# MYOPIA TREATMENT STUDY (MTS1)

# Low-Dose Atropine for Treatment of Myopia

**PROTOCOL**

**Protocol Identifying Number: MTS1**

**IND Sponsor: Jaeb Center for Health Research, Inc.**

**Version Number: v5.1**

**April 6, 2020**

## PROTOCOL AMENDMENT IV (24 Mar 2020)

This amendment provides for the following protocol changes:

**Protocol Change # 1**

Original Protocol
Office visits are conducted at 6, 12, and 18-months post-randomization.

Protocol Change
A virtual visit may be completed at 6, 12, or 18-months in the event that an in-person office visit cannot be completed by the participant. Data collected during a virtual visit are a subset of the data that are collected at an in-office visit (summarized in section 4.9) that can be collected by means of a phone call, or other smartphone or computer based video/audio method of communication such as teleconferencing.

Rationale for Change and Impact on Study Design
Due to the coronavirus (COVID-19) pandemic, participating clinical centers may be unable to see research participants for in-office study visits in the coming months. The protocol is being amended to allow for a virtual visit to be completed at 6, 12, or 18-months instead of an office visit. Given that these visits are prior to the 24-month primary outcome visit, the overall scientific integrity of the study is maintained.

Effect of Change on Informed Consent Form and Study Participants
No changes are needed to the current informed consent or assent forms. The data collected by virtual visit are a subset of the data that would be collected at an in-office visit already described in the consent form.

**Protocol Change # 2**

Original Protocol
Females who have experienced menarche will undergo a urine pregnancy test at each follow up visit after randomization. Study medication will be discontinued if the test result is positive.

Protocol Change
A pregnancy test will be performed at home if an office visit cannot be completed. Pregnancy testing is being omitted at the 30-month visit which occurs 6 months after study medication has been discontinued.

Rationale for Change and Impact on Study Design
Female participants who have experienced menarche must not be pregnant to continue on study medication. The protocol has been revised to require a pregnancy test to be performed at home instead of in the office if an in-person office visit cannot be completed by the participant.

Effect of Change on Informed Consent Form and Study Participants
No changes are needed to the current informed consent form as the form states that pregnancy tests are required at 6, 12, and 18-months for females who have experienced menarche.

## PROTOCOL AMENDMENT III (25 Feb 2019)

This amendment provides for the following protocol changes:

**Protocol Change #1**

Original Protocol

Potential participants with systemic diseases, the specified eye abnormalities, or the inability to perform study testing were not explicitly excluded from the study.

Protocol Change

The following items have been added as exclusion criteria in section 2.2.:

- Diseases known to affect accommodation, vergence, or ocular motility (e.g., multiple sclerosis, Grave's disease, myasthenia gravis, diabetes mellitus, Parkinson's disease)
- Existing ocular conditions (e.g., retinal disease, cataracts, ptosis) or systemic/neurodevelopmental conditions (e.g., Down syndrome) which may influence refractive development.
- Any condition that in the judgement of the investigator could potentially influence refractive development.
- Existing conditions that may affect the long-term health of the eye or require regular pharmacologic treatment that may adversely interact with study medication (e.g., JIA, glaucoma, diabetes mellitus, pre-diabetes).
- Inability to comprehend and/or perform any study-related clinical tests.

Rationale for Change

The reasons for excluding certain diseases and/or conditions are specified in the criteria to aid investigators in understanding the exclusions. The inability to comprehend and/or perform any study-related clinical tests by a potential participant would prevent the study from collecting necessary valid and complete data.

**Protocol Change #2**

Original Protocol

Section 4.1 includes the following two statements:

- A central pharmacy will *compound* the atropine and placebo eyedrops based on a participant-specific treatment group and will package them in identical single-use ampules to maintain masking.
- The atropine eyedrops will consist of 0.01% atropine. The placebo eyedrops will consist of 0.5% hydroxypropol methylcellulose and 1:10,000 benzalkonium chloride.

Protocol Change

A separate section 4.1 has been added to better describe Study Medication.

Nevakar is manufacturing the study drug (0.01% atropine) and placebo and packaging both in identical-appearing single-use ampules. In addition to 0.01% atropine, the ampules contain a buffer similar to artificial tears while the placebo contains just the buffer similar to artificial tears. The atropine and placebo ampules are sent to a central pharmacy, which will label and

package multiple atropine or placebo ampules into three month supply packages to maintain masking. The packages of ampules will be shipped to participating sites in insulated shipping boxes designed to maintain study drug at 59 to 77 degrees F during shipping. Participating sites will store study drug at room temperature (between 68 and 77 degrees F) prior to dispensing study medication packages to study participants. Additional study medication details are summarized within a separate investigational product manual.

Rationale for Change

The terms "compound" and "1:10,000 benzalkonium chloride" were inadvertent holdovers from a previous draft protocol that was written when the study was expected to use a compounding pharmacy to produce the atropine eyedrops. No compounding or preservative is needed for the study medication currently manufactured in single-use ampules (monitored by US FDA) which are shipped directly from the manufacturer.

**Protocol Change #3**

Original Protocol

Section 4.3 on phone calls stated that "Two weeks following randomization (±3 days), the site will contact parents *to confirm receipt of study medication* and question the parent as to whether the child is experiencing any issues with treatment."

Protocol Change

The phrase "to confirm receipt of study medication" has been omitted.

Rationale for Change

There is no need to confirm receipt of study medication on the 2-week phone call because study medication is handed directly to participants at their office visit at the time of randomization. The "*to confirm receipt of study medication"* wording was an inadvertent holdover from a previous draft protocol which was written when the study was expected to mail study medication to participants.

**Protocol Change #4**

Original Protocol

Although a negative urine pregnancy test is required for enrollment of any female who had reached menarche, no pregnancy testing was described during follow up.

Protocol Change

A pregnancy test is now required at every post-randomization follow up visit for females who have experienced menarche.

Rationale for Change

Pregnancy testing during post-randomization follow up (section 4.9) was felt necessary to enforce the existing requirement that study medication be discontinued in the event of pregnancy during the study.

**Protocol Change #5**

Original protocol

One inclusion criteria for randomization was interocular difference <= 0.1 logMAR (<= 5 letters by E-ETDRS testing).

Protocol change

This inclusion criteria has been changed to interocular difference <= 0.2 logMAR (<= 10 letters by E-ETDRS testing) in sections 1.11, 1.12, and 3.4.

Rationale for Change

The intent of the exclusion criteria for interocular difference was to exclude children with amblyopia; however, the previous interocular difference of 0.1 (5 letters) is within test-retest variability for E-ETDRS visual acuity testing. The criteria was expanded to allow enrollment of children with interocular differences up to 0.2 logMAR (10 letters), the threshold that is used to define amblyopia in several other PEDIG studies of intermittent exotropia.

## PROTOCOL AMENDMENT II (12 Jun 2018)

This amendment provides for the following protocol changes:

**Protocol Change #1**

Original Protocol

It was not an inclusion criterion that participants were required to have excellent compliance with spectacle correction either to be enrolled into the run-in phase or to be eligible for randomization. Participants who were not currently wearing refractive correction were eligible for the study and could have spectacle correction initiated during the run-in phase.

Protocol Change

Excellent compliance with refractive correction (76% to 100% of waking hours) for at least one month will be an eligibility criterion for enrollment into the run-in phase (sections 1.11, 1.12, and 2.2). Similarly, excellent compliance with refractive correction during the run-in phase will be encouraged and will be required to be eligible for randomization (sections 1.11, 1.12, 2.5, 2.6, 3.2, 3.3, and 3.4).

Rationale for Change

It is not known whether spectacle compliance could interact with the effect of atropine eyedrops, but limiting the study to children who are compliant with refractive correction will guard against the possibility of having lowered statistical power for analysis should such an interaction exist. It was also felt that children who are compliant with refractive spectacle correction might also be more likely to be compliant with nightly eyedrops for two years than children who are not compliant with refractive correction. It is acknowledged that the study results will be generalizable only to children who are compliant with refractive correction.

**Protocol Change #2**

Original Protocol

The original protocol indicated that "It is the investigators' opinion that the protocol's level of risk falls under DHHS 46.404, which is research not involving greater than minimal risk." (section 6.4.3)

Protocol Change

The revised protocol states that "The Jaeb Center Institutional Review Board has classified the protocol as research involving greater than minimal risk using the federal definition under 45 CFR 46.102i."

Rationale for Change

The protocol was assigned the risk level of "research involving greater than minimal risk" by the Jaeb Center for Health Research Institutional Review Board when it approved the protocol.

**Protocol Change #3**

Original Protocol

Mean corneal radius was one of the biometric parameters to be measured. Three summary measurements of axial length, mean corneal radius, anterior chamber depth and lens thickness were to be taken using an optical biometer (e.g. IOLMaster, LENSTAR).

Protocol Change

Flat corneal radius will be measured instead of mean corneal radius because that is what both optical biometers can measure. The first summary measurement of axial length, flat corneal radius, anterior chamber depth and lens thickness will be collected, with each value based on the individual instrument's method of taking and then averaging multiple measures.

Rationale for Change

For corneal curvature, the only common measurement and unit of measure for the two optical biometers being used is flat corneal radius and diopter. To avoid increasing the testing burden for participants, a single measurement was deemed sufficient for these four biometric parameters.

**In addition, the following minor corrections/clarifications have been made.**

- Typos were corrected in protocol change #1 in protocol amendment I and in section 7.4.2 to reflect that near visual acuity is measured binocularly, not in each eye.

- Clarification that the *average* spherical equivalent between eyes is used for the primary analysis of myopia progression (section 1.1)

- In section 3.4 concerning eligibility for randomization, clarified that participants who do not meet eligibility criteria will be withdrawn from the study *without being randomized*.

- Clarified in section 6.4.2 that it refers to the *24-month* primary outcome in the section pertaining to participants develops adverse effects serious enough to discontinue study medication.

- The enrollment visit has been added to the list of visits that are paid for by the study (section 5.4); it was originally omitted in error.

- In section 7.1.1 regarding the 24-month on-treatment primary analysis
  - Clarified that adjustment covariates are included to improve power for the treatment group comparison, as well as to account for potential residual confounding
    Clarified that baseline spherical equivalent refractive error (SER) will be included in the analysis model as an adjustment factor, while the change in SER at all follow-up visits up to and including the 24-month visit will be included in the longitudinal outcome vector. Further details, including handling of missing data, will be included in the separate Statistical Analysis Plan.

- Section 7.6 has been updated based on recent decision from the Data Safety and Monitoring Committee that evaluation of whether an interim monitoring is needed would be made after 6 months of recruitment and before any outcome data are reviewed.

- In Section 6.4.2, clarified that the reason for trying progressive lenses is to address adverse events related to near focusing problems.

- In the statistical analysis chapter, a few minor corrections have been made to the data for two previous studies (CLEERE and ATOM2) that are cited as background data for estimating sample size (sections 7.8.2. 7.8.3). Note that none of these minor changes affected the sample size calculation.

- In section 7.8.5, a few minor corrections have been made to the numbers in Table 2 on the expected width of confidence intervals on the treatment group comparisons of myopia progression in racial subgroups. None of these minor changes were substantive.

- In section 7.8.1, the purpose of the general considerations for sample size section was clarified. In addition, two sentences were omitted here as they were already covered elsewhere in section 7.8.

- In section 2.4, some details of the cycloplegic autorefraction and other biometry measurements have been omitted and moved to a separate manual of procedures.

## PROTOCOL AMENDMENT I (11 Dec 2017)

**This amendment provides for the following protocol change:**

**Protocol Change #1**

Original Protocol
Binocular near visual acuity will be assessed at the 6-month visit only. The analysis plan consisted of tabulating 6-month binocular near visual acuity by treatment group.

Protocol Change
Binocular near visual acuity will be assessed at both the Randomization visit and the 6-month visit (section 3.2). The analysis plan was changed to calculate the proportion of participants with loss of best corrected near vision >1 logMAR line at 6 months (sections 1.1, 1.12, and 7.4.2).

Rationale for Change
Binocular near visual acuity is an important outcome to assess the safety of low-dose atropine. In order to interpret any change in binocular near visual acuity between randomization to six months, a baseline measure is needed at the time of randomization.

**Protocol Change #2**

Original Protocol
The eye drop questionnaire will be completed at each follow up visit.

Protocol Change
The eye drop questionnaire will be completed at each follow up visit except the 30-month visit (sections 1.1.1, 1.12, 4.8, and 7.4.1).

Rationale for Change
The eye drop questionnaire is not relevant to the 30-month visit as eye drops are to be discontinued at the 24-month visit.

**Protocol Change #3**

Original Protocol
The criterion for a serious adverse event did not include a congenital anomaly/birth defect.

Protocol Change
The criterion for a serious adverse event now includes a congenital anomaly/birth defect (section 6.2).

Rationale for Change
Congenital anomalies and birth defects are part of the Food and Drug Administration definition of a serious adverse event.

