

# Myopia Control With Positively Aspherized Progressive Addition Lenses: A 2-Year, Multicenter, Randomized, Controlled Trial

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**PURPOSE.** To evaluate the effect of newly designed positively aspherized progressive addition lenses (PA-PALs), which reduce both lag of accommodation and hyperopic defocus on the peripheral retina, on the progression of early-onset myopia.

**METHODS.** Positively aspherized-PALs have near addition and high positive distance zone aspherization comparable to the addition power. One hundred ninety-seven children were enrolled, 6 to 12 years of age, with spherical equivalent refraction from  $-1.00$  to  $-4.50$  diopters (D). The children were randomized to receive one of three lenses: single vision lenses (SVLs), PA-PALs with  $+1.0$  D addition, or PA-PALs with  $+1.5$  D addition. Follow-up visits occurred every 6 months for 2 years. The primary outcome was myopia progression evaluated by cycloplegic autorefraction.

**RESULTS.** One hundred sixty-nine (86%) children completed the follow-up. Statistical analysis of adjusted progression rates showed a mean ( $\pm$ SE) progression of  $-1.39 \pm 0.09$  D in the control group wearing SVLs at the 24-month visit. Statistically significant ( $P = 0.017$ ) retardation of myopia progression ( $0.27 \pm 0.11$  D during 24-month period or reduction ratio of 20%) by  $+1.5$  D add PA-PALs relative to the SVLs was found, which was within the range of the percentage efficacy of myopia retardation by the conventional PALs in earlier trials over the same follow-up period. Nearly all retardation occurred in the first 12 months with no significant efficacy in the second year. Positively aspherized-PALs with  $+1.0$  D addition showed negligible efficacy.

**CONCLUSIONS.** To the extent that has been tested and that can be tolerated by wearers of spectacle lenses, the high positive aspherization of the distance zone added to PALs does not enhance their therapeutic efficacy in slowing myopia progression. (<http://www.anzctr.org.au/> number, ACTRN12608000566336).

**Keywords:** myopia, refractive development, spectacles, peripheral refraction, axial elongation

Recent epidemiologic surveys from different parts of the world have documented an increased prevalence of myopia.<sup>1-3</sup> It is particularly prevalent in some countries in East Asia (e.g., Taiwan [Lin et al.<sup>4,5</sup>] and Korea [Jung et al.<sup>6</sup>]), which have experienced unprecedented increases in prevalence in younger generations with up to 97% of 19-year-olds being myopic. Myopia not only makes distance vision blurry but also, by way of pathologic changes in the retina and choroid associated with extensive elongation of the eye, increases the risks for developing macular degeneration, retinal detachment, and glaucoma in the latter half of life.<sup>7,8</sup> Nowadays, we have some impressive choices to correct refractive errors, such as excimer laser refractive surgery or intraocular lens, but neither of these can reduce the risk of the diseases associated with high myopia. Hence, there is a great deal of interest in finding a preventive treatment for myopia with few adverse effects in childhood when myopia progression and axial elongation are most prominent.

On the basis of results from experiments with a monkey model, Hung et al.<sup>9</sup> and Smith and Hung,<sup>10</sup> among others, suggest that axial length of the developing eye is regulated by visual conditions. Their results predict that hyperopic retinal defocus would elongate the axial length of the eye, leading to the progression of myopia, while an image clearly focused on the retina or in front of it would work as a stop signal for the elongation. If this is correct, some optical methods could slow myopia progression by eliminating such hyperopic retinal defocus. In 1999, Leung and Brown<sup>11</sup> reported that progressive addition lenses (PALs) effectively slow down myopia progression in children. Because PALs reduce accommodative demand and, consequently, lag of accommodation, that is, hyperopic defocus during near work, it seems plausible that PALs would have a preventive effect on myopia progression. However, subsequent randomized controlled trials have concluded that the treatment effect of PALs is statistically significant but

clinically insufficient: reduction ratios of 11% to 21% compared with single vision lenses (SVLs) have been reported.<sup>12-16</sup>

Interestingly, recent experiments with monkeys have indicated that hyperopic defocus in the peripheral retina alone can cause elongation of the eyeball.<sup>17-20</sup> Similar conditions may be encountered clinically, as off-axis refractive errors often differ from these central (foveal) values, for which SVLs may be used to correct<sup>21,22</sup> (see Ref. 23 for review). In particular, myopic eyes tend to display less myopia in the retina's peripheral region than in its foveal region. For example, Mutti et al.<sup>24</sup> have found that mean ( $\pm$ SD) relative peripheral refractions (RPRs) for the myopic eyes of 58 children at the 30° field angle nasally produce  $+0.80 \pm 1.29$  diopters (D) of spherical equivalent. Other studies<sup>25,26</sup> since then have confirmed the common presence of a relative hyperopic shift in the periphery of myopic eyes.

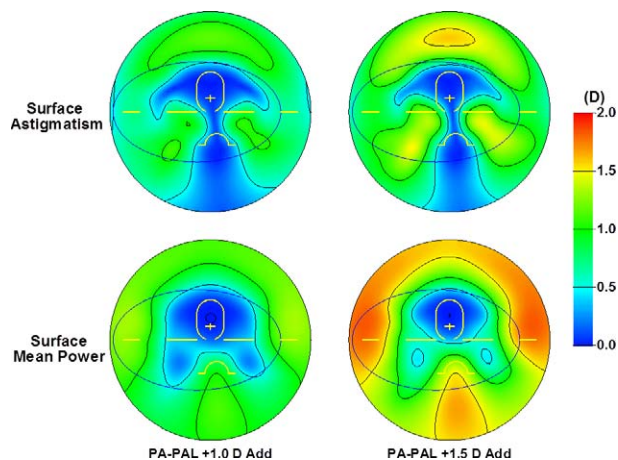
Radial refractive gradient (RRG) design lenses, which have gradually increasing plus power surrounding the lens center, are theoretically one possible way to reduce hyperopic RPR.<sup>21</sup> Using RRG lenses and one alternate design, Sankaridurg et al.<sup>26</sup> in 2010 ran the first randomized controlled trial with highly aspherized single vision lenses to control myopia progression. Reportedly, one of the test lenses, which is not an RRG design (type III in their study), reduces myopia progression by 30% compared with control SVLs. However, a statistically significant effect is found only in the subgroup of children aged 6 to 12 years with parental myopia, and thus the result is not conclusive. Furthermore, it is not known if this retarding effect would have continued over a longer period of time because this trial was terminated at 12 months. Generally, RRG design lenses have plus-power addition in the lower part of the lens like PALs, but this part involves high levels of astigmatism and is visually undesirable: Children are restricted to using the nonaspherized part at the center of the lens (or clear aperture), regardless of the viewing distance.

Positively aspherized PALs (PA-PALs) are newly designed spectacle lenses, aiming to reduce both of the possible stimuli for myopia progression: lag of accommodation during near work and hyperopic defocus in the peripheral retina when looking through the distance portion of the lens. This randomized controlled trial was undertaken to evaluate the possible treatment effect of PA-PALs compared with SVLs on slowing myopia progression in Asian children.

