Safety and Efficacy of 2% Pirenzepine Ophthalmic Gel in Children With Myopia

A 1-Year, Multicenter, Double-Masked, Placebo-Controlled Parallel Study

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Objective: To evaluate the safety and efficacy of the relatively selective M₁ antagonist pirenzepine hydrochloride in slowing the progression of myopia in school-aged children.

Methods: This was a parallel-group, placebo-controlled, double-masked study in healthy children, aged 8 to 12 years, with a spherical equivalent of −0.75 to −4.00 diopters (D) and astigmatism of 1.00 D or less. Patients underwent a baseline complete eye examination and regular examinations during a 1-year period. The setting was 13 US academic clinics and private practices. Patients were randomized in a 2:1 ratio to receive 2% pirenzepine ophthalmic gel or a placebo control twice daily for 1 year.

Results: At study entry, the spherical equivalent was mean ± SD −2.098 ± 0.903 D for the pirenzepine group (n=117) and −1.933 ± 0.825 D for the placebo group (n=57, P= .22). At 1 year, there was a mean increase in myopia of 0.26 D in the pirenzepine group vs 0.53 D in the placebo group (P< .001). No patients in the placebo group and 13 (11%) of 117 patients in the pirenzepine group discontinued participation in the study because of adverse effects (5 [4%] of 117 due to excessive antimuscarinic effects).

Conclusions: Pirenzepine is effective and relatively safe in slowing the progression of myopia during a 1-year treatment period.

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Myopia, one of the most common ocular disorders in the world, is a significant global public health problem. It affects at least 25% of the adult population in the United States.¹⁻³ Myopia is among the 5 conditions that have been identified as immediate priorities by the World Health Organization in its Global Initiative for the Elimination of Avoidable Blindness.

Probably the most widely studied pharmacological treatment for myopia has been the use of atropine, a nonselective muscarinic antagonist. Several recent controlled clinical trials have provided evidence that atropine can retard myopia progression in children.⁵⁻⁷ Animal studies suggest that this retardation occurs independent of the effect of atropine on accommodation.⁸⁻¹² Pirenzepine hydrochloride, another muscarinic receptor antagonist, has long been used orally in Europe to treat dyspepsia and pediatric endocrine disorders and has an extensive clinical history and excellent safety profile.¹³ Unlike atropine, which is equipotent in binding to M₃ (accommodation and mydriasis) and M₁ muscarinic receptors, pirenzepine is relatively selective for the M₁ muscarinic receptor¹⁴,¹⁵ and thus less likely than atropine to cause mydriasis and cycloplegia. Since Stone et al¹² first suggested study of pirenzepine as an agent to decrease myopic progression, animal research has demonstrated that it reduced the development of deprivation-induced myopia and axial elongation in animals.¹⁶⁻¹⁸ Based on previous phase 1 trials of the safety and tolerability of pirenzepine solution in adults¹⁹ and pirenzepine ophthalmic gel in children,²⁰ we undertook a double-masked, multicenter, placebo-controlled phase 2 trial to evaluate the safety and efficacy of pirenzepine ophthalmic gel in slowing the progression of myopia in school-aged children. The maximally tolerated concentration in the previous study, 2% pirenzepine,²⁰ was selected for evaluation in the present study.
This was a parallel-group, placebo-controlled, double-masked study conducted from March 1, 2000, to February 28, 2002, at 13 US sites (academic clinics and private practices). Children were randomized in a 2:1 ratio to receive 2% pirenzepine twice daily or placebo control for 1 year. The 2:1 randomization schema was used to increase the chance of a patient being randomized to the active treatment arm, while maintaining sufficient power. A central coordinating center was located at Valley Forge Pharmaceuticals Inc (Irvine, Calif). Clinical research monitors for each site were provided via Clinical Studies Management Group, Tulsa, Okla.

