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Secondary 12-Month Ocular Outcomes of a Phase 1 Dosing Study of Bevacizumab for Retinopathy of Prematurity

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Key Points

Question

What were ocular outcomes at 12 months' corrected age for eyes that received a dose of 0.625 mg to 0.031 mg of bevacizumab for type 1 retinopathy of prematurity?

Findings

In this cohort study of 46 infants (87 eyes), 12 eyes had myopia greater than −5.00 D spherical equivalent, and 2 eyes had hyperopia greater than 5.00 D spherical equivalent. Abnormalities of the cornea, lens, or anterior segment were reported in 1 eye, 3 eyes, and 3 eyes, respectively.

Meaning

Ocular abnormality rates at 1 year were consistent with those reported in other studies with higher bevacizumab dosages.

Abstract

Importance

Lower bevacizumab dosages are being used for type 1 retinopathy of prematurity, but there are limited data on long-term ocular outcomes with lower doses.

Objective

To evaluate ocular outcomes at 12 months' corrected age for eyes that received a dose of 0.625 mg, 0.25 mg, 0.125 mg, 0.063 mg, or 0.031 mg of bevacizumab for type 1 retinopathy of prematurity.

Design, Setting, and Participants

This prospective cohort study used a masked, multicenter, phase 1 dose de-escalation study design and was conducted from April 2016 to October 2017. Study eyes were treated with a dose of 0.25, 0.125, 0.063, or 0.031 mg of bevacizumab; fellow eyes were treated with a dosage 1 level higher than the study eye. Additional treatment after 4 weeks was at investigator discretion. Data analysis occurred from November 2018 to March 2019.

Interventions

Intravitreous bevacizumab injections of 0.625 mg to 0.031 mg.

Main Outcomes and Measures

Visual fixation, amblyopia, alignment, nystagmus, cycloplegic refraction, and ocular examinations were assessed at 12 months' corrected age as preplanned secondary outcomes. The primary outcome 4 weeks after treatment and secondary outcomes after 6 months' corrected age have been previously reported.

Results

Forty-six of 61 infants (75%) had a 12-month follow-up examination (46 study eyes and 43 fellow eyes; median [interquartile range] birth weight, 650 [590-760] g). Of 87 eyes with a cycloplegic refraction, 12 (14% [95% CI, 7%-27%]) had myopia of more than −5.00 D spherical equivalent; 2 (2%; [95% CI, 0%-8%]) had hyperopia greater than 5.00 D spherical equivalent; and 5 infants (11% [95% CI, 4%-24%]) had anisometropia greater than 1.50 D spherical equivalent. Abnormalities of the cornea, lens, or anterior segment were reported in 1 eye (1% [95% CI, 0%-6%]), 3 eyes (3% [95% CI, 1%-10%]), and 3 eyes (3% [95% CI, 1%-10%]), respectively. Optic nerve atrophy was identified in 11 eyes (13% [95% CI, 6%-26%]), and 1 eye (1% [95% CI, 0%-6%]) had total retinal detachment. Strabismus was reported in 13 infants (30% [95% CI, 17%-45%]), manifest nystagmus in 7 infants (15% [95% CI, 6%-29%]), and amblyopia in 3 infants (7% [95% CI, 1%-18%]). Overall, 98% of infants had central fixation in each eye (44 of 45 eyes).

Conclusions and Relevance

In this study of low-dose bevacizumab, the secondary outcomes of high myopia, strabismus, retinal detachment, nystagmus, and other ocular abnormalities at 1 year were consistent with rates reported in other studies with higher dosages.