## METHODS

### Subjects

A total of 303 children who met the below-mentioned criteria were recruited between July 2008 and June 2009: 120 in Wenzhou (China), 77 in Okayama (Japan), and 106 in Seoul (South Korea). Written informed consent from the parents and assent from the children were obtained after written explanations and verbal discussion of the nature of the trial and the possible risks and benefits. The children and parents agreed to accept the random assignment of PA-PALs or SVLs, wear the study glasses during all waking hours, and attend the follow-up visits as appointed. The process of obtaining consent was in accordance with the Declaration of Helsinki and was approved by the institutional ethics committees (Okayama University Medical School, Eye Hospital of Wenzhou Medical College, and Eulji University). However, the trial in Korea was terminated after 12-months wear because of trial protocol violations that led to the unmasking of the main investigator; therefore, we used the data from only 197 children originally enrolled in the trial in China and Japan in this analysis.



**FIGURE 1.** Contour plots of surface astigmatism (*top*) and mean surface power offset by the base curve (*bottom*) in PA-PALs with +1.0 D addition and +1.5 D addition. Both designs have a base curve of 2.50 D. The diameter of the lens shown is 60 mm. The overlay of a typical oval child's frame is 50 × 30 mm, and the fitting position is inset by 4 mm nasally, while the fitting cross is located 4 mm above the frame datum. Note that along the radial line up from the fitting cross the positive aspherization inside the illustrated frame will have mean addition power < 0.50 D. The plots of control SVLs are not shown here, because the SVLs used have a spherical front surface, that is, constant surface power without astigmatism.

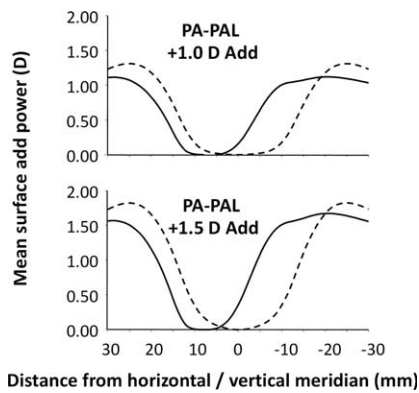
### Inclusion and Exclusion Criteria

The following inclusion criteria were applied when subjects were recruited: (1) age of 6 to 12 years at the baseline visit, (2) spherical equivalent refractive error (SER) determined by cycloplegic autorefractometry of  $-0.50$  D to  $-4.50$  D, in both eyes, (3) astigmatism of not more than  $-1.50$  D in both eyes, (4) anisometropia of not more than 1.50 D in spherical and cylindrical error, (5) best-corrected visual acuity of 6/9 (20/30) or better in each eye, (6) normal ocular health other than myopia, (7) no prior use of bifocal or progressive lenses in the previous 12 months, and (8) no rigid gas-permeable contact lens experience before enrolment in this trial.

Exclusion criteria encompassed any systemic diseases that may affect refractive error as well as manifest strabismus. Subjects were recruited through advertisements and interested families were asked to contact the research ophthalmologist or optometrist to determine if the child met the selection criteria. If so, the family was invited to attend the baseline examination.

### Lens Design

One of the authors (SRV) designed the special PALs to provide a relative plus power in a peripheral zone of the lens compared with the central region, and in which the power and surface astigmatism are distributed to provide clear distance vision in the central region and clear near vision in the lower part of the peripheral zone that is likely to be used for a wearer's near vision tasks (Figs. 1-3). The peripheral zone provides a positive mean addition power in the upper portion of the lens (corresponding approximately to the near addition power), intended as a stop signal for myopia progression. The region of the peripheral zone providing low astigmatism includes a near viewing zone that is connected to the central region via a nearly umbilic corridor, as per conventional PALs. Both designs have a very short power progression corridor adapted for juvenile use with the full nominal addition being reached 14 mm below the fitting point. The provisions of the corridor and the near viewing zone reduce the need to tilt the head when



**FIGURE 2.** Surface addition power profiles of PA-PALs along the vertical eye path (*solid line*) and the horizontal line passing through the distance reference point (*dashed line*). Minus indicates the lower or nasal direction. The distance reference point is located 8 mm, and the fitting cross is located 4 mm, above the geometric center of the lens.

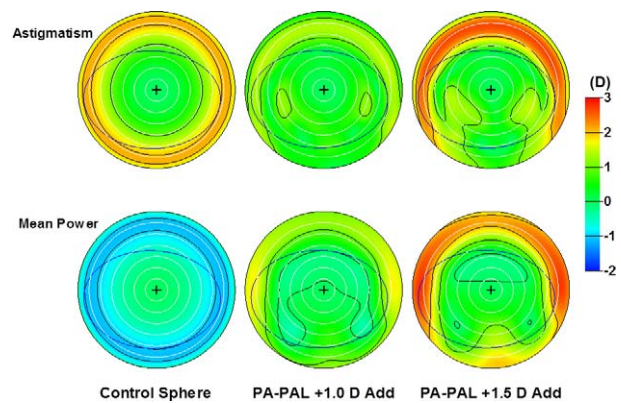
reading, making the lens more comfortable to wear. After running some small-scale acceptance trials, we selected two designs with different near additions (+1.00 and +1.50 D) and corresponding distance zone aspherization levels to be tested in this trial. Lenses with the higher addition and faster power ramp in the positively aspherized upper region tested in the acceptance trial have been almost universally rejected by the wearers as unsatisfactory. None of the tested lenses are commercially available.

When comparing contour plots of mean addition power between Figures 1 and 3, it is worth noting that the ray-trace in the latter figure evaluates the oblique angle power of the lens with rays at highly variable angles to the lens surfaces (i.e., actual relative plus sphere equivalent power seen by the eye), whereas the former figure effectively corresponds to lens powers from rays that are perpendicular to the lens front surface at every point (i.e., amount of plus power the lens is delivering over and above the SVL). As can be seen from the contour plots of the control spherical SVL ray-traced for the static eye looking straight ahead (first column of Fig. 3), this configuration provides considerable relative hyperopic shift and oblique astigmatism in the periphery even for a spherical lens having constant surface power. The PA-PALs of similar base curve need to compensate for this SVL-induced hyperopic shift before delivering any positive addition power to the peripheral retina. As a consequence, in this trial we shifted the correction on the peripheral retina toward significantly more positive values relative to controls.

### Study Design

The study involved a parallel-designed, randomized, controlled clinical trial. As shown in Figure 4, the children were randomly divided into three groups of wearers: control 3 D base spherical SVLs, PA-PALs with +1.0 D addition, and PA-PALs with +1.5 D addition. The children attended follow-up visits every 6 months for a period of 2 years.