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# LIST OF ABBREVIATIONS

| ABBREVIATION | DEFINITION |
|---|---|
| ANCOVA | Analysis of Covariance |
| ATOM | Atropine for the Treatment of Childhood Myopia Study |
| CFR | Code of Federal Regulations |
| CI | Confidence Interval |
| CLEERE | Collaborative Longitudinal Evaluation of Ethnicity and Refractive Error |
| CRF | Case Report Form |
| DSMC | Data Safety and Monitoring Committee |
| FDA | Food and Drug Administration |
| GCP | Good Clinical Practice |
| ICH | International Council for Harmonisation |
| IRB | Institutional Review Board |
| MCMC | Monte Carlo Markov Chain |
| PI | Principle Investigator |
| PEDIG | Pediatric Eye Disease Investigator Group |
| QA | Quality Assurance |
| QC | Quality Control |
| RBM | Risk Based Monitoring |
| SE | Spherical equivalent |
| SER | Spherical equivalent refractive error |
| SVL | Single vision lenses |

# Chapter 1: BACKGROUND AND SUMMARY

This study is being conducted by the Pediatric Eye Disease Investigator Group (PEDIG) and funded through a cooperative agreement from the National Eye Institute of the National Institutes of Health.

## 1.1 Epidemiology and Clinical Characteristics:

Myopia is one of the most commonly occurring ocular disorders, with an estimated prevalence of 13% to 49% in adult population-based studies.[1, 2] In children, the prevalence of myopia in population-based studies worldwide ranges from 1.2% to 59.1%,[1, 3, 4] with variations due to age and race and definition used to classify myopia. In the US, in children 6-72 months of age, prevalence has been reported at 0.7 -1.2% in Non-Hispanic white children,[5, 6] 3.98% in Asian children,[6] 5.5-6.6% in African American children[5, 7] and 3.7% in Hispanic children.[7] Not only is the prevalence of myopia in adults relatively high, but it is increasing in the US[8] (http://www.nei.nih.gov/eyedata/myopia.asp#4) and around the world.[9]

Progression of myopia primarily occurs due to elongation of the axial length of the eye. The average increase in myopia has been estimated at 0.5 diopters per year (personal communication with the Collaborative Longitudinal Evaluation of Ethnicity and Refractive Error (CLEERE) study group between November 2015 and April 2016).[10-12] Retarding progression of myopia has been the focus of much research, since high levels of myopia (>-6.00D) are associated with retinal and vitreous detachment, myopic macular degeneration, and increased risk of glaucoma and cataract.[13, 14] A recent report for the US Population estimated the prevalence of high myopia and myopic choroidal neovascularization to be 3.92% (95% confidence interval [CI], 2.82-5.60) and 0.017% (95% CI, 0.010-0.030), respectively, among adults in the United States aged 18 years and older in 2014.[15] This translated into a population burden of approximately 9 614 719 adults with high myopia, and 41 111 adults with myopic choroidal neovascularization.

## 1.2 Retardation of Myopia Progression:

Treatment to retard myopia progression is important for preventing the development of high myopia and associated sequelae. Various management approaches have been reported, with varying success, including the use of anti-muscarinic pharmacological agents (atropine, pirenzepine, cyclopentolate), bifocals, progressive additional lenses, contact lenses, contact lenses with peripheral myopic defocus, under-correction or part-time optical correction, and orthokeratology.[16,17] Some studies have found that an increase in the amount of time spent outdoors may have a protective effect on the progression of myopia.[18-20] In a recent Cochrane Systematic Review entitled Interventions to Slow Progression of Myopia in Children,[16] anti-muscarinic pharmacological treatments were found to be more effective than other treatments. Nevertheless, side-effects from mydriasis and cycloplegia with atropine 1% were significant. More conclusive evidence is needed regarding optimal dose (i.e., dose with meaningful treatment effect with minimal side-effects), lasting effects of treatment, and efficacy of anti-muscarinic pharmacological treatments combined with other treatment modalities, such as bifocals.[16]

## 1.3 Atropine Treatment:

Use of topical atropine for treatment of myopia has been advocated since the 1800s.[21] Summarizing a wealth of knowledge on atropine treatment for reduction of myopia progression,

1% atropine daily with or without multi-focal spectacles is most commonly used, resulting in an average reduction of myopia progression of 90%.[22] The mechanism by which atropine slows myopia progression is largely unknown, but has been hypothesized to occur via elimination of accommodation, local retinal effects that slow progression, or potential biochemical changes brought about through binding of atropine with the muscarinic receptors.[16] Another possible mechanism of slowing myopic progression with atropine may be via increased UVA exposure[23] as a result of a dilated pupil, which exposure has been shown to strengthen the sclera via crosslinking of scleral collagen,[24] potentially limiting axial lengthening. Although this last mechanism is somewhat speculative, the general impression from the literature is that, regardless of mechanism, 1% atropine appears to be very effective.

### 1.4 Previous Randomized Trials of Atropine Treatment to Reduce Myopia Progression:

Several randomized trials of prevention of myopia progression using atropine have been conducted in recent years.

- Yen and colleagues[25] in 1989 compared one year of 1% atropine every other night, 1% cyclopentolate every night, and normal saline every night in 96 children aged 6 to 14 years with myopia ranging from -0.50D to -4.00D. Children in the atropine group had a mean myopia progression over 1 year of -0.219D, whereas children receiving cyclopentolate progressed -0.578D and children receiving normal saline progressed -0.914D.
- In 1999, Shih and colleagues[26] reported a study of 200 children aged 6 to 13 years with myopia ranging from -0.50D to -6.75D that compared 0.5%, 0.25%, and 0.1% atropine to 5% tropicamide. Children received atropine or tropicamide eyedrops nightly for up to 2 years. At the end of 2 years, all atropine-treatment groups had less myopia progression (-0.04±0.63 D/year, -0.45±0.55D/year, and -0.47± 0.91D/year, respectively) than the tropicamide group (-1.06±0.61D/year).
- Subsequently, Shih and colleagues[27] studied the effect of multi-focal glasses with and without atropine to control progression of myopia. The study randomized 227 children to 18 months of 0.5% atropine + multifocal lenses, multi-focal lenses alone, or single vision glasses. Myopia progressed only -0.42D±0.07D with atropine + multi-focal lenses compared with -1.19D±0.07D with multi-focal lenses and -1.40D±0.09D with single vision lenses, leading the authors to conclude that atropine treatment is effective for slowing the progression of myopia and may act via a mechanism of accommodation inhibition.
- More recently, the Atropine for the Treatment of Childhood Myopia (ATOM) study was a RCT comparing nightly administration of 1% atropine to vehicle (0.5% hydroxypropyl methylcellulose and 1:10,000 benzalkonium chloride) over 2 years in 400 children ages 6 to 12 years with myopia ranging from -1.00D to -6.00D.[28] Only one eye of each child was chosen for treatment. After 2 years, myopia in children receiving 1% atropine had progressed -0.28D±0.92D versus -1.20D±0.69D in the placebo-treated eye (Figure 1). Axial length was also reduced in atropine-treated eyes compared with placebo-treated eyes (-0.02±0.35mm vs 0.38±0.38mm).
- The ATOM2 study[29] compared 3 doses of atropine (0.5%, 0.1% and 0.01%) in 400 children with myopia of at least -2.00D and found 2-year myopia progression of -0.30±0.60D, -0.38±60D, and -0.49±0.63D respectively (Figure 1). Although there was no control group, myopia progression was significantly lower than that observed in controls

in ATOM1 (-1.20D±0.69D), but was not different from the 1% atropine-treated cohort (-0.28D±0.92D). Axial length growth was lower in both 0.5% and 0.1% groups compared with the 0.01% group (0.27 ± 0.25mm, 0.28 ±0.27mm, and 0.41±0.32mm respectively, P<0.001).

The effect of treatment on myopia progression and axial length in these randomized trials is compiled in Table 1. Although there were good overall results with atropine treatment, a logistic regression analysis of ATOM1 data suggested that there is a subgroup of participants (younger participants with higher levels of myopia and trending towards progression) whose myopia progressed significantly despite atropine treatment.[30]

**Table 1: Summary of Randomized Trials Evaluating Effect of Atropine on Myopia Progression**

| Study | Ethni-city | Treatment Group ** | N | Time point | Change in Myopia (D) | Change in Axial Length (mm) | Comments |
|---|---|---|---|---|---|---|---|
| Yen[25] | Asian | Control (saline) | 32 | 1 yr | -0.914 ± 0.581 | not reported | Only about 40% (96/247) of randomized participants included in analysis. Excluded participants with less than 100% compliance. |
| | | Atropine 1%*** | 32 | 1 yr | -0.219 ± 0.538 | not reported | |
| | | Cyclopentolate 1% | 32 | 1 yr | -0.578 ± 0.490 | not reported | |
| Shih[26] | Asian | Atropine 0.5% | 41 | ≤2 yr | -0.04 ± 0.63 | not reported | Likely confounded by refractive correction as "suggested" bifocals in atropine 0.5%, under-correction in atropine 0.25, and full correction in atropine 0.1%. Outcomes by cycloplegic autorefraction. Length of treatment/follow-up not well defined. |
| | | Atropine 0.25% | 47 | ≤2 yr | -0.45 ± 0.55 | not reported | |
| | | Atropine 0.1% | 49 | ≤2 yr | -0.47 ± 0.91 | not reported | |
| | | Tropicamide | 49 | ≤2 yr | -1.06 ± 0.61 | not reported | |
| Shih[27] | Asian | Control (SVL)**** | 61 | 1.5 yr | -1.40 ± 0.09 | 0.59 ± 0.04 | Double blind randomization. |
| | | Multifocal lenses | 66 | 1.5 yr | -1.19 ± 0.07 | 0.49 ± 0.03 | |
| | | Atropine 0.5% + multifocal lenses | 61 | 1.5 yr | -0.42 ± 0.07 | 0.22 ± 0.03 | |
| ATOM[28] | Asian | Control | NR | 1 yr | -0.76 ± 0.44 | 0.20 ± 0.30 | Outcomes by masked cycloplegic autorefraction.<br>Number of participants analyzed at 1yr not specified but suspect similar to number analyzed at 2yrs. |
| | | | 190 | 2 yr | -1.20 ± 0.69 | 0.38 ± 0.38 | |
| | | Atropine 1% | NR | 1 yr | 0.03 ± 0.50 | -0.14 ± 0.28 | |
| | | | 166 | 2 yr | -0.28 ± 0.92 | -0.02 ±0.35 | |
| ATOM2[29] | Asian | Atropine 0.5% | NR | 1 yr | -0.17 ± 0.47 | 0.11 ± 0.17 | Outcomes by cycloplegic autorefraction, but no control group.<br>Number of participants analyzed at 1yr not specified but suspect similar to number analyzed at 2yrs. |
| | | | 139 | 2 yr | -0.30 ± 0.60 | 0.27 ± 0.25 | |
| | | Atropine 0.1% | NR | 1 yr | -0.31± 0.50 | 0.13 ± 0.18 | |
| | | | 141 | 2 yr | -0.38 ± 0.60 | 0.28 ± 0.27 | |
| | | Atropine 0.01% | NR | 1 yr | -0.43 ± 0.52 | 0.24 ± 0.19 | |
| | | | 75 | 2 yr | -0.49 ± 0.60 | 0.41 ± 0.32 | |
| ATOM2[31] | Asian | Atropine 0.01% | 17 | 5 yr | -2.25 ± 1.11 | 1.21 ± 0.54 | Children progressing more than 0.50 D during washout year three were started back on atropine 0.01% for two additional years. |
| | | Atropine 0.1% | 82 | 5 yr | -2.34 ± 1.07 | 1.08 ± 0.53 | |
| | | Atropine 0.5% | 93 | 5 yr | -2.32 ± 1.04 | 1.03 ± 0.47 | |

*N = number with outcome data. NR = not reported. **Daily treatment unless otherwise noted ***Treatment every other day. ****SVL = single vision lenses

**Figure 1: Summary of Findings from ATOM[28] and ATOM2[29] Studies***

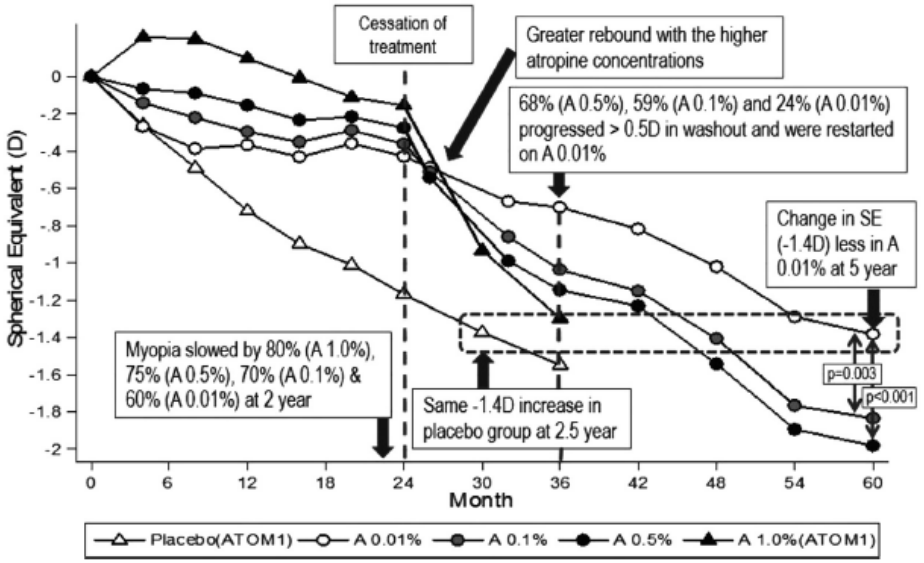



**Figure 6.** Summary of findings from the ATOM1 and ATOM2 studies: change in spherical equivalent (SE). ATOM = Atropine for the Treatment of Myopia; D = diopter.

