One-Year Multicenter, Double-Masked, Placebo-Controlled, Parallel Safety and Efficacy Study of 2% Pirenzepine Ophthalmic Gel in Children with Myopia

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Objective: To evaluate the safety and efficacy of the relatively selective M_1-antagonist, pirenzepine ophthalmic gel (gel), in slowing the progression of myopia in school-aged children.

Design: Parallel-group, placebo-controlled, randomized, double-masked study.

Participants: Three hundred fifty-three healthy children, 6 to 12 years old, with a spherical equivalent (SE) of −0.75 to −4.00 diopters (D) and astigmatism of ≤1.00 D. Subjects underwent a baseline complete eye examination, and regular examinations over a 1-year period. The study was conducted at 7 academic centers and clinical practices in Asia.

Intervention: Subjects received 2% gel twice daily (gel/gel), 2% gel daily (evening, placebo/gel), or vehicle twice daily (placebo/placebo) in a 2:2:1 ratio, respectively, for 1 year.

Main Outcome Measure: Spherical equivalent under cycloplegic refraction.

Results: At study entry, mean SE refraction was −2.4±0.9 D. At 12 months, there was a mean increase in myopia of 0.47 D, 0.70 D, and 0.84 D in the gel/gel, placebo/gel, and placebo/placebo groups, respectively ($P<0.001$ for gel/gel vs. placebo/placebo). Discontinued from the study for adverse events were 11% (31/282) of pirenzepine-treated subjects. Of the 15 serious adverse events reported in 12 subjects (all in the active groups), none was ophthalmic in nature, all subjects recovered, and only 1 (abdominal colic preceded by a flu) was judged possibly related to treatment.

Conclusions: Gel (2% twice daily) was effective and relatively safe in slowing the progression of myopia over a 1-year treatment period. *Ophthalmology 2005;112:84–91 © 2005 by the American Academy of Ophthalmology.*

Myopia, one of the most common ocular disorders in the world, is a significant global public health concern. Grouped under the term *uncorrected refractive error,* together with cataract, macular degeneration, infectious disease, and vitamin A deficiency, it is among the leading causes of blindness and visual impairment in the world.[1] In Asia, prevalence rates of myopia are highest, and are rising rapidly.[2–4] In Singapore, Taiwan, and Hong Kong, the prevalence rate of myopia in young adults ranges from 60% to 80%, as compared with prevalence rates of 20% to 50% in older adults in Europe and the United States.[4–8]

Refractive surgery, spectacles, and contact lenses can eliminate the refractive condition of myopia. However, they do not treat the underlying pathophysiological condition, essentially one of abnormal scleral elongation, and, thus, do not decrease the risk of developing the sight-threatening complications of retinal detachment (RD), macular degeneration, and glaucoma associated with high myopia.[9,10]

Originally received: February 11, 2004.
Accepted: June 28, 2004. Manuscript no. 240108.

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Presented in part as a poster at: Association of Research in Vision and Ophthalmology meeting, May 2003; Fort Lauderdale, Florida, and American Academy of Pediatric Ophthalmology and Strabismus meeting, March, 2004; Washington, DC.

The study reported here was supported by Valley Forge Pharmaceuticals, Inc., the developers of Pirenzepine Ophthalmic Gel, and Novartis Ophthalmics AG, its licensee. Ms Edmondson and Ms Buteyn were employees of Valley Forge Pharmaceuticals, Inc. at the time this study was conducted. Drs Novack and Crockett are consultants to Valley Forge Pharmaceuticals, Inc. The clinical investigators were contractors to Valley Forge Pharmaceuticals, Inc. for this clinical study. Neither are stockholders, nor have any other investigators received consulting fees from Valley Forge Pharmaceuticals, Inc.

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ISSN 0161-6420/05/$–see front matter
doi:10.1016/j.ophtha.2004.06.038

Thus, the scientific community has sought a treatment to slow or even to arrest the development of myopia in children. Several recent controlled clinical trials have provided evidence that atropine, a classic muscarinic antagonist equipotent in binding to M_3 (accommodation and mydriasis) and M_1 muscarinic receptors (putative myopia), can retard myopia progression in children.[11–13] Based upon animal studies using muscarinic antagonists of varying selectivity, and the nicotinic rather than muscarinic nature of avian accommodative muscles, the efficacy of atropine seems to occur independent of its effect on accommodation.[14–18] This is consistent with studies on dopaminergic agonists, which do not alter accommodation.[19–21]

Pirenzepine is a relatively selective M_1 muscarinic receptor antagonist,[22,23] and thus less likely than atropine to cause mydriasis and cycloplegia. Pirenzepine reduced the development of deprivation-induced myopia and axial elongation in animals relative to vehicle-treated controls.[14,24–26] It has long been used orally in Europe to treat dyspepsia and pediatric endocrine disorders as well, and has an extensive clinical history and excellent safety profile.[27] Based upon previous phase I trials of the safety and tolerability of up to 2% pirenzepine solution in adults (Invest Ophthalmol Vis Sci 39:S279, 1998) and pirenzepine ophthalmic gel in children,[28] we undertook a double-masked, multicenter, placebo-controlled phase II trial to evaluate the safety and efficacy of 2% pirenzepine ophthalmic gel (gel) twice daily and once daily in slowing the progression of myopia in school-aged Asian children.

