A Randomized Placebo-controlled Trial of Spectacles with Highly Aspherical Lenslets or 0.05% Atropine to Slow Progression of Myopia in Children

Protocol Identifying Number: MTS2
IND Sponsor: Jaeb Center for Health Research
IND #: 137441

Funded by: National Eye Institute, National Institutes of Health; EssilorLuxottica provided partial support

Version Number: 1.0
June 12, 2025

CONFIDENTIAL

KEY ROLES

JCHR Principal Investigator	
Name, degree	Danielle Chandler, MSPH
Title	Epidemiologist
Institution Name	Jaeb Center for Health Research 15310 Amberly Drive, Suite 350 Tampa, FL 33647 Phone: 1-888-797-3344 Fax: 1-888-697-3344 Email:dchandler@jaeb.org http://www.pedig.net
Signature/date	
Protocol Co-Chair	
Name, degree	Lori Ann F. Kehler, OD
Title	Associate Professor of Ophthalmology
Institution Name	Vanderbilt University Medical Center Vanderbilt Eye Institute 2311 Pierce Avenue Nashville, TN 37232 Phone: 615-936-2020 Email: lori.ann.kehler@vumc.org
Signature/date	
Protocol Co-Chair	
Name, degree	Katherine A. Lee, MD, PhD
Title	Consultant
Institution Name	Jaeb Center for Health Research 15310 Amberly Drive, Suite 350 Tampa, FL 33647 Phone: 1-888-797-3344 Fax: 1-888-697-3344 Phone: 1-888-797-3344 Email: kathlee058@gmail.com
Signature/date	
Medical Monitor	
Name, degree	Michael X. Repka, MD, MBA
Title	Medical Monitor
Institution Name	Wilmer Eye Institute 233 Wilmer Institute, 600 N Wolfe St Baltimore, MD 21287 Phone: (410) 955-8314 Fax: (410) 955-0809 Email: mrepka@jhmi.edu
Signature/date	

VERSION HISTORY

VERSION NUMBER	AUTHOR	APPROVER	EFFECTIVE DATE	REVISION DESCRIPTION
1.0			29Apr2025	Original document*

*Version in effect at study initiation

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
ANCOVA	Analysis of covariance
ATS	Amblyopia Treatment Study
BCVA	Best-corrected visual acuity
CI	Confidence interval
CFR	Code of Federal Regulations
CRF	Case report form
D	Diopter
DHHS	Department of Health and Human Services
DSMC	Data safety and monitoring committee
eCRF	Electronic case report form
FDA	Food and Drug Administration
GCP	Good clinical practice
HAL	Spectacles with Highly Aspherical Lenslets
HRQOL	Health-related quality of life
ICH	International Council for Harmonisation
IOD	Interocular difference
IRB	Institutional Review Board
JCHR	Jaeb Center for Health Research
logMAR	Logarithm of the minimal angle of resolution
NIH	National Institutes of Health
ODM	Occlusion dose monitor
PACT	Prism and alternate cover test
PEDIG	Pediatric Eye Disease Investigator Group
QA	Quality assurance
QC	Quality control
RBM	Risk-based monitoring
RCT	Randomized clinical trial
SER	Spherical equivalent refractive error

SITE PRINCIPAL INVESTIGATOR STATEMENT OF COMPLIANCE

Protocol Title: A Randomized Placebo-controlled Trial of Spectacles with Highly Aspherical Lenslets or 0.05% Atropine to Slow Progression of Myopia in Children

Protocol Version/Date: 1.0 12Jun2025

I have read the protocol specified above. In my formal capacity as a Site Principal Investigator, my duties include ensuring the safety of the study participants enrolled under my supervision and providing the Jaeb Center for Health Research, which serves as the JCHR for the protocol, with complete and timely information, as outlined in the protocol. It is understood that all information pertaining to the study will be held strictly confidential and that this confidentiality requirement applies to all study staff at this site.

This trial will be carried out in accordance with ICH E6 Good Clinical Practice (GCP) and as required by the following: United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812).

As the Principal Investigator, I will assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the Institutional Review Board (IRB), or other approved Ethics Committee, except where necessary to eliminate an immediate hazard(s) to the trial participants.

All key personnel (all individuals responsible for the design and conduct of this trial) have completed Human Participants Protection Training and Good Clinical Practice Training. Further, I agree to ensure that all staff members involved in the conduct of this study are informed about their obligations in meeting the above commitments.