Trial Registration

ClinicalTrials.gov identifier: NCT02390531

Introduction

Retinopathy of prematurity (ROP) is an important cause of childhood vision loss in the United States.[1] Historically, severe ROP has been primarily treated with laser photocoagulation of the peripheral avascular retina.[2,3] More recently, intravitreal bevacizumab (IVB) has been used increasingly in the United States and internationally as treatment for severe type 1 ROP, in particular for aggressive posterior ROP.[4,5]

Lower dosages are being used to treat type 1 ROP, but there are limited data on long-term ocular outcomes. The Pediatric Eye Disease Investigator Group (PEDIG) is conducting a phase 1 trial of bevacizumab treatment for severe retinopathy of prematurity (the ROP1 study) to evaluate the effectiveness of dosages of bevacizumab that are lower than those typically used to treat ROP. Details of drug dilution and injection, 4-week outcomes, and any additional retreatments for ROP were reported previously.[6,7] In brief, 61 infants with ROP received 0.25 mg, 0.125 mg, 0.063 mg, or 0.031 mg in the study eye, and the study found that the lowest dosage of 0.031 mg was effective after 4 weeks.[6] Each dosage was planned to be used in up to 14 infants to ensure that at least 10 infants had 4-week outcomes. After 6 months' corrected age, 25 infants (41% [95% CI, 29%-54%]) received additional treatment: 3 infants (5% [95% CI, 1%-14%]) for early failure (within 4 weeks), 11 infants (18% [95% CI, 9%-30%]) for late recurrence of ROP (after 4 weeks), and 11 infants (18% [95% CI, 9%-30%]) for persistent avascular retina.[7] The study continues to evaluate dosage levels of 0.016 mg, 0.008 mg, 0.004 mg, 0.002 mg, and 0.001 mg, and those results are pending. The objectives of this article are to report ocular findings at 12-months' corrected age for the 61 infants treated with the first 4 lower dosages of IVB (0.25 mg, 0.125 mg, 0.063 mg, and 0.031 mg) and to explore whether there are any associations between ocular findings and total dosage of IVB received at the eye or infant level. Ocular and neurological findings for a subset of infants whose parents consented for an examination at 24 months' corrected age are pending completion and will be reported separately.

Methods

The cohort for this article was limited to the 61 patients treated in the study eye with the first 4 dose levels in the ROP1 PEDIG phase 1 study (0.25 mg, 0.125 mg, 0.063 mg, and 0.031 mg).[6] The study was conducted at 10 institution-based clinical sites and approved by the respective institutional review boards.

A parent or guardian of each study infant gave written informed consent. The study is listed on ClinicalTrials.gov (NCT02390531). The complete study protocol is available on the PEDIG website (http://www.pedig.net). Additional details are available in the Trial Protocol in Supplement 1.

Treatment was initiated by the investigator when 1 or both eyes reached type 1 severity, defined as any stage ROP in zone I with plus disease, stage 2 or 3 ROP in zone II with plus disease, or stage 3 ROP in zone I without plus disease.[8] One eye (called *the study eye*) of 61 infants received the study-specified dosage of IVB: 11 eyes received 0.25 mg, 16 eyes received 0.125 mg, 24 eyes received 0.063 mg, and 10 eyes received 0.031 mg. Fifty-seven nonstudy fellow eyes received IVB at a dosage that was 1 level higher than the study eye (ie, the last dosage found to be effective in the study; eg, 0.063 mg in the fellow eye when 0.031 mg was injected into the study eye). The remaining 4 fellow eyes did not have ROP severe enough to warrant treatment.

Infants were examined at 1 day (and 4 days if needed) and 1, 2, 3, and 4 weeks' postinjection in the study eye. Beginning 4 weeks after the initial bevacizumab injection, any additional treatment was at investigator discretion. After 6 months' corrected age, medical records were reviewed to collect data on ROP recurrences, additional treatments, timing of and indications for treatment, and retinal structural outcomes. After 4 weeks, follow-up examinations and additional treatments were at investigator discretion, with the exception of a study-mandated examination completed at 12 months' (±2 weeks') corrected age, subsequently referred to as the *12-month examination*. Preplanned secondary outcomes of visual fixation, amblyopia, ocular alignment, nystagmus, cycloplegic refraction, and anterior and posterior segment examinations were assessed at the 12-month examination.