Following the study of Gwiazda et al. (the Correction of Myopia Evaluation Trial, COMET),<sup>14</sup> subjective noncycloplegic refraction was used to specify the spectacle prescription worn by children in all groups. The prescription was changed when either of the following criteria was met in at least one eye at the scheduled visit and nonscheduled visits when children reported some problems: a change in sphere equivalent to 0.50 D or more was recorded in subjective noncycloplegic refraction, or a drop of distance visual acuity of 0.2 logMAR or more was found. The spectacle frames were fitted so that

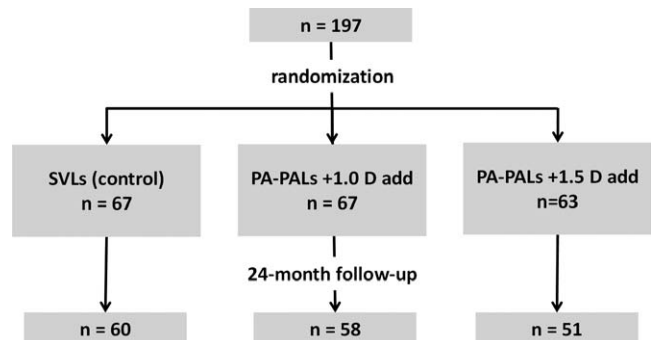


**FIGURE 3.** Ray-traced astigmatism (*top*) and mean power (*bottom*) as a function of field angle referenced to the entrance pupil center when looking straight ahead through the fitting cross of the lenses. The diameter of the field is 140°, and the gray rings are plotted in 10° increments. The outlines of the ray-traced spectacle frame 50 × 30 mm and the fitting cross are overlaid. Simulation when the lens power is −2.50 D and the distance between the back vertex point of the lens and the entrance pupil center is 15 mm.

the fitting point of the lenses would be just at the center of the entrance pupil with a vertex distance between 10 and 14 mm and a pantoscopic angle of not less than 0°. No instructions were given to the children regarding preferred eye or head positions while using the glasses because such instructions would be difficult for young children to follow. The children and parents were asked to be careful about misalignment of the spectacles and encouraged to consult our opticians for readjustment if they noticed it. The study glasses were provided free of charge.

### Randomization and Masking

One of the authors (unmasked investigator) made a lens allocation table by using the Microsoft Excel (Microsoft, Redmond, WA, USA) function “INT(RAND()\*2.99),” which was used to generate random integers between 0 and 2. These numbers denote each lens design. This page was refreshed to change the seed of the RAND function until the allocation ratio was approximately 1:1:1. The results were copied and pasted as values into a new spreadsheet (master allocation table). The masked investigator at each study center sent prescriptions with the subject ID to the unmasked investigator who, in turn, assigned the lens design from the master allocation table according to the subject ID and placed the order with the Zeiss surfacing laboratory.



**FIGURE 4.** Study flow and random assignment of subjects.



Enrolled children and their parents were not told of their group allocation; we emphasized the importance of full-time proper wear of the assigned spectacles, as if they were wearing PA-PALs. In the follow-up period, only one pair of lenses was given to the children at any time. All lenses had semivisible engravings indicating the lens design, but no masked investigator or optician having direct contact with the participants was allowed to check the engravings or was told their meaning. However, the rate of unmasking and its potential impact on the study results are not known.

### Primary and Secondary Outcome Measures

The primary outcome measure was the central (foveal) SER determined by cycloplegic autorefraction, and the secondary outcome measure was the axial length of the eye determined by partial coherence interferometry (IOLMaster; Carl Zeiss, Jena, Germany). The treatment effect was the mean difference in myopia progression or axial elongation between PA-PAL- and SVL-wearing groups, and the reduction ratio (%) was defined as the ratio of the mean difference between the two groups to the mean myopia progression or axial elongation found in the control SVL group.

The cycloplegic agent used in the Japan trial comprised a combination of eyedrops of 0.5% tropicamide and 0.5% phenylephrine (Mydrin-P; Santen, Osaka, Japan), administered 5 minutes apart. Autorefraction measures were taken 30 minutes after the initial eyedrop. In the China trial, 1% tropicamide eyedrops were used instead. Objective assessment of residual accommodation have confirmed that both types of eyedrops are effective cycloplegic agents in myopic children.<sup>27,28</sup> Open-field autorefractors (Grand-Seiko WV-500 [Grand-Seiko, Fukuyama, Japan] in Japan and a different model of the device made by the same company, WAM-5500, in China) were used with a fixation target at 500 cm to measure the refractive error in both eyes. The autorefractors were calibrated according to the manufacturer's specifications at weekly intervals. Four reliable readings were taken, and the average (produced by the instrument) was considered as a representative value.

### Relative Peripheral Refraction and Heterophoria

The RPR was estimated at the baseline visit because we wanted to use RPR data as an independent variable in statistical modeling to ascertain if hyperopic defocus in the periphery is the real driver of myopia progression and whether any intervention with highly aspherized spectacle lenses indicates the negation of this driver through significant interaction between lens and RPR. While the children were undergoing cycloplegia, we measured refraction, from each eye in turn, using the open-field autorefractor while subjects monocularly looked at a point source of light placed along the horizontal meridian ( $0^\circ$ ,  $\pm 5^\circ$ ,  $\pm 15^\circ$ ,  $\pm 25^\circ$ , and  $\pm 30^\circ$ ). The target distance was 33 cm in China and 50 cm in Japan, and therefore there is a possibility that the children were slightly accommodating owing to an incomplete cycloplegic effect of those eyedrops. The RPR was estimated by subtracting the central refraction from that at each peripheral gaze direction. The average of temporal and nasal  $5^\circ$  values was regarded as the central refraction for Chinese children because they were unfortunately not measured under this condition. We regarded the RPR at the  $30^\circ$  nasal field point (i.e., in the temporal retina) as a representative value. This choice was based on the recently reported finding of a significant association between relative peripheral eye length at the same location in the temporal retina and progression of myopia in children with steeper retinas displaying greater myopia progression.<sup>29</sup>

Horizontal heterophoria (in prism diopters) at distances of 33 and 300 cm was measured through distance-corrective lenses by using Howell Phoria Cards. When ocular misalignment was found, the cover and uncover test was performed to determine whether it was heterophoria or heterotropia.

### Statistical Analyses

From previous studies,<sup>11,13-16</sup> we assumed that mean myopia progression in the control (SVL-wearing) group was  $-1.34$  D with a SD of 0.75 D over a 2-year period. Because we were aiming for a minimal acceptable reduction of 33% or a difference of 0.45 D during 2 years, 73 subjects in each group were required to have a 5% alpha level and 95% power. In anticipation of dropout of 10% of the subjects, the required sample size was 240. Only 169 subjects completed the study. For the comparison between the control group having 60 subjects completing the trial and the smallest group of 51 subjects wearing the +1.5 D add PA-PAL at the end of the trial, the power of the experiment was just under 88%.

