Valganciclovir for Symptomatic Congenital Cytomegalovirus Disease

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Running Head: Long-term oral valganciclovir therapy in congenital CMV disease

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ABSTRACT

Background: Treatment of symptomatic congenital cytomegalovirus (CMV) disease with 6 weeks of ganciclovir improves audiologic outcomes at 6 months, but benefits wane over time.

Methods: Randomized, placebo-controlled trial of 6 months or 6 weeks of valganciclovir in symptomatic congenital CMV disease. Primary endpoint was change in best ear hearing between baseline and 6 months. Secondary endpoints included change in hearing between baseline and 12 and 24 months and neurodevelopmental outcomes, each adjusted for baseline central nervous system involvement.

Results: 96 neonates were enrolled of whom 86 completed 6 months of therapy. Best-ear hearing outcomes at 6 months were similar for the groups [2 improved, 36 unchanged, 5 worse for 6-month group, versus 3, 37, and 3 respectively for 6-week group (p=0.41)]. Total ear hearing was more likely to be improved or remain normal at 12 months in the 6-month group (73.4%) versus the 6-week group (57.1%) (p=0.01). Benefit in total ear hearing was maintained at 24 months (77.1% vs. 63.8%, respectively; p=0.04]. The 6-month group had higher Bayley III Language Composite (84.6 vs. 72.5, p<0.01) and Receptive Communication Scale (7.3 vs. 5.2, p<0.01) neurodevelopmental scores at 24 months. Grade 3 or 4 neutropenia occurred in 19.3% during the first 6 weeks, and 21.3% (6-month group) vs. 26.5% (6-week group) during the next 4.5 months of treatment (p=0.64).

Conclusions: Treating symptomatic congenital CMV disease with 6 months of valganciclovir, compared with 6 weeks, does not improve short-term hearing but appears to modestly improve longer-term hearing and developmental outcomes. (ClinicalTrials.gov number, NCT00466817)

Congenital cytomegalovirus (CMV) infection is the leading non-genetic cause of sensorineural hearing loss (SNHL)[1-4] and the most frequent known viral cause of mental retardation,[5] affecting 0.6% to 0.7% of live births in industrialized countries.[6-8] 10% of congenitally infected neonates have symptomatic disease at delivery, of whom 35% have SNHL, up to two-thirds have neurologic deficits, and 4% die in the newborn period.[7-11] Overall, congenital CMV is a rare infection but accounts for 21% of hearing loss at birth and 24% of hearing loss at four years of age.[1, 12]

The National Institute of Allergy and Infectious Diseases (NIAID) Collaborative Antiviral Study Group (CASG) demonstrated that 6 weeks of intravenous ganciclovir for symptomatic congenital CMV disease involving the central nervous system (CNS) improved audiologic outcomes at 6 months of life, but there was suggestion that this benefit could wane over the first 2 years of life.[13] Treated infants had fewer developmental delays by Denver Developmental Evaluations.[14] In a follow-up study, the CASG determined the dose of oral valganciclovir (ganciclovir's prodrug) that achieves similar systemic ganciclovir exposure as intravenous ganciclovir.[15] Six weeks of therapy with intravenous ganciclovir or oral valganciclovir is now an accepted treatment option for symptomatic congenital CMV disease involving the CNS.[16]

METHODS

Study Design and Population

Neonates with symptomatic congenital CMV disease, with or without CNS involvement, were eligible for enrollment. Given the disease rarity, 40 study sites participated and each was anticipated to contribute only a few subjects. All study subjects had CMV detected from urine or

throat swab specimens by culture, shell vial, or polymerase chain reaction (PCR). Symptomatic disease was defined as ≥ one of the following: thrombocytopenia, petechiae, hepatomegaly, splenomegaly, intrauterine growth restriction, hepatitis, or CNS involvement such as microcephaly, intracranial calcifications, abnormal cerebrospinal fluid (CSF) indices, chorioretinitis, SNHL, or detection of CMV DNA in CSF. Subjects had a gestational age ≥ 32 weeks, were ≤ 30 days of age, and weighed ≥ 1800 grams at initiation of therapy.