*Figure reproduced from Chia et al, 2016.[31]

### 1.5 Persistence of Atropine Effect:

Following cessation of atropine treatment, there appears to be a rebound of myopia progression, although the rate of myopia progression differs between studies and depending on which dose of atropine was used. In a prospective long-term study, Brodstein and colleagues[32] followed 253 children treated with atropine for up to 9 years. They found a rebound in myopia progression, but the rate was no higher than observed in control participants. In a retrospective population-based study of atropine treatment for myopia, 214 children in Olmsted County, MN were followed for a mean of 11.7 years, along with age-matched controls. Final refraction data at age 20 years indicated that benefits of atropine treatment remain after atropine treatment was discontinued. Nevertheless, length of treatment and follow-up was not standardized in this retrospective study. In the ATOM1 study, children were followed off atropine treatment, and myopia progression was reported after 1 year.[33] A higher rate of myopia progression in atropine-treated eyes following cessation of atropine compared with control fellow eyes was reported (-1.14±0.80D vs -0.38±0.39D in 1 year) (Figure 1). However, overall myopia remained less severe in atropine-treated eyes at the end of 3 years. In the subsequent ATOM2 study,[34] 356 of the 400 children enrolled in ATOM2 were followed for an additional year after stopping atropine. Myopia progression off atropine was greatest following treatment with 0.5% atropine (-0.87±0.52D), with less progression off treatment with 0.1% (-0.68±0.45D) and 0.01% (-0.28±0.33D), leading to the conclusion that the effect of 0.01% atropine is more sustained following treatment than with higher doses (Figure 1). The 0.01% atropine was restarted in a subgroup that progressed more than 0.5 D in the washout year (year 3) for two additional years. The resumption of atropine 0.01% treatment showed a lower progression in the subgroup treated initially with atropine 0.01%, compared with higher doses in the first phase of the study (years one and two).[31]

### 1.6 Atropine and Race:

Early in the 1900's, differences in dilation response to mydriatic drugs (although not specifically atropine) were reported between different races, with African American and Asian participants requiring a longer time for mydriasis than White participants.[35] This phenomenon has become a common clinical experience and has been reproduced by the works of others.[36] Work by Salazar et al explored the mechanism by which this racial difference may occur, reporting that atropine is rapidly taken up by melanocytes and released over time, leading to a longer time required to achieve mydriasis and a prolonged mydriatic effect in heavily-pigmented eyes as atropine is released over an extended period of time.[37] In a meta-analysis of atropine for slowing progression of myopia, Li et al[38] report that atropine slows the progression of myopia more in Asian populations of children than it does for populations of white children, but note that comparisons are limited by the lack of studies in non-Asian populations. They conclude that further studies to determine ethnic differences in the effect of atropine for slowing the progression of myopia are needed.

### 1.7 Safety of Atropine Treatment:

Atropine use is associated with photophobia, mydriasis, accommodative paralysis, and allergic or hypersensitivity reactions. In an effort to reduce these side effects, Shih et al[26] used 3 lower doses of atropine than the commonly used 1% concentration (i.e., 0.5%, 0.25%, 0.1%), reporting that 0.25% and 0.1% atropine were well-tolerated throughout their 2-year study (no systemic or ocular complications identified). The ATOM2 study also tested lower concentrations of atropine

(0.5%, 0.1%, and 0.01%), reporting that allergic conjunctivitis and dermatitis occurred in the 0.5% and 0.1% groups, but were absent in the 0.01% group, which only reported 1 case of near blur and 1 case of irritation.[29] The authors reported that 7% of children receiving atropine 0.01% requested glasses for blur or for photosensitivity in years one and two. In the further extension study to 5 years, no child required glasses for blur at near or for photosensitivity.[31] Cooper at al[39] conducted a study to determine the maximal dose of atropine that is not associated with clinical symptoms associated with higher doses, reporting that a dose of 0.02% atropine is the maximum effective dose without clinical signs or symptoms. A recent study in 14 white university students found atropine 0.01% to be well tolerated.[40]

Below (Table 2) is a summary of side effects reported with various doses of atropine for the treatment of myopia progression in children.

**Table 2. Side Effects/Safety of Atropine Treatment of Myopia**

| Study | Ethnicity / Eye Color | Study Type* | N** | Dose*** | Side effects |
|---|---|---|---|---|---|
| Yen 1989[25] | Asian | Pro | 32 | 1% **** | All experienced photophobia. No systemic or ocular complications reported. |
| Kennedy 2000[41] | Minnesota --mainly white | Retro | 214 | 1% | Photophobia (40.2%), Blurred vision (10.7%), Ocular allergic reaction (3.7%), Ocular discomfort (3.7%), Headache (2.3%), Bad taste in mouth (2.3%), Dry mouth (1.9%), Dry eyes (1.4%), Psychological problems (0.5%), Dizziness (0.5%) |
| ATOM1 (Chua 2006) [28] | Asian | Pro | 200 | 1% | No serious adverse events. Study withdrawals due to allergic or hypersensitivity reaction (4.5%), glare (1.5%), and blurred vision (1%) |
| ATOM1 recovery (Tong 2009)[33] | Asian | Pro | 158 | 1% | Small decrease in best-corrected visual acuity from baseline, but ≤3 letters in all participants (occurred in controls as well). No reduction in near visual acuity compared with controls. No lens opacities. |
| Shih 1999[26] | Asian | Pro | 41<br>47<br>49 | 0.5%<br>0.25%<br>0.1% | **0.5%:** light sensitivity persisting >3 months in 22%, 2 children with intolerable photophobia, 2 children with fear of long-term effects, 1 child with recurrent blepharitis.<br>**0.25%:** light sensitivity >4 weeks in 7%. No systemic or ocular complications.<br>**0.1%:** No light sensitivity beyond 4 weeks. No systemic or ocular complications. |
| ATOM2 (Chia 2012)[29] | Asian | Pro | 139<br>141<br>75 | 0.5%<br>0.1%<br>0.01% | **0.5%:** Reduced accommodation, impaired near visual acuity, and pupil size increased >3mm. Allergic conjunctivitis (6.2%). Serious adverse reactions (2%)<br>**0.1%:** Reduced accommodation, impaired near visual acuity, and pupil size increased >3mm. Allergic conjunctivitis (4.5%). Serious adverse reactions (2%)<br>**0.01%:** Serious adverse reactions (1%). Minimally reduced accommodation. No allergic conjunctivitis or dermatitis. |
| ATOM2 recovery (Chia 2014)[34] | Asian | Pro | 138<br>139<br>71 | 0.5%<br>0.1%<br>0.01% | **0.5%:** Accommodation reduced for 1 year after stopping (2 years administration). Near acuity reduced for an additional month.<br>**0.1%:** No effects after stopping<br>**0.01%:** No effects after stopping. 7% were given glasses for blur or photosensitivity[31] |
| Wu 2011[42] | Asian | Retro | 97 | 0.05% for 6 months, then 0.1% | No reports of cataract or retinopathy noted during study period. Complaints of near blurring were "uncommon" |
| Cooper 2013[39] | Brown iris U.S. race not specified | Pro | 3<br>6<br>3 | 0.05%<br>0.025%<br>0.012% | **0.05%:** Accommodation deficits- no accommodation in 1 participant, 6D accommodation in 2 participants.<br>**0.025%:** borderline accommodation in 2 of 6 participants, clinically significant pupil dilation in 4 of 6 participants and minimal in 2 of 6.<br>**0.0125%:** 2 of 3 with subnormal accommodation (but no blurred vision). |
| Lee 2006[43] | Asian | Retro | 21 | 0.05% | **33%** had morning photophobia (1 into afternoon). 10% had hampered near vision. No irritation or allergic effects. |
| Fang 2010[44] | Asian | Retro | 24 | 0.025% | **16%** complained of photophobia with atropine vs 8% in control (p=0.4). No complaints of blurred vision. No systemic side effects. |
| Ekdawi 2015 (AAPOS Poster 2015) | Mostly Caucasian | Retro | 7 | 0.01% | 1(14%) participant had headaches and discontinued treatment after 7 months. Participants (number not specified) had difficulty with reading in the first weeks that did not persist past 4-6 weeks with continued use. |

*Study type: Pro = prospective study Retro = retrospective study
**N = number with outcome data.
***Treatment is daily unless otherwise noted
****Treatment is every other day.

## 1.8 Why is Another RCT Needed?

To date, randomized trials of atropine for slowing the progression of myopia in children have been primarily conducted on Asian populations. A meta-analysis comparing the effect of atropine on myopia progression in Asian and White children using data from both RCTs and prospective cohort studies concluded that atropine may have a greater effect in Asian populations.[38] A potential explanation of the observed differences of myopia progression between Asian and White children may be the mydriatic differences observed between highly pigmented and lowly pigmented eyes in response to atropine.[35-37] Although results of current RCTs are promising, additional studies in non-Asian populations are needed[38] to test the efficacy of atropine in counteracting myopia progression, including dose studies.

## 1.9 Public Health Importance

The increasing prevalence of myopia and the unresolved problem of myopia progression pose significant healthcare concerns. Increasing axial length and especially high levels of myopia (>-6.00D) are associated with serious ocular co-morbidities, often resulting in visual impairment or even blindness.[45] These include retinal detachment, myopic maculopathy, glaucoma and cataract. While much research has considered the impact of preventing high myopia development, there are relatively few participants who progress to those levels that would benefit from reduction in progression. What is omitted from that discussion is the impact on reducing the proportion of participants who progress even to moderate myopia. Many individuals would retain the ability to function without correction for some activities of daily living and not be constantly dependent on vision correction. But far more important to this research is the recognition that there is a large number of individuals who progress to moderate myopia and who by doing so are at increased risk for the same myopic complications compared with emmetropic individuals. While the risk of each adverse impact from myopia is lower at lesser amounts of myopia on an individual basis, the risk affects many more participants and thus slowing progression could protect more participants than from just preventing high myopia.

Flitcroft has opined that it is important to slow progression even in the moderate range of -1.00 to -6.00 D as those levels of myopia are also significantly associated with an increased risk of a range of ocular pathologies from glaucoma to retinal detachment[46] compared with emmetropia. Similarly, in the Blue Mountains Eye Study, the odds ratio for myopic maculopathy was 9.7 when comparing myopia -3.00 to -4.99D with emmetropia.[47] Tideman et al found that the risk of visual impairment went up with increasing spherical myopia. They noted that the lifetime risk at 75 years of age of was 3.0%.[45]

Many existing treatments to slow the progression of myopia have proven either ineffective or unacceptable to the participant when administered for many years. Low-dose atropine treatment has the potential to reduce the prevalence of high myopia, reduce myopic progression among children with moderate myopia, and thereby reduce the incidence of undesirable sequelae associated with myopia.

## 1.10 Study Objectives

The objectives for this randomized trial are:

1. To determine the efficacy of daily low-dose atropine (0.01%) for slowing myopia progression over a two-year treatment period in children aged 5 to less than 13 years with myopia -1.00 to -6.00D at the time of enrollment (Primary Outcome On-Treatment).
2. To determine the efficacy of atropine treatment on myopia progression 6 months following cessation of low-dose atropine treatment (Secondary Outcome Off-Treatment).

## 1.11 Synopsis of Study Design

The current study is designed as an efficacy study, making effort to maximize adherence to treatment group assignments. After a run-in phase during which all participants are treated with daily artificial tear eyedrops for 2-4 weeks (and glasses are updated if required) to assess their ability to adhere to daily eye drops, participants are randomly assigned to daily atropine or placebo for 24 months, followed by 6 months off treatment.

Major Eligibility Criteria for Run-in Phase (*see section 2.2 for a complete listing*)

- Age 5 years to <13 years at time of enrollment. Children within 4 weeks of their 13th birthday are not eligible.
- Refractive error meeting the following by cycloplegic *autorefraction:*
  - Myopia -1.00D to -6.00D spherical equivalent (SE) in both eyes
  - Astigmatism <=1.50D in both eyes
  - Anisometropia <1.00D SE
- Currently wearing refractive correction (single vision eyeglasses or contact lenses)
- Excellent compliance with refractive correction (more than 75% of all waking hours) for at least one month, based on investigator judgment after discussion with parent.
- No current or previous myopia treatment with atropine, pirenzepine or other anti-muscarinic agent.
- No current or previous use of bifocals, progressive-addition lenses, or multi-focal contact lenses.
- No current or previous use of orthoK, rigid gas permeable, or other contact lenses being used to reduce myopia progression.
- No known atropine allergy.