Investigator's Signature _____ Date: _____ / _____ / _____
dd mmm yyyy

Investigator's Name: _____

Site Name/Number: _____

PROTOCOL SUMMARY

PARTICIPANT AREA	DESCRIPTION
Title	A Randomized Placebo-controlled Trial of Spectacles with Highly Aspherical Lenslets or 0.05% Atropine to Slow Progression of Myopia in Children
Précis	To date, randomized trials of low-concentration atropine eyedrops and specially designed spectacle lenses to slow the progression of myopia are limited in number and results are inconsistent in non-Asian children. Although results of some recent randomized clinical trials outside the US are promising, additional studies in children are needed to test the safety and efficacy of low-concentration atropine and specially designed spectacle lenses as treatments to slow the progression of myopia during the peak years for eye growth. After a run-in phase to demonstrate adherence with nightly eyedrops (artificial tears) and spectacle correction, children 5 to <12 years old with myopia of 0.75D to 6.00D cycloplegic spherical equivalent refractive error (SER) and at least 0.75D myopia in both principal meridians of each eye will be randomized in a 2x2 factorial design to treatment with 1) nightly 0.05% atropine or placebo eyedrops, and 2) spectacles with highly aspherical lenslets (HAL) or single vision spectacles, and followed every six months for 24 months. Change in axial length over 24 months and change in SER over 24 months are the primary and secondary outcomes, respectively. All children will return for a visit at 30 months (after 6 months of no treatment other than single-vision spectacles alone between 24 and 30 months).
Investigational Drug	Atropine 0.05% eyedrops
Investigational Device	Spectacle lenses with highly aspherical lenslets (HAL)
Treatment Groups	Eligible participants will be randomly assigned 1:1:1:1 to four treatment groups for 24 months: • Daily low-concentration atropine (0.05%) eyedrops plus spectacles with single vision lenses (SVL) (hereafter **ATROPINE** group) • Daily placebo eyedrops plus spectacles with single-vision lenses (SVL) (hereafter **PLACEBO** group) • Daily placebo eyedrops plus spectacles with highly aspherical lenslets (hereafter **HAL** group) • Daily low-concentration atropine (0.05%) eyedrops plus spectacles with highly aspherical lenslets (hereafter **COMBINED** group)
Objectives	**Primary 24-Month Timepoint (On Treatment) Objective** To compare the effectiveness of **ATROPINE** versus **PLACEBO and of HAL vs. PLACEBO** for slowing myopia progression in axial length (AL) over a two-year treatment period in children aged 5 to less than 12 years with SER myopia of 0.75D to 6.00D and at least 0.75D myopia in both principal meridians of each eye at the time of enrollment. **Secondary 24-Month Timepoint (On Treatment) Objective** To compare the effectiveness of **ATROPINE** versus **PLACEBO and HAL** versus **PLACEBO** for slowing myopia progression in SER over a two-year treatment period in children aged 5 to less than 12 years with SER myopia of 0.75D to 6.00D and at least 0.75D myopia in both principal meridians of each eye at the time of enrollment. **Exploratory 30-Month Timepoint (Off-Treatment) Objectives** All analyses described for the 24-month primary timepoint will be repeated as exploratory analyses at 30 months to evaluate the progression of myopia over 30 months (after 6 months of no treatment other than single-vision spectacles alone between 24 and 30 months).

PARTICIPANT AREA	DESCRIPTION
	Exploratory Objectives at the Primary 24-Month Timepoint (On Treatment) To compare the effectiveness of **COMBINED** therapy versus **PLACEBO** for slowing myopia progression over a two-year treatment period in children aged 5 to less than 12 years with SER myopia of 0.75D to 6.00D and at least 0.75D myopia in both principal meridians of each eye at the time of enrollment. To compare the effectiveness of **COMBINED** therapy versus **HAL** for slowing myopia progression over a two-year treatment period in children aged 5 to less than 12 years with SER myopia of 0.75D to 6.00D and at least 0.75D myopia in both principal meridians of each eye at the time of enrollment. To compare the effectiveness of **COMBINED** therapy versus **ATROPINE** for slowing myopia progression over a two-year treatment period in children aged 5 to less than 12 years with SER myopia of 0.75D to 6.00D and at least 0.75D myopia in both principal meridians of each eye at the time of enrollment.
Study Design	Multicenter Phase III Randomized Clinical Trial
Number of Sites	18 to 40
Endpoints	**Primary Efficacy Outcome (On-Treatment):** Change in axial length from baseline to 24 months (on-treatment) as measured by a masked examiner using cycloplegic biometry. **Key Secondary Efficacy Outcome (On-Treatment):** Change in spherical equivalent refractive error (SER) from baseline to 24 months (on-treatment), as measured by a masked examiner using cycloplegic autorefraction. **Exploratory Efficacy Outcomes (Off-Treatment):** Change in axial length and SER from baseline to 30 months. **Key Safety Outcomes:** • Proportion of adverse events reported in each group. • Proportion of participants with loss of >2 logMAR lines in best-corrected distance visual acuity in either eye at any follow visit.

Population	**Key Eligibility Criteria for Enrollment Into Run-in Phase:**
	• Age 5 to <12 years at time of enrollment. Children within 4 weeks of their 12th birthday are not eligible.
	• Refractive error meeting the following by cycloplegic autorefraction:
	  ○ Myopia of at least 0.75D in both principal meridians of each eye
	  ○ Myopia 0.75D to 6.00D SER in both eyes
	  ○ Astigmatism <2.50D in both eyes
	  ○ SE Anisometropia <1.50D
	• Investigator has confirmed the following regarding best-corrected distance visual acuity (VA) in habitual spectacles or trial frames using the investigator's preferred optotype VA testing method:
	  ○ VA is age normal in both eyes[1,2]
	  ○ 5-6 years: approximately 20/32 or better, ≤ 0.24 logMAR, ≥ 73 letters
	  ○ 7-12 years: approximately 20/25 or better, ≤ 0.14 logMAR, ≥ 78 letters
	  ○ Interocular difference ≤2 logMAR lines (0.2 logMAR) or ≤ 10 letters
	• Wearing single-vision spectacles ≥90% of waking hours ≥30 days before enrollment
	• Agree to refrain from wearing contact lenses for duration of the study
	• Willing to wear study spectacles full time (i.e at least 10 hours per day)