Materials and Methods

Study Design

This was a parallel-group, placebo-controlled, double-masked study conducted from November 2000 to July 2002 at 7 Asian sites in Singapore, Hong Kong, and Thailand (academic centers and clinical practices; see "Appendix"). Children were randomized in a 2:2:1 ratio to receive 2% gel twice daily (gel/gel), 2% gel daily (placebo/gel; nightly, with vehicle gel in the morning), or a placebo control (vehicle; placebo/placebo), respectively, for 1 year.

Pharmacologic Agents

Gel 2% was formulated with hydroxypropyl methylcellulose and preserved with 0.005% benzalkonium chloride. Gel and the placebo were packaged in identical tubes, whose identities were masked from the children, parents, and investigators. The masking was maintained through the use of a morning tube (yellow label, gel for the gel/gel group and the placebo for the placebo/gel and placebo/placebo groups) and an evening tube (blue label, gel for the gel/gel and placebo/gel groups and the placebo for the placebo/placebo group). Study medications were administered twice daily as about a 6-mm strip in the cul-de-sac of the lower eyelid. Approximately 6 months after the study started, an electronic compliance monitoring device (MEMS SmartCap system, Aardex, Union City, CA) was introduced into the trial at the 2 largest sites. The study medication was placed in an outer standard medication bottle. To access the medication, the SmartCap had to be removed, and the tube of medication removed and used. The device recorded and stored each bottle opening. SmartCap data were retrieved during the subject's regularly scheduled visit.

Subjects

Eligible subjects were healthy children, 6 to 12 years old, with myopia, defined as a spherical equivalent of -0.75 to -4.00 diopters (D), and astigmatism of ≤ 1.00 D in each eye as measured by cycloplegic autorefraction. Additional requirements were round pupils, reactive to light, and best-corrected visual acuity (BCVA) of $\geq$20/25 in each eye by the Early Treatment Diabetic Retinopathy Study (ETDRS) chart.[29] Exclusion criteria were anisometropia of >1.00 D in spherical equivalent (SE); strabismus; current use of either contact lenses or bifocals; and a history of ocular surgery, trauma, or chronic ocular disease (including allergic conjunctivitis), or previous use of atropine for retarding myopia progression. Systemic criteria for exclusion from the study were diseases requiring chronic or regular intermittent medication (e.g., asthma, epilepsy); behavioral or neurological disorders that would interfere with the study; participation in any study involving an investigational drug within the month before enrollment; intolerance or hypersensitivity to topical anesthetics, mydriatics, or components of the formulation (e.g., benzalkonium chloride), or contraindications to antimuscarinic agents; and pregnancy or planned pregnancy. Transient pharmacologic therapy for acute diseases was allowed (e.g., otitis media, pharyngitis).

The protocol, informed consent, and child assent forms were approved by the respective institutional review boards. A parent or guardian of each study subject gave written informed consent, and the subject provided written assent.

Study Procedures

Height and weight were recorded, and a baseline predrug symptom query for symptoms existing before study drug instillation was administered. Monocular and binocular BCVAs were measured at distance and near using the ETDRS charts. Monocular BCVA was measured at distance, followed by testing of binocular BCVA at near. Testing was conducted using the ETDRS charts and an ETDRS testing procedure[30] modified for use in children. For both distance and near, the procedure was modified to start at the 20/50 line of the chart. The child was asked to read all 5 letters on each line of the chart. Testing was stopped when the child missed 3 letters on a line. Visual acuity (VA) was scored as the smallest line of letters on which the child identified 3 letters correctly. For distance acuity testing, if a child missed any letters on the 20/50 line, the child was asked to read the 20/100 line and all letters on subsequent lines until the child missed 3 letters on a line. The logarithm of the minimum angle of resolution value of the last line where the subject missed $\geq$3 letters and the number of letters correctly identified on that line were recorded.