Additional Eligibility Criteria for Randomization

- Compliance with artificial tears at least 90% (days compliant/total days since receiving study medication as evident by review of the compliance calendar and count of unused ampules) during the run-in phase.
- Excellent compliance with refractive correction (more than 75% of all waking hours) during run-in phase, based on investigator judgment after review of compliance calendars and discussion with parent.
- Refractive correction in each eye (single vision eyeglasses or contact lenses with any necessary adjustment for contact lens rotation and vertex distance) that meets the following criteria:
  - Myopia (by spherical equivalent) in both eyes must be corrected to within ±0.50 D of the investigator's cycloplegic measurement of refractive error.
  - Cylinder power in both eyes must be within ±0.50 D of the investigator's standard refraction technique, which can be based on a cycloplegic or non-cycloplegic refraction.

- Cylinder axis for both eyes must be within ±5 degrees of the axis found on the investigator's refraction when cylinder power is >= 1.00 D or within ±15 degrees when the cylinder power is <1.00 D.

Measurement of refractive error for assessing the above criteria may be performed as an over-refraction or without refractive correction.

- Best-corrected distance visual acuity in current correction meeting the following criteria:
  - 20/32 or better in each eye (>=76 letters by E-ETDRS testing)
  - Interocular difference <= 0.2 logMAR (<= 10 letters by E-ETDRS testing)

Treatment Groups

Participants are randomly assigned 2:1 to the following two treatment groups:

- Atropine Group: 0.01% atropine eyedrops administered 1 drop to each eye daily in each eye for 24 months, followed by 6 months off atropine eyedrops
- Placebo Group: Placebo eyedrops administered 1 drop to each eye daily in each eye for 24 months, followed by 6 months off placebo eyedrops

Sample Size

Approximately 186 participants will be randomized in a 2:1 ratio to the two treatment groups (~124 in the atropine group and ~62 in the placebo group).

Visit / Contact Schedule *(timed from randomization unless otherwise specified)*

- Enrollment into run-in phase using daily artificial tear eyedrops for 2-4 weeks (and glasses updated if required)
- Randomization Visit (2-4 weeks after enrollment)
- Phone Calls from site: after 2 weeks (± 3 days), and after 3, 9, 15, 21, and 27 months (± 1 month)
- Office Visits:
  - 6 months ± 2 weeks*
  - 12 months ± 2 weeks*
  - 18 months ± 2 weeks*
  - 24 months ± 4 weeks: Primary Outcome On-Treatment – discontinue treatment after visit
  - 30 months ± 4 weeks: Secondary Outcome Off-Treatment– six months following discontinuation of treatment

*A virtual visit may be completed at 6, 12, or 18-months if an in-person office visit cannot be completed by the participant. If any safety events are identified during a virtual visit, participants will have additional follow up as applicable.

Testing Procedures

Cycloplegic autorefraction, axial length and additional biometry will be measured by a study certified examiner at the enrollment visit and by a masked examiner at all follow up visits using the same instrumentation on the participant throughout the study. Masking will be accomplished by having site personnel administer cyclopentolate to both eyes of each participant before he/she sees the masked examiner.

At randomization and each follow-up exam except the 30-month visit, the effect of eyedrops will be assessed with a questionnaire. Distance visual acuity will be assessed at randomization and

the 30-month visit. Binocular near visual acuity will be assessed at randomization and the 6-month visit.

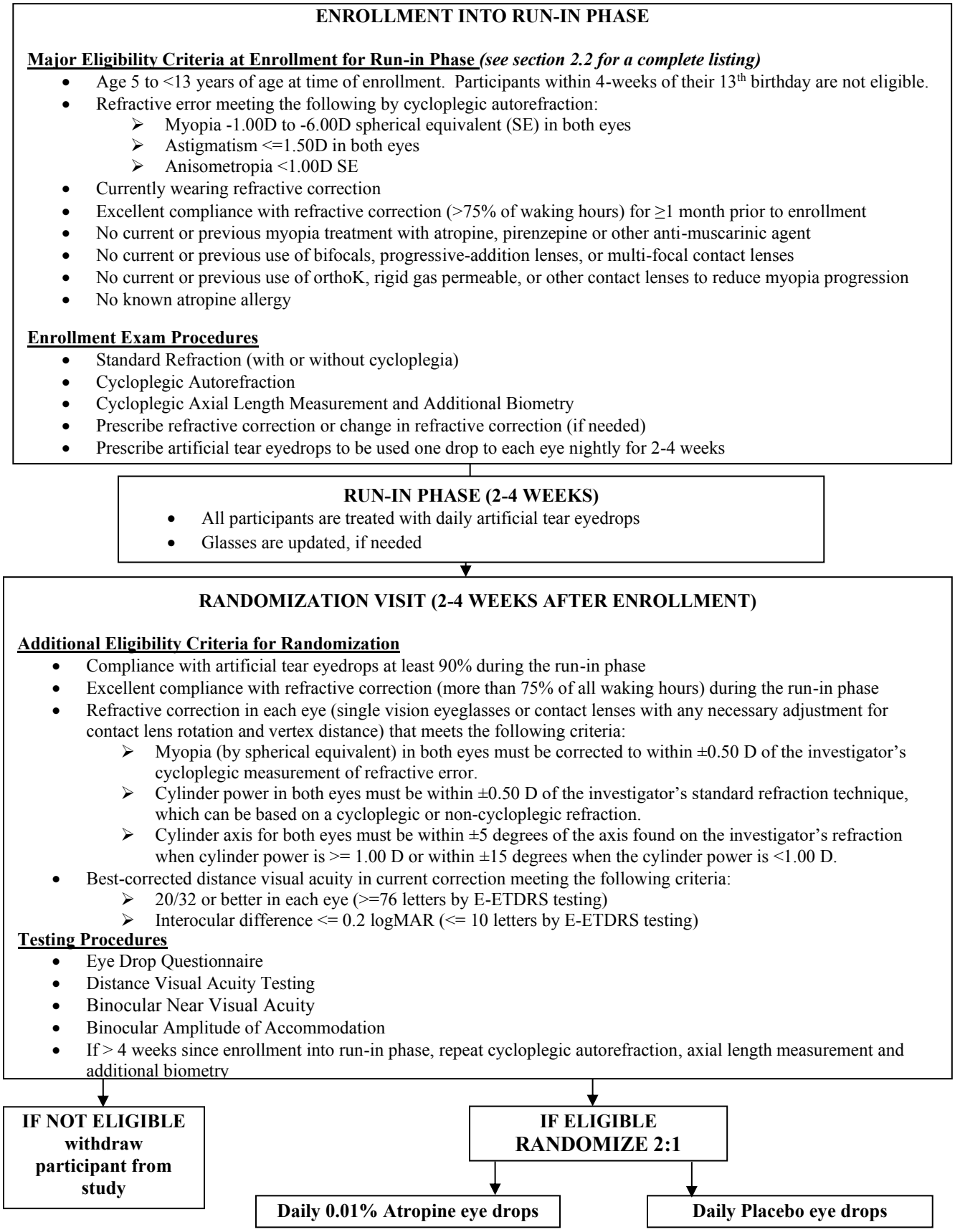
Primary Analysis

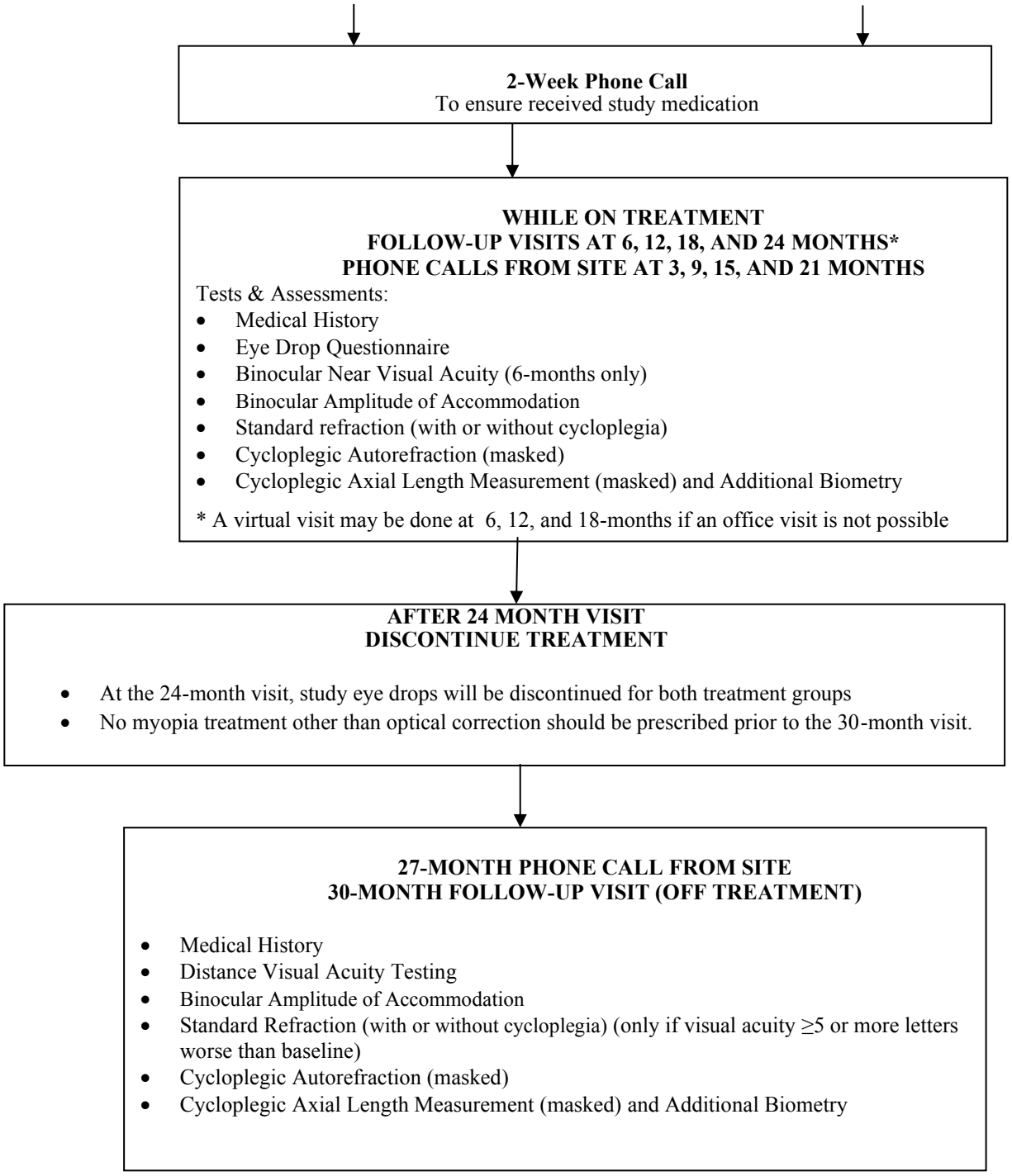
- Treatment group comparison of change from baseline to 24 months in spherical equivalent (average of both eyes) as measured by a masked examiner using cycloplegic autorefraction (on-treatment comparison).

Secondary Analysis

- Treatment group comparison of change from baseline to 30 months in spherical equivalent (average of both eyes) as measured by a masked examiner using cycloplegic autorefraction (off-treatment comparison).

## 1.12 Study Flow Chart




2-Week Phone Call
To ensure received study medication
WHILE ON TREATMENT
FOLLOW-UP VISITS AT 6, 12, 18, AND 24 MONTHS*
PHONE CALLS FROM SITE AT 3, 9, 15, AND 21 MONTHS
Tests & Assessments:
Medical History
Eye Drop Questionnaire
Binocular Near Visual Acuity (6-months only)
Binocular Amplitude of Accommodation
Standard refraction (with or without cycloplegia)
Cycloplegic Autorefraction (masked)
Cycloplegic Axial Length Measurement (masked) and Additional Biometry
* A virtual visit may be done at 6, 12, and 18-months if an office visit is not possible
AFTER 24 MONTH VISIT
DISCONTINUE TREATMENT
At the 24-month visit, study eye drops will be discontinued for both treatment groups
No myopia treatment other than optical correction should be prescribed prior to the 30-month visit.
27-MONTH PHONE CALL FROM SITE
30-MONTH FOLLOW-UP VISIT (OFF TREATMENT)
Medical History
Distance Visual Acuity Testing
Binocular Amplitude of Accommodation
Standard Refraction (with or without cycloplegia) (only if visual acuity ≥5 or more letters worse than baseline)
Cycloplegic Autorefraction (masked)
Cycloplegic Axial Length Measurement (masked) and Additional Biometry

# Chapter 2: ENROLLMENT

## 2.1 Eligibility Assessment and Informed Consent/Assent

The study plans to enroll a maximum of 400 participants into the Run-In Phase for whom informed consent is provided, such that approximately 186 participants will enter the Randomized Trial Phase. The number of participants randomized who self-report as East Asian ethnicity will be limited to no more than 25% of the overall sample (n=47 participants).