Statistical Analysis

For those who completed the 12-month examination, the proportion of infants with each clinical outcome and 95% CIs were tabulated at the eye and infant level. For eye-level outcomes, to account for the correlation between eyes of infants who contribute both eyes to tabulations of ocular characteristics, a logistic regression model was used to compute the log odds of having the ocular characteristic and CIs for those log odds. The inverse logit function was used to calculate the proportion of eyes with the ocular characteristic and the corresponding 95% CI. For infant-level outcomes, binomial proportions were calculated for each ocular outcome along with corresponding exact 95% CIs.

The total dosage of bevacizumab administered per infant in the study eye (and fellow eye if applicable) and the total dosage of bevacizumab administered per eye prior to the 12-month examination was calculated for each infant. This total bevacizumab dosage included the initial injection into the study eye or fellow eye and any repeated injections as treatment for ROP prior to the 12-month examination. Exploratory analyses were performed to evaluate whether there was any association between the total dosage of bevacizumab received (in either the infant or the eye, depending on whether the outcome was eye level or infant level) and each 12-month outcome. For continuous 12-month outcomes, a linear mixed model adjusting for the correlation between eyes (for spherical equivalent of the cycloplegic refraction) or linear regression model (for anisometropia) was used to evaluate the association between total dose and each continuous 12-month outcome. For categorical 12-month outcomes (percentages of the study population with hyperopic spherical equivalent >5.00 diopters [D], myopic spherical equivalent <−5.00 D, an abnormal ocular examination finding of the cornea or lens, optic nerve atrophy, macular ectopia, retinal detachment, retinal fold, constant strabismus at distance or near, manifest nystagmus, and amblyopia), a generalized linear model adjusting for the correlation between eyes (if the variable was at an eye level) or logistic regression (if on a participant level) was used to evaluate the association between total dosage and each binary outcome. Given the secondary and exploratory nature of these analyses, *P* values of .05 or less were considered suggestive of but not definitive for associations that may merit further study.

Additional exploratory analyses evaluated whether there was any association between spherical equivalent cycloplegic refractive error at the 12-month examination and location of ROP in zone I or zone II at baseline and any association between spherical equivalent cycloplegic refractive error at the 12-month examination and prior laser treatment or no laser treatment after the initial bevacizumab injection. Analyses were conducted using SAS version 9.4 (SAS Inc). More details are available in the Statistical Analysis Plan in Supplement 2.

Results

Forty-six of 61 infants (75%) completed the 12-month examination. Infants initially treated in the study eye with lower dosages of bevacizumab were less likely to return for the 12-month examination than infants initially treated in the study eye with higher dosages of bevacizumab (11 of 11 infants initially treated with 0.25 mg [100%], 13 of 16 infants treated with 0.125 mg [81%], 16 of 24 infants treated with 0.063 mg [67%], and 6 of 10 infants treated with 0.031 mg [60%]; Table 1). Characteristics of the 46 infants who completed the 12-month examination, as well as the 15 infants who did not complete the 12-month examination (of whom 6 had died prior to 12 months from causes not associated with the study drug) are summarized in Table 1. The 46 infants who completed the 12-month examination tended to have higher birth weights than those who did not (median [interquartile range (IQR)], 650 [590-760] g vs 610 [545-790] g) and were more likely to have a preexisting condition associated with neurodevelopment (22 [48%] vs 4 [27%]) than those who did not complete the 12-month examination. The 46 infants with 12-month outcomes had 89 eyes (46 study eyes and 43 fellow eyes) treated with bevacizumab.