PATIENTS

Eligible patients were healthy children, aged 8 to 12 years, with myopia, defined as a spherical equivalent (SEQ) of −0.75 to −4.00 diopters (D) and astigmatism of 1.00 D or less in each eye as measured by cycloplegic refraction. Also required were normal pupils and best-corrected visual acuity of 20/25 or better in each eye by Early Treatment Diabetic Retinopathy Study (ETDRS) charts.21 A modified ETDRS procedure was used to measure visual acuity monocularly at distance and binocularly at near. Starting with the 20/50 line (or 20/100 line when any letter was missed on the 20/50 line), the child read all 5 letters on each subsequent line until he/she missed 3 or more letters on a line. Visual acuity was scored as the logMAR score for the line plus 0.02 times the total number of letters missed on that line. Ocular exclusion criteria were anisometropia greater than 1.00 D in SEQ, any manifest tropia, current use of either contact lenses or bifocals, and a history of ocular surgery, trauma, or chronic ocular disease, including allergic conjunctivitis. Systemic criteria for exclusion from the study were diseases that required long-term or regular intermittent medication use (eg, asthma, epilepsy); behavioral or neurological disorders that would interfere with the study; participation in any study that involved an investigational drug within the month before enrollment; intolerance or hypersensitivity to topical anesthetics, mydriatics, or components of the formulation (eg, benzalkonium chloride); contraindications to antimuscarinic agents; and pregnancy or planned pregnancy. Transient pharmacologic therapy for acute diseases was allowed (eg, otitis media, pharyngitis).

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

PHARMACOLOGIC AGENTS

We formulated 2% pirenzepine with hydroxypropyl methylcellulose and preserved it with 0.003% benzalkonium chloride. Both pirenzepine and placebo (identical formulation except for the pirenzepine) were packaged in identical tubes, the identity of which was masked from the children, parents, and investigators. The product that contained active drug and the vehicle were identical in appearance. Study medications were administered twice daily as an approximately ⅛-in (6-mm) strip in the cul-de-sac of the lower eyelid. Approximately 9 months after study began, an electronic monitoring device (MEMS SmartCap system; Aardec, Union City, Calif) was introduced into the trial. The study medication was placed into an outer standard medication bottle. To access the medication, the SmartCap had to be removed. The device recorded and stored a bottle opening event (limit 1 per 15-minute period to reduce double counts). SmartCap data were retrieved during the patient’s regularly scheduled visit.

STUDY PROCEDURES

Height and weight were recorded, and a baseline, predrug symptom query for symptoms that existed before study drug instillation was administered. Monocular and binocular best-corrected visual acuity was measured at distance and near using the ETDRS charts. A comprehensive eye examination, including measurement of intraocular pressure, was performed to rule out any exclusion criteria. Autorefraction (Speedy 1; Nikon, Melville, NY) was performed 30 to 60 minutes after instillation of 0.3% proparacaine hydrochloride, 1.0% cyclopentolate hydrochloride, and 1.0% tropicamide in each eye with 1 minute of eyelid closure. A-scan ultrasonography was used to measure axial length via the standard fashion of each site. All qualified patients were provided with a demonstration by the clinical staff of how to properly instill the study medication using a tube of placebo gel. They were then provided with a tube of the placebo gel to take home to practice instillation to ensure that the child and parents were able to use the gel. The child then returned within 1 week for randomization.

Before randomization, individuals were queried regarding ability to administer the agent and any potential adverse effects. No child or parent reported any problems with administration or use of the vehicle gel. Eligible patients were randomized either to active or placebo treatment using a sponsor-prepared, computer-generated randomization list stratified by site (PROC PLAN; SAS version 8, SAS Institute Inc, Cary, NC). 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 biomicroscopy performed. Subsequent visits were scheduled at 15 days and 1, 3, 6, 9, and 12 months. At each visit, a symptom query was administered and visual acuity, pupil size, anterior segment evaluation, intraocular pressure, heart rate, and blood pressure were measured. At months 3, 6, and 12, cycloplegic autorefration and A-scan ultrasonography were performed. Autorefration was also performed at month 9.

STATISTICAL ANALYSIS

The primary outcome measure was SEQ. We assumed that the progression in the placebo group would be at least −0.3±0.3 D/y (Karla Zadnik, OD, PhD, Orinda Longitudinal Study of Myopia, National Institutes of Health, National Eye Institute, grant 10-EY08893, unpublished data, 1980-2000), with an arbitrary 30% difference between treatments in change from baseline in SEQ cycloplegic refraction. The study had 90% power to detect a mean difference between treatment groups of approximately 0.17 D in myopia (α=.05, 1-tailed, SD=0.3 D, t test), assuming 144 evaluable children at 1 year (96 pirenzepine patients and 48 placebo patients). The secondary outcome measure was axial length.