Myopia progression rates can be influenced by a range of independent factors such as age, parental myopia, and sex.<sup>30-34</sup> Randomized assignment of lenses to children should help to achieve an approximate balance, but any residual imbalances in confounding independent variables among the groups can be adjusted statistically. Analysis of variance (ANOVA) was used to compare the amount of variance explained by the model with two-way interactions to that explained by the model with the main effects only. If ANOVA showed a statistically significant improvement in the model fit to the data with all two-way interactions, this model was trimmed to remove interaction terms with  $P > 0.1$ . Another ANOVA comparison was then made between the trimmed model with selected significant two-way interactions and that with the main effects only. If the trimmed model maintained a statistically significant advantage in explaining the variance in the data compared with the main effects model, then the trimmed model was retained as the most representative model of the adjusted progression rates. Since one of the hypotheses of our study was that correcting peripheral hyperopic defocus may retard the progression of myopia, we included the factor reflecting the peripheral refractive state of the eye. In addition, since there was some intersubject variation in the actual wear time from the nominal 24 months, the wear time calculated from the data at the baseline and final visits was included in the model to normalize the progression rates to the nominal wear time. We also included the interactions between these factors and main effects that were significant at the 10% level provided that the ANOVA test for the coefficients of the additional interaction terms being zero gave  $P < 0.05$ . To make full use of the measurements from both eyes, we built linear mixed-effects models where each eye was used as the case, assuming that data from the left and right eyes were highly correlated. The public domain statistical software R with the lme() package was used for this analysis.<sup>35-38</sup> In addition, we planned a subgroup analysis to compare progression of myopia and treatment effect by baseline clinical characteristics, similarly to our previous trial using PALs.<sup>15</sup>

### Questionnaire Survey

To clarify visual symptoms associated with the use of PA-PALs (usability), a questionnaire survey was conducted in the Japan trial. It consisted of seven questions, and the children were requested to respond to each of the questions on a scale of 1 (very bad) to 5 (very good). Question (Q) 1 evaluated the general impression of the study glasses. Questions 2, 3, and 4 evaluated the image clarity for near, intermediate, and distance vision, respectively. Question 5 evaluated difficulty in walking

TABLE 1. Baseline Characteristics of the Subjects Who Completed the 2-Year Follow-up by Study Group

	Total	Group			P Value
		SVLs, Control	PA-PALs +1.0 D Add	PA-PALs +1.5 D Add	
N	169	60	58	51	-
Age, y	10.3 ± 1.4	10.4 ± 1.2	10.6 ± 1.5	10.0 ± 1.5	0.18
SER, D	-2.61 ± 1.00	-2.55 ± 0.96	-2.52 ± 1.01	-2.80 ± 1.02	0.22
Axial length, mm	24.64 ± 0.79	24.64 ± 0.73	24.56 ± 0.90	24.71 ± 1.02	0.66
Distance phoria, PD*	-0.7 ± 2.0	-0.9 ± 1.7	-0.3 ± 1.6	-0.9 ± 2.7	0.97
Near phoria, PD*	-0.5 ± 4.8	-1.1 ± 3.9	0.2 ± 5.0	-0.5 ± 5.5	0.49
RPR, D	1.16 ± 0.83	1.22 ± 0.97	1.08 ± 0.70	1.19 ± 0.79	0.82
Parental myopia†	115 (68%)	36 (60%)	43 (74%)	36 (71%)	0.23
Chinese	97 (57%)	35 (58%)	32 (55%)	30 (59%)	0.91
Girl	74 (44%)	24 (40%)	30 (52%)	20 (39%)	0.32

Mean ± SD values for the average of both eyes are presented. PD, prism diopters.

\* Minus sign indicates exophoria.

† Numbers of children who have at least one myopic parent. P values were obtained by one-way ANOVA or  $\chi^2$  tests.

or in sports activity. Question 6 evaluated the adaptability at the beginning of spectacle use, and Q7 evaluated image distortion in lateral gaze. The questionnaire was mailed to the children 1 month after the baseline visit, and answers, with the parents' assistance, were obtained from all 77 children.

## RESULTS

### Trial Profile

Of the 197 children enrolled in the trial, 120 were from China and 77 were from Japan. Clinical characteristics at baseline are shown in Table 1. They are reasonably balanced, with no significant or clinically relevant differences between the study

groups. All children adapted successfully to the study glasses. One hundred sixty-nine (86%) children completed the 2-year follow-up: 23 (19%) children from China and five (6%) children from Japan dropped out of the trial. The reasons for discontinuation included a complaint about the time-consuming examination (10 children), moving to another city (four children), desire for other treatment (four children), refusal to undergo cycloplegia (two children), lost contact (two children), and could not adapt to the test lenses (one child); the reason was unknown in five children. Data for another three children in Japan could not be used in the analysis because they were erroneously dispensed lenses with a trial design different from that assigned to them at least once during the trial. We have included these three children in the overall number of dropouts. Of the dropouts, five were assigned to the SVL group, nine to the +1.0 D add PA-PAL group, and 14 to the +1.5 D PA-PAL group. After performing a test of the dropout proportions, there was no clear evidence for loss of randomization ( $P = 0.076$ ).

### Relative Peripheral Refraction at Baseline

In agreement with previous studies,<sup>25,26,39,40</sup> we found a nearly symmetrical pattern of spherical equivalent RPR with an axis of the primary gaze position, and an averaged hyperopic RPR reaching 1 to 1.5 D at the gaze angle of 30° (Fig. 5). There was large intersubject variation in the amount of RPR, but its association with neither central refraction nor axial length was significant.

### Effect of Treatment on Myopia Progression

During the 2-year follow-up period, myopia significantly progressed in all groups (two-tailed paired *t*-test,  $P < 0.0001$ ). The mean (±SD) myopia progressions (when eye was treated as the case) were  $-1.38 \pm 0.61$  D ( $n = 120$ ),  $-1.32 \pm 0.59$  D ( $n = 116$ ), and  $-1.19 \pm 0.49$  D ( $n = 102$ ) in SVL, +1.0 D add PA-PAL, and +1.5 D add PA-PAL groups, respectively.

Results of the linear mixed-effects model fitting to SER data are shown in Table 2. Chosen confounding factors were age, sex, parental myopia, RPR, SER at baseline, deviation of the wear time from the nominal 24 months, and near phoria, as well as some of their interactions. The interaction terms were included in the model only if the estimated standard deviation of the errors in the model with the interaction terms was significantly smaller ( $P < 0.05$ ) than that for the model without the interaction terms.

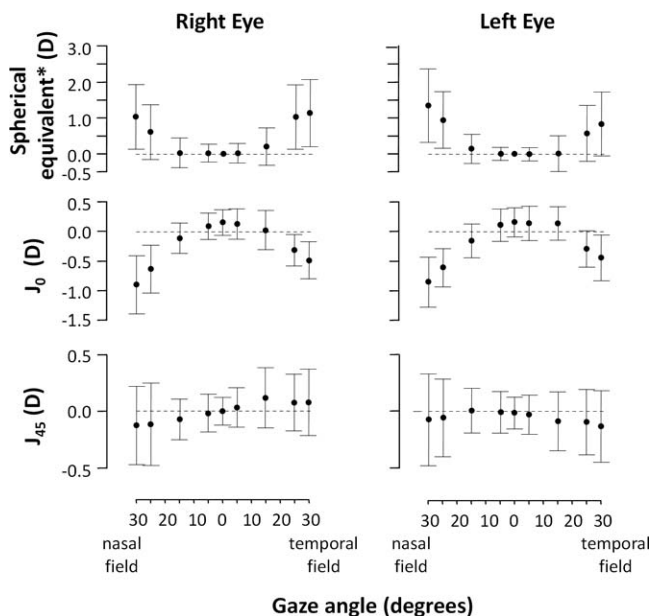


FIGURE 5. Relative peripheral refraction at baseline for all children ( $n = 169$ ). \*Spherical equivalent is shown as a relative value obtained by subtracting the refractive measurement at the primary position from that at each gaze position. Plus sign indicates less myopic.  $J_0$  and  $J_{45}$  (dioptric power of a Jackson cross cylinder with axis at 0° and 45°, respectively) are absolute values and were calculated by using the power vector approach. Error bars represent mean ± SD.