PARTICIPANT AREA	DESCRIPTION
	• No current or past pharmacologic agents or light therapy used for myopia treatment • No current or previous use of bifocals, progressive-addition lenses, multi-focal contact lenses, or focus- or contrast-modifying spectacle lenses • No current or previous use of orthokeratology, rigid gas permeable, or other contact lenses used to slow myopia progression
Sample Size	87 participants per group (348 total)
Phase	Phase III Randomized Clinical Trial
Participant Duration	31 months
Study Duration Planned (1st participant in to last out)	46 months
Protocol Overview/Synopsis	Upon signing informed consent and assent (if needed), eligible children are considered enrolled into a 2 to 4-week run-in phase designed to determine adherence with nightly eyedrops (artificial tears) and spectacle correction. If adherence criteria are met (≥90% of expected days with eyedrops administered), and the participant still meets eligibility criteria, they will be randomized to 1 of 4 treatments described above (ATROPINE, HAL, PLACEBO, or COMBINED groups) for 24 months. Four weeks after randomization, each participant will return for a Treatment Initiation Visit to be fitted with a new pair of spectacles and receive study eyedrops. Four weeks after initiating randomized treatment, sites will contact the parent to check for treatment problems and to encourage adherence with the prescribed treatment. Study visits will occur at 6, 12, 18, and 24 months (on-treatment primary outcome), and 30 months (off-treatment outcome) from randomization. Study glasses will be changed every 6 months and dispensed at glasses fitting visits occurring four weeks after every follow up visit except the 30-month final study visit. After the Treatment Initiation Visit, Eyedrops will be dispensed at each 6, 12, and 18-month office visits.

STUDY SUMMARY FLOW CHART

ENROLLMENT INTO RUN-IN PHASE

Major Eligibility Criteria at Enrollment for Run-in Phase

- Age 5 to <12 years of age at enrollment. Children within 4 weeks of their 12th birthday are not eligible.
- Refractive error meeting the following by cycloplegic autorefraction:
  - Myopia of 0.75D to 6.00D SER and at least 0.75D in both principal meridians of each eye
  - Astigmatism <2.50D in both eyes
  - Anisometropia <1.50D SE
  - Wearing single-vision spectacles ≥90% of waking hours ≥30 days duration before enrollment. (Exception exists for subjects with broken or lost spectacles. Details in section 2.3.)
- Investigator has confirmed the following regarding best-corrected distance visual acuity (VA) in habitual spectacles or trial frames using the investigator's preferred optotype VA testing method:
  - VA is age normal in both eyes (ref)
    - 5-6 years: approximately 20/32 or better, ≤ 0.24 logMAR, ≥ 73 letters
    - 7-12 years: approximately 20/25 or better, ≤ 0.14 logMAR, ≥ 78 letters
  - Interocular difference ≤2 logMAR lines (0.2 logMAR) or ≤ 10 letters
- Willing to wear study spectacles for at least 10 hours per day,6 days per week
- No current or past pharmacologic agents or light therapy used for myopia treatment
- No current or previous use of bifocal spectacles, progressive-addition lenses, defocus or contrast modifying spectacle lenses, or multi-focal contact lenses
- No current or previous use of orthokeratology, rigid gas permeable, or other contact lenses being used to slow myopia progression
- Agree to refrain from wearing contact lenses for duration of the study
- No known atropine allergy
- No strabismus other than a phoria

Enrollment Exam Procedures

- Cycloplegic Autorefraction
- Cycloplegic Axial Length Measurement
- Spectacle Prescription Determination with Cycloplegia (using investigators usual method) to prescribe new spectacles if necessary (broken, lost, or not meeting tolerances)
- Prescribe artificial tear eyedrops to be used one drop to each eye until run-in follow up/randomization visit in 2-4 weeks

↓

RUN-IN PHASE (2-4 WEEKS)

- Run in phase starts the day after enrollment for all participants.
- All participants are treated with nightly artificial tear eyedrops
- Habitual spectacles are continued until the Randomization Visit or until new spectacles are obtained, if prescribed

↓

RANDOMIZATION VISIT (2-4 WEEKS AFTER ENROLLMENT)

assessed in new spectacles (if prescribed); otherwise, habitual spectacles. Trial frames if spectacles out of tolerances.