Institutional review boards at each study center approved the protocol. After written informed consent from the parent(s) or legal guardian(s), subjects received 6 weeks of valganciclovir (16 mg/kg orally twice daily),[15] followed by 1:1 randomization to continued valganciclovir or placebo for 4.5 months. Study medication dose was adjusted monthly for growth. Study medication was provided by Hoffmann-La Roche Inc. (Nutley, NJ), which had no input on study design, analyses, or manuscript development. Study personnel and families were blinded to randomization assignment.

The protocol pre-specified primary endpoint was change in hearing in best ear between baseline and the 6 month follow-up.[13] Protocol pre-specified secondary endpoints included change in hearing in total ears between baseline and 6, 12, and 24 months; change in hearing in best ear between baseline and 12 and 24 months; neurologic impairment at 12 and 24 months; and adverse events leading to permanent discontinuation of therapy. Tertiary endpoints included correlation of whole blood viral load with audiologic and neurodevelopmental outcomes, adverse events related to study medication, and characterization of ganciclovir blood concentrations.

Audiologic Assessments

Brainstem evoked response (BSER) was performed at entry, and BSER or visual reinforcement audiometry (VRA) was performed at 6, 12, and 24 months. Hearing thresholds were defined as: normal hearing 0-20 decibel (dB) thresholds, mild hearing loss 21-45 dB thresholds, moderate hearing loss 46-70 dB thresholds, and severe hearing loss ≥ 71 dB thresholds.[3, 10, 13] An independent audiologist, masked to randomization assignment, reviewed all audiometry reports and classified evaluable ears by hearing thresholds, giving "total ear" classifications. The study audiologist then assigned the "best ear" classification for the subject at that study visit; for example, if a subject had mild hearing loss in their left ear and severe hearing loss in their right ear, then the "best ear" classification was mild hearing loss. Odd numbers of total ears by treatment category are reported because a patient may have only one evaluable ear [e.g., otitis media on one side (nonevaluable), normal ear on the other (evaluable)].

Neurodevelopmental Assessments

The Bayley Scales of Infant and Toddler Development™ Third Edition was administered at 12 and 24 months by a neuropsychologist at each site masked to randomization assignment.[17]

Virologic Assessments

Whole blood for CMV viral load[18] was obtained at baseline, weekly for four weeks, every two weeks for eight weeks, and monthly for four months.

Safety Assessments

White blood cell count and differential, hemoglobin, platelet count, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, and creatinine measurements were conducted serially. Toxicity assessments were quantified with the NIAID Division of AIDS Toxicity Tables.[19]

Statistical Analyses

The primary objective was to assess best ear hearing change from baseline to 6 months of age between 6-week versus 6-month therapy groups. For the primary endpoint, the Wilcoxon/Mann-Whitney test was used; linear models were used for secondary outcomes adjusting for covariates. For sample size purposes, 37 subjects per group produced a power of 85% to detect an effect size of 0.169 from the null value of 0.5. With an expected 15% of subjects not eligible for randomization at 6 weeks and another 10% failing to complete the 6 month hearing evaluation, the original sample size was 94. During the course of the study, the DSMB suggested that the sample size be increased to achieve the targeted 37 per group, due to inadequate baseline or 6 month data. The sample size then was increased to 104 in order to accommodate 10% unevaluable outcomes due to inadequate baseline or 6 month hearing data. A 5% over-enrollment was allowed for operational purposes.

