0.2495 (adjusted for therapy)

Change in Best Ear Hearing	Randomized					Active					Placebo				
	N	Mean	SD	10th Pctl	90th Pctl	N	Mean	SD	10th Pctl	90th Pctl	N	Mean	SD	10th Pctl	90th Pctl
Normal to Normal	15	0.548	1.143	-.885	2.223	6	0.311	1.594	-1.66	2.339	9	0.705	0.792	0.000	2.223
No Change Abnormal Worsened	12	0.098	0.787	-.753	0.891	6	0.200	0.588	-.753	0.891	6	-.003	0.996	-1.38	1.714

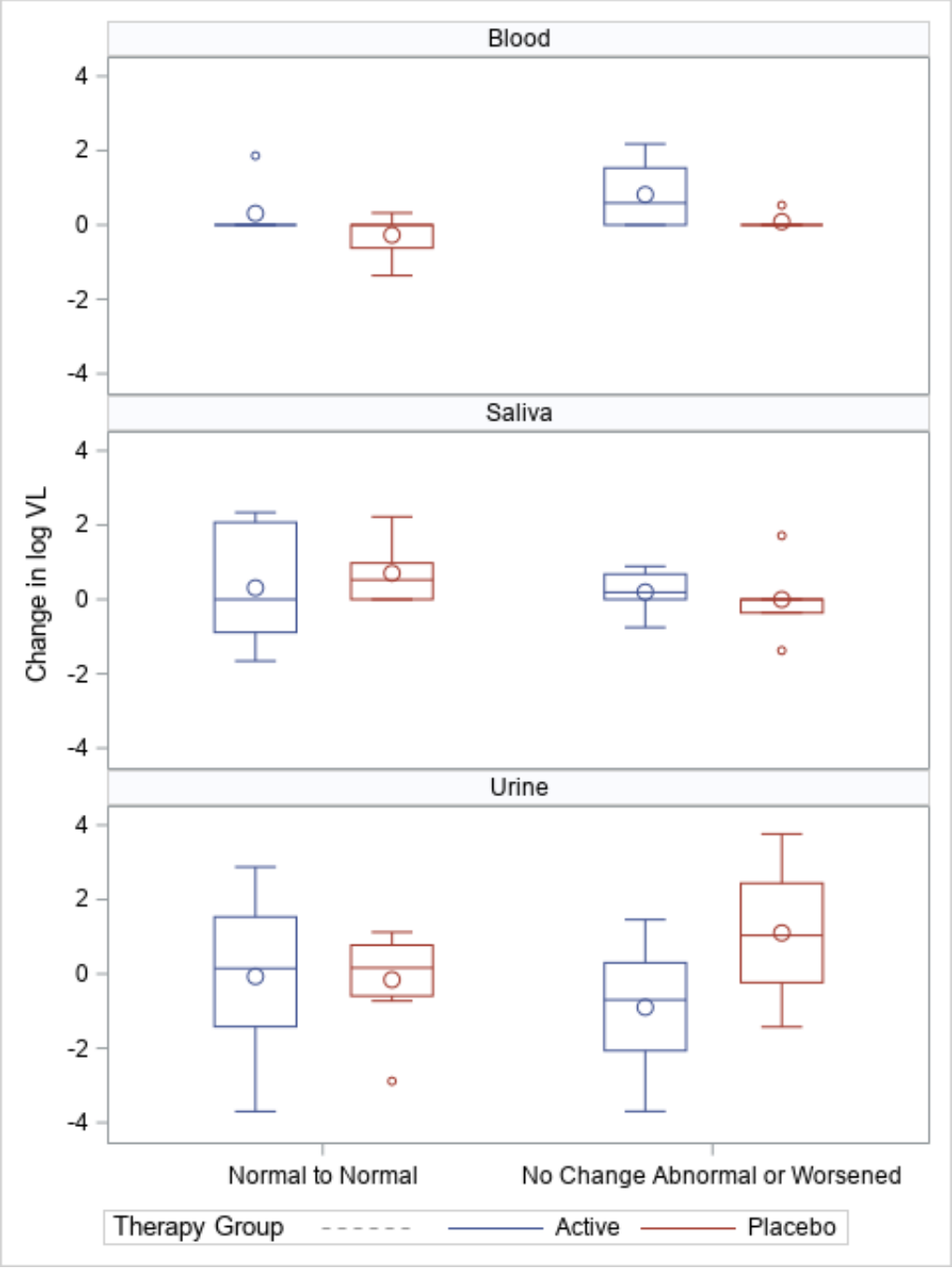
URINE: p-value*=0..9741 (unadjusted); p-value*= 0.8127 (adjusted for therapy)

Change in Best Ear Hearing	Randomized					Active					Placebo				
	N	Mean	SD	10th Pctl	90th Pctl	N	Mean	SD	10th Pctl	90th Pctl	N	Mean	SD	10th Pctl	90th Pctl
Normal to Normal	15	-.122	1.655	-2.89	1.533	6	-.070	2.297	-3.70	2.875	9	-.157	1.222	-2.89	1.122
No Change Abnormal Worsened	10	-.099	2.117	-2.88	2.611	6	-.899	1.857	-3.70	1.459	4	1.102	2.121	-1.43	3.763

[#]Viral load values below detection limit were replaced by 10 (i.e. 1 in log10 units); Change in viral load = (Month6 log10 VL – Baseline log10 VL); For subjects without the month-6 viral load, the last visit with available viral load was used.

*p-values for association between change in log10 VL and change in hearing based on fitting generalized linear model.

Figure 15: Boxplots: Change in Log10 VL and Change (Binary) in Best Ear Hearing



Hearing Assessment Listing

Active

		BASELINE			MONTH 6			
ID	**Therapy**	**Left Ear**	**Right Ear**	**Best Ear**	**Left Ear**	**Right Ear**	**Best Ear M6**	**Best Ear Change**
13TX	Active	Severe	Severe	Severe	Severe	Not Evaluable	Not Evaluable	
17EH	Active	Severe	Moderate	Moderate			Withdrew	
19DC	Active	Normal	Severe	Normal	Normal	Not Evaluable	Normal	Normal to Normal
1YEM	Active	Moderate	Mild	Mild	Severe	Severe	Severe	Worsened
1YXH	Active	Severe	Severe	Severe	Severe	Severe	Severe	No Change Abnormal
2AH3	Active	Mild	Severe	Mild	Severe	Not Evaluable	Not Evaluable	
2TA3	Active	Normal	Severe	Normal	Normal	Severe	Normal	Normal to Normal
2ZGU	Active	Severe	Severe	Severe	Severe	Severe	Severe	No Change Abnormal
32RK	Active	Mild	Mild	Mild	Mild	Moderate	Mild	No Change Abnormal
3UEF	Active	Severe	Moderate	Moderate	Severe	Severe	Severe	Worsened
573N	Active	Normal	Severe	Normal	Not Evaluable	Severe	Not Evaluable	
5ARV	Active	Normal	Severe	Normal	Normal	Severe	Normal	Normal to Normal
6LEL	Active	Normal	Severe	Normal	Normal	Severe	Normal	Normal to Normal
7QCJ	Active	Normal	Moderate	Normal	Normal	Moderate	Normal	Normal to Normal
974K	Active	Normal	Mild	Normal	Missing*	Missing*	Missing	
9HVF	Active	Severe	Normal	Normal	Severe	Normal	Normal	Normal to Normal
9PGH	Active	Severe	Mild	Mild	Severe	Severe[#]	Severe[#]	Worsened

[*]Participant hospitalized and died around Month 6 so hearing assessment was not done.
[#]Cochlear implant done after baseline and before Month 6; hearing on both ears at Month 6 assigned as “Severe”.