In this bilateral treatment study, continuous measures (eg, sphere, pupil size) were averaged between eyes for analysis. Change from baseline refractive error and axial length was analyzed by a mixed-model analysis of covariance with baseline as the covariate; treatment group, site, and their interaction as between-patient factors in the model; and the repeated measures (visits and right and left eyes) and their interaction with the between-patient factors as within-patient factors. Nonsignificant interactions were dropped from the model used to estimate treatment effect.
Safety measures made on continuous scales were analyzed in a manner similar to the efficacy measures. The analysis of safety measures made on categorical or frequency scales was based on $\chi^2$ statistics. All analyses were performed using PC-SAS (version 8.1; SAS Institute Inc.). A planned interim analysis was conducted when 50% of patients reached the primary end point (12 months). The null hypothesis of no treatment effect was tested with a $P$ value of .05 and not rejected. The criterion $P$ value for statistical significance in the final analysis was adjusted to .048 to maintain an experiment-wise type I error of less than .05.

### RESULTS

Demographics and baseline characteristics of the 174 patients enrolled are given in Table 1.

#### PATIENTS

We screened 277 patients and enrolled 174 patients, of which 145 completed the trial. Twenty-six (22%) of 117 patients randomized to pirenzepine did not complete the study compared with 3 (5%) of the 57 patients in the placebo group (Figure 1, $P = .005$). Thirteen of the 26 pirenzepine-treated patients stopped participation in the study due to an adverse event: allergic reaction or conjunctivitis, 7; accommodation or blurred vision at near, 5; and stinging, 1. Thirteen patients (11%) randomized to pirenzepine did not complete the study for reasons other than adverse events: noncompliance with medication, 3; lost to follow-up, 2; and other reasons, 8 (missed visits, withdrew consent, “didn’t like study medication,” moved, use of prohibited concomitant systemic medication, or personal reasons). Three patients (5%) randomized to placebo did not complete the study due to the following reasons: noncompliance with medication, 1; and other reasons, 2 (patient unable to accept ultrasound, patient “got tired of using the gel”). For 5 of the 29 patients, discontinuation occurred within the first few days due to either intolerance to the study medication or the study procedures. However, for the most part, discontinuation occurred after the patients were in the study for several months or more. When a compliance measurement was introduced partway through the study, the mean compliance ratio for each group was 79%. No patient’s treatment was unmasked early.

#### REFRACTIVE STATUS

At study entry, mean $\pm$ SD SEQ refraction was $-2.098 \pm 0.903$ D for the pirenzepine group and $-1.933 \pm 0.825$ D for the placebo group ($P = .22$). As shown in Figure 2, during the 1-year study, the mean SEQ refraction became more myopic in both treatment groups. At 3, 6, 9, and 12 months, the mean increase in myopia was significantly higher ($P \leq .006$) in the placebo group compared with the pirenzepine group (Table 2). At 12 months, there was a mean increase in myopia of 0.26 D in the pirenzepine group vs 0.53 D in the placebo group for treatment effect in favor of pirenzepine of 0.260 D ($P < .001$). There was no evidence for a difference among study sites (analysis of variance test for homogeneity across treatment by investigative site, $P = .52$ at baseline and $P = .95$ for change from baseline). Age, sex, iris color, and refraction at entry were not predictive of treatment difference. Additional methods were used to impute missing values due to patients who discontinued the study. In all 3 methods used (last observation carried forward, visit-to-visit extrapolation using median of respective treatment, and visit-to-visit extrapolation using median of pla-