Additional Eligibility Criteria for Randomization

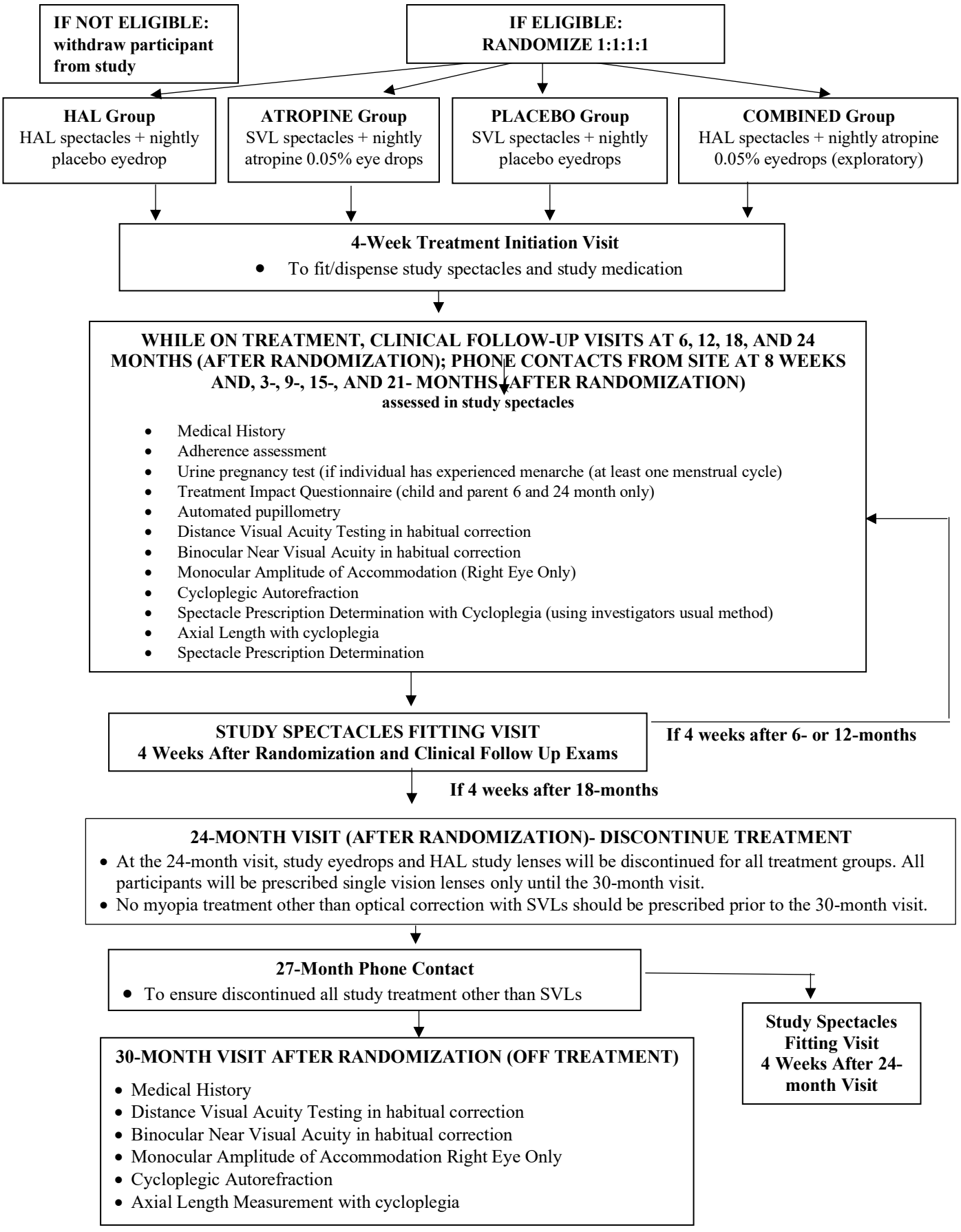
Best-corrected distance visual acuity (VA) meeting the following:

- VA is age normal in both eyes
- 5-6 years: approximately 20/32 or better **by ATS-HOTV**
- 7-12 years: approximately 20/25 or better, ≤ 0.14 logMAR, ≥ 78 letters using E-ETDRS
- Interocular difference ≤2 logMAR lines (0.2 logMAR) or ≤ 10 letters

- Current spectacles meet refractive error tolerances
- At least 90% adherent with artificial tear eyedrop installation

Testing Procedures

- Distance Visual Acuity Testing (ATS-HOTV for children <7 years old; E-ETDRS for children ≥7 years old)
- Binocular Near Visual Acuity
- Monocular Amplitude of Accommodation (Right Eye Only)
- Automated pupillometry (for sites with equipment deemed study qualified)
- Urine Pregnancy Test (for all individuals who have experienced menarche (i.e. at least one menstrual cycle)


IF NOT ELIGIBLE: withdraw participant from study
IF ELIGIBLE: RANDOMIZE 1:1:1:1
HAL Group
HAL spectacles + nightly placebo eyedrop
ATROPINE Group
SVL spectacles + nightly atropine 0.05% eye drops
PLACEBO Group
SVL spectacles + nightly placebo eyedrops
COMBINED Group
HAL spectacles + nightly atropine 0.05% eyedrops (exploratory)
4-Week Treatment Initiation Visit
To fit/dispense study spectacles and study medication
WHILE ON TREATMENT, CLINICAL FOLLOW-UP VISITS AT 6, 12, 18, AND 24 MONTHS (AFTER RANDOMIZATION); PHONE CONTACTS FROM SITE AT 8 WEEKS AND, 3-, 9-, 15-, AND 21- MONTHS (AFTER RANDOMIZATION)
assessed in study spectacles
Medical History
Adherence assessment
Urine pregnancy test (if individual has experienced menarche (at least one menstrual cycle)
Treatment Impact Questionnaire (child and parent 6 and 24 month only)
Automated pupillometry
Distance Visual Acuity Testing in habitual correction
Binocular Near Visual Acuity in habitual correction
Monocular Amplitude of Accommodation (Right Eye Only)
Cycloplegic Autorefraction
Spectacle Prescription Determination with Cycloplegia (using investigators usual method)
Axial Length with cycloplegia
Spectacle Prescription Determination
STUDY SPECTACLES FITTING VISIT
4 Weeks After Randomization and Clinical Follow Up Exams
If 4 weeks after 6- or 12-months
If 4 weeks after 18-months
24-MONTH VISIT (AFTER RANDOMIZATION)- DISCONTINUE TREATMENT
At the 24-month visit, study eyedrops and HAL study lenses will be discontinued for all treatment groups. All participants will be prescribed single vision lenses only until the 30-month visit.
No myopia treatment other than optical correction with SVLs should be prescribed prior to the 30-month visit.
27-Month Phone Contact
To ensure discontinued all study treatment other than SVLs
Study Spectacles Fitting Visit 4 Weeks After 24-month Visit
30-MONTH VISIT AFTER RANDOMIZATION (OFF TREATMENT)
Medical History
Distance Visual Acuity Testing in habitual correction
Binocular Near Visual Acuity in habitual correction
Monocular Amplitude of Accommodation Right Eye Only
Cycloplegic Autorefraction
Axial Length Measurement with cycloplegia