Hearing Assessment Listing

Placebo

		BASELINE			MONTH 6			
ID	**Therapy**	**Left Ear**	**Right Ear**	**Best Ear**	**Left Ear**	**Right Ear**	**Best Ear M6**	**Best Ear Change**
1K5D	Placebo	Severe	Severe	Excluded*			Excluded*	
1KUH	Placebo	Normal	Moderate	Normal	Normal	Moderate	Normal	Normal to Normal
2674	Placebo	Mild	Normal	Normal	Not Evaluable	Normal	Normal	Normal to Normal
2Q49	Placebo	Severe	Severe	Severe	Severe	Severe	Severe	No Change Abnormal
337J	Placebo	Normal	Normal	Normal	Not Evaluable	Normal	Normal	Normal to Normal
3FG4	Placebo	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate	No Change Abnormal
3RJM	Placebo	Missing	Missing	Excluded*			Excluded*	
3ZGW	Placebo	Normal	Severe	Normal	Normal	Severe	Normal	Normal to Normal
46WG	Placebo	Normal	Severe	Normal	Normal	Severe	Normal	Normal to Normal
4JKU	Placebo	Severe	Severe	Severe	Severe	Severe	Severe	No Change Abnormal
5HPK	Placebo	Severe	Mild	Mild	Severe	Mild	Mild	No Change Abnormal
5NTX	Placebo	Moderate	Normal	Normal	Moderate	Normal	Normal	Normal to Normal
5RT2	Placebo	Normal	Severe	Normal	Normal	Severe	Normal	Normal to Normal
64X3	Placebo	Severe	Severe	Severe	Severe	Severe	Severe	No Change Abnormal
6GED	Placebo	Severe	Severe	Severe	Severe	Severe	Severe	No Change Abnormal
77VL	Placebo	Severe	Normal	Normal	Not Evaluable	Normal	Normal	Normal to Normal
7HG6	Placebo	Moderate	Normal	Normal	Moderate	Normal	Normal	Normal to Normal
9AJ7	Placebo	Severe	Mild	Mild	Not Evaluable	Severe	Not Evaluable	

*Dropped after randomization and did not take study drug – excluded from the analyses.

Specimen Shipment Tracking

Blood Specimen Shipment

	Enrollment	Whole Blood Specimen		Blood Specimens Status			
	# Enrolled	# of Blood Specimen	# of Blood Specimen Not Collected	# of Specimen Shipped	# of Pending Specimen Shipment	# of Specimen Received	# of Specimen not yet Received but Shipped
All Sites	35 (100%)	215 (100%)	10 (100%)	218 (100%)	0 (0.0%)	218 (100%)	0 (0.0%)
001	2 (5.7%)	13 (6%)	1 (10%)	13 (6%)	0 (0.0%)	13 (6%)	0 (0.0%)
002	1 (2.9%)	1 (0.5%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	1 (0.5%)	0 (0.0%)
019	2 (5.7%)	14 (6.5%)	0 (0.0%)	14 (6.4%)	0 (0.0%)	14 (6.4%)	0 (0.0%)
086	2 (5.7%)	14 (6.5%)	0 (0.0%)	14 (6.4%)	0 (0.0%)	14 (6.4%)	0 (0.0%)
273	3 (8.6%)	19 (8.8%)	2 (20%)	19 (8.7%)	0 (0.0%)	19 (8.7%)	0 (0.0%)
280	5 (14.3%)	34 (15.8%)	1 (10%)	34 (15.6%)	0 (0.0%)	34 (15.6%)	0 (0.0%)
281	2 (5.7%)	13 (6%)	0 (0.0%)	13 (6%)	0 (0.0%)	13 (6%)	0 (0.0%)
283	5 (14.3%)	29 (13.5%)	0 (0.0%)	29 (13.3%)	0 (0.0%)	29 (13.3%)	0 (0.0%)
285	1 (2.9%)	6 (2.8%)	1 (10%)	6 (2.8%)	0 (0.0%)	6 (2.8%)	0 (0.0%)
286	3 (8.6%)	21 (9.8%)	0 (0.0%)	21 (9.6%)	0 (0.0%)	21 (9.6%)	0 (0.0%)
292	4 (11.4%)	23 (10.7%)	5 (50%)	23 (10.6%)	0 (0.0%)	23 (10.6%)	0 (0.0%)
294	1 (2.9%)	7 (3.3%)	0 (0.0%)	7 (3.2%)	0 (0.0%)	7 (3.2%)	0 (0.0%)
296	3 (8.6%)	14 (6.5%)	0 (0.0%)	17* (7.8%)	0 (0.0%)	17* (7.8%)	0 (0.0%)
297	1 (2.9%)	7 (3.3%)	0 (0.0%)	7 (3.2%)	0 (0.0%)	7 (3.2%)	0 (0.0%)

*For site# 296 for one subject, two additional frozen specimen were shipped and received for Study Day 42 and one additional frozen specimen was shipped and received for Study Day 28. This accounts for the shipped to be three more than the specimen collected.

Specimen Shipment Tracking

Saliva Specimen Shipment

	Enrollment	Saliva Specimen		Saliva Specimens Status			
	# Enrolled	# of Saliva Specimen	# of Saliva Specimen Not Collected	# of Specimen Shipped	# of Pending Specimen Shipment	# of Specimen Received	# of Specimen not yet Received but Shipped
All Sites	35 (100%)	225 (100%)	0 (0.0%)	225 (100%)	0 (0.0%)	225 (100%)	0 (0.0%)
001	2 (5.7%)	14 (6.2%)	0 (0.0%)	14 (6.2%)	0 (0.0%)	14 (6.2%)	0 (0.0%)
002	1 (2.9%)	1 (0.4%)	0 (0.0%)	1 (0.4%)	0 (0.0%)	1 (0.4%)	0 (0.0%)
019	2 (5.7%)	14 (6.2%)	0 (0.0%)	14 (6.2%)	0 (0.0%)	14 (6.2%)	0 (0.0%)
086	2 (5.7%)	14 (6.2%)	0 (0.0%)	14 (6.2%)	0 (0.0%)	14 (6.2%)	0 (0.0%)
273	3 (8.6%)	21 (9.3%)	0 (0.0%)	21 (9.3%)	0 (0.0%)	21 (9.3%)	0 (0.0%)
280	5 (14.3%)	35 (15.6%)	0 (0.0%)	35 (15.6%)	0 (0.0%)	35 (15.6%)	0 (0.0%)
281	2 (5.7%)	13 (5.8%)	0 (0.0%)	13 (5.8%)	0 (0.0%)	13 (5.8%)	0 (0.0%)
283	5 (14.3%)	29 (12.9%)	0 (0.0%)	29 (12.9%)	0 (0.0%)	29 (12.9%)	0 (0.0%)
285	1 (2.9%)	7 (3.1%)	0 (0.0%)	7 (3.1%)	0 (0.0%)	7 (3.1%)	0 (0.0%)
286	3 (8.6%)	21 (9.3%)	0 (0.0%)	21 (9.3%)	0 (0.0%)	21 (9.3%)	0 (0.0%)
292	4 (11.4%)	28 (12.4%)	0 (0.0%)	28 (12.4%)	0 (0.0%)	28 (12.4%)	0 (0.0%)
294	1 (2.9%)	7 (3.1%)	0 (0.0%)	7 (3.1%)	0 (0.0%)	7 (3.1%)	0 (0.0%)
296	3 (8.6%)	14 (6.2%)	0 (0.0%)	14 (6.2%)	0 (0.0%)	14 (6.2%)	0 (0.0%)
297	1 (2.9%)	7 (3.1%)	0 (0.0%)	7 (3.1%)	0 (0.0%)	7 (3.1%)	0 (0.0%)