As the enrollment goal into the Randomized Trial Phase approaches 186 participants, sites will be notified of the end date for recruitment into the Run-In Phase. Participants whose parents have signed an informed consent form may be entered into the Run-in Phase until the end date, which means the expected number for the Randomized Trial Phase might be exceeded during the Run-in Phase. Enrollment into the Run-In Phase may be temporarily halted if necessary until it is determined how many participants in the Run-in Phase will enter the Randomized Trial Phase. The anticipated randomized total of 186 participants could be exceeded as participants already enrolled into the Run-In Phase become eligible for the Randomized Trial Phase.

The study will be discussed with the child's parent(s) or guardian(s) (referred to subsequently as parent(s)). Parents who express an interest in the study will be given a copy of the informed consent form to read. Written informed consent / assent must be obtained from the parent and child prior to performing any study-specific procedures that are not part of routine care.

## 2.2 Eligibility Criteria for Enrollment into Run-in Phase

The following criteria must be met for the child to be enrolled into the study:

**Inclusion Criteria**

- Age 5 years to <13 years at time of enrollment. Children within 4 weeks of their 13$^{th}$ birthday are not eligible.
- Refractive error meeting the following by cycloplegic *autorefraction:*
  - Myopia -1.00D to -6.00D spherical equivalent (SE) in both eyes
  - Astigmatism <=1.50D in both eyes
  - Anisometropia <1.00D SE
- Currently wearing refractive correction (single vision eyeglasses or contact lenses)
- Excellent compliance with refractive correction (more than 75% of all waking hours) for at least one month, based on investigator judgment after discussion with parent.
- Gestational age ≥ 32 weeks.
- Birth weight >1500g.
- Parent understands the protocol and is willing to accept randomization to atropine or placebo.
- Is willing to participate in a 2 to 4 week run-in phase using daily artificial tear eyedrops.
- Able to return in 2 to 4 weeks for possible randomization.
- Parent has a phone (or access to phone) and is willing to be contacted by Investigator's site staff.
- Relocation outside of the area of an active PEDIG site within next 32 months is not anticipated.

**Exclusion Criteria**

- Current or previous myopia treatment with atropine, pirenzepine or other anti-muscarinic agent.
- Current or previous use of bifocals, progressive-addition lenses, or multi-focal contact lenses.
- Current or previous use of orthoK, rigid gas permeable, or other contact lenses being used to reduce myopia progression.
- Known atropine allergy.
- Abnormality of the cornea, lens, central retina, iris or ciliary body.
- Current or prior history of manifest strabismus, amblyopia, or nystagmus.
- Prior eyelid, strabismus, intraocular, or refractive surgery.
- Down syndrome or cerebral palsy.
- Diseases known to affect accommodation, vergence, or ocular motility (e.g., multiple sclerosis, Grave's disease, myasthenia gravis, diabetes mellitus, Parkinson's disease)
- Existing ocular conditions (e.g., retinal disease, cataracts, ptosis) or systemic/neurodevelopmental conditions (e.g., Down syndrome) which may influence refractive development.
- Any condition that in the judgement of the investigator could potentially influence refractive development.
- Existing conditions that may affect the long-term health of the eye or require regular pharmacologic treatment that may adversely interact with study medication (e.g., JIA, glaucoma, diabetes mellitus, pre-diabetes)
- Inability to comprehend and/or perform any study-related clinical tests
- Females who are pregnant, lactating, or intending to become pregnant within the next 30 months.
    - A negative urine pregnancy test will be required for all females who have experienced menarche.

### 2.3 Historical Information

Historical information elicited will include the following: date of birth, sex, race, ethnicity, current refractive correction, iris color (brown or not brown), parental history of myopia (0, 1, or 2 parents), current medication use, history of and current medical conditions, and myopia treatment history.

### 2.4 Testing at the Enrollment/Run-in Visit

Testing at the enrollment visit/run-in visit will include the following:

1. Standard Refraction
    - The investigator may use his/her standard refraction technique (with or without cycloplegia) at any time during the visit to ensure that the participant meets eligibility criteria with respect to refractive correction as described in section 2.5.
2. Cycloplegic Autorefraction
    - 1% cyclopentolate – one drop twice to each eye with 5 minutes between drops. The use of proparacaine prior to the cycloplegic drops is at investigator discretion.
    - Three measurements of sphere, cylinder, and axis will be obtained for each eye using autorefraction (see manual of procedures). Each measurement will be converted to a spherical equivalent refractive error (SER) and the mean of the 3 SER values for each eye will be used for confirming eligibility.

- A specific autorefractor model is not required for the study; however, each participant should have their autorefraction assessed using the same instrument during the entire study.
- The cycloplegic autorefraction should occur at 30 minutes ± 5 minutes from the time the second drop of 1% cyclopentolate was instilled.
- If eyes are not sufficiently dilated/cyclopleged and/or if the dilation/cycloplegia has worn off before all cycloplegic procedures have been performed, another drop of 1% cyclopentolate may be administered, followed by an additional 30-minute wait before testing. The use of proparacaine prior to this cycloplegic drop is at investigator discretion.

3. Axial Length Measurement and Additional Biometry
   - One summary reading based on multiple measures with cycloplegia using optical biometry will be documented for the following (see procedures manual):
     - Axial length
     - Flat corneal radius
     - Anterior Chamber depth
     - Lens thickness, if available
   - A specific instrument is not required for the study; however, each participant should have axial length and additional biometry assessments made using the same instrument during the entire study.
   - If eyes are not sufficiently dilated and/or if the dilation has worn off before all cycloplegic procedures have been performed, see procedure for re-dilation in step #2.

## 2.5 Refractive Correction

To be eligible for randomization, the participant must be wearing refractive correction in each eye (single vision eyeglasses or soft, daily wear single vision contact lenses with any necessary adjustment for contact lens rotation and vertex distance) that meets the following criteria:

- Myopia (by spherical equivalent) in both eyes must be corrected to within ±0.50 D the investigator's cycloplegic measurement of refractive error.
- Cylinder power in both eyes must be within ±0.50 D of the investigator's standard refraction technique, which can be based on a cycloplegic or non-cycloplegic refraction.
- Cylinder axis for both eyes must be within ±5 degrees of the axis found on the investigator's standard refraction when cylinder power is >= 1.00 D or within ±15 degrees when the cylinder power is <1.00 D.

Measurement of refractive error for assessing the above criteria may be performed as an over-refraction or without refractive correction.

If the participant meets all eligibility criteria for the run-in phase (see section 2.2) but their current correction does not meet the requirements for randomization, then a change in refractive correction can be prescribed in order to meet the requirements when the participant returns for potential randomization. A change in refractive correction can also be prescribed if the investigator elects to change a smaller amount of refractive error, but the resulting prescription must meet the criteria above. The prescribed correction can be single vision eyeglasses or contact lenses. Single vision lenses will be paid for by the study; contact lenses will be at the participants' own expense. A pair of eyeglasses is recommended for all participants.

## 2.6 Treatment in Run-In Phase

Artificial tears will be dispensed in single-use ampules to be used 1 drop to each eye nightly in each eye for 2-4 weeks. Study personnel will demonstrate for the parent and participant how to instill a drop in each eye prior to the participant leaving the office.

The following will be done to promote compliance with artificial tears during the run-in phase:

- A calendar log will be provided to the parent on which the participant or parent will record whether or not the installation was done each night.
- The parent and participant will be instructed to bring all unused ampules of artificial tears with them when they return in 2-4 weeks.
- A smart phone application may be offered to participants and/or parents who provide consent to be contacted with a nightly prompt asking if the eyedrops were given.

Participants will be encouraged to wear refractive correction for all waking hours. The calendar log used to record artificial tears treatment will also be used to indicate whether refractive correction was worn each day.

# Chapter 3: RANDOMIZATION

The participant should return to assess eligibility for randomization within 2-4 weeks after using nightly artificial tears wearing the optical correction prescribed at the enrollment visit. If the participant is unable to return for possible randomization within 6 weeks of enrollment into the run-in, the participant will be withdrawn from the study.

## 3.1 Assessment of Compliance with Artificial Tears

Calendar logs will be reviewed to assess the level of compliance with artificial tears eyedrops during the run-in phase. The number of unused artificial tears eyedrop ampules will be counted.

To be eligible for randomization, participants must have used artificial tear eyedrops in both eyes for at least 2 weeks and must have been at least 90% compliant with instilling the drops in both eyes (days compliant/total days since receiving study medication as evident by review of the compliance calendar and count of unused ampules) in the run-in phase. Participants not able to return both the unused ampules of artificial tears eyedrops and the calendar log, and participants returning the log who are not compliant at least 90% will be withdrawn from the study.

In addition, the parent (or participant) must demonstrate the ability to instill an eyedrop in both eyes on their own prior to being considered for randomization. Participants who can't demonstrate successful instillation of eyedrops (either by themselves or by their parent) will be withdrawn from the study.

## 3.2 Assessment of Compliance with Refractive Correction

Calendar logs will be reviewed to assess the level of compliance with refractive correction during the run-in phase. Compliance with refractive correction will be classified as excellent (76% to 100% waking hours), good (51% to 75%), fair (26% to 50%), or poor (0 to 25%) based on investigator judgment after review of the compliance calendar and discussion with parent. Participants with excellent (greater than 75% compliance) will be eligible for randomization. Participants 75% compliant or less will be withdrawn from the study.

## 3.3 Testing at the Randomization Visit

Participants judged to be compliant with eyedrops and refractive correction will have the following assessed:

1. Eye Drop Questionnaire
   - To be completed by the child prior to any other testing to evaluate effect of eye drops on the child
2. Distance Visual Acuity Testing: Monocular distance visual acuity testing tested at the start of the exam without cycloplegia in current correction meeting the requirements in section 2.5.
   - Measurement of best corrected visual acuity in each eye by a study certified visual acuity tester using the E-ETDRS testing protocol.
3. Binocular Near Visual Acuity Testing: Binocular near visual acuity is measured using the ATS4 Near Acuity Test with the participant wearing current refractive correction and prior to administration of cycloplegia.

4. Binocular Amplitude of Accommodation: Measured with a study-specified and provided accommodation near-point rule (e.g. Gulden's near-point rule) and the participant in their current spectacle or contact lens correction.

Cycloplegic autorefraction, axial length and additional biometric assessments (following the same procedure as described for enrollment in section 2.4) must be repeated if the enrollment visit was completed more than 4 weeks (>28 days) prior to randomization. If repeated, these will be considered the participant's "baseline" measurements; otherwise the measurements from the enrollment/run-in phase visit will be considered the "baseline" measurements.

### 3.4 Confirmation of Eligibility for Randomization

Visual acuity testing to assess eligibility for randomization must be performed in the participant's current refractive correction.

Randomization will occur at the conclusion of the randomization exam after confirming that the participant meets the following eligibility criteria:

- Best-corrected distance visual acuity in current correction meeting the following criteria:
  - 20/32 or better in each eye (>=76 letters by E-ETDRS testing)
  - Interocular difference <= 0.2 logMAR (<= 10 letters by E-ETDRS testing)

- Refractive error meeting the following by cycloplegic *autorefraction (only if repeated on day of randomization):*
  - Myopia -1.00D to -6.00D spherical equivalent (SE) in both eyes
  - Astigmatism <=1.50D in both eyes
  - Anisometropia <1.00D SE

- Refractive correction that is being worn for each eye (single vision eyeglasses or contact lenses with any necessary adjustment for contact lens rotation and vertex distance) must meet the following criteria:
  - Myopia (by spherical equivalent) in both eyes must be corrected to within ±0.50 D of the investigator's cycloplegic measurement of refractive error.
  - Cylinder power in both eyes must be within ±0.50 D of the investigator's standard refraction technique, which can be based on a cycloplegic or non-cycloplegic refraction.
  - Cylinder axis for both eyes must be within ±5 degrees of the axis found on the investigator's refraction when cylinder power is >= 1.00 D or within ±15 degrees when the cylinder power is <1.00 D.

  Measurement of refractive error for assessing the above criteria may be performed as an over-refraction or without refractive correction.
- Compliant with artificial tears eyedrops during run-in phase (*see definition in section 3.1*)
- Compliant with refractive correction during run-in phase (*see definition in section 3.2*).

Participants who do not meet eligibility criteria will be withdrawn from the study without being randomized.

Prior to randomization, the study requirements should again be discussed with the parent so that site staff have reasonable assurance that the participant will be adherent to the protocol.

## 3.5 Randomization

Eligible participants will be randomly assigned 2:1 to the atropine (0.01%) or placebo group (administering one drop nightly for 24 months), respectively, using a permuted block design stratified by iris color (brown vs non-brown) and by site. The number of participants randomized who self-report as East Asian ethnicity will be limited to no more than 25% of the overall sample (n=47 participants).

A participant is officially enrolled in the randomized trial when the website randomization process is completed.