SCHEDULE OF STUDY CALLS, VISITS, AND PROCEDURES

	Enrollment Visit	Random-ization Visit	4-Week Treatment Initiation Visit	6-Month Clinical Visit	12-Month Clinical Visit	18-Month Clinical Visit	24-Month Clinical Visit	30-Month Clinical Visit	Spectacle Fittings After Each Clinical Visit[1]	Phone Calls[2]
Consent/assent (Enrollment)	I									
Medical history	I			I	I	I	I	I		
Adverse events				I[3]	I[3]	I[3]	I[3]	I		CT or CO
Demographics	CO, CT or I									
Urine pregnancy test[4]		CO, CT or I		CO, CT or I[3]	CO, CT or I[3]	CO, CT or I[3]	CO, CT or I[3]			
Treatment Impact Questionnaire (parent and child versions)				CO, CT or I			CO, CT or I			
Lensometry		CO, CT or I	SF	CT	CT	CT	CT	CT or I	SF	
Automated pupillometry		CT or I		CT	CT	CT	CT	CT or I		
Monocular distance visual acuity		CT or I		CT	CT	CT	CT	CT or I		
Binocular near visual acuity		CT or I		CT	CT	CT	CT	CT or I		
Monocular amplitude of accommodation		CT or I		CT	CT	CT	CT	CT or I		
Dilating eye drop instillation[5]	CO, CT or I			CO or CT	CO or CT	CO or CT	CO or CT	CO, CT or I		
Cycloplegic autorefraction[5]	CT, BT or I			BT or I	BT or I	BT or I	BT or I	CT, BT or I		
Axial length with cycloplegia[5]	CT, BT or I			BT or I	BT or I	BT or I	BT or I	CT, BT or I		
Refractive error determination with cycloplegia	I			I	I	I	I	I		
Initiate run-in phase[6]	I									
Assess eligibility / randomize participant		I								
Dispense study spectacles			SF						SF	
Dispense study medication			CT or CO	CT or CO	CT or CO	CT or CO				
Collect unused study medication and empty bottles				CT or CO	CT or CO	CT or CO	CT or CO			
Collect study spectacles (when new spectacles fitted)[7]									CT, CO, or SF	
Review treatment and encourage adherence										CT or CO

There is a minimum of two study personnel required to conduct this study; roles may also be split into additional personnel. Backup personnel are encouraged.

1) Investigator/Biometry Tester
2) Coordinator/Certified Tester/Spectacles Fitter

I = Investigator (MD, DO, or OD). For all post-randomization visits, the Investigator may not see the participant before dilating eyedrops are administered, unless the participant is wearing stereo spectacles (to prevent observation of pupils before dilating eyedrops are administered). After dilating eyedrops have been administered, the Investigator may see the participant without the participant wearing stereo spectacles. The Investigator may also serve as Biometry Tester, but may not serve as Coordinator, Certified Tester, or Spectacles Fitter. **CT** = Certified Tester. The CT may be the Coordinator, Spectacles Fitter, or other person also trained and certified in study procedures. The Certified Tester may not be the Biometry Tester or the Investigator. **BT** = Biometry Tester. The BT is trained and certified in autorefraction and biometry. For all post-randomization visits, autorefraction and biometry must be performed by either the Investigator or a Biometry Tester. The BT will only see the participant after dilating eyedrops have been administered. The Investigator may serve as BT, but the BT may not be the Coordinator, Certified Tester, or Spectacles Fitter. **CO** = Coordinator. The Coordinator may also serve as Certified Tester and/or Spectacles Fitter, but not as Biometry Tester or Investigator. **SF** = Spectacles Fitter. The study Spectacles Fitter will be trained and certified to fit, dispense, and repair study spectacles. The Spectacles Fitter may be the Coordinator, Certified Tester, or another person trained to handle study spectacles. The Spectacles Fitter is unmasked to type of spectacles and may not be the Biometry Tester or the Investigator.

[1]There will be a spectacles dispensing visit 4 ±2 weeks after each semi-annual clinical research visit conducted by the Coordinator or Certified Tester and Spectacles Fitter.
[2]Phone calls will occur at 8 weeks and at, 3, 9, 15, 21, and 27 months to review treatment, manage any problems encountered and encourage compliance.
[3]Participant should wear stereo spectacles to prevent Investigator from observing pupils.
[4]For all individuals who have experienced menarche.
[5]Testing is repeated at randomization only if >28 days since enrollment (consent/assent).
[6]At the end of the Enrollment Visit, the participant will begin nightly artificial tears for 2 to 4 weeks.
[7]The SVL spectacles prescribed at 24-months may be kept by participants after the study ends.

Chapter 1: Background Information

1.1 Epidemiology and Clinical Characteristics

Myopia is one of the most commonly occurring ocular disorders, with an estimated prevalence in children of 1.2% to 59.1%,[3-5] in population-based studies conducted worldwide with variation attributed to age, race, and definition of myopia. In children 6-72 months of age in the US, population-based prevalence has been reported at 0.7-1.2% in non-Hispanic white children,[6,7] 3.98% in Asian children,[7] 5.5-6.6% in African American children,[6,8] and 3.7% in Hispanic children.[8] 50% of children aged 11 to 13 years enrolled in a large health plan in California who had eye examinations with refraction were found to have myopia[9] Longitudinal studies demonstrate a relatively high and increasing prevalence of myopia in adults.[10-12] In a study of white children and black children between 12 and 17 years of age, the US prevalence of myopia increased from 24% in 1971-1972 to 34% in 1999-2004.[8]

Progression of myopia primarily occurs due to axial elongation of the eye. In a 2023 Cochrane review[13] of interventions for myopia control in children living mainly in China or other Asian countries (61% of studies) and North America (20% of studies), the meta-analyses of control populations estimated the median progression of myopia to be -0.65D over 1 year (36 studies; 2846 participants analyzed) and −1.02D over 2 years (24 studies; 2282 participants). Retarding progression of myopia has been the focus of much research,[13] given high levels of myopia are associated with retinal and vitreous detachment, myopic macular degeneration, and increased risk of glaucoma and cataract.[14,15]

A report for the US population in 2014 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.[16] This translated into a population burden of approximately 9.6 million adults with high myopia and approximately 41,000 adults with myopic choroidal neovascularization.