Specimen Shipment Tracking

Urine Specimen Shipment

	Enrollment	Urine Specimen		Urine Specimens Status			
	# Enrolled	# of Urine Specimen	# of Urine Specimen Not Collected	# of Specimen Shipped	# of Pending Specimen Shipment	# of Specimen Received	# of Specimen not yet Received but Shipped
All Sites	35 (100%)	173 (100%)	52 (100%)	175 (100%)	0 (0.0%)	175 (100%)	0 (0.0%)
001	2 (5.7%)	12 (6.9%)	2 (3.8%)	12 (6.9%)	0 (0.0%)	12 (6.9%)	0 (0.0%)
002	1 (2.9%)	1 (0.6%)	0 (0.0%)	1 (0.6%)	0 (0.0%)	1 (0.6%)	0 (0.0%)
019	2 (5.7%)	1 (0.6%)	13 (25%)	1 (0.6%)	0 (0.0%)	1 (0.6%)	0 (0.0%)
086	2 (5.7%)	8 (4.6%)	6 (11.5%)	8 (4.6%)	0 (0.0%)	8 (4.6%)	0 (0.0%)
273	3 (8.6%)	12 (6.9%)	9 (17.3%)	12 (6.9%)	0 (0.0%)	12 (6.9%)	0 (0.0%)
280	5 (14.3%)	33 (19.1%)	2 (3.8%)	33 (18.9%)	0 (0.0%)	33 (18.9%)	0 (0.0%)
281	2 (5.7%)	9 (5.2%)	4 (7.7%)	9 (5.1%)	0 (0.0%)	9 (5.1%)	0 (0.0%)
283	5 (14.3%)	26 (15%)	3 (5.8%)	26 (14.9%)	0 (0.0%)	26 (14.9%)	0 (0.0%)
285	1 (2.9%)	7 (4%)	0 (0.0%)	7 (4%)	0 (0.0%)	7 (4%)	0 (0.0%)
286	3 (8.6%)	13 (7.5%)	8 (15.4%)	13 (7.4%)	0 (0.0%)	13 (7.4%)	0 (0.0%)
292	4 (11.4%)	26 (15%)	2 (3.8%)	26 (14.9%)	0 (0.0%)	26 (14.9%)	0 (0.0%)
294	1 (2.9%)	6 (3.5%)	1 (1.9%)	6 (3.4%)	0 (0.0%)	6 (3.4%)	0 (0.0%)
296	3 (8.6%)	12 (6.9%)	2 (3.8%)	14* (8%)	0 (0.0%)	14* (8%)	0 (0.0%)
297	1 (2.9%)	7 (4%)	0 (0.0%)	7 (4%)	0 (0.0%)	7 (4%)	0 (0.0%)

* Two additional samples shipped and received at Site 296, as one subject had two specimen collected, shipped and received at day 1 and day-28.
The site collected 2 samples for these two visits due to not getting sufficient enough sample on the first collection,
which have been documented in Additional Comments F46 as Speciemn Collection F04 allows for only one specimemn details per visit.

Concomitant Medications

Active

Subject #	Study Day	Drug	Start Date	Stop Date	Ongoing	Reason	Regimen Dose,Unit,Freq,Route
17EH	Baseline	MUPIROCIN	06/04/2018		YES	ECZEMA	0001.00,SMALL AMOUNT,3,5
17EH	Baseline	HYDROCORTISONE	04/04/2018		YES	ECZEMA	0001.00,THIN FILM,1,5
17EH	Baseline	AMOXICILLIN	06/06/2018		YES	ECZEMA-INFECTION DUE TO SCRATCHING	0003.00,2,2,1
5ARV	Baseline	CIPRODEX	07/05/2018	07/10/2018		EAR INFECTION	0004.00,6,2,EAR DROPS
6LEL	Baseline	IBUPROFEN	02/21/2019		YES	TEETHING	0001.25,2,5,1
6LEL	Day 14	IBUPROFEN	02/21/2019		YES	TEETHING	0001.25,2,5,1
6LEL	Day 28	IBUPROFEN	04/03/2019		YES	PAIN	0001.25,2,1,1
6LEL	Day 28	IBUPROFEN	02/21/2019	04/03/2019		TEETHING	0001.25,2,5,1
6LEL	Day 42	IBUPROFEN	04/03/2019	04/19/2019		PAIN	0001.25,2,1,1
6LEL	Day 42	VITAMIN D	04/05/2019		YES	BUCKLE FRACTURE OF RIGHT TIBIA AND FIBULA	0001.00,6,1,1
6LEL	Day 70	VITAMIN D	04/05/2019		YES	BUCKLE FRACTURE OF RIGHT TIBIA AND FIBULA	0001.00,6,1,1
573N	Day 14	TRIMETHOPRIM	09/28/2015	09/30/2015		QUERY URINARY TRACT INFECTION	0025.00,1,2,1
573N	Day 14	IBUPROFEN	09/27/2015	09/27/2015		PYREXIA	0060.00,1,5,1
7QCJ	Day 42	PARACETAMOL	10/08/2017	10/19/2017		GASTROENTENITIS	0120.00,1,1,1

Concomitant Medications

Active

Subject #	Study Day	Drug	Start Date	Stop Date	Ongoing	Reason	Regimen Dose,Unit,Freq,Route
2TA3	Day 70	PARACETAMOL	02/27/2018	02/27/2018		FEVER	0060.00,1,5,1
13TX	Day 28	MOVICOL	04/25/2017		YES	CONSTIPATION	0001.00,SACHET,2,1
13TX	Day 42	MOVICOL	04/25/2017		YES	CONSTIPATION	0001.00,SACHET,2,1
13TX	Day 70	MOVICOL	04/25/2017		YES	CONSTIPATION	0001.00,SACHET,2,1
19DC	Baseline	CLENIL MODULITE	07/01/2018		YES	ASTHMA	0050.00,MCG,2,6
19DC	Baseline	LORATIDINE	03/01/2018		YES	HAYFEVER	0005.00,1,1,1
19DC	Baseline	SALBUTAMOL	07/01/2017		YES	ASTHMA	0100.00,MCG,5,6
19DC	Day 14	LORATIDINE	03/01/2018		YES	HAYFEVER	0005.00,1,1,1
19DC	Day 14	SALBUTAMOL	07/01/2017		YES	ASTHMA	0100.00,MCG,5,6
19DC	Day 14	SOFRADEX	07/16/2019		YES	EAR INFECTION	0003.00,6,3 TO 4 TIMES PER DAY,EAR
19DC	Day 14	CLENIL MODULITE	07/01/2018		YES	ASTHMA	0050.00,MCG,2,6
19DC	Day 28	SOFRADEX	07/16/2019	07/24/2019		EAR INFECTION	0003.00,6,3 TO 4 TIMES PER DAY,EAR
19DC	Day 28	SALBUTAMOL	07/01/2017		YES	ASTHMA	0100.00,MCG,5,6
19DC	Day 28	CLENIL MODULITE	07/01/2018		YES	ASTHMA	0050.00,MCG,2,6
19DC	Day 28	LORATIDINE	03/01/2018		YES	HAYFEVER	0005.00,1,1,1
19DC	Day 42	LORATIDINE	03/01/2018		YES	HAYFEVER	0005.00,1,1,1

Concomitant Medications

Active

Subject #	Study Day	Drug	Start Date	Stop Date	Ongoing	Reason	Regimen Dose,Unit,Freq,Route
19DC	Day 42	CLENIL MODULITE	07/01/2018		YES	ASTHMA	0050.00,MCG,2,6
19DC	Day 42	SALBUTAMOL	07/01/2017		YES	ASTHMA	0100.00,MCG,5,6
19DC	Day 70	SALBUTAMOL	07/01/2017		YES	ASTHMA	0100.00,MCG,5,6
19DC	Day 70	LORATIDINE	03/01/2018		YES	HAYFEVER	0005.00,1,1,1
19DC	Day 70	CLENIL MODULITE	07/01/2018		YES	ASTHMA	0050.00,MCG,2,6
2AH3	Day 14	PARACETAMOL	04/16/2019	04/17/2019		VACCINES	0060.00,1,5,1
2AH3	Day 14	BEXERO	04/16/2019	04/16/2019		CHILDHOOD VACCINE	0000.50,2,ONCE,3
2AH3	Day 14	PREVENAR 13	04/16/2019	04/16/2019		CHILDHOOD VACCINE	0000.50,2,ONCE,3
2AH3	Day 14	INFANRIX	04/16/2019	04/16/2019		CHILDHOOD VACCINE	0000.50,2,ONCE,3
2AH3	Day 28	PARACETAMOL	04/27/2019		YES	TEETHING	0060.00,1,5,1
2AH3	Day 42	PARACETAMOL	04/27/2019		YES	TEETHING	0060.00,1,5,1
2AH3	Day 70	PARACETAMOL	04/27/2019	05/13/2019		TEETHING	0060.00,1,5,1
2ZGU	Baseline	MULTIVITAMIN	08/01/2018		YES	VITAMIN SUPPLEMENT - RECOMMENDED FOR UNDER 5 YEAR OLDS	0001.00,TABLET,1,1