A comprehensive eye examination, including measurement of intraocular pressure (IOP), was performed to identify conditions that fell within the exclusion criteria. Autorefraction was performed 30 to 60 minutes after instillation of 0.5% proparacaine, 1.0% cyclopentolate, and 1.0% tropicamide in each eye with 1 minute of eyelid closure. Autorefractors used were the Canon RK-5 (Canon Inc. Ltd., Tochigiken, Japan) (Singapore Eye Research Institute site); the Nikon (Tokyo, Japan) Retinomax K-Plus and Topcon (Tokyo, Japan) KR-7100 (Hong Kong site); and the Nikon NRK-8000, Topcon KR-7000, Topcon RM-A6000, Topcon KR-8100, or Humphrey 599 (Zeiss, Dublin, CA) (other sites). For each patient, the same autorefractor was used at all visits. For each eye, 5 scans were taken at each visit, and the resulting SE values were averaged. The autorefraction was performed by a nurse or technician. A-scan ultrasonography was used to measure axial length via the standard fashion of each site. We considered objectively measuring accommodation at all visits but did not, so as not to increase the respondent burden excessively. All qualified sub-

Table 1. Demographics

	Gel/Gel	Placebo/Gel	Placebo/Placebo	Total
n	142	140	71	353
Age (yrs)				
Mean ± SD	8.6±1.6	8.8±1.6	8.6±1.6	8.7±1.6
Range	6–12	6–13	6–12	6–13
Gender [n (%)]				
Female	67 (47.2)	75 (53.6)	34 (47.9)	176 (49.9)
Male	75 (52.8)	65 (46.4)	37 (52.1)	177 (50.1)
Race [n (%)]				
Asian	142 (100)	138 (98.6)	71 (100)	351 (99.4)
Other	—	2 (1.4)	—	2 (0.6)
Iris color [n (%)]				
Brown	139 (97.9)	135 (96.4)	68 (95.8)	342 (96.9)
Dark hazel	2 (1.4)	4 (2.9)	2 (2.8)	8 (2.3)
Dark gray	—	1 (0.7)	—	1 (0.3)
Other	1 (0.7)	—	1 (1.4)	2 (0.6)

SD = standard deviation.
One child was 12 yrs old at the screening visit but, at the first dosing visit, had reached 13.

jects and their parents were instructed on proper instillation of the study medication by clinical staff using a tube of placebo gel. They were then provided with a tube of the open-label placebo gel to take home to practice instillation, and returned within 48 hours.

At this baseline visit, eligible subjects were randomized to either active (gel/gel or placebo/gel) or placebo (placebo/placebo) treatment using a sponsor-prepared computer-generated randomization list stratified by study site (PROC PLAN, SAS[31]). Study medication was administered by study personnel, and 10 and 60 minutes later, a symptom query was given and vital signs were measured. At 60 minutes, pupil size was recorded and slit-lamp biomicroscopy performed. Subsequent visits were scheduled at 15 days and months 1, 3, 6, 9, and 12. At each visit, a symptom query was administered and VA, pupil size, and anterior segment were evaluated. Intraocular pressure, heart rate, and blood pressure were measured. At months 3, 6, and 12, cycloplegic autorefraction and A-scan ultrasonography were performed. Autorefraction was also performed at month 9. At each visit, subjects were asked "How have you been feeling lately?" and "How have your eyes been lately?"

Statistical Analysis

The primary outcome measure was SE. A priori, we assumed that with 116 subjects per active group and 58 in the placebo group (total sample size, 290), the study had at least 90% power to detect a difference between either of the 2 active treatment groups and placebo of approximately 0.40 D in myopia ($\alpha = 0.05$ over the set of comparisons, 2 tailed; standard deviation [SD], 0.7 D). In anticipation of the potential for patient dropout variations in protocol execution, we enrolled approximately 20% additional subjects. In this bilateral treatment study, continuous measures (e.g., sphere, pupil size) were averaged between eyes for analysis. Change from baseline refractive error and axial length was analyzed by generalized estimating equation methods in which baseline was the covariate, treatment group, site, and their interaction with treatment group and study site served as between-subject factors in the model, and the repeated measures (visits and right and left eyes) and their interaction with treatment group and study site served as within-subject factors. Nonsignificant interactions were dropped from the model used to estimate treatment effect. For descriptive statistic summary tables, the average of values for the two eyes was used as the unit of observation. Safety measures made on continuous scales were analyzed in a manner similar to the efficacy measures. A priori, the frequency of adverse events in the gel/gel group was compared with those of the placebo/gel and the placebo/placebo group using a conservative threshold of $P = 0.150$. The analysis of safety measures made on categorical or frequency scales was based on chi-square statistics. All analyses were performed using PC-SAS.[32] For project administrative purposes, there was a planned interim analysis conducted when 50% of subjects reached the primary end point (12 months). Although

Table 2. Patient Disposition

	Gel/Gel	Placebo/Gel	Placebo/Placebo	Total
Entered	142	140	71	353
Completed (12 mos)	117 (82.4%)	119 (85.0%)	62 (87.2%)	298 (84.4%)
Did not complete	25 (17.6%)	21 (15.0%)	9 (12.7%)	55 (15.6%)
Inadequate efficacy of treatment	—	—	1 (1.4%)	1 (0.3%)
Adverse event	20 (14.1%)	11 (7.9%)	—	31 (8.8%)
Discontinued	5 (3.5%)	10 (7.1%)	8 (11.3%)	23 (6.5%)
Patient lost to follow-up	1 (0.7%)	2 (1.4%)	3 (4.2%)	6 (1.7%)
Patient not adherent to study medication regimen	—	3 (2.1%)	2 (2.8%)	5 (1.4%)
Other	4 (2.8%)	5 (3.6%)	3 (4.2%)	12 (3.4%)