1.2 Treatments to Slow Myopia Progression

Treatments to slow myopia progression could be important for preventing the development of high myopia and associated sequelae although not yet demonstrated to be effective in long-term studies. Various management approaches have been reported to decrease the rate of myopic progression in children, with varying success, including the use of anti-muscarinic pharmacological agents (e.g., atropine, pirenzepine, cyclopentolate), bifocals, progressive additional lenses, contact lenses, contact lenses with peripheral myopic defocus, under-correction or part-time optical correction, and orthokeratology.[13,17]

The Cochrane review[13] primarily compared pharmacological and optical treatments, finding that these interventions may slow myopia and reduce axial elongation over one year. However, results were heterogeneous, with some treatments seeming to be less effective in year 2 compared to year 1.

1.2.1 Atropine Treatment

The mechanism by which atropine slows myopia progression is believed to be unrelated to accommodation but is otherwise largely unknown. Atropine has been hypothesized to modify eye growth regulatory pathways and reduce axial elongation through several mechanisms including locally at the retinal level (potentially through dopamine channels), at the choroidal level (potentially through increasing its thickness), or through other mechanisms including nitric oxide

and gamma-aminobutyric acid (GABA); however, such conclusions on causal relationships between these effects and atropine are mixed.[13,18]

1.2.1.1 Low-Concentration Atropine Eye Drops in Non-Asian Populations

Four studies of 0.01% and 0.02% atropine eye drops have been conducted in largely non-Asian populations in North America, Europe and Australia:

- The Pediatric Eye Disease Investigator Group (PEDIG) randomized trial in the US compared 0.01% atropine to placebo[19] and found no difference in mean (SD) change in SER over 24 months. At the 24-month primary outcome visit, the adjusted mean (95% CI) change in SER from baseline was −0.82D (−0.96 to −0.68) and −0.80D (−0.98 to −0.62) in the atropine and placebo groups, respectively (adjusted difference = −0.02D; 95% CI, −0.19 to +0.15D; $P = 0.83$).
- The Western Australian Atropine for the Treatment of Myopia (WA-ATOM) 2-year randomized trial [20] found myopia progression of -0.64D with 0.01% atropine compared with -0.78D with placebo (adjusted mean difference over 2 years = 0.14D; 95% CI: -0.03 to +0.29D).
- The Childhood Atropine for Myopia Progression (CHAMP) randomized clinical trial[21] conducted at sites across North America and Europe found 0.02% atropine (primary outcome comparison) was not effective for slowing mean SER progression compared with placebo (least squares mean difference, 0.10D; 95% CI, −0.02 to 0.22 D; $P = .10$) at 36 months , whereas efficacy was suggested for 0.01% (secondary outcome comparison) compared with placebo (least squares mean difference, 0.24D; 95% CI, 0.11 to 0.37D; $P < .001$).
- The Myopia Outcome Study of Atropine in Children (MOSAIC)[22] conducted in Ireland found SER change over 24 months was not significantly different between 0.01% atropine and placebo groups (-0.53D in the 0.01% atropine and -0.63D in the placebo group; adjusted difference in SER effect = 0.12 D, $p = 0.07$).

Given the lack of evidence supporting efficacy of the 0.01% and 0.02% atropine eyedrops in slowing myopia progression in the United States, there is a need to evaluate stronger atropine concentrations to determine whether a meaningful treatment effect can be found without unreasonable side effects.

Loughman et al[23] (MOSAIC2) evaluated the effectiveness of 0.05% atropine in a mostly non-Asian population, in a 1-year extension of their original two-year randomized trial[22]: participants originally randomized to two years of placebo eyedrops were given 0.05% atropine eyedrops for the third year (n=61) and participants initially randomized to 0.01% atropine for two years were re-randomized to placebo or tapering of 0.01% for the third year. Over the third year, those using 0.05% atropine showed 0.13D less myopia progression and 0.06mm less axial elongation, compared with the placebo/tapering group, suggesting a possible effect of 0.05% atropine in this group.

There are currently no published randomized trials using 0.05% in largely non-Asian populations. However, as of August 2024, there are two such randomized trials registered on ClinicalTrials.gov indicating active recruitment, one based in the Netherlands comparing 0.05% and 0.50% atropine concentrations (NCT05667454) and the other in France, comparing defocus incorporated multiple segments (DIMS) lenses, 0.05% atropine and single vision lenses (NCT05062031).

1.2.1.2 Low-Concentration Atropine Eye Drops in Asian Populations

The earliest randomized trials of low-concentration atropine for slowing myopia progression were conducted in Asian populations.

- In 1999, Shih and colleagues[24] reported outcomes on 186 children (of 200 randomized) 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 0.5% tropicamide. Children received atropine or tropicamide eyedrops nightly for up to 2 years. All three atropine-treatment groups had less 2-year 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[25] studied the effect of multi-focal spectacles 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 spectacles. Myopia progressed only -0.42D±0.07D with atropine + multi-focal lenses compared with -1.19D±0.07D with multi-focal lenses alone 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.
- The ATOM2 study[26] randomized 400 children (2:2:1) with myopia of at least -2.00D to 3 different concentrations of atropine (0.5%, 0.1% and 0.01%) and found 2-year myopia progression of -0.30±0.60D, -0.38±60D, and -0.49±0.63D respectively. Although there was no control group, myopia progression was significantly lower than that observed in controls in ATOM1[27] (-1.20D±0.69D). 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).