TABLE 2. Results of the Mixed-Effects Models Fitted to 2-Year Change in SER for Both Eyes ( $n = 338$ )

Means	Estimate of Effect, D	Standard Error, D	P Value
The full model			
SVLs	-1.390	0.088	-
PA-PALs +1.0 D add	-1.201	(0.112)	0.094
PA-PALs +1.5 D add	-1.116	(0.114)	0.017*
Incremental effects			
Age, y	0.063	0.036	0.081
RPR, D	0.028	0.030	0.352
Sex, boy/girl	-/+0.009	0.043	0.830
Parental myopia, PM1/PM0†	+/-0.009	0.077	0.909
Wear time, d	-0.001	0.002	0.412
SER at baseline, D	0.006	0.045	0.900
Near phoria	-0.006	0.010	0.504
Incremental interaction effects			
Age by parental myopia, PM1/PM0†	+/-0.090	0.036	0.013*
PA-PALs +1.0 D add by parental myopia, PM1/PM0†	-/+0.184	0.111	0.099
PA-PALs +1.5 D add by parental myopia, PM1/PM0†	+/-0.016	0.113	0.889
SER by parental myopia, PM1/PM0†	-/+0.076	0.044	0.090
The simplified model			
SVLs	-1.353	0.081	-
PA-PALs +1.0 D add	-1.315	(0.101)	0.702
PA-PALs +1.5 D add	-1.102	(0.106)	0.018*
Incremental effects			
Age, y	0.115	0.030	<0.001*
Wear time, d	-0.001	0.002	0.385

Two models are shown: the full model and the simplified model without concomitant variables having  $P > 0.05$ . Numbers in parentheses in the third column are standard errors of the differences between groups: +1.0 D add PA-PALs versus SVLs, and +1.5 D add PA-PALs versus SVLs.

\*  $P < 0.05$ .

† Parental myopia was categorized as children with no myopic parent (PM0) or those with one or two myopic parents (PM1). -/+ or +/- in the estimate of effect column indicates that myopia progressed more or less, respectively, when the child belongs to the former category in parentheses.

Positively aspherized-PALs with +1.5 D addition showed significant retardation of myopia by 0.27 D over a 2-year period ( $P = 0.017$ ), which corresponds to 20% of the control group's mean progression. On the other hand, the effect of +1.0 D add PA-PALs was not statistically significant ( $P = 0.094$ ). These main conclusions are robust to changes in the selection of independent variables in the model and are unchanged for a large range of models, starting from the simplest model that includes only the two lens factors and children's age at baseline through to the model that includes all independent concomitant variables without any interaction terms and ending with the more complex model with all of the reasonable independent variables and three significant interactions shown in Table 2. For the main effects, none of the independent variables was significant at the 5% level. However, there was one two-way interaction term between age and parental myopia that was significant ( $P = 0.013$ ). This indicates that, compared to children with no parental myopia, those who have a myopic parent and are older than the sample mean show a slightly slower progression of myopia while those who are younger than the mean age have faster progression. This essentially implies a steeper fall and saturation in the progression of myopia with age for children with parental myopia and a shallower relationship with a longer tail end for children without it.

### Effect of Treatment on Axial Elongation

The linear mixed model for the axial length data of both eyes is shown in Table 3. Two models are shown in this table. The full model had additional interaction terms that were significant: between parental myopia and age, parental myopia and

baseline SER, as well as relative peripheral refraction and lens type (for the +1.0 D add PA-PALs). In this model, the mean axial elongation for 2 years in children wearing PA-PALs with +1.0 D and +1.5 D addition was smaller than that in the control SVL group by 0.052 mm and 0.082 mm, respectively, but the differences did not reach statistical significance. The simplified model had only two covariate terms included: age and wear time. It confirms the results of the full model: there was no statistically significant retardation of axial elongation with either of the test lenses.

### Change of the Treatment Effects Over Time

Table 4 and Figure 6 show comparisons of myopia progression and axial elongation over the course of the 2-year follow-up among the study groups. Nearly all of the treatment effect of PA-PALs with +1.5 D addition occurred in the first 12 months (0.24 D or reduction ratio of 31%), with no significant efficacy in the second year. In contrast, the treatment effect by +1.0 D add PA-PALs was not significant throughout the follow-up period.

### Relationship Between Axial Elongation and Myopia Progression

Figure 7 shows a comparison of the relationships between change in axial length and SER for the study groups. Only the regression lines for the SVL control and +1.5 D add PA-PAL groups significantly differ from each other (ANOVA,  $P = 0.001$ ).

**TABLE 3.** Results of the Linear Mixed Effects Model Fitted to 2-Year Change in Axial Length for Both Eyes ( $n = 338$ )

Means	Estimate of Effect, mm	Standard Error, mm	P Value
<b>The full model</b>			
SVLs	0.686	0.035	-
PA-PALs +1.0 D add	0.634	(0.045)	0.251
PA-PALs +1.5 D add	0.604	(0.045)	0.074
<b>Incremental effects</b>			
Age, y	-0.057	0.014	<0.001*
RPR, D	0.009	0.015	0.535
Sex, boy/girl	-/+0.009	0.017	0.587
Parental myopia, PM1/PM0	-/+0.030	0.030	0.323
Wear time, d	0.001	0.001	0.404
SER at baseline, D	-0.036	0.016	0.027*
Near phoria	0.005	0.004	0.165
<b>Incremental interaction effects</b>			
Age by parental myopia, PM1/PM0	-/+0.037	0.014	0.009*
PA-PALs +1.0 D add by parental myopia, PM1/PM0	+/-0.084	0.044	0.060
PA-PALs +1.5 D add by parental myopia, PM1/PM0	+/-0.041	0.045	0.369
SER at baseline by parental myopia, PM1/PM0	+/-0.040	0.016	0.014*
PA-PALs +1.0 D add by RPR	-0.060	0.023	0.010*
PA-PALs +1.5 D add by RPR	-0.025	0.025	0.318
<b>The simplified model</b>			
SVLs	0.657	0.033	-
PA-PALs +1.0 D add	0.666	(0.041)	0.828
PA-PALs +1.5 D add	0.607	(0.042)	0.244
<b>Incremental effects</b>			
Age, y	-0.080	0.012	<0.001*
Wear time, d	0.001	0.001	0.360

\*  $P < 0.05$ .