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**Table 1. Demographics and Prestudy Characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Pirenzepine Hydrochloride</th>
<th>Placebo</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>117</td>
<td>57</td>
<td>174</td>
</tr>
<tr>
<td>Age, mean $\pm$ SD (range), y</td>
<td>9.9 ± 1.3 (8-12)</td>
<td>9.9 ± 1.4 (8-12)</td>
<td>9.9 ± 1.3 (8-12)</td>
</tr>
<tr>
<td>Sex, No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>66 (56)</td>
<td>37 (65)</td>
<td>103 (59)</td>
</tr>
<tr>
<td>Male</td>
<td>51 (44)</td>
<td>20 (35)</td>
<td>71 (41)</td>
</tr>
<tr>
<td>Race, No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>86 (74)</td>
<td>41 (72)</td>
<td>127 (73)</td>
</tr>
<tr>
<td>African American</td>
<td>7 (6)</td>
<td>5 (9)</td>
<td>12 (7)</td>
</tr>
<tr>
<td>Asian</td>
<td>4 (3)</td>
<td>3 (5)</td>
<td>7 (4)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>16 (14)</td>
<td>5 (9)</td>
<td>21 (12)</td>
</tr>
<tr>
<td>Other</td>
<td>4 (3)</td>
<td>3 (5)</td>
<td>7 (4)</td>
</tr>
<tr>
<td>Iris color, No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blue</td>
<td>33 (28)</td>
<td>15 (26)</td>
<td>48 (28)</td>
</tr>
<tr>
<td>Green</td>
<td>11 (9)</td>
<td>2 (4)</td>
<td>13 (8)</td>
</tr>
<tr>
<td>Light hazel</td>
<td>9 (8)</td>
<td>6 (10)</td>
<td>15 (9)</td>
</tr>
<tr>
<td>Brown</td>
<td>54 (46)</td>
<td>30 (53)</td>
<td>84 (48)</td>
</tr>
<tr>
<td>Dark hazel</td>
<td>9 (8)</td>
<td>4 (7)</td>
<td>13 (8)</td>
</tr>
<tr>
<td>Dark gray</td>
<td>1 (0.9)</td>
<td>0</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>SEQ, mean $\pm$ SD, diopters</td>
<td>$-2.10 \pm 0.90$</td>
<td>$-1.93 \pm 0.83$</td>
<td>$-2.04 \pm 0.88$</td>
</tr>
<tr>
<td>Axial length, mm</td>
<td>23.88 ± 0.69</td>
<td>23.77 ± 0.76</td>
<td>23.84 ± 0.71</td>
</tr>
<tr>
<td>Family history of myopia, No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative or unknown</td>
<td>29 (24)</td>
<td>17 (30)</td>
<td>46 (26)</td>
</tr>
<tr>
<td>Only father positive</td>
<td>18 (15)</td>
<td>7 (12)</td>
<td>25 (14)</td>
</tr>
<tr>
<td>Only mother positive</td>
<td>33 (28)</td>
<td>14 (25)</td>
<td>47 (27)</td>
</tr>
<tr>
<td>Both positive</td>
<td>37 (32)</td>
<td>19 (33)</td>
<td>54 (31)</td>
</tr>
<tr>
<td>SEQ of spectacles</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OD</td>
<td>$-2.05 \pm 0.90$</td>
<td>$-2.04 \pm 0.93$</td>
<td>$-2.05 \pm 0.91$</td>
</tr>
<tr>
<td>OS</td>
<td>$-2.04 \pm 0.93$</td>
<td>$-2.05 \pm 0.91$</td>
<td>$-2.04 \pm 0.92$</td>
</tr>
</tbody>
</table>

Abbreviation: SEQ, spherical equivalent.

**Figure 1.** Patient disposition.

174 Randomized to Treatment

117 Enrolled in Pirenzepine Hydrochloride Group

57 Enrolled in Placebo Group

26 Did Not Complete

13, Adverse Events

2, Lost to Follow-up

3, Nonadherence

8, Other

91 Completed Study

54 Completed Study

3 Did Not Complete

1, Nonadherence

2, Other


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cebo group), the treatment effect was similar to or greater than in the primary analysis method (0.262-0.343 D). This is not surprising for the first 2 methods, because they correct for the dropout of primarily pirenzepine-treated patients, who had, on average, lower rates of myopic progression.

The proportion of patients whose myopia progressed by at least 0.75 D was 4% (4/99) in the pirenzepine group and 20% (11/56) in the placebo group at 6 months ($P=.004$). At 1 year, the proportions were 11% (10/92) vs 31% (17/54), respectively ($P=.006$, Figure 3).