For the modified intention-to-treat (mITT) analysis population, participants must have taken at least one dose of blinded treatment. The *a priori* study analysis plan dictated that efficacy outcomes be adjusted for CNS involvement. For the primary endpoint, the Wilcoxon/Mann-Whitney test was used. For the secondary audiologic endpoints, hearing results were analyzed based upon two sets of binary outcomes: 1) improved hearing + normal hearing at baseline and follow-up, versus worsened hearing + same degree of hearing loss at baseline and follow-up; and 2) worsened hearing, versus improved hearing + normal hearing at baseline and follow-up + same degree of hearing loss at baseline and follow-up (see Web-only Supplement for additional details). Any hearing assessments completed after cochlear implantation were excluded, as were missing and unevaluable hearing assessments. P-values<0.05 for hearing outcomes and p-

values<0.0071 neurodevelopmental outcomes were considered significant. No adjustments were made for multiplicity. For full details of the study conduct and analyses see the protocol and SAP at NEJM.org.

RESULTS

Subject Demographics and Characteristics

From June 2008 through May 2011, 109 subjects from 31 study sites enrolled; 96 were randomized to blinded study medication (47 active drug, 49 placebo) after receiving 6 weeks of valganciclovir (Figure 1). Nine (6 active, 3 placebo) of the 96 subjects stopped blinded drug before completing 6 months. None discontinued treatment due to adverse events.

Audiologic Outcomes

Primary Study Endpoint

For subjects receiving 6 months of treatment, change in best ear hearing between baseline and 6 months was improved in 2, unchanged in 36, and worse in 5; for subjects receiving 6 weeks of treatment, 3 had improved hearing, 37 were unchanged, and 3 were worse (p=0.41).

Secondary Study Endpoints

Binary assessment of change in best ear hearing between baseline and 6 months was similar between the two treatment groups (p=0.24, adjusting for baseline CNS involvement; Table 2). Analysis of change in best ear hearing between baseline and 12 months and between baseline and 24 months approached statistical significance after adjusting for baseline CNS involvement (p=0.05 and p=0.07, respectively; Table 2).

Total ears from subjects receiving 6 months of valganciclovir were more likely to have improved hearing or maintain normal hearing between baseline and 12 months after adjusting for CNS involvement at baseline [OR (95% CI): 3.04 (1.26, 7.35); p=0.01] (Table 2). Similar results were evident when prematurity and age at treatment initiation were added to the model (p=0.01). The relative risk for improved or protected total ear hearing between baseline and 12 months for the 53 subjects with baseline CNS involvement receiving 6 months of treatment and 6 weeks of treatment was 1.66 (95% CI: 0.92, 2.4), and the risk difference was 0.27 (95% CI: 0.09, 0.45). For the 28 subjects without baseline CNS involvement, the relative risk was 1.22 (95% CI: 0.99, 1.45) and risk difference was 0.16 (95% CI: 0.03, 0.29).

The benefit of longer-term therapy in the total ears analysis was maintained at 24 months, with improved outcomes after adjusting for CNS involvement at baseline [OR (95% CI): 2.61 (1.05, 6.43); p=0.04] (Table 2). Similar results were evident when prematurity and age at treatment initiation were added to the model (p=0.04). The relative risk for improved or protected total ear hearing between baseline and 24 months for the 42 subjects with baseline CNS involvement receiving 6 months of treatment and 6 weeks of treatment was 1.46 (95% CI: 0.87, 2.05), and the risk difference was 0.23 (95% CI: 0.05, 0.41). For the 26 subjects without baseline CNS involvement, the relative risk was 1.19 (95% CI: 0.98, 1.40) and risk difference was 0.14 (95% CI: 0.01, 0.27).

Timing of initiation of valganciclovir within the first month of life (e.g., first three weeks of life versus weeks 3-4 of life) did not correlate with audiologic outcomes at 12 or 24 months (p>0.23).