### Relationship Between Treatment Effect in SER and Clinical Characteristics

Table 5 shows the adjusted myopia progression in different subgroups of children stratified by clinical characteristics at baseline. This analysis shows several interesting outcomes. Age-based subdivision outcomes indicate that most of the retardation of myopia progression occurred in the younger age group (<10 years old). Analysis in the +1.5 D add PA-PAL group at 12 months also found a significant treatment effect only in the younger age group ( $0.36 \pm 0.11$  D, reduction ratio of 57%,  $P = 0.001$ ). Thus, the additional treatment effect in the second

year was merely 0.02 D, indicating that the effect was clearly saturated in this group. The +1.0 D add PA-PALs were only effective in the group of children without parental myopia. Those with near esophoria did not specifically benefit from wearing either of the PA-PALs, although the frequency of children with esophoria in our sample was only 22%. This appears to contradict the findings of some earlier studies,<sup>13,16</sup> where near esophores are the subgroup that show more retardation of myopia progression than others. Another notable outcome was greater efficacy of the +1.5 D add PA-PALs in the subgroup of children with the low RPR of  $\leq 1.25$  D.

**TABLE 4.** Adjusted Mean Myopia Progression and Axial Elongation of Both Eyes for Study Groups at Each Scheduled Visit

Group	SVLs	PA-PALs +1.0 D Add		PA-PALs +1.5 D Add	
<b>Adjusted Mean Myopia Progression, D</b>					
Visit, mo	Progression	Progression	Difference*	Progression	Difference*
6	0.56	0.54	-0.02 (4%)	0.45	-0.10 (19%)
12	0.80	0.71	-0.09 (11%)	0.56	-0.24 (31%)
18	1.10	0.97	-0.13 (12%)	0.88	-0.22 (20%)
24	1.39	1.20	-0.19 (14%)	1.12	-0.27 (20%)
<b>Adjusted Mean Axial Elongation, mm</b>					
Visit, mo	Elongation	Elongation	Difference*	Elongation	Difference*
6	0.22	0.18	-0.04 (16%)	0.19	-0.02 (11%)
12	0.38	0.37	-0.01 (2%)	0.33	-0.05 (13%)
18	0.53	0.53	0.00 (-1%)	0.48	-0.05 (9%)
24	0.69	0.63	-0.05 (8%)	0.60	-0.08 (12%)

\* A difference in progression or elongation between PA-PALs and the control SVLs (the treatment effect). The ratios of reduction compared with SVLs are shown in parentheses.



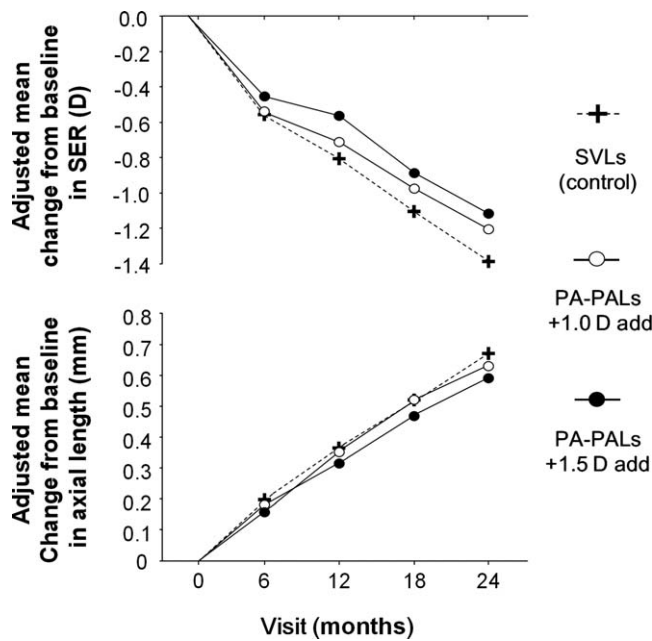


FIGURE 6. Adjusted mean change from baseline in spherical equivalent cycloplegic autorefraction (top) and in axial length (bottom) ( $n = 338$ ).

### Interaction Between +1.0 D Add PA-PALs and Parental Myopia in Myopia Progression

In the model of myopia progression (Table 2), strong interaction between +1.0 D add PA-PALs and parental myopia was observed, adding 0.184 D to the treatment effect for children with no parental myopia. Although this term does not reach statistical significance ( $P = 0.099$ ), it was also demonstrated by subgroup analysis as described above. Therefore, we felt that this issue deserved further analysis.

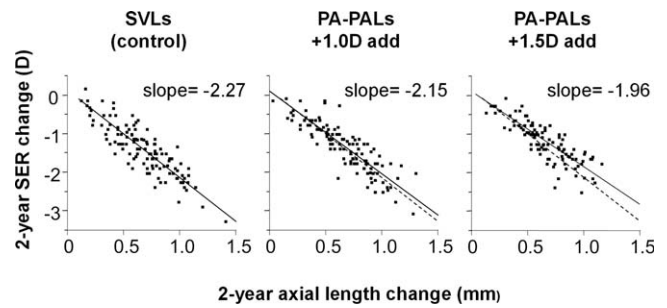


FIGURE 7. Comparison of relationships between 2-year axial elongation and myopia progression among the study groups ( $n = 338$ ). Regression lines were obtained with the Deming regression on the assumption that random errors (SD) of the refraction and axial length measures were 0.16 D<sup>41</sup> and 0.03 mm,<sup>42</sup> respectively (error variance ratio: 28). For comparison, the regression line found in the control group is shown with *dashed lines*.

To verify the effect of +1.0 D add PA-PALs on children with no parental myopia through the interaction between lens type and parental myopia, we ran the mixed-effects model (Table 6). Only the main incremental effects were included, as the addition of any interaction effects did not improve the amount of variance explained by the model. Adjusted SER change over the course of 2-year follow-up is also shown in Figure 8. The estimated mean progression for PA-PALs with +1.0 D addition in this subgroup was slower than that of the subgroup with the +1.5 D addition, a 0.37 D retardation of myopia progression relative to the control group ( $P = 0.04$ , reduction ratio of 26%).

### Safety and Usability Outcomes

No serious adverse events were reported during the 2-year follow-up. The results of the questionnaire survey are summarized in Table 7. The children generally recognized the usability of wearing the study glasses as good (score 4) or

TABLE 5. Adjusted 2-Year Mean Progression of Myopia and Treatment Effect by Baseline Characteristics