Concomitant Medications

Active

Subject #	Study Day	Drug	Start Date	Stop Date	Ongoing	Reason	Regimen Dose,Unit,Freq,Route
2ZGU	Day 14	MULTIVITAMIN	08/01/2018		YES	VITAMIN SUPPLEMENT - RECOMMENDED FOR UNDER 5 YEAR OLDS	0001.00,TABLET,1,1
2ZGU	Day 14	PARACETMOL	03/09/2019	03/09/2019		FELL OVER	0005.00,2,5,1
2ZGU	Day 28	MULTIVITAMIN	08/01/2018		YES	VITAMIN SUPPLEMENT - RECOMMENDED FOR UNDER 5 YEAR OLDS	0001.00,TABLET,1,1
2ZGU	Day 42	SYTRON	03/25/2019		YES	LOW IRON LEVELS	0002.50,2,2,1
2ZGU	Day 42	MULTIVITAMIN	08/01/2018		YES	VITAMIN SUPPLEMENT - RECOMMENDED FOR UNDER 5 YEAR OLDS	0001.00,TABLET,1,1
2ZGU	Day 70	SYTRON	03/25/2019		YES	LOW IRON LEVELS	0002.50,2,2,1
2ZGU	Day 70	MULTIVITAMIN	08/01/2018		YES	VITAMIN SUPPLEMENT - RECOMMENDED FOR UNDER 5 YEAR OLDS	0001.00,TABLET,1,1
3UEF	Baseline	PCV	09/20/2017	09/20/2017		IMMUNISATION	0001.00,DOSE,ONE INJECTION,3
3UEF	Baseline	DTAP IPV HIB	09/20/2017	09/20/2017		IMMUNISATION	0001.00,DOSE,ONE INJECTION,3
3UEF	Baseline	MEN B	09/20/2017	09/20/2017		IMMUNISATION	0001.00,DOSE,ONE INJECTION,3
3UEF	Baseline	PARACETAMOL	10/09/2017	10/11/2017		COUGH AND COLD	0002.50,2,2,1

Concomitant Medications

Active

Subject #	Study Day	Drug	Start Date	Stop Date	Ongoing	Reason	Regimen Dose,Unit,Freq,Route
3UEF	Day 42	ASHTON'S TEETHING POWDER	11/26/2017	11/26/2017		TEETHING PROBLEMS	0130.00,1,2,1
9PGH	Baseline	PHENOBARBITAL	06/12/2017		YES	EPILEPSY	0004.00,MG/ML,2,FEEDING TUBE
9PGH	Baseline	DOCUSATE SODIUM	06/26/2017	07/24/2017		CONSTIPATION	0060.00,MG/15 ML,2,FEEDING TUBE
9PGH	Baseline	TOPIRAMATE	07/14/2017		YES	SEIZURES	0006.00,MG/ML,2,FEEDING TUBE
9PGH	Baseline	LEVETIRACETAM	07/06/2017		YES	SEIZURES	0100.00,MG/ML,2,FEEDING TUBE
9PGH	Baseline	ONDANSETRON	07/07/2017	07/22/2017		EMESIS	0004.00,MG/5 ML,5,FEEDING TUBE
9PGH	Baseline	OMEPRAZOLE	07/10/2017		YES	REFLUX	0002.00,MG/ML,2,FEEDING TUBE
9PGH	Baseline	ALBUTEROL SULFATE	05/21/2017		YES	BREATHING TREATMENT	0002.50,MG/3 ML,5,6
9PGH	Baseline	AMOXICILLIN-CLAVULANATE	07/22/2017		YES	ASPIRATION PNEUMONIA	0457.00,MG/5 ML,1,FEEDING TUBE
9PGH	Day 14	OMEPRAZOLE	07/10/2017		YES	REFLUX	0002.00,MG/ML,2,FEEDING TUBE
9PGH	Day 14	LEVETIRACETAM	07/06/2017		YES	SEIZURES	0100.00,MG/ML,2,FEEDING TUBE

Concomitant Medications

Active

Subject #	Study Day	Drug	Start Date	Stop Date	Ongoing	Reason	Regimen Dose,Unit,Freq,Route
9PGH	Day 14	TOPIRAMATE	07/14/2017		YES	SEIZURES	0006.00,MG/ML,2,FEEDING TUBE
9PGH	Day 14	PHENOBARBITAL	06/12/2017		YES	EPILEPSY	0004.00,MG/ML,2,FEEDING TUBE
9PGH	Day 14	ALBUTEROL SULFATE	05/21/2017		YES	BREATHING TREATMENT	0002.50,MG/3 ML,5,6
9PGH	Day 14	AMOXICILLIN-CLAVULANATE	07/22/2017	07/31/2017		ASPIRATION PNEUMONIA	0457.00,MG/5 ML,1,FEEDING TUBE
9PGH	Day 28	TOPIRAMATE	07/14/2017		YES	SEIZURES	0006.00,MG/ML,2,FEEDING TUBE
9PGH	Day 28	OMEPRAZOLE	07/10/2017		YES	REFLUX	0002.00,MG/ML,2,FEEDING TUBE
9PGH	Day 28	PHENOBARBITAL	06/12/2017		YES	EPILEPSY	0004.00,MG/ML,2,FEEDING TUBE
9PGH	Day 28	LEVETIRACETAM	07/06/2017		YES	SEIZURES	0100.00,MG/ML,2,FEEDING TUBE
9PGH	Day 28	ALBUTEROL SULFATE	05/21/2017		YES	BREATHING TREATMENT	0002.50,MG/3 ML,5,6
9PGH	Day 42	PHENOBARBITAL	06/12/2017		YES	EPILEPSY	0004.00,MG/ML,2,FEEDING TUBE
9PGH	Day 42	DOCUSATE SODIUM	08/18/2017	08/29/2017		CONSTIPATION	0005.00,2,1,1
9PGH	Day 42	OMEPRAZOLE	07/10/2017		YES	REFLUX	0002.00,MG/ML,2,FEEDING TUBE
9PGH	Day 42	SENNOSIDES	08/31/2017		YES	CONSTIPATION	0002.50,2,1,1