$P = 0.6269$ by chi-square (completers vs. noncompleters).

no action was taken in the present study, the criterion P value for statistical significance in the final analysis was adjusted to be 0.048, according to the O'Brien/Fleming method.[33] Before unmasking of the treatment codes, data were reviewed for any substantial variances from protocol. In light of the relatively small proportion of visits at variance, no separate per-protocol population was defined.

Results

Demographic and Prestudy Characteristics

Demographics and baseline characteristics of the 353 subjects enrolled are shown in Table 1.

Subjects

Of the 353 subjects enrolled, 298 (84%) completed the trial. No treatment code was unmasked for any subjects during the study. Of the 55 subjects (16%) not completing the trial, 1 (<1%) was dropped for inadequate efficacy (progression of myopia), 31 (9%) were dropped for adverse events, and 23 (7%) were discontinued for reasons unrelated to the study medication (Table 2). Most of the subjects who dropped for adverse events did so relatively late in the study. All 31 of the subjects who discontinued for adverse events were in the active treatment groups, 20 (14%) in the gel/gel group and 11 (8%) in the placebo/gel group. Of these subjects, most (22/31) were discontinued for signs of local intolerance (giant papillary conjunctivitis, allergy, hypersensitivity, or follicles), 3 for near vision problems, and 6 for other reasons (2, nonspecific body rash, and 1 each, headache, mild dyschromatopsia, possible bilateral posterior lens opacity, and bilateral redness). The subject with a possible opacity in the posterior capsule had a central nuclear opacity at screening, judged congenital, and stable VA. The posterior capsule observation was later judged to be an area of increased reflection, and no opacity was observed on retroillumination.

The one subject dropped for inadequate efficacy was in the placebo/placebo group. The difference in numbers of subjects not completing the study among treatment groups was not statistically significant ($P = 0.627$). Mean compliance (doses taken divided by prescribed doses for subjects reporting) by treatment group at the 2 largest sites was 83%, 89%, and 90% for the gel/gel, placebo/gel, and placebo/placebo groups, respectively.

Refractive Status

At study entry, mean SE was −2.4±0.9 D (mean ± SD) in each treatment group ($P = 0.816$). As shown in Figure 1 and Table 3, over the 1-year study, the mean SE became more negative (myopic) in all treatment groups. At 3, 6, 9, and 12 months, the mean increase in myopia was significantly less ($P<0.001$) in the gel/gel group than in the placebo/placebo group. A statistically significant treatment effect was also seen in the placebo/gel group relative to the placebo/placebo group at 3, 6, and 9 months ($P = 0.04$–0.003). At 12 months, there were mean increases in myopia of 0.47 D in the gel/gel group, 0.70 D in the placebo/gel group, and 0.84 D in the placebo/placebo group. In the gel/gel group, this difference from the placebo/placebo group of approximately 0.37 D (~44%), in favor of less myopic progression with pirenzepine treatment, was statistically significant ($P\leq0.001$). Over all treatment groups, subjects ≤10 years old at entry had a greater mean progression (−0.50 D) than those older than the median age of 10 years (−0.14 D). However, there was no statistical evidence of a treatment-by-age ($P = 0.160$) or gender effect ($P = 0.992$). As nearly all subjects were Asian, of Chinese extraction, race and iris color were not statistically evaluated. We considered statistical methods to impute missing values due to patients who discontinued the study. However, as the proportion of patients not completing was similar across treatment groups (13%–17%; Table 2), any correction would apply similarly to all treatment groups, and thus we did not conduct these analyses.

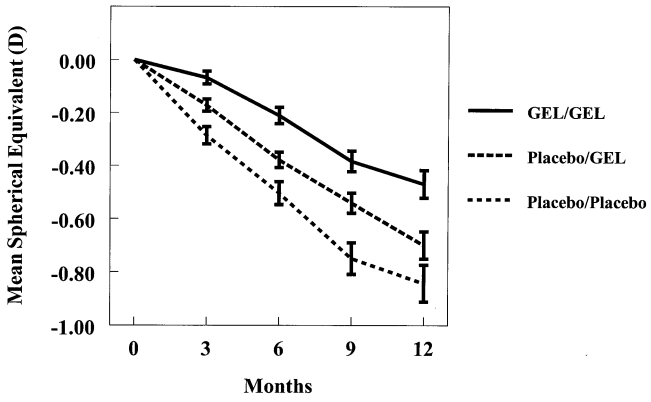

Figure 1. Cycloplegic autorefraction: mean spherical equivalent change from Baseline (D [diopter] ± standard error of the mean). Spherical equivalents at baseline were −2.35±0.86, −2.41±0.89, and −2.35±0.88, for the gel/gel, placebo/gel, and placebo/placebo groups, respectively. At 3, 6, 9, and 12 months, the mean increase in myopia was significantly lower ($P\leq0.001$) in the gel/gel group relative to the placebo/placebo group. Sample sizes were 142, 136, 134, 126, and 118; 140, 133, 128, 125, and 119; and 71, 70, 68, 64, and 62 at baseline, month 3, month 6, month 9, and month 12 for the gel/gel, placebo/gel, and placebo/placebo groups, respectively.