Cycloplegic Refractive Error at 12 Months

Cycloplegic refractive error was measured by retinoscopy in 87 eyes, of which 12 eyes (14% [95% CI, 7%-27%]) had myopia greater than −5.00 D spherical equivalent (SE) and 2 eyes (2% [95% CI, 0%-8%]) had hyperopia greater than 5.00 D SE. The mean (SD) SE refractive error were −0.82 (4.56) D; the median (IQR) SE was 0 (−1.88 to 1.25) D (Table 2). Five infants (11% [95% CI, 4%-24%]) were found to have anisometropia greater than 1.50 D SE (Table 3). The mean (SD) SE cycloplegic refractive error of 38 eyes with a zone I location at baseline was −0.76 (5.25) D, and the median (IQR) was −0.50 (−2.38 to 1.00) D vs a mean (SD) of −0.87 (4.00) D and a median (IQR) of 0.38 (−1.50 to 1.50) D in 49 eyes with a zone II location at baseline (adjusted difference in means, −0.03 D [95% CI, −13.38 to 13.32 D]).

Laser treatment to the avascular retina after initial bevacizumab was performed in 27 eyes prior to the 12-month examination for recurrent ROP (10 eyes) or persistent avascular retina (17 eyes), at a median of 24 (range, 1-45) weeks' corrected age or 64 (IQR, 41-85) weeks' postmenstrual age. Additional details and indications for additional treatments were previously reported.[7] The mean (SD) SE cycloplegic refractive error of the 25 eyes receiving laser treatment after initial bevacizumab was −0.71 (5.77) D and the median (IQR) was −0.75 (−2.38 to 0.75) D vs a mean (SD) of −0.87 (4.02) D and a median (IQR) of 0.25 (−1.50 to 1.50) D in 62 eyes not receiving laser treatment (adjusted difference in means, −0.18 D [95% CI, −14.26 to 13.91 D]).

Ocular Examination at 12 Months

Abnormalities of the cornea, lens, or other anterior segment were reported in 1 eye (1% [95% CI, 0%-6%]), 3 eyes (3% [95% CI, 1%-10%]), and 3 eyes (3% [95% CI, 1%-10%]), respectively (Table 2). Optic nerve atrophy was identified in 11 eyes (13% [95% CI, 6%-26%]); no cases of macular ectopia were reported, and 1 eye (1% [95% CI, 0%-6%]) had a total retinal detachment attributable to severe recurrent disease 10 weeks after initial injection (Table 2). The extent of peripheral retinal vascularization could be determined for 72 of 89 eyes (81%), of which 22 eyes (31% [95% CI, 20%-43%]) were not zone III or fully vascularized (Table 2).

Constant or intermittent strabismus at distance or near fixation was reported in 13 infants (30% [95% CI, 17%-45%]), while manifest nystagmus was reported in 7 infants (15% [95% CI, 6%-29%]), and amblyopia in 3 infants (7% [95% CI, 1%-18%]) (Table 3). Overall, 98% of infants had central fixation in each eye (44 of 45 eyes), and 36 of 45 eyes (80%) had central, steady, and maintained fixation in each eye.

Association With Total Dosage

Following the initial injection, 14 eyes received additional treatment with IVB prior to the 12-month ocular examination (0.125 mg for 1 eye, 0.5 mg for 4 eyes, and 0.625 mg for 9 eyes) at a median of 1 weeks' corrected age (range, −6 to 5 weeks' corrected age) or 41 (IQR, 34-45) weeks' postmenstrual age. There were no associations identified between any ocular examination findings, and the total dose of bevacizumab received prior to the 12-month examination. All *P* values for an association were .10 or greater (Tables 2 and 3).