Once a participant is randomized, that participant will be included in the analysis regardless of whether the assigned treatment is received or not. Participants will remain in the study for 30 months of follow-up. Thus, the investigator must not randomize a participant until he/she is convinced that the parent/participant remains willing to participate and will accept either of the treatment regimens and complete follow-up as previously discussed at enrollment.

Treatment must commence within 1 week following randomization; therefore, a participant should not be randomized until both the investigator and parent are ready to start treatment.

The participant, parents, coordinators, testers and investigators will be masked to treatment group. If the need arises, the investigator may become unmasked after discussion of a specific case with the protocol chair in response to any adverse events.

# Chapter 4: TREATMENT AND FOLLOW-UP IN RANDOMIZED TRIAL

## 4.1 Study Medication

Nevakar is manufacturing the study drug (0.01% atropine) and placebo and packaging both in identical-appearing single-use ampules. In addition to 0.01% atropine, the ampules contain a buffer similar to artificial tears while the placebo contains just the buffer similar to artificial tears. The atropine and placebo ampules are sent to a central pharmacy, which will label and package multiple atropine or placebo ampules into three month supply packages to maintain masking. The packages of ampules will be shipped to participating sites in insulated shipping boxes designed to maintain study drug at 59 to 77 degrees F during shipping. Participating sites will store study drug at room temperature (between 68 and 77 degrees F) prior to dispensing study medication packages to study participants. Additional study medication details are summarized within a separate investigational product manual.

## 4.2 Treatment 0 to 24 Months

Treatment with study medication will be one drop in both eyes each night, including the night before study visits. Participants who are wearing contact lenses will be instructed to remove contact lenses before administering eyedrops and wait at least 30 minutes after eyedrop administration before reinserting contact lenses.

During the first 24 months of the study, no myopia progression prevention treatment other than the study eyedrops is permitted.

## 4.3 Telephone Calls

Two weeks following randomization (±3 days), the site will contact parents to question the parent as to whether the child is experiencing any issues with treatment.

At three months following randomization (±1 month), the site will contact parents to encourage compliance and question the parent as to whether the child is experiencing any issues with treatment.

The site coordinator will make phone calls in between office visits at 9, 15, 21, and 27 months following randomization (±1 month). These calls will be conducted to maintain direct contact with the parents of each participant, to develop and maintain rapport with the participant and/or family, and to assist with the scheduling of study visits if needed.

## 4.4 Masking of Treatment Group

Cycloplegic autorefraction, axial length, and additional biometry will be measured by a masked examiner at all follow-up visits using the same instrumentation on the participant throughout the study. Masking will be accomplished by having site personnel administer cyclopentolate to both eyes of each participant and wait 30 minutes before he/she sees the masked examiner. The masked examiner may be a technician or an investigator and must be certified to complete these measurements.

## 4.5 Compliance with Study Treatment

Unused study medication ampules will be brought to all visits while on randomized treatment and will be counted as a measure of treatment compliance.

To promote compliance with eyedrops, a calendar will be provided on which the child/parent will record the treatment received each day. At each visit, an assessment of compliance will be recorded on the Follow-up Examination Form after review of the calendars and an interview with the parent and child.

If a participant is noncompliant with study eyedrops, the parents and participants should be encouraged to persist with their efforts to treat to the best of their ability.

### 4.6 Off-Treatment Phase >24 to 30 Months

At the 24-month visit, study eyedrops will be discontinued and no myopia treatment other than optical correction should be prescribed prior to the 30-month visit.

### 4.7 Side Effects of Treatment

Reporting of adverse events is described in Chapter 6. In cases of vision-related adverse events, distance visual acuity should be measured using the E-ETDRS testing protocol (see section 4.8). Prior to deviating from the treatment protocol or prescribing non-protocol treatment, the situation should be discussed with the Protocol Chair.

### 4.8 Follow-up Visit Schedule in Randomized Trial

The follow-up visit schedule consists of the following office visits timed from randomization:

- 6 months ± 2 weeks*
- 12 months ± 2 weeks*
- 18 months ± 2 weeks*
- 24 months ± 4 weeks: On-Treatment Primary Outcome – discontinue treatment after visit
- 30 months ± 4 weeks: Off-Treatment Secondary Outcome – six months following discontinuation of treatment

*A virtual visit may be completed at 6, 12, or 18-months if an in-person office visit cannot be completed by the participant. If any safety events are identified during a virtual visit, participants will have additional follow up as applicable.

Additional visits may be scheduled at investigator discretion. Adverse event data may be reported and collected at any time during the study.

### 4.9 Follow-up Visit Testing Procedures

At each office visit the following tests and assessments will be done with the participant wearing their current refractive correction:

1. Medical History - including questioning about the occurrence of adverse effects of treatment. Concomitant medications will be recorded, as well as current eyeglasses or contact lenses correction.
2. Compliance Assessment
    - All unused study medication ampules since the last visit (if brought to the visit) will be counted as a measure of compliance.
    - Home calendar logs (if brought to the visit) will be reviewed and assessments of compliance with eyedrops and with refractive correction will be recorded on the Follow-up Examination Form

3. Eye Drop Questionnaire (all follow up visits except the 30-month visit)
    - To be completed by the child prior to any other testing to evaluate the effect of eye drops on the child.
4. Distance Visual Acuity Testing (30-month visit only): Monocular distance visual acuity tested at the start of the exam without cycloplegia in current correction.
    - Measurement of best corrected visual acuity in each eye by a study certified visual acuity tester using the E-ETDRS testing protocol.
    - If the vision is more than one line (>=5 letters) worse than baseline, retest using trial frames or phoropter with the most recent subjective refraction.
5. Binocular Near Visual Acuity Testing (6-month visit only): Binocular near visual acuity is measured using the ATS4 Near Acuity Test with participant wearing current refractive correction prior to administration of cycloplegia.
6. Binocular Amplitude of Accommodation: Measured in their current correction without cycloplegia with a study-specified and provided accommodation near-point rule (e.g. Gulden's near-point rule).
7. Standard Refraction
    - The investigator may use their standard refraction technique (with or without cycloplegia) at any time during the visit to ensure that refractive correction meets study criteria at each visit (see section 4.9 below).
    - At 30-month visit, only required if the vision is more than one line (>=5 letters) worse than baseline.
8. Following cycloplegia, at all visits an examiner masked to treatment group will perform:
    - Cycloplegic Autorefraction – (*see section 2.4)*
    - Cycloplegic Axial Length Measurement and Additional Biometry (*see section 2.4)*

If a virtual visit is completed, only items 1 through 3 above will be completed. If any safety events are identified during a virtual visit, participants will have additional follow up as applicable.

In addition, females who have experienced menarche will undergo a urine pregnancy test at each follow up visit except the 30-month visit (or at home if a virtual visit is completed).

- In the case of pregnancy during the study, study eyedrops will be discontinued although the subject will be retained in the study.

### 4.10 Management of Refractive Error

Spectacle or contact lenses correction must be updated whenever the investigator's standard refraction technique reveals a change in refractive error. A change in refractive error is defined as any of the following amounts:

- A difference of ≥0.75 D sphere
- A difference of ≥0.75D cylinder
- A difference of ≥0.50D in SE anisometropia
- A difference in axis of 6 degrees or more when the cylinder is ≥1.00D.

Whether to update the correction for smaller differences in refraction is at investigator discretion. Glasses required by a contact lens user should be updated when their contact lenses are updated, and these glasses will be paid for by the study.

If updated, the refractive correction must meet the requirements described in section 2.5.

Daily wear single vision contact lenses may be used for correction of refractive error full time or alternating with spectacle correction. Contact lenses should not differ from a cycloplegic over-refraction by more than +/- 0.50D SE. Uncorrected astigmatism should not exceed 1.00D. OrthoK, rigid gas permeable, and other contact lenses being used to affect myopia progression are not allowed. Contacts must be removed from the eyes prior to study medication administration and not reinserted for at least 30 minutes.

### 4.11 Non-Randomized Treatment Other than Refractive Correction

Non-randomized treatment for myopia other than changes in refractive error as described above is not permitted during the study. The investigator must call the protocol chair to discuss the case and obtain approval for an exception prior to initiating non-randomized treatment (including OrthoK, rigid gas permeable, and other contact lenses being prescribed to affect myopia progression).

### 4.12 General Considerations

The study is being conducted in compliance with the policies described in the study policies document, with the ethical principles that have their origin in the Declaration of Helsinki, with the protocol described herein, and with the standards of Good Clinical Practice.

There is no restriction on the number of participants to be enrolled by each site towards the overall recruitment goal.

# Chapter 5: MISCELLANEOUS CONSIDERATIONS IN FOLLOW-UP

## 5.1 Participant Withdrawals

Parents may withdraw their child from the study at any time. If the parents indicate that they want to withdraw their child from the study, the investigator should attempt to speak with the parents personally to determine the reason. If their interest is in transferring the child's care to another eye care provider, every effort should be made to comply with this and at the same time try to keep the participant in the study under the new provider's care.

## 5.2 Discontinuation of Study

The study may be discontinued by the Steering Committee (with approval of the Data and Safety Monitoring Committee) prior to the pre-planned completion of enrollment and follow-up for all participants.

## 5.3 Travel Reimbursement

The parent of each participant will be compensated $50 (by merchandise/money card or check) upon completion of the enrollment exam, the randomization exam, and each study visit at 6, 12, 18, 24, and 30 months following randomization, for a maximum of $350. If there are extenuating circumstances and/or the participant is unable to complete study visits without additional funds due to travel costs, additional funds may be provided.

## 5.4 Costs Covered by the Study

The study will pay for the office visits that are part of the study (enrollment, randomization visit, and visits at 6, 12, 18, 24, and 30 months). The study will pay for virtual visits. Any other visits that are part of routine care will be the parent(s) or their insurance company's responsibility.

The study will pay for the following:

- Study eyedrops (artificial tears, atropine and placebo) will be provided to the participants at no cost.
- Eyeglasses will be provided at enrollment (if needed), and at 12 and 24-month visits if obtained from a study optician.
- Lens changes will be provided at 6 and 18-month visits if a change is required (see Section 4.10) and the lenses are obtained from a study optician.
- The study will pay for bifocals (progressive-addition lenses) if prescribed by the investigator because of difficulties seeing up close when doing schoolwork or reading.

## 5.5 Costs Not Covered by the Study

The study will not pay for eyeglasses obtained from a non-study optician. The study will not pay for contact lenses.

# Chapter 6: ADVERSE EVENTS AND RISKS

The study will be performed under an Investigation New Drug Application to the FDA of the US. Specific reporting requirements for adverse events are summarized below.

## 6.1 Recording of Adverse Events

The participant and parent will be queried as to whether or not they have experienced ocular side effects of treatment including lid/conjunctival irritation, light sensitivity, or near blur and/or reading difficulty; as well as any systemic side effects of treatment presenting within one hour following administration of atropine, including dry skin/mouth, tachycardia, fever, flushing, irritability, mental confusion, constipation, aggravation of asthma, or seizures. In addition, all serious adverse events will be recorded.

The study investigator will assess the relationship of each adverse event to be *related* or *unrelated* by deciding if there is a reasonable possibility that the adverse event may have been caused by the treatment.

To ensure consistency of adverse event causality assessments, investigators should apply the following general guideline when determining whether an adverse event is related:

> Yes
> There is a plausible temporal relationship between the onset of the adverse event and administration of the study treatment and the adverse event cannot be readily explained by the participant's clinical state, intercurrent illness, or concomitant therapies; and/or the adverse event follows a known pattern of response to the study treatment.
>
> No
> Evidence exists that the adverse event has an etiology other than the study treatment (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the adverse event has no plausible temporal relationship to study treatment administration.

The maximum intensity that occurred since the onset of an adverse event will be rated on a three-point scale: (1) mild, (2) moderate, or (3) severe, categorized as follows:

Mild - Symptom(s) barely noticeable to participant or does not make participant uncomfortable; does not influence performance or functioning; prescription drug not ordinarily needed for relief of symptom(s).

Moderate - Symptom(s) of sufficient severity to make participant uncomfortable; performance of daily activity is influenced; participant is able to continue in study; treatment for symptom(s) may be needed.

Severe - Symptom(s) cause severe discomfort; severity may cause cessation of treatment with study medication or device; treatment for symptom(s) may be given and/or participant hospitalized.

It is emphasized that the term severe is a measure of intensity: thus, a severe adverse event is not necessarily serious. For example, itching for several days may be rated as severe, but may not be clinically serious.

Adverse events that continue after the study participant's discontinuation or completion of the study will be followed until their medical outcome is determined or until no further change in the condition is expected.

## 6.2 Reporting Serious or Unexpected Adverse Events

A serious adverse event is any untoward occurrence that:

- Results in death.
- Is life-threatening; (a non-life-threatening event which, had it been more severe, might have become life-threatening, is not necessarily considered a serious adverse event).
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions (sight-threatening).
- Is a congenital anomaly/birth defect.
- Is considered a significant medical event by the investigator based on medical judgment (e.g., may jeopardize the participant or may require medical/surgical intervention to prevent one of the outcomes listed above).