**AXIAL LENGTH**

At study entry, there was no significant difference in mean axial length between groups (Table 3, 23.88 mm vs 23.77 mm, $P=.41$). At 12 months, there was a mean increase in axial length of 0.19 mm in the pirenzepine group and 0.23 mm in the placebo group. This difference of approximately 0.04 mm, in favor of less myopic progression in the active treatment group, was not statistically significant ($P=.60$).
SAFETY

Adverse Events

Adverse events for both groups are provided in Table 4. In general, they were mild or moderate in severity. The 3 most frequent systemic events were headache, common cold, and flu syndrome. The 3 nonophthalmic adverse events that differed statistically at the conservative $P = .15$ cutoff level were common cold, rhinitis, and sinusitis, which were actually more frequent in the placebo treatment group. The 3 most frequent ocular events were mydriasis, erythema of the eyelids, and ocular itching. Six ophthalmic adverse events differed at the criterion $P$ value: (1) symptoms of decreased accommodation, (2) increase in papillae and follicles, (3) decreased visual acuity (primarily near), (4) mydriasis and (5) eye discomfort, which were more common in the pirenzepine group, and (6) medication residue on eyelids or eyelashes, which was more common in the placebo group. Most reports of blurred or decreased vision (primarily near) and other symptoms of accommodative abnormalities began during the first month of the study. There was 1 serious adverse event reported during the study; a patient in the pirenzepine group was thrown from a horse and hospitalized for surgical repair of a fractured right arm. During the study, no differences of note occurred between groups with respect to height, weight, heart rate, or blood pressure.

Ocular Signs

At study entry, the mean pupil diameter in room light was 5.0 mm in both treatment groups ($P = .62$). Sixty minutes after the first instillation, the mean mydriasis in pupil diameter was 1.5 mm in the pirenzepine group and 0.2 mm in the placebo group ($P < .005$, Figure 4). For the most part, there were few reports of abnormal biomicroscopic results that were not present at baseline. Mild conjunctival erythema was noted in 4 piren-
Pirenzepine patients and 1 patient randomized to placebo at 1 or more visits. Conjunctival edema was noted in 2 pirenzepine patients at 6 months, and the severity was mild and moderate; mild edema was noted in 1 pirenzepine patient at 9 months. No edema was reported in placebo patients.

Medication residue was similar in both treatment groups and was described as mild to moderate for both groups (45 [38%] of 117 pirenzepine patients and 30 [53%] of 57 placebo patients). Only one instance of severe conjunctival erythema was reported during the study; the observation occurred in a pirenzepine patient at 3 months. No abnormalities of the lens or posterior segment were noted at any time in any patient. Of the patients with objective conjunctival papillae and follicles, few reports of ocular symptoms of discomfort occurred (11 [9%] of 117 pirenzepine patients and 2 [4%] of 57 placebo patients). Of the patients found to have increased conjunctival follicles and papillae, 9 (19%) of 47 in the pirenzepine group and 2 (20%) of 10 in the placebo group experienced an increase of 2 grades or more. From a mean baseline intraocular pressure of 15 mm Hg, there was a mean decrease of up to 1 to 2 mm Hg in each eye for both treatment groups, with little apparent effect of treatment duration (1 day vs 1 year) or interval from instillation (0 or 60 minutes).

VISUAL ACUITY

At study entry, mean best-corrected distance visual acuity was approximately 0.01 logMAR (equivalent to approximately 20/20 Snellen) in both treatment groups. During the study, mean changes in distance visual acuity were much less than 1 line ETDRS, with mean acuity at 12 months similar to entry −0.03 ± 0.089 (pirenzepine) and −0.01 ± 0.118 (placebo). Near visual acuity was approximately 0.06 at entry in both groups, and mean changes were less than 1 line ETDRS. At each visit, the proportion of patients who reported loss of 3 or more lines in distance or near vision was 0% to 3% (all in the pirenzepine group).

Figure 4. Mean change from baseline in pupil diameter. Time shown is baseline or approximately 12 hours after last instillation. Error bars indicate standard error of the mean. P values are < .001, < .001, < .001, < .001, < .001, and .005 at week 2 and months 1, 3, 6, 9, and 12, respectively.