Group	SVLs			PA-PALs +1.0 D Add			PA-PALs +1.5 D Add		
	N	Mean $\pm$ SE, D	N	Mean $\pm$ SE, D	Effect, D	N	Mean $\pm$ SE, D	Effect, D	
Age, y									
6–9	23	-1.55 $\pm$ 0.14	23	-1.35 $\pm$ 0.17	0.20 $\pm$ 0.17	26	-1.17 $\pm$ 0.17	0.38 $\pm$ 0.17*	
10–12	37	-1.17 $\pm$ 0.11	35	-1.23 $\pm$ 0.13	-0.06 $\pm$ 0.13	25	-1.04 $\pm$ 0.14	0.13 $\pm$ 0.14	
Parental myopia									
0	24	-1.40 $\pm$ 0.15	15	-1.03 $\pm$ 0.17	0.37 $\pm$ 0.17*	15	-1.15 $\pm$ 0.17	0.25 $\pm$ 0.17	
1 or 2	36	-1.31 $\pm$ 0.08	43	-1.27 $\pm$ 0.10	0.03 $\pm$ 0.10	36	-1.07 $\pm$ 0.11	0.24 $\pm$ 0.11*	
SER of the right eye									
> -2.5 D	30	-1.29 $\pm$ 0.14	29	-1.26 $\pm$ 0.16	0.03 $\pm$ 0.16	19	-0.92 $\pm$ 0.18	0.37 $\pm$ 0.18*	
$\leq$ -2.5 D	30	-1.47 $\pm$ 0.13	29	-1.23 $\pm$ 0.16	0.23 $\pm$ 0.16	32	-1.17 $\pm$ 0.16	0.29 $\pm$ 0.16	
Near phoria with full correction									
Exo, $\leq$ -2 PD	22	-1.48 $\pm$ 0.15	20	-1.33 $\pm$ 0.16	0.15 $\pm$ 0.16	17	-1.10 $\pm$ 0.17	0.38 $\pm$ 0.17*	
Ortho, -1 to 1 PD	29	-1.40 $\pm$ 0.15	22	-1.41 $\pm$ 0.19	-0.02 $\pm$ 0.19	22	-1.08 $\pm$ 0.19	0.31 $\pm$ 0.19	
Eso, $\geq$ 2 PD	9	-1.27 $\pm$ 0.20	16	-1.11 $\pm$ 0.24	0.16 $\pm$ 0.24	12	-1.18 $\pm$ 0.24	0.09 $\pm$ 0.24	
RPR of the right eye									
$\leq$ 1.25 D	36	-1.35 $\pm$ 0.12	40	-1.29 $\pm$ 0.14	0.06 $\pm$ 0.14	27	-0.95 $\pm$ 0.16	0.40 $\pm$ 0.16*	
> 1.25 D	24	-1.55 $\pm$ 0.15	18	-1.22 $\pm$ 0.19	0.34 $\pm$ 0.19	24	-1.27 $\pm$ 0.17	0.29 $\pm$ 0.17	
Overall	60	-1.39 $\pm$ 0.09	58	-1.20 $\pm$ 0.11	0.19 $\pm$ 0.11	51	-1.12 $\pm$ 0.11	0.27 $\pm$ 0.11*	

Subgroup analysis adjusted for main effects only.  
\*  $P < 0.05$ .



**TABLE 6.** Results of the Mixed Effects Model Fitting to 2-Year SER Change for Both Eyes in the Subgroup of Children With No Parental Myopia ( $n = 108$ )

Means	Estimate of Effect, D	Standard Error, D	P Value
SVLs	-1.403	0.147	-
PA-PALs +1.0 D add	-1.034	(0.175)	0.040*
PA-PALs +1.5 D add	-1.147	(0.175)	0.151
Incremental effects			
Age, y	-0.020	0.058	0.729
RPR, D	0.088	0.046	0.060
Sex, boy/girl	-/+0.035	0.073	0.636
Wear time, d	-0.0004	0.003	0.898
SER at baseline, D	0.077	0.070	0.278
Near phoria	-0.014	0.018	0.421

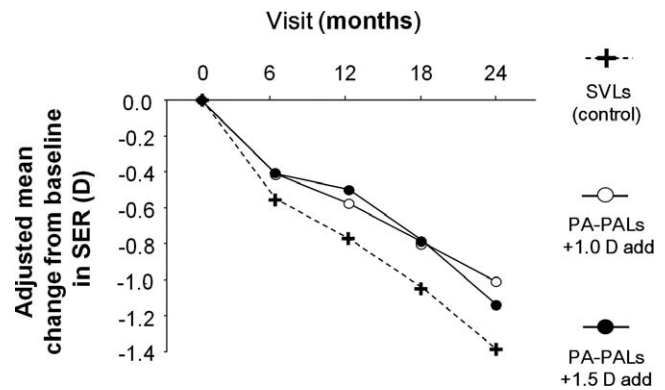
\*  $P < 0.05$ .

very good (5). There was no difference in the median score in any of the questions among the study groups.

## DISCUSSION

Our 2-year randomized controlled trial showed that PA-PALs with +1.5 D addition significantly slowed the progression of myopia in children, with an average of 20% reduction ( $0.27 \pm 0.11$  D) of SER derived from cycloplegic autorefractometry. We did not directly compare the treatment effect between PA-PALs and conventional (marginally aspherized) PALs in this study, but the reduction ratio was not better than that of 11% to 21% reported by 2-year trials in Asian children with PALs having the same addition power (SOLA MC PAL; Carl Zeiss Vision, Aalen, Germany).<sup>13,15,16</sup> In addition, most of the retardation effect was observed in the first 12 months of the trial with virtually no effect in the second 12 months. These results to the extent tested do not support the hypothesis that the high positive aspherization imposed on PALs enhances their therapeutic efficacy by reducing hyperopic defocus in the peripheral retina.

Since the applied aspherization was rotationally symmetrical over the upper hemisphere of the lens, its effect was similar to RRG-design lenses (lens types I and II) tested by Sankaridurg et al.<sup>26</sup> These two designs, which had 1 and 2 D positive aspherization, respectively, were found to be ineffective in slowing the progression of myopia. Therefore, it seems plausible that the treatment effect of PA-PALs was attributable to the positive add power available for clear near vision in the lower portion of the lens rather than any effect of aspherization on peripheral imaging on the retina. This is corroborated by the lack of significance for the RPR term and its interactions with the test lenses in the regression model for the myopia

**FIGURE 8.** Adjusted mean SER change in the subgroup of children with no parental myopia ( $n = 108$ ).

progression at the 24-month visit, although there is still controversy as to whether a +1.0 or +1.5 D near addition applied to myopic children reduces lag of accommodation to a satisfactory level.<sup>43,44</sup>

This conclusion can be challenged by arguing that the amount of the plus power delivered to the peripheral retina by the lens inside the smallish typical children's frame was mostly not sufficient to compensate for the relative peripheral hyperopic defocus of the myopic eyes. Such conclusion might be drawn by comparing Figures 3 and 5. To test this argument, we have calculated the fraction of the area of the lens inside a typical children's frame that delivers  $\geq 1.0$  D of relative plus power to the eye, based on the static eye ray-trace illustrated in Figure 3. We have carried out this calculation for two +1.5 D addition progressive lenses, the efficacy of which to control progression of myopia has been tested in clinical trials: MC PAL and the PA-PAL tested in this trial. As was pointed out earlier, both of these lenses appeared to have similar efficacy in slowing down progression of myopia but the fraction of the lens area was different: 4% and 22%, respectively. Given that both of these lenses reduce accommodation demand to the same level, the agreement in efficacy appears to favor the accommodation theory of myopia rather than the peripheral hyperopic defocus theory.