Two recent randomized trials[28-30] provide data on 0.05% atropine eye drops for slowing myopia progression in Asian populations.

The LAMP study[29,31] randomized 438 children aged 4-12 years with at least -1.00D of myopia to 0.05%, 0.025%, 0.01% atropine, or placebo eye drops For the 383 (87%) children completing the 12-month outcome,[28] the mean change in spherical equivalent refractive error from baseline was -0.27D, -0.46D, -0.59D in the 0.05%, 0.025%, and 0.01% atropine groups respectively compared with 0.81D in the placebo group (p <0.001); the mean change in axial length from baseline was 0.20mm, 0.29mm, 0.36mm in the 0.05%, 0.025%, and 0.01% atropine groups compared with 0.41mm in the placebo group (<0.001).

For the 93 children completing 24 months (85% of 109 randomized) of treatment and follow up,[29] the mean change in spherical equivalent refractive error from baseline was -0.55D, -0.85D, -1.12D and in the 0.05%, 0.025%, and 0.01% atropine groups, respectively. (There were no placebo controls after 12 months). The mean change in axial length from baseline was 0.39 mm, 0.50 mm, 0.59mm and in the 0.05%, 0.025%, and 0.01% atropine groups, respectively.

Zhu et al[30] enrolled 142 children aged 7-12 years with -1.00 D to -6.00 D of myopia and randomized to 0.05% atropine or placebo eye drops. For the 72 children using 0.05% for 24 months, the mean change in spherical equivalent refractive error was -0.46±0.30D vs -1.72±1.12D in children using placebo (n=70), for a mean difference of 1.26±0.08D (*95% CI 1.10 to 1.42 D calculated using reported standard error of ±0.08;* P<0.001); mean change in axial length was 0.26±0.30 mm in the 0.05% atropine group vs 0.76±0.62 mm with placebo, for a mean difference of 0.05±0.04 mm (*95% CI 0.42 to 0.58 D calculated using reported standard error of* ±0.04; P=0.002).

Four additional ongoing randomized trials of 0.05% atropine (versus either the Stellest lens, the DIMS lens, 0.01% atropine or 0.025% atropine) in Asian populations are on ClinicalTrials.gov (NCT06344429, NCT06282848, NCT02130167, NCT05597163).

1.2.1.3 Higher Atropine Concentrations (>0.05%)

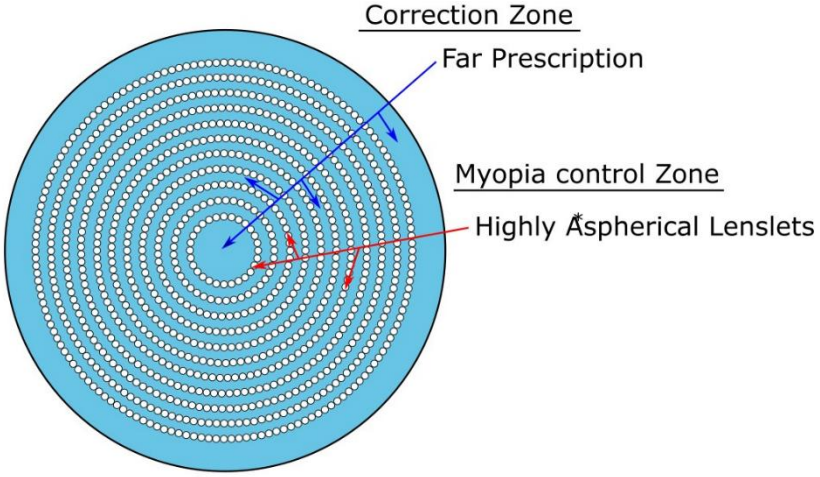
Higher concentrations of atropine (>0.05%) have been studied and appear to be more effective at reducing myopia progression,[13] but are also associated with considerable side effects[13] and, therefore, were not further considered for this study.

1.2.2 Spectacles with Highly Aspherical Lenslets (HAL)

The utilization of optical defocus technology for slowing myopia progression has gained momentum in recent years.

One example utilizing defocus technology is spectacle lenses with Highly Aspherical Lenslets (HAL), which provide 1) myopia correction through a single vision zone, and 2) myopia progression control through a constellation of highly aspherical contiguous lenslets spread on 11 rings. The light rays passing through the lenslets create a volume of non-focused light in front of the retina following its shape which result in slowing the elongation of the eye in myopic children.

Schematic describing a spectacle lens with Highly Aspherical Lenslets



1.2.2.1 HAL Lens Mechanism of Action

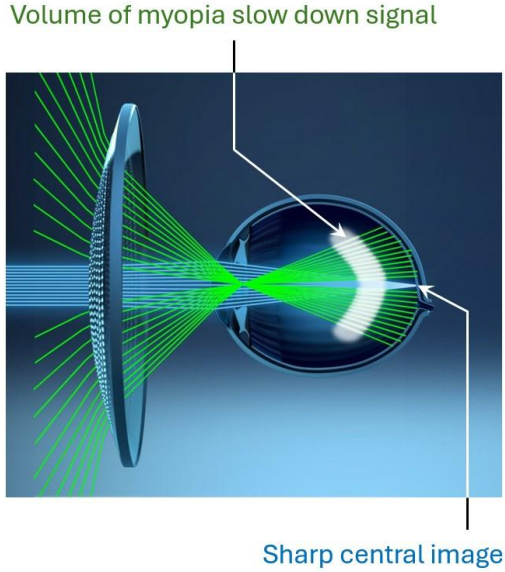
Studies in various animal species have shown that hyperopic defocus in the central part of the retina stimulates eye elongation.[32,33] Additionally, research indicates that relative peripheral hyperopia can promote the development of central axial myopia in primates, even when clear central retinal images are present.[33,34] These findings highlight the critical role of the peripheral retina in regulating eye growth.