Neurodevelopmental Outcomes

Adjusting for CNS involvement at baseline, subjects randomized to 6 months of valganciclovir had higher Bayley III Language Composite (p=0.0046) and Receptive Communication Scale (p=0.0031) scores at 24 months compared with subjects randomized to 6 weeks of treatment (Table 3). No significant interaction effects were found when outcome and baseline CNS involvement were incorporated in a single model, indicating similar treatment benefits for both groups (with and without CNS involvement). These differences were maintained when age at treatment initiation and prematurity were added to the model (P-values of 0.0037 and 0.0027, respectively). All other components of the Bayley assessments trended toward improved outcomes for subjects randomized to 6 months of therapy.

Virologic Results

Whole blood viral loads decreased in parallel during the first 6 weeks of open-label valganciclovir therapy, then diverged following randomization (Figure 2). Adjusting for interaction effect between treatment and viral load area-under-the-curve (AUC), lower viral loads correlated with better hearing outcomes at 6, 12, and 24 months for subjects receiving 6 months of treatment ($p<0.01$) but not for those receiving 6 weeks of treatment ($p>0.68$). No correlation existed between viral load AUC and neurodevelopmental outcomes beyond that provided by treatment.

Safety Assessments

Twenty-one (19.3%) of the 109 subjects experienced Grade 3 or 4 neutropenia during the first 6 weeks of open-label valganciclovir therapy. Between week six and month six, ten (21.3%) of the 47 active subjects experienced Grade 3 or 4 neutropenia compared with 13 (26.5%) of 49 placebo subjects (p=0.64). Three subjects had drug temporarily held for ANCs < 500 cells/mm^3;

all treatment interruptions occurred within the first 6 weeks and resolved, following which treatment was continued.

ALT and AST both increased slightly at Months 4 and 5 in the group receiving active drug, although differences were not statistically ($p>0.59$ for both ALT and AST) or clinically (mean ± SE values all < 90 U/L) significant. No deaths occurred. There were no significant differences in adverse events between the treatment groups.

DISCUSSION

Only one previous randomized controlled trial of antiviral treatment of symptomatic congenital CMV disease, also from the NIAID CASG, has been conducted.[13] Other reports in the literature involve individual cases[20-24] or small uncontrolled case series.[25-27] The earlier randomized controlled trial demonstrated benefit of 6 weeks of parenteral ganciclovir therapy on best-ear hearing outcomes between baseline and 6 months, but there was suggestion that this benefit wanes over the first 2 years of life.[13] Based on these data, change in best-ear hearing between baseline and 6 months was selected as the primary endpoint of this trial. This positioned the current study to extend our knowledge of the impact of antiviral therapy on hearing, and allowed for sample size assessments in protocol development. We also selected numerous clinically relevant secondary endpoints prior to initiation of the study to explore the impact of longer-term antiviral treatment on longer-term hearing improvement. These included change in best ear and total ear hearing between baseline and 12 months and between baseline and 24 months in order to more completely ascertain the impact of antiviral treatment on shorter-term (first 6 months) and longer-term (to 2 years of age) time frames. No previous study had prospectively assessed

the impact of antiviral treatment on neurodevelopmental outcome, so formal neurodevelopmental outcomes were incorporated as secondary endpoints in the study.

We did not meet the primary study outcome of change in best ear hearing between baseline and 6 months, with both study groups achieving similar results. Total ear hearing between baseline and 6 months also was similar between the groups. However, the secondary study outcomes of change in total ear hearing between baseline and 12 months and between baseline and 24 months were statistically significantly different between the groups, with subjects receiving the longer course of therapy having improved hearing outcomes compared with subjects receiving 6 weeks of treatment. Data from our *a priori* secondary endpoints suggest that 6 months of antiviral treatment modestly improves longer-term hearing outcomes, but provides no additional benefit on shorter-term outcomes over that of 6 weeks of treatment. The magnitude of the longer-term benefit can be viewed in different ways. Using odds ratios, patients receiving longer therapy have 3-times the odds of improved hearing or protection of normal hearing at 12 months and 2.6-times the odds at 24 months versus patients receiving shorter therapy. Using relative risk, subjects with CNS involvement at baseline have a 65% and 46% increased likelihood of having better outcomes between baseline and 12 and 24 months, respectively, while for subjects without CNS involvement these values are 22% and 19%, respectively. Risk differences between the groups range from 0.14 to 0.27, depending on baseline CNS involvement and follow-up interval. We encourage caution that spurious findings may have arisen from the multiple statistical tests conducted for the secondary hearing outcomes considered in this report.