Discussion

Among the 46 infants treated with dosages of intravitreal bevacizumab ranging from 0.25 to 0.031 mg who later completed a 12-months' corrected-age outcome examination, the rates of high myopia, strabismus, nystagmus, retinal detachment, and other ocular findings were low and consistent with rates reported for infants treated with higher dosages of bevacizumab and laser ablative treatment. Chen et al[9] treated 57 eyes with 0.625 mg (0.025 mL) of bevacizumab and follow-up laser treatment if needed and reported that 9 eyes (16%) had high myopia of −5.00 D or greater when the patients were 2 years of age, which was similar to the rate of 14% observed in this study. Harder et al[10] found the prevalence of high myopia to be 9% in 23 eyes treated with either 0.375 mg or 0.625 mg of bevacizumab, which was also similar to the rate of 14% observed in this study. Among 22 eyes treated with 0.625 mg of IVB, Hwang et al[11] reported a mean SE refractive error of −3.7 D for eyes with ROP in zone I vs 0.6 D for eyes with ROP in zone II; these were contrary to our findings of no difference in SE refractive error between zone I and II locations. Our results were based on the mean (−0.76 D for zone I vs −0.87 D for zone II) and might be subject to the changes caused by small numbers and outliers. Our results using the median refractions are consistent with those of Hwang et al[11] with respect to those with a zone I location being more myopic (medians: −0.50 D for eyes with ROP in zone I; 0.38 D for eyes with ROP in zone II).

VanderVeen et al[12] reported rates of 30% with strabismus after laser ablative treatment, similar to the rate of 30% in infants receiving IVB in this study. In the Early Treatment for Retinopathy of Prematurity Study (ETROP) study, which used laser ablation, Wheeler et al[3] reported a similar rate of nystagmus (17%), a lower rate of strabismus (16%), and a higher rate of high myopia (32%) compared with the infants in this study, who received IVB. A report by Good et al[13] that also used the ETROP study data reported similar rates of optic atrophy (9%), cataract (5%), macular ectopia (6%), retinal fold (3%), and retinal detachment (3%) at age 6 years in eyes treated with lasers for ROP. Fixation behavior in eyes treated with lasers was reported as uncentral eccentric fixation in 12% of participants and unsteady fixation in 22% of participants, which was consistent with the rates observed in the infants in this study, who were treated with IVB.

Limitations

This study has several limitations. First, the sample size was small overall and in each dosage-defined subgroup, limiting our ability to evaluate the frequency of outcomes with high precision as well as whether outcomes differed between total dosage levels of bevacizumab. This study also did not use fluorescein angiography to document the peripheral vasculature. Another limitation is that infants treated with lower dosages in the study eye were more likely not to have completed the 12-months' corrected-age examination; however, we suspect this occurred by chance. This further limited our ability to assess the

association between the total injected dosage of bevacizumab and clinical and/or ocular findings, and it potentially biased results, because those infants not completing the 12-month examination differed from those completing the examination. The current observed 12-month ocular findings are generalizable only to those treated with low dosages of 0.25 mg, 0.125 mg, 0.063 mg, and 0.031 mg. Because study eyes could not be treated with 0.625 mg and fellow eyes could not be treated with 0.031 mg per the study protocol, the total number of eyes treated with those dosages was particularly small. In addition, almost half of treated eyes received retreatment with lasers (27 eyes) or additional injections (14 eyes) prior to the 12-month examination. In addition, we had no control group because this was a phase 1 study.

Conclusions

In conclusion, in this long-term study of low-dose bevacizumab for type I ROP, the rates of high myopia, strabismus, retinal detachment, nystagmus, and other ocular abnormalities at 1 year (corrected age) were consistent with rates reported for higher dosages of bevacizumab and laser ablative treatment. A larger future study with a randomized comparison group not receiving anti–vascular endothelial growth factor therapy is necessary to assess the effectiveness and relative risk for developing comorbidities in infants.

Notes

Supplement 1.

Trial Protocol.

Supplement 2.

Statistical Analysis Plan.

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Figures and Tables

Table 1.