Concomitant Medications

Active

Subject #	Study Day	Drug	Start Date	Stop Date	Ongoing	Reason	Regimen Dose,Unit,Freq,Route
9PGH	Day 42	LEVETIRACETAM	07/06/2017		YES	SEIZURES	0100.00,MG/ML,2,FEEDING TUBE
9PGH	Day 42	TOPIRAMATE	07/14/2017		YES	SEIZURES	0006.00,MG/ML,2,FEEDING TUBE
9PGH	Day 42	ALBUTEROL SULFATE	05/21/2017		YES	BREATHING TREATMENT	0002.50,MG/3 ML,5,6
9PGH	Day 70	ALBUTEROL SULFATE	05/21/2017		YES	BREATHING TREATMENT	0002.50,MG/3 ML,5,6
9PGH	Day 70	SENNOSIDES	08/31/2017		YES	CONSTIPATION	0002.50,2,1,1
9PGH	Day 70	TOPIRAMATE	07/14/2017		YES	SEIZURES	0006.00,MG/ML,2,FEEDING TUBE
9PGH	Day 70	LEVETIRACETAM	07/06/2017		YES	SEIZURES	0100.00,MG/ML,2,FEEDING TUBE
9PGH	Day 70	PHENOBARBITAL	06/12/2017		YES	EPILEPSY	0004.00,MG/ML,2,FEEDING TUBE
9PGH	Day 70	OMEPRAZOLE	07/10/2017		YES	REFLUX	0002.00,MG/ML,2,FEEDING TUBE
1YEM	Day 14	PARACETAMOL	07/19/2019	07/19/2019		LOW GRADE PYREXIA	0120.00,1,STAT,1
1YEM	Day 14	BEXSERO IMMUNISATION	07/18/2019	07/18/2019		ROUTINE IMMUNISATION	0000.50,2,STAT,3
1YEM	Day 14	INFRANRIX HEXA IMMUNISATION	07/18/2019	07/18/2019		ROUTINIE IMMUNISATION	0000.50,2,STAT,3

Concomitant Medications

Active

Subject #	Study Day	Drug	Start Date	Stop Date	Ongoing	Reason	Regimen Dose,Unit,Freq,Route
1YEM	Day 14	PREVENAR 13 IMMUNISATION	07/18/2019	07/18/2019		ROUTINE IMMUNISATION	0000.50,2,STAT,3
1YEM	Day 28	PARACETAMOL	07/20/2019		YES	VIRAL ILLNESS AND POST IMMUNISATION	0060.00,1,5,1
1YEM	Day 42	PARACETAMOL	07/20/2019		YES	VIRAL ILLNESS AND POST IMMUNISATION	0060.00,1,5,1
1YEM	Day 70	PARACETAMOL	07/20/2019		YES	VIRAL ILLNESS AND POST IMMUNISATION	0060.00,1,5,1
974K	Baseline	CYCLOPENTOLATE 0.5%	03/21/2018	03/21/2018		RETINOPATHY SCREEN	0001.00,6,5,INSTILLED INTO BOTH EYES
974K	Baseline	INFANRIX HEXA	04/05/2018	04/05/2018		VACCINATION	0000.50,2,ONCE ONLY STAT,3
974K	Baseline	SYTRON	01/17/2018		YES	SUPPLEMENT - PREMATURITY	0001.00,2,1,1
974K	Baseline	LEVOTHYROXIN	03/13/2018		YES	HYPTHYROIDISM	0012.50,MICROGRAMS,ONCE A DAY FOR 4 DAYS PER WEEK,1
974K	Baseline	URSODEOXYCHOLIC ACID	02/15/2018	03/13/2018		TREATMENT FOR LIVER FUNTION ABNORMALITIES	0013.00,1,2,1
974K	Baseline	PHENYLEPHRINE 2.5%	03/21/2018	03/21/2018		RETINOPATHY SCREEN	0001.00,6,5,INSTILLED INTO BOTH EYES

Concomitant Medications

Active

Subject #	Study Day	Drug	Start Date	Stop Date	Ongoing	Reason	Regimen Dose,Unit,Freq,Route
974K	Baseline	LEVOTHYROXIN	03/13/2018		YES	HYPTHYROIDISM	0025.00,MICROGRAMS,ONCE A DAY FOR 3 DAYS PER WEEK,1
974K	Baseline	FOLIC ACID	01/17/2018		YES	SUPPLEMENT - PREMATURITY	0500.00,MICROGRAMS,ONCE A WEEK,1
974K	Baseline	GENTAMICIN	04/07/2018	04/07/2018		SUSPECTED SEPSIS	0013.00,1,ONE DOSE,2
974K	Baseline	ABIDEC	01/01/2018		YES	SUPPLEMENT - PREMATURITY	0000.60,2,1,1
974K	Baseline	CHLOROTHIAZIDE	04/01/2018		YES	PDA	0027.00,1,1,1
974K	Baseline	CAFFEINE CITRATE	02/15/2018	03/12/2018		PROPHYLAXIS - PREVENTION OF APNOEAS. IMPROVE RESPIRATORY EFFORT.	0013.00,1,1,1
974K	Baseline	FLUCLOXACILLIN	04/07/2018	04/08/2018		SUSPECTED SEPSIS	0068.00,1,4,2
974K	Baseline	ROTARIX	04/05/2018	04/05/2018		VACCINATION	0001.50,2,ONCE ONLY STAT,1
974K	Baseline	OXYBUPROCAINE 0.4%	03/21/2018	03/21/2018		RETINOPATHY SCREEN	0001.00,6,5,INSTILLED INTO BOTH EYES
974K	Baseline	SODIUM CHLORIDE	02/16/2018		YES	LOW SODIUM LEVELS. ON SPIRONOLACTONE	0004.00,MMOLS,4,1

Concomitant Medications

Active

Subject #	Study Day	Drug	Start Date	Stop Date	Ongoing	Reason	Regimen Dose,Unit,Freq,Route
974K	Baseline	ALFACALCIDOL	03/13/2018	04/10/2018		VITAMIN D DEFICIENCY	0002.00,6,1,1
974K	Baseline	SILDENAFIL	03/30/2018		YES	SECONDARY PULMONARY HYPERTENSION	0000.70,1,3,1
974K	Baseline	SPIRONOLACTONE	04/01/2018		YES	PDA	0002.70,1,1,1
974K	Baseline	COLECALCIFEROL	03/03/2018		YES	VITAMIN D DEFICIENCY	1000.00,UNITS,1,1
974K	Baseline	PARACETAMOL	04/05/2018	04/05/2018		PAIN	0052.00,1,ONCE ONLY STAT,1
974K	Day 14	ABIDEC	01/01/2018		YES	SUPPLEMENT - PREMATURITY	0000.60,2,1,1
974K	Day 14	FOLIC ACID	01/17/2018		YES	SUPPLEMENT - PREMATURITY	0500.00,MICROGRAMS,ONCE A WEEK,1
974K	Day 14	SYTRON	01/17/2018		YES	SUPPLEMENT - PREMATURITY	0001.00,2,1,1
974K	Day 14	SODIUM CHLORIDE	02/16/2018	04/21/2018		LOW SODIUM LEVELS. ON SPIRONOLACTONE	0004.00,MMOLS,4,1
974K	Day 14	CHLOROTHIAZIDE	04/01/2018		YES	PDA	0027.00,1,1,1
974K	Day 14	CALCIUM CARBONATE	04/17/2018		YES	SUPPLEMENT	0000.75,MMOLS,4,1

Concomitant Medications

Active

Subject #	Study Day	Drug	Start Date	Stop Date	Ongoing	Reason	Regimen Dose,Unit,Freq,Route
974K	Day 14	LEVOTHYROXIN	03/13/2018		YES	HYPTHYROIDISM	0012.50,MICROGRAMS,ONCE A DAY FOR 4 DAYS PER WEEK,1
974K	Day 14	LEVOTHYROXIN	03/13/2018		YES	HYPTHYROIDISM	0025.00,MICROGRAMS,ONCE A DAY FOR 3 DAYS PER WEEK,1
974K	Day 14	SILDENAFIL	03/30/2018		YES	SECONDARY PULMONARY HYPERTENSION	0000.70,1,3,1
974K	Day 14	SPIRONOLACTONE	04/01/2018		YES	PDA	0002.70,1,1,1
974K	Day 14	COLECALCIFEROL	03/03/2018		YES	VITAMIN D DEFICIENCY	1000.00,UNITS,1,1
974K	Day 28	COLECALCIFEROL	03/03/2018	04/16/2018		VITAMIN D DEFICIENCY	1000.00,UNITS,1,1
974K	Day 28	SPIRONOLACTONE	04/01/2018	04/20/2018		PDA	0002.70,1,1,1
974K	Day 28	CHLOROTHIAZINE	04/21/2018	05/06/2018		PDA	0032.00,1,1,1
974K	Day 28	CHLOROTHIAZINE	05/07/2018		YES	PDA	0036.00,1,1,1
974K	Day 28	COLECALCIFEROL	04/17/2018		YES	VITAMIN D DEFICIENCY	0400.00,UNITS,1,1
974K	Day 28	SILDENAFIL	05/07/2018		YES	SECONDARY PULMONARY HYPERTENSION	0001.80,1,3,1