Unexpected adverse events are those that are not identified in the current Clinical Investigator's Brochure.

Serious or unexpected adverse events must be reported to the Coordinating Center immediately via completion of the online serious adverse event form.

The Coordinating Center will notify all participating investigators of any adverse event that is both serious and unexpected. Notification will be made within 10 days after the Coordinating Center becomes aware of the event.

Each principal investigator is responsible for reporting serious study-related adverse events and abiding by any other reporting requirements specific to their Institutional Review Board.

## 6.3 Data and Safety Monitoring Committee Review of Adverse Events

A Data and Safety Monitoring Committee will approve the protocol, template informed consent form, and substantive amendments, and provide independent monitoring of adverse events. Cumulative adverse event data will be tabulated for review by the DSMC at intervals determined by the coordinating center and the DSMC. Following each DSMC data review, a summary will be made available for submission to Institutional Review Boards.

## 6.4 Risks

### 6.4.1 Risks of Examination Procedures

The procedures in this study are part of daily eye care practice in the United States and pose no additional risks.

### 6.4.2 Risk of Atropine Therapy

The effects of long-term use of bilateral atropine eye drops when used as treatment for myopia progression depend on the strength of atropine used. Side effects are uncommon with the 0.01% dosage to be used in this protocol, based on a series of 84 participants treated with 0.01% atropine for 2 years (ATOM2). In most cases the events were deemed not related to the treatment. Six children had eye symptoms felt related to the therapy, 1 case of irritation and 1 case of blurred vision in the 0.01% group. Further treatment for two additional years was not associated with side-effects.

A common side effect of atropine 1% is blurry vision, particularly at near, which may cause problems with reading at school and near work. The 0.01% dosage used in this study is not expected to be frequently associated with reading problems or blur at near.

Following atropine administration, local side effects of minimal severity include allergic lid reactions, local irritation, conjunctival hyperemia, and follicular conjunctivitis. In the ATOM2 series, 1% of participants had irritation sufficient to warrant discontinuation of treatment; no cases of allergic conjunctivitis or allergic dermatitis were reported.

Potential systemic side effects include dry skin and mouth, tachycardia, fever, flushing and irritability. These effects were not reported (ATOM2), but rather some more minor complaints such as blurring and some light sensitivity with atropine 0.1% and 0.5% in the first two years of treatment. The only severe adverse event with 0.01% was 1 participant (1%) with acute gastric pain which was not felt to be related to the atropine (ATOM2).

Atropine 1% produces dilation of the pupil, which increases the light that enters the eye. Although it has not been demonstrated that atropine used for 2 years could have harmful ocular effects, excessive exposure to light theoretically could be toxic to the retina. The strength used in this study is expected to have minimal effect on pupil dilation.[39] If there is light sensitivity, clip-on or flip-up sunglasses or photochromic lenses will be provided. The use of hats with brims or visors will be encouraged along with sunglasses.

Participants who experience problems with schoolwork or significant symptoms when reading may be prescribed progressive bifocals paid for by the study. These will be provided irrespective of treatment assignment after consultation with the protocol chair.

Atropine in various dosages from 0.01% to 1% has been used long-term to prevent the progression of myopia without any lasting adverse effect on visual acuity.[32, 41, 49, 50] In the ATOM2 trial, the most common side effect in the 0.01% atropine group was loss of one or more lines of distance visual acuity (13%) but this was reversible upon discontinuing medication.

If a participant develops adverse effects serious enough to discontinue study medication prior to the 24-month on-treatment primary outcome exam, the Investigator should call the Protocol Chair to discuss the case. Progressive lenses should be tried for near focusing problems before stopping therapy. Reading glasses may be prescribed for participants using contact lenses. If study medication is discontinued, the participant will continue in follow-up.

In the case of pregnancy during the study, study eyedrops will be discontinued although the subject will be retained in the study.

### 6.4.3 Risk Assessment

The Jaeb Center Institutional Review Board has classified the protocol as research involving greater than minimal risk using the federal definition under 45 CFR 46.102i.

# Chapter 7: SAMPLE SIZE ESTIMATION AND STATISTICAL ANALYSIS

The approach to sample size and statistical analyses are summarized below. A detailed statistical analysis plan will be written and finalized without knowledge of study data. The analysis plan synopsis in this chapter contains the framework of the anticipated final analysis plan.

## 7.1 Primary Objective: Efficacy on Atropine Treatment (24 Months)

The primary objective is to determine the efficacy of atropine for slowing progression of myopia after 24 months of treatment.

### 7.1.1 Primary Analysis – Refractive Error at 24 Months (On-Treatment)

The primary analysis will be a treatment group comparison of change from baseline to 24-months in spherical equivalent refractive error (SER), as measured by a masked examiner using cycloplegic autorefraction, using a longitudinal discrete time mixed model, which allows for interaction between time and treatment group, and adjusts for baseline SER, age, iris color (brown vs. non-brown) and East Asian vs. non-East Asian race, to account for potential residual confounding and improve power for the treatment comparison. At baseline and all follow-up visits, including the 24-month visit, the mean of the three readings from autorefraction in each eye will be calculated and then the mean of both eyes for each participant will be used for the analysis. If fewer than 3 readings are available in each eye, the mean of available readings will be used for each eye to obtain the mean of both eyes for each participant. The baseline SER will be included in the analysis model as an adjustment factor, while the change in SER at all follow-up visits up to and including the 24-month visit will be included in the longitudinal outcome vector. Further details, including handling of missing data, will be included in the Statistical Analysis Plan.

The treatment group difference (atropine – placebo) and a 95% confidence interval will be calculated based on the model estimates at 24 months.

The primary analysis will follow the intention-to-treat principle. All randomized participants will be analyzed according to their randomized treatment group regardless of whether/what treatment was received, including non-randomized treatment for myopia (section 4.109).

#### 7.1.1.1 Sensitivity Analyses

As a sensitivity analysis, the primary analysis will be repeated using an analysis of covariance model (ANCOVA) model in which SER at 24 months is adjusted for SER at baseline. Multiple imputation with the Monte Carlo Markov Chain (MCMC) method will be used to impute missing change in SER for participants who missed the 24-month visit or did not complete cycloplegic autorefraction testing at the 24-month visit. In addition, change in SER will also be imputed for participants who start non-randomized treatment.

### 7.1.2 Secondary Outcomes at 24 Months (On-Treatment)

Each secondary analysis below will be conducted using the same approaches as defined above for the primary analysis unless otherwise specified.

#### 7.1.2.1 Proportion of Participants with Progression >=2D at 24 Months

The relative risk of progression of myopia SER >= 2D from baseline between participants in the atropine group and the placebo group will be estimated using a Cox proportional hazards model,

which adjusts for baseline SER, age, iris color (brown vs. non-brown) and East Asian vs. non-East Asian race. An alternative analysis method will be used if the proportional hazards assumption is not met.

#### 7.1.2.2 Change in Axial Length at 12 and 24 Months

Axial length will be reported as the distributions of baseline length, 12-month length, 24-month length, and change in axial length from baseline to 12 and 24 months. A treatment group comparison of the change from baseline to 12 months and 24 months in axial length will be performed using a longitudinal discrete time mixed model, which allows for interaction between time and treatment group, and adjusts for baseline axial length, age, iris color (brown vs. non-brown) and East Asian vs. non-East Asian race. At baseline and all follow-up visits, including the 12 and 24-month visits, the mean of the axial length readings in both eyes for each participant will be used for the analysis. The treatment group difference (atropine – placebo) and a 95% confidence interval will be calculated based on the model estimates at 12 months and 24 months.

#### 7.1.2.3 Compliance

Compliance with study medication will be assessed at the 6-month, 12-month, 18-month, and 24-outcome exams. For each of these exams, the distribution of number of calendar days that study medication was reported used and the distribution of the number of unused study medication ampules will be compared between treatment groups.

Compliance with refractive correction will be assessed at every follow up visit. After discussion with the parent and child, study personnel will classify the proportion of time refractive error was worn will be described as excellent (76% to 100%), good (51% to 75%), fair (26% to 50%), or poor (≤ 25%). The distribution of refractive correction compliance will be compared between treatment groups.

### 7.1.3 Secondary Outcomes at 12 Months (On-Treatment)

Each secondary analysis below will be conducted using the same approaches as defined above for the primary analysis unless otherwise specified.

#### 7.1.3.1 Refractive Error at 12 Months

The model used for the primary analysis at 24 months will also be used to perform a treatment group comparison of change from baseline to 12-months in spherical equivalent refractive error (SER), as measured by a masked examiner using cycloplegic autorefraction.

#### 7.1.3.2 Proportion of Participants with Progression >=1D at 12 Months

The relative risk of progression of myopia SER >= 1D from baseline between participants in the atropine group and the placebo group will be estimated using a Cox proportional hazards model, adjusting for baseline SER, age, iris color (brown vs. non-brown) and East Asian vs. non-East Asian race. An alternative analysis method will be used if the proportional hazards assumption is not met.

## 7.2 Secondary Objective: Efficacy off Atropine Treatment (30 Months)

The secondary objective of the study is to determine the efficacy of atropine treatment for slowing progression of myopia after a period of 6 months off treatment. All analyses as described in section 7.1 above will be repeated using data from the 30-month off-treatment visit.

## 7.3 Additional Analyses

### 7.3.1 Treatment Effect in Subgroups

The treatment difference for spherical equivalent refractive error (SER) change from baseline to 24 and 30 months within the following subgroups will be explored:

- Baseline SER
- Brown iris versus non-brown iris
- Race/ethnicity
- Baseline age
- Baseline age and baseline SER

These planned subgroup analyses will repeat the primary analysis, including the baseline factor and the baseline factor by treatment interaction. In general, statistical power will be low for detection of interactions unless the interaction is very large.

Subgroup analyses will be interpreted with caution, particularly if the corresponding overall analysis does not demonstrate a significant treatment group difference.

### 7.3.2 Treatment Effect over Time

The treatment effect on change in spherical equivalent refractive error (SER) from baseline through the first year will be compared with the treatment effect on change in SER from end of first year through the second year, by constructing the appropriate contrasts in the primary analysis model.

### 7.3.3 Exploratory Analyses of Additional Ocular Biometric Parameters

As exploratory analyses at 24 and 30 months, change in flat corneal radius, anterior chamber depth, and lens thickness will each be compared between treatment groups at 24 and 30 months using a longitudinal discrete time mixed model which allows for interaction between time and treatment group, and adjusts for the baseline value of the parameter, age, iris color (brown vs. non-brown), and East Asian vs. non-East Asian race.

## 7.4 Safety Analyses

### 7.4.1 Adverse Effects of Eye Drops

An eyedrops questionnaire will be administered at randomization and at each follow-up visit except the 30-month visit. The distribution of scores on each survey item will be summarized by treatment group at the time of randomization and at each follow-up exam up until and including the 24-month visit. The average of the item responses at the 24-month visit will be calculated and compared with a t-test for difference in means between treatment groups.

### 7.4.2 Visual Acuity

The proportion of participants with loss of best corrected distance vision >1 logMAR line at 30 months in either eye will be compared between treatment groups using Barnard's test. The proportion of participants with loss of best corrected near binocular vision >1 logMAR line at 6 months will be compared between treatment groups using Barnard's test.

## 7.5 Need for Bifocals

The proportion of participants needing bifocals in both groups will be evaluated.

## 7.6 Interim Analysis

As specified by the DSMC, the decision of whether an interim analysis will be conducted will be evaluated after 6 months of recruitment and before any outcome data is reviewed. An interim monitoring plan will be developed at that point if circumstances warrant.

## 7.7 Data Tabulations and Other Analyses

The following tabulations will be performed according to treatment group:

- Baseline demographics and clinical characteristics
- A flow chart accounting for all participants for all visits and phone calls
- Visit and phone contact completion rates for each follow-up visit
- Protocol deviations

## 7.8 Sample Size

### 7.8.1 General Considerations

The goal of this section is to summarize data from prior studies of myopia progression, use these data to formulate assumptions about the expected treatment effect and its standard deviation, and to calculate the sample size needed to provide at least 90% power for each of the 2 hypothesis tests corresponding to the 24-month on treatment (primary) and 30-month off-treatment secondary objectives.

To collect more safety data from participants using atropine, sample size was based on a 2:1 allocation (2 participants will be randomized to the atropine group for every 1 participant randomized to the placebo group).

### 7.8.2 Sample Size for Primary Objective: Efficacy on Atropine Treatment

**Comparison of SER at 24 months**

Sample size calculations for the on-treatment comparison of refractive error at 24 months were based upon data from the CLEERE group and ATOM1 for untreated participants meeting similar eligibility criteria, and data from participants treated with atropine 0.01% in the ATOM2 study.[28, 31, 51] The participants in these studies were 6 to <13 years old with refractive error of -1.00D to -6.00D spherical equivalent and astigmatism of -1.50D or less. The ATOM1 and ATOM2 studies were conducted in Asian populations whereas the race/ethnicity of participants in the CLEERE study was more reflective of the US population.