Characteristics of Infants, Stratified by Completion of the 12-Month Outcome Examination

Characteristics	No. (%)	
	Completed Examination (n = 46)	Did Not Complete Examination (n = 15)
Female	20 (43)	6 (40)
Race/ethnicity		
White	23 (50)	8 (53)
Black/African American	8 (17)	3 (20)
Hispanic/Latino	8 (17)	2 (13)
Asian/American Indian/Alaska Native	2 (4)	1 (7)
>1 Race	3 (7)	1 (7)
Unknown/not reported	2 (4)	0
Gestational age, wk		
Mean (SD)	24.9 (1.7)	24.8 (1.4)
Median (IQR)	24.9 (23.7-25.9)	24.1 (23.9-26.0)
Initial intravitreal bevacizumab dose in study eye, mg		
0.25	11 (24)	0
0.125	13 (28)	3 (20)
0.0625	16 (35)	8 (53)
0.03125	6 (13)	4 (27)
Stage of retinopathy of prematurity in study eye at baseline		
Stage 2 or 3 in zone II with plus disease	26 (57)	8 (53)
Stage 3 in zone I without plus disease	5 (11)	3 (20)
Any stage in zone I with plus disease	15 (33)	4 (27)
Birth weight, g		
Mean (SD)	727 (336)	656 (162)
Median (IQR)	650 (590-760)	610 (545-790)

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Abbreviations: IQR, interquartile range; NA, not applicable.

[a]Preexisting conditions that could affect neurodevelopmental milestones were included, such as intraventricular hemorrhage, periventricular leukomalacia, and hydrocephalus.

Table 2.

Clinical Testing and Ocular Examination Findings at the 12-Month Outcome Examination (Study and Fellow Eyes Combined)

Characteristic	Eyes, No. (%)					*P* Value[a]
	Overall	Total Dosage of Bevacizumab Injected Into Eye Prior to 12 mo, mg				
		≤0.0625	0.125	0.25	>0.25	
Eyes, No.[b]	89	24	24	25	16	NA
Cycloplegic refraction (spherical equivalent)						
Not done	2 (2)	0	0	1 (4)	1 (6)	NA
<−5.00 D	12 (13)	3 (13)	3 (13)	3 (12)	3 (19)	
−5.00 D to ≤−1.00 D	17 (19)	6 (25)	3 (13)	3 (12)	5 (31)	
>−1.00 D to <1.00 D	30 (34)	10 (42)	8 (33)	8 (32)	4 (25)	
≥1.00 D to ≤5.00 D	26 (29)	5 (21)	9 (38)	9 (36)	3 (19)	
>5.00 D	2 (2)	0	1 (4)	1 (4)	0	
Mean (SD) [95% CI], D	–0.82 (4.56) [–1.79 to 0.15]	–1.74 (4.43) [–3.61 to 0.12]	0.13 (4.41) [–1.74 to 1.99]	0.05 (4.62) [–1.90 to 2.00]	–2.24 (4.69) [–4.84 to 0.36]	.16[c]
Median (IQR) [range], D	0.00 (–1.88 to 1.25) [–16.25 to 14.50]	–0.06 (–2.44 to 0.75) [–16.25 to 2.25]	+0.75 (–1.06 to +1.63) [–8.88 to +14.50]	0.13 (–1.06 to 2.06) [–10.50 to 14.50]	–1.00 (–1.88 to 0.88) [–12.00 to 3.50]	
Ocular clinical examination findings, No. (%) [95% CI]						
Abnormal						
Anterior segment	3 (3) [1-10][d]	1 (4) [0-21]	1 (4) [0-21]	1 (4) [0-20]	0 (0) [0-21]	.99[e]
Cornea	1 (1) [0-6][d]	0 (0) [0-14]	0 (0) [0-14]	1 (4) [0-20]	0 (0) [0-21]	.99[e]
Lens	3 (3) [1-10][d]	0 (0) [0-14]	1 (4) [0-21]	1 (4) [0-20]	1 (6) [0-30]	.87[e]
Optic nerve atrophy	11 (12) [6-21]	3 (13) [3-32]	3 (13) [3-32]	4 (16) [5-36]	1 (6) [0-30]	.49[f]
Macular ectopia	0 (0) [0-4]	0 (0) [0-14]	0 (0) [0-14]	0 (0) [0-14]	0 (0) [0-21]	NA

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Abbreviations: IQR, interquartile range; NA, not applicable.