Employing the Bayley III[17]and utilizing the Bonferroni adjustment for multiple testing, the communicative outcomes of language composite score and receptive communication scale were

improved with longer treatment, with low average results among subjects treated for 6 months but borderline results among subjects treated for 6 weeks following adjustment for factors that could impact development. All other components of the Bayley Scales also were higher in the 6 month treatment group (Table 3), although statistically significant. No significant interaction effects were found, indicating similar neurologic treatment benefits for groups with and without CNS involvement.

Subjects receiving oral valganciclovir had lower rates of Grade 3 or Grade 4 neutropenia during the first 6 weeks of treatment (19.3%) than treated subjects in previous CASG studies of 6 weeks of intravenous ganciclovir (63.0%)[13] or of two weeks of intravenous ganciclovir and four weeks of oral valganciclovir (37.5%),[15] perhaps due to the C_{max} of intravenous versus oral drug delivery. From week six to month seven in the current trial, subjects randomized to continuation of valganciclovir had similar incidence of Grade 3-4 neutropenia compared with subjects randomized to placebo (21.3% versus 26.5%; p=0.64). Thus, drug-induced neutropenia is of primary concern during the first 6 weeks of treatment, and the risk appears to be lower when treatment is solely with oral valganciclovir.[13] Ganciclovir is gonadal toxic and carcinogenic in animal models,[28] and while these toxicities have not been seen in humans they should be conveyed to families of babies for whom valganciclovir therapy is being considered.

These controlled data suggest moderately favorable impact of 6 months of oral valganciclovir on longer-term audiologic and neurodevelopmental outcomes adjusting for baseline CNS involvement in infants with symptomatic congenital CMV disease, without excess risk of neutropenia or the risk associated with maintaining intravenous access for prolonged periods of time. These data do not apply to infants with asymptomatic congenital CMV infection, since

there are no controlled studies documenting benefit in this population and the possibility of harm exists. Since CMV-associated sensorineural hearing loss fluctuates over time in more than one-third of patients as part of the natural history of disease, prospective, controlled trial designs are critical to assess treatment benefit in congenital CMV infections.

Disclosure:

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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Figure Legends

Figure 1. Randomization and Follow-up of Study Participants

Figure 2. Whole Blood CMV DNA Viral Load for Subjects receiving 6 Months (green) and 6 Weeks (red) of Therapy; viral load <100 was replaced by viral load =10 in the figure

Table 1. Baseline Demographics*

	6 Months of Therapy (N=47)	6 Weeks of Therapy (N=49)	P-value
Gestational Age by Category [N (%)]			
Preterm (32 to ≤ 37 weeks gestational age)	24 (51.1)	22 (44.9)	0.68
Term (> 37 weeks gestational age)	23 (48.9)	27 (55.1)	
Age at enrollment (by grouping) [N (%)]			
< 7 days	6 (12.8)	7 (14.3)	0.08
7-14 days	19 (40.4)	12 (24.5)	
15-21 days	10 (21.3)	6 (12.2)	
21- < 30 days	12 (25.5)	24 (49.0)	
Extent of CMV Disease† [N (%)]			
Thrombocytopenia	38 (80.8)	34 (69.4)	0.24
Petechiae	22 (46.8)	20 (40.8)	0.68
Hepatomegaly	26 (55.3)	21 (42.9)	0.31
Splenomegaly	23 (48.9)	22 (44.9)	0.84
Intrauterine growth restriction	17 (36.2)	22 (44.9)	0.41
Hepatitis (elevated transaminases or bilirubin)	21 (44.7)	25 (51.0)	0.55
Central nervous system involvement	34 (72.3)	29 (59.2)	0.20
Microcephaly	14 (29.8)	17 (34.7)	0.19
Chorioretinitis	2 (4.3)	1 (2.0)	1.00
Neuroimaging Results (MRI, CT, HUS) [N (%)]			
Normal	9 (20.0)	12 (25.5)	0.62
Abnormal	36 (80.0)	35 (74.5)	
Baseline BSER (best ear) for subjects evaluable at 6 months [N (%)]			
	N=43	N=43	0.17
Normal	32 (74.4)	25 (58.1)	
Mild	5 (11.6)	8 (18.6)	
Moderate	3 (7.0)	2 (4.7)	
Severe	3 (7.0)	8 (18.6)	