- In 404 untreated participants from CLEERE (N=214) and ATOM1 (N=190), the mean progression after 24 months was 1.12D (95% CI = 1.05 to 1.18D) with standard deviation (SD) of 0.69D (95% CI = 0.65 to 0.75D).

- In 75 participants treated with 0.01% atropine from ATOM2, the mean progression after 24 months was 0.49D (95% CI = 0.35 to 0.63D) with SD of 0.60D (95% CI = 0.52 to 0.72).

The on-treatment effect after 24 months in our study is estimated to be 0.50D based on a conservative estimate of 1.00D 24-month progression in untreated participants and an estimated 0.50D 24-month progression in participants treated with 0.01% atropine.

Assuming a conservative standard deviation of 0.80D (based on CLEERE), and using a 2-sided t-test with alpha = 0.05, a sample size of 123 participants (82 in the atropine group and 41 in the placebo group) is needed to detect a difference in mean change in SER (atropine – placebo) at 24 months with 90% power, assuming the true mean difference is 0.50D or larger (Table 1). Since the correlation between baseline refractive error and change in refractive error at 24 months in the CLEERE data was low (r=0.05), no reduction in sample size was taken to account for the correlation between baseline and the outcome at 24 or 30 months. Accounting for up to 10% loss to follow-up over 24 months, the sample size *for this objective* is 138 participants overall (92 in the atropine group and 46 in the placebo group).

**Table 1: Total Sample Size Estimates for Various Treatment Group Differences in Mean SER Score at 24 Months or 30 Months***

| Standard Deviation Mean SER Change from Baseline to 24 Months or 30 Months(D) | True Treatment Group Difference (D) in Mean SER Change between Baseline and 24 Months or 30 Months | | | |
|---|---|---|---|---|
| | **0.40** | **0.50** | **0.60** | **0.625** |
| **0.60** | 111 (74:37) | 72 (144:72) | 51 (34:17) | 48 (32:16) |
| **0.70** | 147 (98:49) | 96 (64:32) | 69 (46:23) | 63 (42:21) |
| **0.80** | 192 (128:64) | 123 (82:41) | 87 (58:29) | 81 (54:27) |
| **0.90** | 243 (162:81) | 156 (104:52) | 111 (74:37) | 102 (68:34) |
| **1.00** | 300 (200:100) | 192 (128:64) | 135 (90:45) | 123 (82:41) |

Cells indicate total sample size needed assuming a 2:1 randomization. (Numbers in parenthesis reflect number needed in each group atropine:placebo).

*Sample sizes based on a t-test to evaluate a difference between treatment groups in mean change from baseline at 24-months, with a 2-sided alpha=0.05, and power=90%.

### 7.8.3 Sample Size for Secondary Objective: Efficacy off Atropine Treatment

**Comparison of SER at 30 months**

In CLEERE, the mean progression after 36 months was 1.50D in 127 untreated participants (95% CI = 1.34 to 1.66 D) with a SD of 0.89D (95% CI = 0.79 to 1.02 D). If the rate of progression in our study is similar (approximately 0.25D every 6 months), then the progression rate between baseline and 30-months in placebo participants is estimated to be 1.25D.

In ATOM2, the 71 participants who stopped atropine at 24 months progressed a mean of 0.28D (SD = 0.33D) after 12 months off treatment (95% CI for mean change = 0.20 to 0.36 D); and their mean progression from baseline to 36 months was 0.72D (95% CI = 0.55 to 0.89 D) with SD of 0.72D (95% CI = 0.62 to 0.86 D).

*If atropine group participants progress at the same rate as ATOM2 participants between 24 and 30 months*

If atropine participants progress at the same rate as ATOM2 participants between 24 and 30 months (estimated to be about 0.125 D over six months), then the estimated progression rate

between baseline and 30-months in the atropine group is 0.625D (0.50D at 24 months plus 0.125D between 24 and 30 months). Compared with the estimated 1.25D progression rate in the placebo group between baseline and 30-months (based on CLEERE data), the treatment group difference would be expected to be 0.625D in favor of the atropine group.

Assuming a slightly larger standard deviation of 0.90D at 30-months, and using a 2-sided t-test with alpha = 0.05, a sample size of 102 participants (68 in the atropine group and 34 in the placebo group) is needed to detect a mean difference in SER (atropine – placebo) at 30 months with 90% power, if the magnitude of the true mean difference is 0.625D or larger (Table 1). Accounting for up to 15% loss to follow-up over 30 months, the sample size *for this objective* is 120 participants overall (80 in the atropine group and 40 in the placebo group) under this scenario.

*If atropine group participants progress at the same rate as placebo participants in CLEERE between 24 and 30 months*

If atropine participants progress at the same rate as placebo participants in CLEERE (i.e. no treatment effect) between 24 and 30 months (0.25D), then the estimated progression rate between baseline and 30-months in the atropine group is 0.75D (0.50D at 24 months plus 0.25D between 24 and 30 months). Compared with the estimated 1.25D progression rate in the placebo group between baseline and 30-months (based on CLEERE data), the treatment group difference would be expected to be 0.50D in favor of the atropine group.

Assuming a slightly larger standard deviation of 0.90D at 30-months, and using a 2-sided t-test with alpha = 0.05, a sample size of 156 participants (104 in the atropine group and 52 in the placebo group) is needed to detect a mean difference in SER (atropine – placebo) at 30 months with 90% power, if the magnitude of the true mean difference is 0.50D or larger (Table 1). Accounting for up to 15% loss to follow-up over 30 months, the sample size *for this objective* is 186 participants overall (124 in the atropine group and 62 in the placebo group) under this scenario.

### 7.8.4 Summary of Sample Size Estimation

To be conservative, sample size for the study was chosen based upon the comparison of SER at 30 months (secondary objective) assuming that atropine group participants will progress at the same rate as placebo between 24 and 30 months and that expected treatment group difference between baseline and 30 months will be 0.50D, the scenario which has the largest sample size requirement.

The total sample size for the study will be 186 participants (124 in the atropine group and 62 in the placebo group).

### 7.8.5 Precision within Racial Subgroups

Table 2 below summarizes the expected ½-width of a 2-sided 95% confidence interval on the treatment group difference of myopia progression for the exploratory analysis within subgroups defined by race/ethnicity with an overall sample size of 156 participants completing the 30-month primary outcome exam.

For example: if participants of East Asian race/ethnicity make up 25% of the total sample (26 in atropine group and 13 in placebo group) and the standard deviation of progression in this group

is 0.80D, then the expected width of 2-sided 95% confidence interval for the treatment group difference in East Asians is ±0.55D.

**Table 2. Expected width of 2-sided 95% confidence interval on the treatment group comparison of myopia progression as a function of the standard deviation of progression and sample size per race/ethnicity subgroup***

| Race/Ethnicity Subgroup as Proportion of Total Sample Size | Standard Deviation of Mean SER Change from Baseline** (D) | | | | | | |
|---|---|---|---|---|---|---|---|
| | **0.8** | **0.9** | **1.0** | **1.1** | **1.2** | **1.3** | **1.4** |
| **10% n=15** | ±0.95 | ±1.06 | ±1.18 | ±1.30 | ±1.42 | ±1.54 | ±1.66 |
| **20% n=30** | ±0.63 | ±0.71 | ±0.79 | ±0.87 | ±0.95 | ±1.03 | ±1.11 |
| **25% n=39** | **±0.55** | ±0.62 | ±0.69 | ±0.76 | ±0.83 | ±0.89 | ±0.96 |
| **30% n=48** | ±0.49 | ±0.55 | ±0.62 | ±0.68 | ±0.74 | ±0.80 | ±0.86 |
| **40% n=63** | ±0.43 | ±0.48 | ±0.53 | ±0.59 | ±0.64 | ±0.69 | ±0.75 |
| **50% n=78** | ±0.38 | ±0.43 | ±0.48 | ±0.53 | ±0.57 | ±0.62 | ±0.67 |
| **60% n=93** | ±0.35 | ±0.39 | ±0.44 | ±0.48 | ±0.52 | ±0.57 | ±0.61 |
| **70% n=108** | ±0.32 | ±0.36 | ±0.40 | ±0.45 | ±0.49 | ±0.53 | ±0.57 |
| **80% n=126** | ±0.30 | ±0.34 | ±0.37 | ±0.41 | ±0.45 | ±0.49 | ±0.52 |
| **90% n=141** | ±0.28 | ±0.32 | ±0.35 | ±0.39 | ±0.42 | ±0.46 | ±0.49 |

*Cells show the expected ½-width of 2-sided 95% confidence interval on the treatment group comparison of myopia progression as a function of the standard deviation of progression and sample size per race/ethnicity subgroup.

**The range of standard deviation was based on the standard deviation of progression in CLEERE group data at 36-months, stratified by race/ethnicity group. At 36 months, the standard deviations of progression in Asian, Black, Hispanic, and White populations were 1.02D (95% CI =0.82 to 1.36D), 0.61D (95% CI =0.47 to 0.88D), 0.82D (95% CI =0.67 to 1.05D), and 0.92D (95% CI =0.70 to 1.36D) respectively.

# Chapter 8: DATA COLLECTION AND MONITORING

## 8.1 Case Report Forms and Device Data

The main study data are collected through electronic case report forms (CRFs). These electronic CRFs from the study website are considered the primary source documentation.
When data are directly collected in electronic case report forms, this will be considered the source data. Each participating site will maintain appropriate medical and research records for this trial, in compliance with ICH E6 and regulatory and institutional requirements for the protection of confidentiality of participants.

## 8.2 Study Records Retention

Study documents will be retained for a minimum of 3 years following the submission of the final financial report for the last grant cycle for which the study is conducted or 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or if not approved, 2 years after the IND is withdrawn, whichever is later. No records will be destroyed without the written consent of the sponsor. It is the responsibility of the sponsor to inform the investigators when study documents no longer need to be retained.

## 8.3 Quality Assurance and Monitoring

Designated personnel from the Coordinating Center will be responsible for maintaining quality assurance (QA) and quality control (QC) systems to ensure that the clinical portion of the trial is conducted and data are generated, documented and reported in compliance with the protocol, Good Clinical Practice (GCP) and the applicable regulatory requirements. Adverse events will be prioritized for monitoring.

A risk-based monitoring (RBM) plan will be developed and revised as needed during the course of the study, consistent with the FDA "Guidance for Industry Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring" (August 2013). Study conduct and monitoring will conform with 21 Code of Federal Regulations (CFR) 812.

The data of most importance for monitoring at the site are participant eligibility and adverse events. Therefore, the RBM plan will focus on these areas. As much as possible, remote monitoring will be performed in real-time with on-site monitoring performed to evaluate the verity and completeness of the key site data. Elements of the RBM may include:

- Qualification assessment, training, and certification for sites and site personnel
- Oversight of Institutional Review Board (IRB) coverage and informed consent procedures
- Central (remote) data monitoring: validation of data entry, data edits/audit trail, protocol review of entered data and edits, statistical monitoring, study closeout
- On-site monitoring (site visits): source data verification, site visit report
- Communications with site staff
- Patient retention and visit completion
- Quality control reports

- Management of noncompliance
- Documenting monitoring activities
- Adverse event reporting and monitoring

Coordinating Center representatives or their designees may visit the study facilities at any time in order to maintain current and personal knowledge of the study through review of the records, comparison with source documents, observation and discussion of the conduct and progress of the study.

## 8.4 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, GCP, or procedure requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

The site PI/study staff is responsible for knowing and adhering to their IRB requirements. Further details about the handling of protocol deviations will be included in the monitoring plan.

# Chapter 9: ETHICS/PROTECTION OF HUMAN PARTICIPANTS

## 9.1 Ethical Standard

The investigator will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Participants of Research codified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and/or the ICH E6.

## 9.2 Institutional Review Boards

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent/assent forms must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent and/or assent form will be IRB approved; a determination will be made regarding whether previously consented participants need to be re-consented.

## 9.3 Informed Consent Process

### 9.3.1 Consent Procedures and Documentation

Informed consent (and assent if required) is a process that is initiated prior to the parent and child agreeing to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of participation will be provided to the participants and their families. Consent forms and assent forms if required will be IRB-approved and the parent and child if required will be asked to read and review the document. The investigator will explain the research study to the parent and child and answer any questions that may arise. All parent(s) will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their child's rights as research participants. Parent(s) will have the opportunity to carefully review the written consent form and ask questions prior to signing.

The parent(s) and child should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The parent will sign the informed consent document prior to any procedures being done specifically for the study. The participants may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

### 9.3.2 Participant and Data Confidentiality

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The study monitor, other authorized representatives of the Jaeb Center for Health Research, or representatives of the IRB may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and Institutional regulations. Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the Jaeb Center for Health Research. Individual participants and their research data will be identified by a unique study identification number.

The study data entry and study management systems used by clinical sites and by the Jaeb Center for Health Research Coordinating Center research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the Jaeb Center for Health Research and made available to the public.

# Chapter 10: REFERENCES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