[a]If there were 0 events, *P* values are not reported; if data are presented as both a continuous and categorical outcome, then a *P* value is only presented for the outcome as a continuous measure.

[b]Number of eyes treated initially with bevacizumab examined at the 12-month examination. Total dosages were grouped into 4 groups.

[c]The *P* value from linear mixed model are presented after accounting for any correlation between eyes for an

association between the continuous factors and total dosage as a categorical factor.

[d]Seven eyes of 4 infants; 1 infant had a smaller corneal diameter than normal in the study eye, with inferior and superior anterior synechiae after receiving subsequent laser treatment; 1 infant had corectopia in both eyes; 1 infant had bilateral aphakia after receiving subsequent laser treatment; and 1 infant had a tiny corneal opacity in the fellow eye.

[e]Since there is a limited number of outcomes, the *P* value is from a Fisher exact test without accounting for any correlation between eyes for an association between the binary outcome and total dose as categorical factor.

[f]The *P* value from logistic regression was presented after accounting for any correlation between eyes for an association between the binary outcome and total dosage as categorical factor.

Table 3.

Clinical Test Findings at the 12-Month Outcome Examination for Infants

Outcome	No. (%)				*P* Value[a]
	Overall	Total Dosage of Bevacizumab Injected Into Both Eyes Prior to 12 mo, mg			
		≤0.1875	0.25-0.375	≥0.50	
Eyes, No.[b]	46	19	13	14	NA
Ocular Alignment at Distance					
Strabismus					
Constant	3 (7)	2 (11)	1 (8)	0 (0)	NA
Intermittent	1 (2)	1 (5)	0 (0)	0 (0)	
Orthotropic	33 (72)	15 (79)	8 (62)	10 (71)	
Unable	9 (20)	1 (5)	4 (31)	4 (29)	
Ocular Alignment at Near					
Strabismus					
Constant	5 (11)	3 (16)	2 (15)	0 (0)	NA
Intermittent	8 (17)	2 (11)	4 (31)	2 (17)	
Orthotropic	33 (72)	14 (74)	7 (54)	12 (86)	
Unable	0	0	0	0	
Constant or intermittent at distance or near, No. (%) [95% CI]	13 (30) [17-45]	5 (26) [9-51]	6 (46) [19-75]	2 (14) [2-48]	.27[c]
Manifest nystagmus, No. (%) [95% CI]	7 (15) [6-29]	2 (11) [1-33]	1 (8) [0-36]	4 (29) [8-58]	.37[d]
Amblyopia, No. (%) [95% CI]	3 (7) [1-18]	0 (0 [0-18]	2 (15) [2-45]	1 (8) [0-36]	.25[d]
Anisometropia					
Refraction not done	1 [Reference]	0	0	1 [Reference]	NA
0 D	19 (42)	10 (53)	6 (46)	3 (23)	
>0-≤1.50 D	21 (47)	7 (37)	6 (46)	8 (62)	
>1.50 D	5 (11)	2 (10)	1 (8)	2 (15)	

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Abbreviations: IQR, interquartile range; NA, not applicable.

[a]The *P* values were reported for constant or intermittent alignment at distance or near. Where data are presented as both a continuous and categorical outcome, a *P* value is only presented for the outcome as a continuous measure.
[b]Number of infants treated initially with bevacizumab examined at the 12-month examination. Total dosage of bevacizumab grouped into 3 groups.
[c]The *P* value from logistic regression for an association between the binary outcome and total dosage as a categorical factor.

[d]Since there is a limited number of outcomes, the *P* value is from a Fisher exact test without accounting for any correlation between eyes for an association between the binary outcome and total dose as categorical factor.
[e]This *P* value is from a linear model for an association between the continuous factor and the total dosage as a categorical factor.