Concomitant Medications

Active

Subject #	Study Day	Drug	Start Date	Stop Date	Ongoing	Reason	Regimen Dose,Unit,Freq,Route
974K	Day 28	ORABASE	04/23/2018	05/06/2018		NAPPY RASH	0001.00,APPLICATION,WITH NAPPY CHANGES,5
974K	Day 28	PARACETAMOL	05/05/2018	05/06/2018		PAIN	0053.00,1,3,1
974K	Day 28	PREVENAR 13	05/05/2018	05/05/2018		IMMUNISATION	0000.50,2,ONCE ONLY,3
974K	Day 28	BEXSERO	05/05/2018	05/05/2018		IMMUNISATION	0000.50,2,ONCE ONLY,3
974K	Day 28	CALCIUM CARBONATE	04/17/2018	04/27/2018		SUPPLEMENT	0000.75,MMOLS,4,1
974K	Day 28	CHLOROTHIAZIDE	04/01/2018	04/20/2018		PDA	0027.00,1,1,1
974K	Day 28	SPIRONOLACTONE	05/07/2018		YES	PDA	0003.60,1,1,1
974K	Day 28	SILDENAFIL	03/30/2018	04/21/2018		SECONDARY PULMONARY HYPERTENSION	0000.70,1,3,1
974K	Day 28	INFANTRIX	05/05/2018	05/05/2018		IMMUNISATION	0000.50,2,ONCE ONLY,3
974K	Day 28	SILDENAFIL	04/22/2018	05/07/2018		SECONDARY PULMONARY HYPERENSION	0001.50,1,3,1
974K	Day 28	SPIRONOLACTONE	04/21/2018	05/06/2018		PDA	0003.20,1,1,1
974K	Day 28	ABIDEC	01/01/2018		YES	SUPPLEMENT - PREMATURITY	0000.60,2,1,1

Concomitant Medications

Active

Subject #	Study Day	Drug	Start Date	Stop Date	Ongoing	Reason	Regimen Dose,Unit,Freq,Route
974K	Day 28	FOLIC ACID	01/17/2018		YES	SUPPLEMENT - PREMATURITY	0500.00,MICROGRAMS,ONCE A WEEK,1
974K	Day 28	SYTRON	01/17/2018		YES	SUPPLEMENT - PREMATURITY	0001.00,2,1,1
974K	Day 28	LEVOTHYROXIN	03/13/2018		YES	HYPTHYROIDISM	0012.50,MICROGRAMS,ONCE A DAY FOR 4 DAYS PER WEEK,1
974K	Day 28	LEVOTHYROXIN	03/13/2018		YES	HYPTHYROIDISM	0025.00,MICROGRAMS,ONCE A DAY FOR 3 DAYS PER WEEK,1
974K	Day 42	SPIRONOLACTONE	05/17/2018		YES	PDA	0004.00,1,1,1
974K	Day 42	CHLORTHIAZIDE	05/17/2018		YES	PDA	0040.00,1,1,1
974K	Day 42	ABIDEC	01/01/2018		YES	SUPPLEMENT - PREMATURITY	0000.60,2,1,1
974K	Day 42	FOLIC ACID	01/17/2018		YES	SUPPLEMENT - PREMATURITY	0500.00,MICROGRAMS,ONCE A WEEK,1
974K	Day 42	SYTRON	01/17/2018		YES	SUPPLEMENT - PREMATURITY	0001.00,2,1,1
974K	Day 42	LEVOTHYROXIN	03/13/2018		YES	HYPTHYROIDISM	0012.50,MICROGRAMS,ONCE A DAY FOR 4 DAYS PER WEEK,1

Concomitant Medications

Active

Subject #	Study Day	Drug	Start Date	Stop Date	Ongoing	Reason	Regimen Dose,Unit,Freq,Route
974K	Day 42	LEVOTHYROXIN	03/13/2018		YES	HYPTHYROIDISM	0025.00,MICROGRAMS,ONCE A DAY FOR 3 DAYS PER WEEK,1
974K	Day 42	CHLOROTHIAZINE	05/07/2018	05/16/2018		PDA	0036.00,1,1,1
974K	Day 42	COLECALCIFEROL	04/17/2018	05/15/2018		VITAMIN D DEFICIENCY	0400.00,UNITS,1,1
974K	Day 42	SPIRONOLACTONE	05/07/2018	05/16/2018		PDA	0003.60,1,1,1
974K	Day 42	SILDENAFIL	05/17/2018		YES	SECONDARY PULMONARY HYPERTENSION	0002.00,1,3,1
974K	Day 42	GAVISCON	05/22/2018		YES	REFLUX	0001.00,SACHET,WITH MILK FEEDS,1
974K	Day 42	FUROSEMIDE	05/21/2018	05/21/2018		DIURESIS	0004.00,1,ONCE ONLY,1
974K	Day 42	ORABASE	05/15/2018		YES	NAPPY RASH	0001.00,4,WITH NAPPIES,5
974K	Day 42	SILDENAFIL	05/07/2018	05/17/2018		SECONDARY PULMONARY HYPERTENSION	0001.80,1,3,1
974K	Day 70	SPIRONOLACTONE	05/29/2018	06/15/2018		PDA	0004.40,1,2,1
974K	Day 70	CHLORTHIAZIDE	05/29/2018	06/15/2018		PDA	0044.00,1,2,1

Concomitant Medications

Active

Subject #	Study Day	Drug	Start Date	Stop Date	Ongoing	Reason	Regimen Dose,Unit,Freq,Route
974K	Day 70	SPIRONOLACTONE	06/16/2018		YES	PDA	0004.80,1,2,1
974K	Day 70	CHLORTHIAZIDE	06/16/2018		YES	PDA	0048.00,1,2,1
974K	Day 70	LEVOTHYROXIN	03/13/2018		YES	HYPTHYROIDISM	0012.50,MICROGRAMS,ONCE A DAY FOR 4 DAYS PER WEEK,1
974K	Day 70	LEVOTHYROXIN	03/13/2018		YES	HYPTHYROIDISM	0025.00,MICROGRAMS,ONCE A DAY FOR 3 DAYS PER WEEK,1
974K	Day 70	CHLORTHIAZIDE	05/17/2018	05/28/2018		PDA	0040.00,1,1,1
974K	Day 70	DEXAMETHASONE	06/16/2018		YES	CHRONIC LUNG DISEASE	0096.00,MCG,2,1
974K	Day 70	DEXAMETHASONE	06/12/2018	06/15/2018		CHRONIC LUNG DISEASE	0034.00,MCG,2,1
974K	Day 70	DEXAMETHASONE	06/08/2018	06/11/2018		CHRONIC LUNG DISEASE	0034.00,MCG,ONCE DAILY,1
974K	Day 70	ABIDEC	01/01/2018		YES	SUPPLEMENT - PREMATURITY	0000.60,2,1,1
974K	Day 70	FOLIC ACID	01/17/2018		YES	SUPPLEMENT - PREMATURITY	0500.00,MICROGRAMS,ONCE A WEEK,1
974K	Day 70	SYTRON	01/17/2018		YES	SUPPLEMENT - PREMATURITY	0001.00,2,1,1