The only trial outcome indicative of the aspherization having some effect on the progression of myopia is in the subgroup analysis showing that the subgroup of children with lower RPR ( $\leq 1.25$  D) had their myopia progression slowed down more with +1.5 D add PA-PALs than the group with higher RPR (the treatment effect was significant only in the former subgroup). It could be argued that these lenses had sufficient aspherization to compensate for the peripheral hyperopic defocus only in children with lower RPR. This

**TABLE 7.** Results of Questionnaire Survey Comparing Usability of the Worn Spectacles ( $n = 77$ )

Group	SVLs	PA-PALs +1.0 D Add	PA-PALs +1.5 D Add
Q1 general impression	4.43 (5)	4.55 (4.5)	4.50 (5)
Q2 image clarity at near	4.17 (4)	4.05 (4)	4.45 (5)
Q3 image clarity at intermediate distance	4.17 (4)	4.32 (5)	4.35 (5)
Q4 image clarity at distance	4.35 (4)	4.14 (5)	4.45 (5)
Q5 difficulty in walking or sports activity	4.13 (4)	4.23 (5)	4.30 (4.5)
Q6 adaptability	3.78 (4)	3.82 (4)	3.80 (4)
Q7 distortion in lateral gaze	3.74 (4)	3.64 (3)	4.10 (4)

The children responded to questions 1 to 7 on a scale of 1 (very bad) to 5 (very good), and the average (median) scores are shown. Mann-Whitney  $U$  test indicated that, in all of the questions, the responses were not significantly different between groups: +1.0 D add PA-PALs versus SVLs, or +1.5 D add PA-PALs versus SVLs.

result may point to the need for individually customized correction of the peripheral vision for the lenses to be more effective; however, to our knowledge, such studies have yet to be carried out.

The results for +1.0 D add PA-PALs appeared to be different. These lenses were effective only for children with no parental myopia. In addition, the treatment effect did not show clear signs of saturation after the first 12 months of wear, differently from +1.5 D add PA-PALs. The treatment effect of 0.37 D for 2 years would be clinically significant, assuming 0.5 D retardation during 3 years as the threshold for clinical significance, if a similar rate of retardation of progression continued in the third year. It is possible that the +1.00 D addition had the closest optimal addition power for oculomotor balance in the absence of horizontal prism in the near zone, as Cheng et al.<sup>43</sup> have argued for the +1.125 D addition, and thus provided better oculomotor balance for the wearer. However, the positive effect of the +1.0 D add PA-PALs observed in this subgroup is only suggestive and would require a confirmation trial targeted at such children.

Why was the treatment effect of PA-PALs limited? First, PA-PALs are effective in theory while the eyes are in the primary or downward eye position. When the eyes are located in eccentric positions, lens aspherization affects the central and peripheral refraction in various ways. However, studies about human eye-head coordination<sup>45,46</sup> suggest that eccentric eye positions are usually transient: when changing fixation from a visual target at the front to an eccentrically placed target, gaze is initially displaced by a saccade movement only. After a delay of 50 ms, head movement starts, and the eye simultaneously counter-rotates in the orbit to maintain the gaze direction by the action of the vestibular-ocular reflex. Hence, the eyes come close to the primary eye position usually in 500 ms, even though the eye does not always adopt this position under steady-state conditions. The comparison of the children's responses to Qs 2 to 4 (image clarity) and Q7 (image distortion in lateral gaze) found no difference between PA-PAL and SVL groups. These results indicate that children wearing PA-PALs do not experience image blur in daily life and indirectly support the validity of the above-mentioned assumption.

Secondly, the aspherization imposed on PALs would increase astigmatism in the peripheral retina. As shown in Figure 5, the eye's optical system suffers from off-axis astigmatism peripherally with the tangential image surface lying anterior to the sagittal image surface. Unfortunately, this is in the same direction as the optical image of PA-PALs, as well as RRG design lens, which means that these lenses reduce the hyperopic defocus at the expense of an increase of astigmatism. An experiment with monkeys has reported that form-deprivation myopia is a graded phenomenon and can be triggered by a modest degree of chronic image degradation.<sup>47</sup> We do not know how off-axis astigmatism is involved in the visual regulation of axial length mechanism,<sup>48</sup> but PA-PALs may produce mild form-deprivation myopia contrary to our original expectations. Another drawback with PA-PALs may be that, when looking through the near zone during near work, the peripheral retina may be exposed to a hyperopic shift due to the add power falling down laterally away from the center of the near zone.

Finally, ray-tracing simulation for a static eye (Fig. 3) shows that PA-PALs provide +0.50 D of relative plus power at best for a field angle of 40°. Our autorefractor was only able to measure peripheral refraction to 30°. It is known that peripheral refraction of myopes still tends to be relatively hyperopic beyond the 40° field angle,<sup>49</sup> and this is where the PA-PALs attempt to compensate for it. On the other hand, Queirós et al.<sup>50</sup> have reported that overnight orthokeratology produces a myopic shift of SER starting from around a 15° field angle

corresponding to the value of +0.50 D from the center. Orthokeratology lenses are reported to produce a more robust treatment effect in slowing axial elongation.<sup>51,52</sup> The different eccentricity of the optical effect between PA-PALs and orthokeratology lenses may explain the difference in the result.

For the secondary outcome measures, or the axial length of the eye, the linear mixed model has interaction terms that were significant: between parental myopia and age, parental myopia and baseline SER, as well as RPR, but only for the +1.0 D add PA-PAL (Table 3). In this model, the adjusted 2-year axial elongation in the +1.5 D add PA-PAL group was smaller than that in the control SVL group by 0.082 mm, although the difference was not significant at the 5% level ( $P = 0.074$ ). The difference was approximately 30% smaller than expected from the treatment effect found in SER (0.119 mm, when converting this with the myopia progression/axial elongation ratio of 2.27 D/mm found in the control group). The discrepancy in treatment effects was also depicted by the different regression lines among the study groups in Figure 7. Since the children in our trial are too old to experience any further significant corneal flattening,<sup>53</sup> it is possible that factors related to the amount of power the crystalline lens provides to the eye are affected by the continuous wearing of PA-PALs. The cessation of crystalline lens thinning may play a role in the onset of juvenile myopia.<sup>54,55</sup> For example, Zadnik et al.<sup>56</sup> have noted that the lens thinning stops around the age of 10 in children with a wide range of refractive errors. Our age-based analysis is consistent with this hypothesis because it indicates that only children in the younger age group (6–9 years at baseline) showed a significant treatment effect.

Compliance in wearing PA-PALs was good. The parents reported at every scheduled visit that the children had worn the study spectacles for most of their waking hours. The trial protocol warranted exchange of spectacle types from PA-PALs to SVLs if a child reported difficulty in the use of these spectacles, but we did not see such a case. In the responses of the children to Q1 (general impression), PA-PALs and SVLs had equally high average scores (4.43–4.55). Similarly to the case of conventional PALs,<sup>57,58</sup> the children seemed to use PA-PALs comfortably in the follow-up period, except for the early adaptation stage, which is demonstrated by the slightly low average scores (3.82 and 3.80 for +1.0 and +1.5 D add PA-PALs, respectively) in Q6 (adaptability).

In conclusion, the myopia-retarding effect of PA-PALs with +1.5 D addition after 2 years was statistically significant, but was similar to that found in earlier studies with conventional PALs having the same addition power. It appears that the high positive aspherization of the distance zone imposed on PALs does not markedly enhance their therapeutic efficacy in slowing myopia progression. However, the aspherization was not sufficient to correct the hyperopic defocus across a large area of peripheral retina in most myopic children, and thus we cannot rule out peripheral defocus as a driver for myopia progression and correction of it as a potentially viable method to slow the progression of myopia.

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