* See Table S1 in Web-only Supplement for full tabulation of Baseline Demographics

† Subjects could have multiple manifestations of CMV disease

Table 2. Improvement and protection in hearing among best ear and total ears between baseline and follow-up

	6 Month Follow-up				12 Month Follow-up				24 Month Follow-up			
	Best Ear Analysis (Primary Endpoint)*		Total Ears Analysis (Secondary Endpoint)*		Best Ear Analysis (Secondary Endpoint)*		Total Ears Analysis (Secondary Endpoint)*		Best Ear Analysis (Secondary Endpoint)*		Total Ears Analysis (Secondary Endpoint)*	
Duration of Valganciclovir Therapy	**6 months (n=43)**	**6 weeks (n=43)**	**6 months (n=82)**	**6 weeks (n=84)**	**6 months (n=41)**	**6 weeks (n=40)**	**6 months (n=79)**	**6 weeks (n=77)**	**6 months (n=37)**	**6 weeks (n=31)**	**6 months (n=70)**	**6 weeks (n=58)**
Improved Hearing	2 (4.7%)	3 (7.0%)	6 (7.3%)	7 (8.3%)	2 (4.9%)	2 (5.0%)	6 (7.6%)	4 (5.1%)	2 (5.4%)	2 (6.5%)	6 (8.6%)	2 (3.5%)
Normal Hearing at Baseline and Follow-up	28 (65.1%)	23 (53.5%)	46 (56.1%)	39 (46.4%)	30 (73.2%)	23 (57.5%)	52 (65.8%)	40 (50.6%)	30 (81.1%)	20 (64.5%)	48 (68.6%)	35 (60.3%)
Same Degree of Hearing Loss at Baseline and Follow-Up	8 (18.6%)	14 (32.6%)	19 (23.2%)	29 (34.5%)	6 (14.6%)	10 (25.0%)	15 (19.0%)	23 (29.9%)	2 (5.4%)	7 (22.6%)	8 (11.4%)	16 (27.6%)
Worsened Hearing	5 (11.6%)	3 (7.0%)	11 (13.4%)	9 (10.7%)	3 (7.3%)	5 (12.5%)	6 (7.6%)	10 (13.0%)	3 (8.1%)	2 (6.5%)	8 (11.3%)	5 (8.6%)
Improved/Protected Hearing versus Other,† Unadjusted Analysis	p=0.50 OR (95% CI): 1.51 (0.62, 3.68) RR (95% CI): 1.15 (0.84, 1.58) RD (95%CI): 0.09 (-0.11, 0.29)		p=0.34 OR (95% CI): 1.45 (0.67, 3.15) RR (95% CI): 1.17 (0.85, 1.61) RD (95% CI): 0.09 (-0.10, 0.28)		p=0.15 OR (95% CI): 2.13 (0.80, 5.67) RR (95% CI): 1.25 (0.93, 1.67) RD (95% CI): 0.16 (-0.04, 0.35)		p=0.08 OR (95% CI): 2.18 (0.92, 5.18) RR (95% CI): 1.32 (0.97, 1.79) RD (95% CI): 0.18 (-0.01, 0.37)		p=0.14 OR (95% CI): 2.62 (0.77, 8.87) RR (95% CI): 1.22 (0.94, 1.58) RD (95% CI): 0.16 (-0.04, 0.35)		p=0.13 OR (95% CI): 1.99 (0.82, 4.83) RR (95% CI): 1.23 (0.93, 1.62) RD (95% CI): 0.14 (-0.04, 0.33)	
Improved/Protected Hearing versus Other, † Adjusted for CNS involvement at baseline‡	p=0.24 OR (95% CI): 1.75 (0.69, 4.43)		p=0.20 OR (95% CI): 1.69 (0.76, 3.73)		p=0.05 OR (95% CI): 2.81 (0.99, 7.99)		p=0.01 OR (95% CI): 3.04 (1.26, 7.35)		p=0.07 OR (95% CI): 3.28 (0.91, 11.9)		p=0.04 OR (95% CI): 2.61 (1.05, 6.43)	