Using a categorical analysis with a bifurcation at ≥0.75 D of progression, after 6 months of treatment, proportions of subjects meeting this criterion were 5%, 13%, and 21% in the gel/gel, placebo/gel, and placebo/placebo groups, respectively ($P = 0.001$). At 12 months, proportions of subjects meeting this criterion were 29%, 41%, and 57%, respectively ($P = 0.005$; Fig 2).

Axial Length

At study entry, mean axial length was 24.2 mm in all treatment groups ($P = 0.986$). At 12 months, there was a mean increase in axial length, numerically greatest in the placebo/placebo, followed by the placebo/gel then gel/gel groups (0.33, 0.30, and 0.20 mm, respectively). In a repeated-measures analysis of variance, there was a statistically significant treatment effect ($P = 0.008$; Fig 3).

Safety

Adverse Events. Adverse events for all groups are listed in Table 4. In general, they were mild or moderate in severity. The most frequent treatment emergent adverse events in the gel/gel and placebo/gel groups were papillae/follicles (59% and 51%, respectively, compared with 14% in the placebo/placebo group), medication residue (52% and 54%, compared with 49% in the placebo/placebo group), abnormality of accommodation (44% and 21%, compared with 3% in the placebo/placebo group), increased cough (23% and 21%, compared with 23% in the placebo/placebo group), and respiratory infection (21% and 14%, compared with 18% in the placebo/placebo group). Events meeting the conservative threshold of $P = 0.150$ for gel/gel versus placebo/placebo were papillae/follicles, abnormality of accommodation, VA decreased (subjectively), and abdominal pain, all higher in the gel/gel group.

Table 3. Cycloplegic Autorefraction (Spherical Equivalent Diopters): Mean of Subjects' Eyes

Month	Treatment	n	Mean	SD	Minimum	Maximum
Baseline	Gel/gel	142	−2.35	0.86	−4.03	−0.75
	Placebo/gel	140	−2.41	0.89	−4.06	−0.75
	Placebo/placebo	71	−2.35	0.88	−4.01	−0.90
3	Gel/gel	136	−2.41	0.91	−4.41	−0.10
	Placebo/gel	133	−2.61	0.97	−4.64	−0.10
	Placebo/placebo	70	−2.65	0.93	−4.39	−0.93
6	Gel/gel	134	−2.55	0.92	−4.53	−0.61
	Placebo/gel	128	−2.82	0.99	−5.21	−1.00
	Placebo/placebo	68	−2.87	0.94	−5.16	−1.19
9	Gel/gel	126	−2.74	0.99	−4.91	−0.23
	Placebo/gel	125	−2.97	1.02	−5.53	−0.74
	Placebo/placebo	64	−3.19	0.96	−5.73	−1.08
12	Gel/gel	118	−2.82	1.02	−5.05	−0.55
	Placebo/gel	119	−3.13	1.10	−6.00	−0.70
	Placebo/placebo	62	−3.29	0.99	−5.55	−1.13

SD = standard deviation.

Eyes averaged within subject. One gel/gel subject whose treatment was interrupted periodically was determined by the investigator as not completing the study. However, there was a 12-mo observation of this patient. Thus, the sample size for the observation here was 118, whereas the number of patients completing was 117 (Table 2).

Events meeting the conservative threshold of $P = 0.150$ for placebo/gel versus placebo/placebo were papillae/follicles, abnormality of accommodation, ocular itching, VA decreased (subjectively), and rash—all higher in the placebo/gel group, except for ocular itching. Many of the ocular events were expected, as they were related to the pharmacology of the active drug. There were 15 serious adverse events reported in 12 subjects (all in the active groups). None of these events was ophthalmic in nature, all subjects recovered, and only one (abdominal colic preceded by a flu) was judged possibly related to treatment.

Ocular Signs. From a mean pupil diameter of 5.2 to 5.3 mm in each group at baseline ($P = 0.122$), either on the first dose or after 1 month of dosing, when measured 1 hour after dosing, there was a mydriatic effect in the groups receiving the active drug of approximately 1.0 to 1.5 mm relative to the group receiving the vehicle. Twelve hours after the last dose, there was a mydriatic effect of approximately 0.5 to 0.8 mm in the groups receiving the active drug relative to the group receiving the vehicle (Fig 4). Treatment was a statistically significant factor in postbaseline visits ($P<0.001$). When pairwise comparisons were performed, the gel/gel group statistically significantly differed from both the placebo/gel and placebo/placebo groups at each follow-up visit. The placebo/gel group statistically significantly differed from the placebo/placebo group at visits from month 3 onward.