Concomitant Medications

Active

Subject #	Study Day	Drug	Start Date	Stop Date	Ongoing	Reason	Regimen Dose,Unit,Freq,Route
974K	Day 70	SPIRONOLACTONE	05/17/2018	05/28/2018		PDA	0004.00,1,1,1
974K	Day 70	GAVISCON	05/22/2018		YES	REFLUX	0001.00,SACHET,WITH MILK FEEDS,1
974K	Day 70	ORABASE	05/15/2018		YES	NAPPY RASH	0001.00,4,WITH NAPPIES,5
974K	Day 70	DEXAMETHASONE	05/29/2018	06/07/2018		CHRONIC LUNG DISEASE	0034.00,MCG,2,1
974K	Day 70	SILDENAFIL	05/17/2018		YES	SECONDARY PULMONARY HYPERTENSION	0002.00,1,3,1
974K	Day 70	BUDESONIDE	06/14/2018	06/14/2018		CHRONIC LUNG DISEASE	0001.00,1,2,1
1YXH	Day 14	FLU VACCINE	01/15/2019	01/15/2019		FLU VACCINATION BOOSTER	UNKNOWN,UNKNOWN,1,4
1YXH	Day 42	UNKNOWN	02/14/2019	02/14/2019		12 MONTH IMMUNISATIONS	UNKNOWN,UNKNOWN,1,UNKNOWN

CONCOMITANT MEDICATIONS

Placebo

Subject #	Study Day	Drug	Start Date	Stop Date	Ongoing	Reason	Regimen Dose,Unit,Freq,Route
5RT2	Day 28	CHILDRENS TYLENOL ACETAMINOPHEN	07/17/2018	07/20/2018		FEVER	0160.00,1,5,1
2Q49	Baseline	LIQUID MULTIVITAMIN	10/10/2016		YES	SUPPLEMENT	0001.00,DROPPER,1,G-TUBE
2Q49	Day 14	LIQUID MULTIVITAMIN	10/10/2016		YES	SUPPLEMENT	0001.00,DROPPER,1,G-TUBE
2Q49	Day 28	LIQUID MULTIVITAMIN	10/10/2016		YES	SUPPLEMENT	0001.00,DROPPER,1,G-TUBE
2Q49	Day 42	LIQUID MULTIVITAMIN	10/10/2016		YES	SUPPLEMENT	0001.00,DROPPER,1,G-TUBE
3FG4	Baseline	FLINTSTONES VITAMINS WITH IRON	01/01/2016		YES	SUPPLEMENT	0001.00,CHEWABLE,1,1
3FG4	Baseline	MELATONIN	12/01/2016		YES	SLEEP	0001.00,1,1,1
3FG4	Day 14	MELATONIN	12/01/2016		YES	SLEEP	0001.00,1,1,1
3FG4	Day 14	FLINTSTONES VITAMINS WITH IRON	01/01/2016		YES	SUPPLEMENT	0001.00,CHEWABLE,1,1
3FG4	Day 28	FLINTSTONES VITAMINS WITH IRON	01/01/2016		YES	SUPPLEMENT	0001.00,CHEWABLE,1,1
3FG4	Day 28	MELATONIN	12/01/2016		YES	SLEEP	0001.00,1,1,1
3FG4	Day 42	MELATONIN	12/01/2016		YES	SLEEP	0001.00,1,1,1
3FG4	Day 42	FLINTSTONES VITAMINS WITH IRON	01/01/2016		YES	SUPPLEMENT	0001.00,CHEWABLE,1,1
337J	Day 14	GLYCERIN	04/04/2016		YES	CONSTIPATION	0001.00,SLIVER,5,PR
337J	Day 14	CLOVE OIL	03/28/2016		YES	TEETHING	0001.00,PINCH,1,1
337J	Day 14	IBUPROFEN	03/30/2016		YES	FUSSINESS	0001.25,2,1,1
337J	Day 28	GLYCERIN	04/04/2016		YES	CONSTIPATION	0001.00,SLIVER,5,PR
337J	Day 28	TYLENOL	04/13/2016		YES	EASE PAIN ASSOCIATED WITH CONSTIPATION	0003.60,2,5,1

CONCOMITANT MEDICATIONS

Placebo

Subject #	Study Day	Drug	Start Date	Stop Date	Ongoing	Reason	Regimen Dose,Unit,Freq,Route
337J	Day 28	IBUPROFEN	03/30/2016		YES	FUSSINESS	0001.25,2,1,1
337J	Day 28	MILK OF MAGNESIA	04/20/2016		YES	CONSTIPATION	0001.00,3,1,1
337J	Day 28	CLOVE OIL	03/28/2016		YES	TEETHING	0001.00,PINCH,1,1
337J	Day 42	MILK OF MAGNESIA	04/20/2016		YES	CONSTIPATION	0001.00,3,1,1
337J	Day 42	GLYCERIN	04/04/2016	04/26/2016		CONSTIPATION	0001.00,SLIVER,5,PR
337J	Day 42	TYLENOL	04/13/2016	04/26/2016		EASE PAIN ASSOCIATED WITH CONSTIPATION	0003.60,2,5,1
337J	Day 42	AMOXICILLIN	04/26/2016	05/05/2016		EAR INFECTION	0004.00,2,2,1
337J	Day 42	CLOVE OIL	03/28/2016		YES	TEETHING	0001.00,PINCH,1,1
337J	Day 42	IBUPROFEN	03/30/2016		YES	FUSSINESS	0001.25,2,1,1
337J	Day 70	IBUPROFEN	03/30/2016		YES	FUSSINESS	0001.25,2,1,1
337J	Day 70	MILK OF MAGNESIA	04/20/2016		YES	CONSTIPATION	0001.00,3,1,1
337J	Day 70	CLOVE OIL	03/28/2016		YES	TEETHING	0001.00,PINCH,1,1
46WG	Baseline	PARACETAMOL	03/11/2019		YES	TEETHING	0005.00,2,5,1
46WG	Day 14	TEETHA TEETHING GRANULES	03/16/2019		YES	TEETHING	0001.00,SATCHET,5,1
46WG	Day 14	PARACETAMOL	03/11/2019		YES	TEETHING	0005.00,2,5,1
46WG	Day 28	PARACETAMOL	03/11/2019		YES	TEETHING	0005.00,2,5,1
46WG	Day 28	TEETHA TEETHING GRANULES	03/16/2019		YES	TEETHING	0001.00,SATCHET,5,1
46WG	Day 42	PARACETAMOL	03/31/2019	03/31/2019		TEETHING	0005.00,2,5,1
46WG	Day 42	PARACETAMOL	04/15/2019	04/15/2019		TEETHING	0008.00,2,5,1
46WG	Day 42	TEETHA TEETHING GRANULES	03/16/2019		YES	TEETHING	0001.00,SATCHET,5,1