OR: Odds Ratio; RR: Risk Ratio; RD: Risk Difference; CI: Confidence Interval

* All of the analyses for the primary and secondary endpoints were pre-specified in the protocol

† Improved hearing or normal at baseline and follow-up, versus worsened hearing or same degree of hearing loss at baseline and follow-up

‡ Adjustment for CNS involvement at baseline was determined a priori

Table 3. Treatment Effects on Neurological Outcomes by Randomization Group*

Bayley III Component	Month 12 Follow-up			Month 24 Follow-up		
	6 Months of Therapy	6 Weeks of Therapy	P-Value	6 Months of Therapy	6 Weeks of Therapy	P-Value
Cognitive Composite						
N	43	45	0.0128	42	41	0.0236
Mean ± SE	89.6 ± 3.0	79.5 ± 2.8		84.4 ± 2.6	76.0 ± 2.6	
(Min-Max)†	55-115	9.5-120		55-135	55-110	
Language Composite						
N	41	43	0.0090	41	41	0.0037
Mean ± SE	87.6 ± 3.0	76.8 ± 2.9		84.6 ± 2.9	72.5 ± 2.9	
(Min-Max)†	47-118	11-112		47-121	47-103	
Receptive Communication Scale						
N	41	43	0.0544	41	41	0.0027
Mean ± SE	7.5 ± 0.5	6.1 ± 0.5		7.3 ± 0.5	5.2 ± 0.5	
(Min-Max)†	1-14	1-12		1-14	1-10	
Expressive Communication Scale						
N	41	44	0.0224	41	41	0.0158
Mean ± SE	8.0 ± 0.5	6.5 ± 0.5		7.3 ± 0.5	5.5 ± 0.5	
(Min-Max)†	1-13	1-13		1-13	1-11	
Motor Composite						
N	42	44	0.0289	41	40	0.0130
Mean ± SE	82.6 ± 3.2	73.2 ± 3.0		85.5 ± 3.3	74.1 ± 3.2	
(Min-Max)†	46-112	11-112		46-121	46-121	
Fine Motor Scale						
N	41	44	0.1132	42	40	0.0566
Mean ± SE	7.3 ± 0.6	6.0 ± 0.6		8.0 ± 0.6	6.4 ± 0.6	
(Min-Max)†	1-11	0.1-13		1-15	1-19	
Gross Motor Scale						
N	42	44	0.0672	42	40	0.0198
Mean ± SE	6.7 ± 0.5	5.4 ± 0.5		7.0 ± 0.5	5.3 ± 0.5	
(Min-Max)†	1-14	0.1-15		1-13	1-12	

* Adjusted for CNS involvement at baseline, prematurity, and age at treatment initiation. P-values < 0.0071 (= 0.05/7) considered statistically significant, using Bonferroni adjustment for multiple testing.

† Minimum and maximum values of the raw data