For the most part, there were few reports of abnormal biomicroscopic observations that were not present at baseline. Consistent with the reported adverse events, there were reports of papillae/follicles and medication residue. Of the subjects with signs of conjunctival papillae and follicles, there were only a few reports of ocular symptoms of discomfort. Mean IOPs at baseline were 15.86±2.30, 15.53±2.29, and 15.61±2.33 mmHg for the gel/gel, placebo/gel, and placebo/placebo groups, respectively ($P = 0.400$). At follow-up visits, there was a mean decrease of up to .1 mmHg in each treatment group, with little apparent effect of treatment duration (1 day vs. 1 year), interval from instillation (0 or 60 minutes), or treatment group ($P = 0.289$). There were no

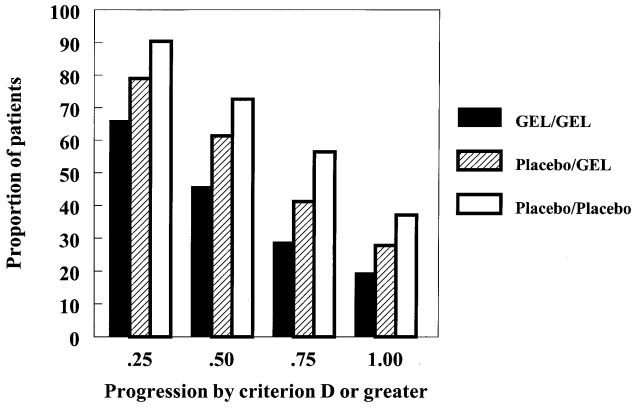

Figure 2. Cycloplegic autorefraction: categorical evaluation of spherical equivalent change from baseline (proportion of subjects with different levels of progression at 12 months). Calculated on the basis of the mean of subjects' eyes. Among-treatment *P* values were <0.001, <0.001, <0.001, and 0.03 for 0.25, 0.50, 0.75, and 1.00 diopters (D), respectively. Sample sizes were 118, 119, and 62 for the gel/gel, placebo/gel, and placebo/placebo groups, respectively.

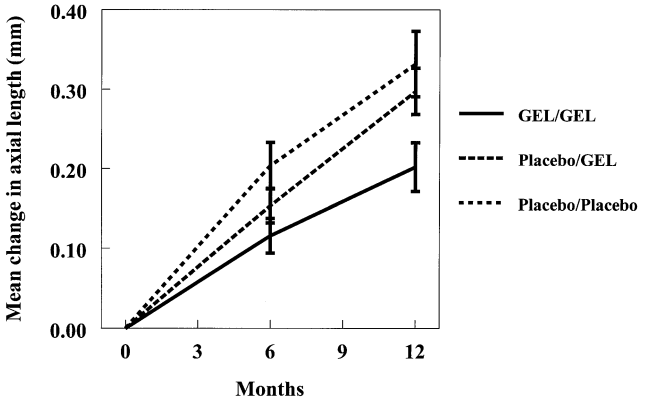

Figure 3. Ultrasound: mean axial length − mean change from baseline (mm). Means ± standard deviations at baseline were 24.17±0.75, 24.19±0.72, and 24.18±0.79 for the gel/gel, placebo/gel and placebo/placebo groups, respectively.

Table 4. Adverse Events: Treatment Emergent Adverse Events by Descending Incidence: Most Frequent (≥5% in Active Group)