In this large, placebo-controlled study in children 8 to 12 years of age, pirenzepine was more effective than the placebo gel in retarding both the mean increase in SEQ and proportion of patients who showed myopic progression. These clinical data are consistent with the efficacy observed in animal models. No serious adverse events related to drug use occurred, and mydriasis and cycloplegia, as might be expected from a nonselective muscarinic antagonist, prompted withdrawal in only 5 (4%) of the 117 pirenzepine-treated patients. Conjunctival allergic reactions were more common in the pirenzepine group but again prompted withdrawal in only 7 (6%) of these 117 patients. Medication residue was frequently observed by the investigator and also reported by patients in the preceding study. Conjunctival follicles, observed in both study arms, occur with high frequency in this age group; it is possible that in many cases both the appearance of follicles and changes in grade are related to environmental and individual immune factors rather than to either the study drug or the vehicle. Mydriasis, although expected and consistent with the pharmacology of pirenzepine, was relatively small in magnitude (average dilation of 1.3 mm at 15 minutes after dosing and 0.5 mm at 12 hours after dosing). As demonstrated in a previous study, pupils in children treated with pirenzepine remain reactive to light, unlike what typically occurs with atropine. Therefore, patients in this study were not required to use photochromic spectacles and concern for lens and/or retinal phototoxicity was minimized.

Potential limitations of the study include lack of formal accommodation testing and phoria quantification in this protocol. However, accommodation was measured in the preceding study, and no individual with any manifest strabismus was permitted to enroll. There was a slight difference in baseline myopia between the pirenzepine and placebo groups. However, this difference was not statistically significant, but myopic progression between the 2 groups was. Additionally, the entry level of myopia was not predictive of degree of progression to a statistically significant level. Also, there was no difference in family history of myopia between the 2 groups. Thus, despite these limitations, we believe that the results of our study are applicable to the general population.

Although there is little doubt that preventing progression of myopia beyond 5 or 6 D decreases the risk of retinal detachment, peripheral retinal degenerations, and glaucoma, preventing even lesser degrees of myopia is also of great clinical significance. From a public health standpoint, the incidence of these myopic complications certainly increases with refractive errors between −1.00 and −5.00 D, although not as significantly as at higher refractive errors (eg, a patient with −2.00-D myopia has less risk of developing retinal detachment than a patient with −4.00-D myopia). Additionally, quality-of-life issues become important with increasing dependence on constant refractive correction with higher de-
addition lenses, this implicates a muscarinic, cholinergic pathway that does not involve M3 receptor activation and is supportive of a neural mechanism that may be based in the retina. A scleral-based mechanism, however, is also conceivable; cholinergic amacrine cells may be based in the retina. A scleral-based mechanism, however, is also conceivable; cholinergic amacrine cells may not be required for the progression of form-deprivation myopia in chicks, and muscarinic antagonists (in somewhat high concentrations) inhibit chick sceral chondrocytes. Alternatively, both retinal and scleral sites may play a role. Regardless of the site(s) of action, the results of this study and prior work with pirenzepine argue against an accommodative mechanism in the development of pediatric myopia and also serve to validate the use of form-deprivation myopia to study this entity.

In conclusion, results of this study serve to establish the safety and efficacy of administration of pirenzepine ophthalmic gel in myopic children in slowing the progression of myopia during a 1-year treatment period. We are continuing to treat and evaluate these patients, because 84 have elected to continue with a second year of controlled evaluation.

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Drees of myopia. A child with a refractive error of −1.00 D may do fine scholastically and athletically with only wearing glasses part time, but a patient with −2.00-D myopia needs correction all the time.

The magnitude of efficacy seen in the present study, approximately 50% reduction in progression or 0.3 D during 12 months in this US population, is of similar magnitude to that reported by atropine in an Asian population3 and greater than that reported by the use of progressive addition lenses.78 The M3 muscarinic antagonistic ocular effects of 0.1% to 0.5% atropine (eg, mydriasis and loss of accommodation) would be expected to be greater than that seen with 2% pirenzepine in the present study. Also, patients in the present study were not allowed to wear bifocals. The apparent ability of long-term pirenzepine treatment to retard the development of myopia without predominant M3 muscarinic antagonism is contrary to an accommodative basis for the development of pediatric myopia. Rather, like studies with dopaminergic agonists, the efficacy of muscarinic agents in chicks in which the intraocular muscles are nicotinic in nature, and the Correction of Myopia Evaluation Trial (COMET) using progressive addition lenses, this implicates a muscarinic, cholinergic pathway that does not involve M2 receptor activation and is supportive of a neural mechanism that may be based in the retina. A scleral-based mechanism, however, is also conceivable; cholinergic amacrine cells may
Ala (Dr Crockett); and PharmaLogic Development, Inc, San Rafael, Calif (Dr Novack).

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REFERENCES