CONCOMITANT MEDICATIONS

Placebo

Subject #	Study Day	Drug	Start Date	Stop Date	Ongoing	Reason	Regimen Dose,Unit,Freq,Route
46WG	Day 42	PARACETAMOL	03/11/2019		YES	TEETHING	0005.00,2,5,1
46WG	Day 42	TIXYLIX GLYCEROL COUGH SYRUP	04/23/2019	04/24/2019		COUGH	0010.00,2,1,1
46WG	Day 42	PARACETAMOL	04/16/2019	04/16/2019		TEETHING	0005.00,2,5,1
46WG	Day 70	PARACETAMOL	04/28/2019	04/30/2019		COUGH	0005.00,2,5,1
46WG	Day 70	TEETHA TEETHING GRANULES	03/16/2019	03/16/2019		TEETHING	0001.00,SATCHET,5,1
46WG	Day 70	PARACETAMOL	03/11/2019	03/27/2019		TEETHING	0005.00,2,5,1
64X3	Day 14	PARACETAMOL	09/26/2018	09/27/2018		FEVER	0005.00,2,1,1
64X3	Day 14	LACTULOSE	09/07/2018		YES	CONSTIPATION	0002.50,2,2,1
64X3	Day 28	LACTULOSE	09/07/2018	10/12/2018		CONSTIPATION	0002.50,2,2,1
64X3	Day 42	LACTULOSE	10/18/2018		YES	CONSTIPATION	0002.50,2,2,1
64X3	Day 70	LACTULOSE	10/18/2018	11/26/2018		CONSTIPATION	0002.50,2,2,1
64X3	Day 70	AMOXICILLIN	11/27/2018		YES	OTITIS MEDIA	0005.00,2,3,1
64X3	Day 70	CALPOL	11/21/2018	11/28/2018		FEVER	0005.00,2,4,1
64X3	Day 70	IBUPROFEN	11/21/2018	11/28/2018		FEVER	0005.00,2,4,1
7HG6	Baseline	OMEPRAZOLE	01/15/2017		YES	ACID REFLUX	0010.00,1,1,1
7HG6	Baseline	VENTOLIN	12/15/2017		YES	HELP WITH BREATHING	0100.00,MCG/PUFF,AS NEEDED,6
7HG6	Baseline	CIRCADIN	06/15/2017		YES	HELP WITH SLEEPING	0002.00,1,1,1
7HG6	Baseline	AZITHROMYCIN	06/15/2017		YES	PROPHALACTIC ANTIBIOTIC	0200.00,1,3XA WEEK EVERY OTHER WEEK,1
7HG6	Baseline	FLIXOTIDE	06/15/2017		YES	HELP WITH BREATHING	0050.00,MCG/PUFF,AS NEEDED,6

CONCOMITANT MEDICATIONS

Placebo

Subject #	Study Day	Drug	Start Date	Stop Date	Ongoing	Reason	Regimen Dose,Unit,Freq,Route
7HG6	Day 14	VENTOLIN	12/15/2017		YES	HELP WITH BREATHING	0100.00,MCG/PUFF,AS NEEDED,6
7HG6	Day 14	OMEPRAZOLE	01/15/2017		YES	ACID REFLUX	0010.00,1,1,1
7HG6	Day 14	CIRCADIN	06/15/2017		YES	HELP WITH SLEEPING	0002.00,1,1,1
7HG6	Day 14	CALPOL	11/28/2018	11/28/2018		UNSETTLED	0007.50,2,ONCE,1
7HG6	Day 14	FLIXOTIDE	06/15/2017		YES	HELP WITH BREATHING	0050.00,MCG/PUFF,AS NEEDED,6
7HG6	Day 14	AZITHROMYCIN	06/15/2017		YES	PROPHALACTIC ANTIBIOTIC	0200.00,1,3XA WEEK EVERY OTHER WEEK,1
7HG6	Day 28	OMEPRAZOLE	01/15/2017		YES	ACID REFLUX	0010.00,1,1,1
7HG6	Day 28	CALPOL	12/11/2018	12/11/2018		PAIN	0007.50,2,ONCE ONLY,1
7HG6	Day 28	VENTOLIN	12/15/2017		YES	HELP WITH BREATHING	0100.00,MCG/PUFF,AS NEEDED,6
7HG6	Day 28	FLIXOTIDE	06/15/2017		YES	HELP WITH BREATHING	0050.00,MCG/PUFF,AS NEEDED,6
7HG6	Day 28	AZITHROMYCIN	06/15/2017		YES	PROPHALACTIC ANTIBIOTIC	0200.00,1,3XA WEEK EVERY OTHER WEEK,1
7HG6	Day 28	CIRCADIN	06/15/2017		YES	HELP WITH SLEEPING	0002.00,1,1,1
7HG6	Day 28	PHENOXYMETHYLPENECILLIN	12/11/2018		YES	TONSILLITIS	0005.00,2,4,1
7HG6	Day 42	VENTOLIN	12/15/2017		YES	HELP WITH BREATHING	0100.00,MCG/PUFF,AS NEEDED,6
7HG6	Day 42	OMEPRAZOLE	01/15/2017		YES	ACID REFLUX	0010.00,1,1,1
7HG6	Day 42	PHENOXYMETHYLPENECILLIN	12/11/2018	12/21/2018		TONSILLITIS	0005.00,2,4,1

CONCOMITANT MEDICATIONS

Placebo

Subject #	Study Day	Drug	Start Date	Stop Date	Ongoing	Reason	Regimen Dose,Unit,Freq,Route
7HG6	Day 42	FLIXOTIDE	06/15/2017		YES	HELP WITH BREATHING	0050.00,MCG/PUFF,AS NEEDED,6
7HG6	Day 42	AZITHROMYCIN	06/15/2017		YES	PROPHALACTIC ANTIBIOTIC	0200.00,1,3XA WEEK EVERY OTHER WEEK,1
7HG6	Day 42	CIRCADIN	06/15/2017		YES	HELP WITH SLEEPING	0002.00,1,1,1
7HG6	Day 70	OMEPRAZOLE	01/15/2017		YES	ACID REFLUX	0010.00,1,1,1
7HG6	Day 70	VENTOLIN	12/15/2017		YES	HELP WITH BREATHING	0100.00,MCG/PUFF,AS NEEDED,6
7HG6	Day 70	FLIXOTIDE	06/15/2017		YES	HELP WITH BREATHING	0050.00,MCG/PUFF,AS NEEDED,6
7HG6	Day 70	CALPOL	01/20/2019		YES	GENRALLY UNWELL	0007.50,2,5,1
7HG6	Day 70	AZITHROMYCIN	06/15/2017		YES	PROPHALACTIC ANTIBIOTIC	0200.00,1,3XA WEEK EVERY OTHER WEEK,1
7HG6	Day 70	CIRCADIN	06/15/2017		YES	HELP WITH SLEEPING	0002.00,1,1,1
5NTX	Baseline	PARACETAMOL	03/14/2018	03/14/2018		COUGH	0120.00,1,5,1
5NTX	Day 28	PARACETAMOL	04/06/2018		YES	COUGH	0060.00,1,5,1
5NTX	Day 42	PARACETAMOL	04/10/2018		YES	COUGH	0060.00,1,5,1
5NTX	Day 70	PARACETAMOL	04/10/2018	04/26/2018		COUGH	0060.00,1,5,1
1KUH	Baseline	IBUPROFEN	06/23/2019	06/26/2019		PAIN WHILE TEETHING	0100.00,1,5,1
1KUH	Baseline	PARACETAMOL	06/23/2019	06/26/2019		FEVER WHILE TEETHING	0180.00,1,5,1
1KUH	Day 14	PIRITON	07/05/2019	07/05/2019		RHINITIS	0002.50,2,5,1

CONCOMITANT MEDICATIONS

Placebo

Subject #	Study Day	Drug	Start Date	Stop Date	Ongoing	Reason	Regimen Dose,Unit,Freq,Route
1KUH	Day 70	PARACETAMOL	09/08/2019		YES	SORE THROAT	0007.50,2,4,1
9AJ7	Day 42	PARACETAMOL	04/08/2016	04/16/2016		CHICKEN POX	0005.00,2,4,1
2674	Day 28	BENALYN	07/28/2018	07/28/2018		VIRAL ILLNESS	0000.00,SPRAY,5,1
2674	Day 28	DEXTROMETHORPHAN	07/28/2018	07/28/2018		COUGH	0005.00,2,1,1
2674	Day 28	SODIUM CHLORIDE SOLUTION	07/24/2018	07/25/2018		VIRAL COLD	0000.00,NASAL SPRAY; NO DOSAGE SPECIFIED,1,6
3ZGW	Day 28	PARACETAMOL	05/25/2018	05/26/2018		VIRAL INFECTION	0005.00,2,5,1
4JKU	Day 14	PARACETOMOL	05/21/2016	05/26/2016		CORYZAL SYMPTOMS	0180.00,1,5,1
4JKU	Day 28	PARACETOMOL	06/01/2016		YES	TEETHING PAIN	0180.00,1,5,1
4JKU	Day 42	PARACETOMOL	001/2016	06/24/2016		TEETHING PAIN	0180.00,1,5,1