	Gel/Gel (n = 142)				Placebo/Gel (n = 140)				Placebo/Placebo (n = 71)		
	No. with Event	*% of Patients*	*Total Events*	*P (vs. Placebo/Placebo)*	*No. with Event*	*% of Patients*	*Total Events*	*P (vs. Placebo/Placebo)*	*No. with Event*	*% of Patients*	*Total Events*
Ocular											
Papillae/follicles	83	58.5	104	<0.001*	72	51.4	86	<0.001*	10	14.1	11
Medication residue on eyelids or eye	74	52.1	75	0.772	75	53.6	75	0.564	35	49.3	36
Abnormality of accommodation†	63	44.4	75	<0.001*	31	22.1	32	<0.001*	2	2.8	2
Itching, eye	26	18.3	29	1.000	14	10.0	15	0.125*	13	18.3	14
Visual acuity decreased (subjectively)	24	16.9	24	<0.001*	20	14.3	20	0.003*	1	1.4	1
Injection	23	16.2	31	0.548	20	14.3	21	0.835	9	12.7	11
Fluorescein staining	18	12.7	18	1.000	21	15.0	22	0.835	9	12.7	9
Burn/sting, eye, on instillation	12	8.5	13	0.395	2	1.4	2	0.338	3	4.2	3
Conjunctivitis	8	5.6	9	0.502	9	6.4	10	0.341	2	2.8	2
Eye/vision, blurred	8	5.6	8	0.755	8	5.7	8	0.754	3	4.2	3
Corneal abnormality	6	4.2	6	0.429	7	5.0	9	0.272	1	1.4	1
Systemic											
Cough increased	33	23.2	45	1.000	30	21.4	50	0.861	16	22.5	21
Infection, respiratory, NOS	30	21.1	34	0.719	19	13.6	28	0.418	13	18.3	15
Rhinitis	27	19.0	34	0.332	18	12.9	25	1.000	9	12.7	17
Fever	16	11.3	23	0.819	21	15.0	25	0.392	7	9.9	9
Abdominal pain	12	8.5	13	0.065*	6	4.3	6	0.428	1	1.4	1
Headache	10	7.0	12	0.778	6	4.3	6	0.736	4	5.6	4
Diarrhea	8	5.6	9	0.277	1	0.7	1	1.000	1	1.4	2
Dizziness	8	5.6	9	0.277	0	0.0	0	0.336	1	1.4	1
Flu syndrome	7	4.9	7	1.000	7	5.0	8	1.000	4	5.6	4
Pharyngitis	6	4.2	7	1.000	9	6.4	9	0.755	3	4.2	4
Rash	5	3.5	5	0.666	10	7.1	10	0.104*	1	1.4	1

$P = H_o$: no association between gel/gel or placebo/gel compared with placebo/placebo, Fisher exact test. NOS = not otherwise specified.
*$P<0.150$.
†Used as a term to describe a number of patient responses, which included "blurred near vision," "decrease in near visual acuity," and "removal of specs for near work."

subjects with an increase in IOP of ≥10 mmHg, nor were there any adverse events of increased IOP.

Visual Acuity. At screening, mean monocular distance VA was 20/20 in each treatment group ($P = 0.404$). Mean changes from baseline in each treatment group were <0.05 (<0.5 line), with no statistically significant differences among treatments ($P = 0.140$; Fig 5). At screening, mean monocular near VA was 20/20 in all treatment groups ($P=0.884$). Mean ± SD changes at follow-up were <1 line in the active groups (0.008 ± 0.104 and -0.052 ± 0.067 in the gel/gel and placebo/gel groups, respectively) and low in the placebo/placebo group (-0.039 ± 0.059, $P<0.0001$; Fig 6).

Systemic Measures. During the study there were no differences of note between treatments in height, weight, heart rate, or blood pressure.

Discussion

In this large placebo-controlled study in children 6–12 years old, pirenzepine ophthalmic gel was more effective than the placebo gel in both the mean change in SE and proportion of subjects showing myopic progression. These clinical data are consistent with the efficacy observed in animal models.[14,24–26] Axial length measurements were consistent with treatment effect on refractive measurements but of limited magnitude, most likely due to the limit of resolution of the ultrasonography, which is approximately 100 μm.[34,35]

Only one serious adverse event possibly related to drug use occurred (abdominal pain). Mydriasis and cycloplegia, effects associated with a nonselective muscarinic antagonist, prompted withdrawal of treatment in only a few subjects in the active treatment groups (2/142 in the gel/gel group and 1/140 in the placebo/gel group). Conjunctival allergic reactions were more common in the pirenzepine-treated groups but, again, prompted withdrawal of treatment in only 8% (22/282) of children in these treatment groups. Papillae and follicles are commonly reported in children the age of our subject population.[36] As there was no a priori standardized system of grading these observations, the incidence during the study may represent an over-reporting in all groups. However, the incidence was greater in the active groups (59% [83/142] in the gel/gel group and 51% [72/140] in the placebo/gel group) than in the vehicle group (14% [10/71]). Medication residue was frequently observed

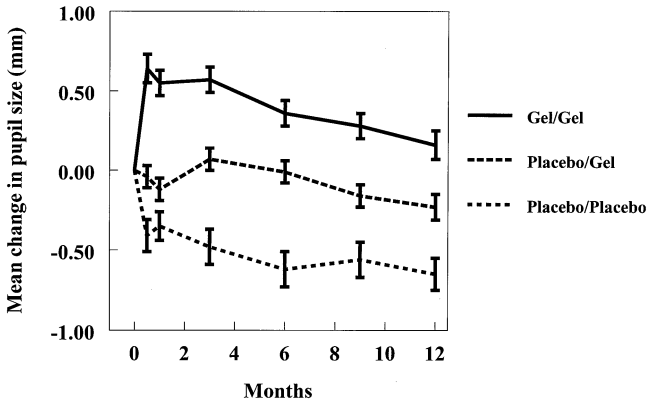

Figure 4. Pupil diameter: mean change from baseline (mm, ± standard error of the mean). Shown is mean pupil size at time 0 (approximately 12 hours after last instillation). $P<0.001$ for each active drug compared with placebo at all time points. Sample sizes were 142, 141, 140, 137, 133, 126, and 118; 140, 137, 134, 133, 128, 125, and 119; and 71, 71, 71, 70, 68, 64, and 61 at baseline, week 2, month 3, month 6, month 9, and month 12 for the gel/gel, placebo/gel, and placebo/placebo groups, respectively.

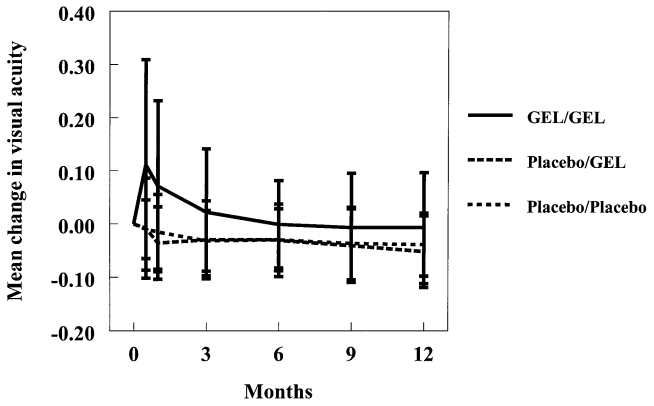

Figure 6. Near visual acuity: mean change from baseline (logarithm of the minimum angle of resolution [logMAR]). Means ± standard deviations at baseline were −0.006±0.066, −0.006±0.065, and −0.010±0.061 logMAR units for the gel/gel, placebo/gel, and placebo/placebo groups, respectively. Near vision was measured in both eyes. Hour 0.

by the investigators in this study, and also reported by subjects in the preceding study.[28] Although medication residue is probably not a clinically significant effect, it may be cosmetically unappealing. Nevertheless, this may be easily remedied by simply washing the lids and face around the eyes.

Myopia is an important ocular condition that is associated with increased risks for RD, peripheral retinal degenerations, and glaucoma. These increased risks are associated with all levels of myopia, but increase substantially with high levels of refractive error.[37,38] Additionally, the loss of visual function associated with increasing levels of myopia creates quality-of-life issues for patients. The increasing dependence on continuing refractive correction impacts patients' daily activities. In a study using a self-reported questionnaire in patients with refractive error (mean, −5.4±3.5 D; range, −18.4 to +3.8 D), patients with more refractive error had significantly lower (worse) quality of life scores.[39]

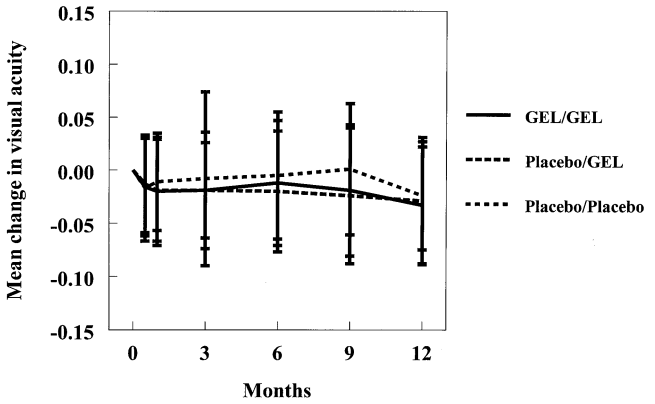

Figure 5. Distance visual acuity: mean change from baseline (logarithm of the minimum angle of resolution [LogMAR]). Means ± standard deviations at baseline were −0.001±0.059, −0.011±0.055, and −0.004±0.057 logMAR units for the gel/gel, placebo/gel, and placebo/placebo groups, respectively. The data from the two eyes were averaged so that there is one score per patient. Hour 0.

The magnitude of efficacy seen in the present study, approximately a 50% reduction (0.35 D) over the course of 12 months in this population, is of greater magnitude than that reported with the use of progressive additive lenses in a United States population.[40] Subjects in the present study were not allowed to wear bifocals. The M_3 muscarinic antagonistic ocular effects of atropine 0.1% to 0.5% (e.g., mydriasis and loss of accommodation) would be expected to be greater than that seen with pirenzepine ophthalmic gel 2% in the present study. The apparent ability of chronic pirenzepine treatment to delay the development of myopia without predominant M_3 muscarinic antagonism is supportive of a neural mechanism that may be based in the retina, rather than an accommodative basis for the development of pediatric myopia.

In conclusion, results of this study serve to establish the safety and efficacy of administration of pirenzepine ophthalmic gel to myopic children in slowing the progression of myopia over a 1-year treatment period.

Acknowledgments. The authors dedicate this study to the memory of Sek-Jin Chew, FRCS, PhD.

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