Further animal studies have demonstrated that when exposed to competing defocus (simultaneous myopic and hyperopic defocus), the emmetropization process is more influenced by myopic defocus than hyperopic defocus, protecting the eye against elongation.[33,35] Two other studies investigated in animals the effects of aspherical lenses with a power gradient on emmetropization .[36,37] Unlike competing defocus lenses, which focus light on two distinct surfaces, these aspherical lenses redirect light rays continuously in a nonlinear manner, creating a three-dimensional quantity of light in front of the retina known as the volume of myopic defocus. Greater asphericity, corresponding to a larger volume of myopic defocus, has been shown to reduce lens-induced myopia in chicks.[36,37]

Based on these findings:

- The light rays passing through the far prescription zone of the lens focuses a first signal on the retina to ensure a sharp perception of the world.
- The light rays passing through the Highly Aspherical Lenslets create a volume of non-focused light in front of the retina. The asphericity of the lenslets is calculated differently for each ring, ensuring that this volume of non-focused light follows the shape of the myopic retina. This second signal acts as a signal to slow down axial elongation due to myopia progression.

Schematic describing how light rays penetrating through a spectacle lens with Highly Aspherical Lenslets split into two different signals. The first signal (blue) is focused on the retina to grant sharp vision and corresponds to the correction signal. The second one (white) is a volume of non-focused light displayed inside the retina and corresponds to the myopia progression control signal.



1.2.2.2 Characteristics of HAL Lens

- Material: polycarbonate
- Coating: Crizal(R) Rock TM
- Back surface: Single vision (spherical or toric) digitally surfaced
- Front surface: Highly Aspherical Lenslets
- Anti-reflective coating

1.2.2.3 HAL Lens Clinical Trial Data

Highly aspherical lenslets (HAL) lenses have been studied in two randomized trials in Asian populations (China and Vietnam).[38-40] One study evaluated outcomes after 12 months or more.[38,39] Two lens designs were initially evaluated: highly aspherical lenslets and slightly aspherical lenslets. Because a greater treatment effect between the two was seen for the HAL design, this design is the subject of ongoing research.

In a study of 170 children 8 to 13 years old randomized to either highly aspherical, slightly aspherical, or single-vision lenses, the change in SER with the highly aspherical (HAL) lenses over 12 months was -0.30D (SE 0.06) (n=54) compared with the change of -0.81 (SE 0.06) with single-vision lenses (N=52).[38] The change in axial length was 0.13mm (SE 0.02) for the HAL lenses and 0.36mm (SE 0.02) for single-vision lenses.

Over 24 months, the mean change in SER was -0.68 (SE 0.07) D with HAL lenses (n=54) and -1.45 (SE 0.08) D for single vision lenses (n=50), whereas the change in axial length was 0.34 (SE 0.03) mm with HAL lenses and 0.69 (SE 0.04) mm with single vision lenses.[39]

The selection of the HAL lenses for use in this study was based on several factors. Three brands of spectacle lenses that had shown promise in slowing myopia progression in European and Asian populations were reviewed by the study planning committee. Factors that were considered included:

- Mechanism of action and robustness of scientific rationale
- Effectiveness: mean change in both SER and AL
- Developmental status and the availability of multi-year data
- Competing studies in US
- Safety/adverse events data publicly available
- Frame selection and the manner in which spectacles were fit
- Data publicly available on rebound effect
- Data publicly available on adherence
- Inventory availability in US
- Feasibility of collaboration agreement
- US Food and Drug Administration designation as breakthrough investigational device

The HAL lenses had data at two and three years (with four- and five-year data in progress) that showed promise in treatment effect, adherence, rebound effect, and safety at the time of review (May 2024). Both PEDIG and Essilor were optimistic that terms of the collaboration agreement could be agreed upon. The HAL spectacle lenses received breakthrough device designation by the FDA in May 2021. As such, the HAL lenses were chosen over the other two lens designs considered.

1.2.3 Combined Atropine and HAL Lenses

Emerging data suggests an additive effect of low-concentration atropine and HAL lenses.[41,42] An abstract by Vagge et al[41] reported outcomes from a retrospective study of Italian children age 6 to 13 years old (mean 9.2 years) with myopia (range not defined). Children were grouped according to the treatment(s) used: HAL only (N=41), 0.01% atropine only (N=34), combined HAL and 0.01% atropine (N=33) and SVL "controls" (N=35). The three treatment groups each significantly slowed SER myopia progression and AL elongation at 12 months compared with the SVL group ($p< 0.001$). At 12 months, the combined HAL and atropine group significantly reduced SER progression compared with the HAL-only group and the atropine group (p values < 0.03). The combined HAL and atropine group showed reduced AL elongation compared with 0.01% atropine group (p value < 0.05) at 12 months, but showed no difference compared with the HAL group ($p=0.52$).

A one-year non-randomized prospective study of combined HAL and atropine treatment was included in a non-peer-reviewed article.[42] The study included 50 Singaporean children age 6-11 years old, with myopia -1.50D to -6.00D and astigmatism <2.00D, who were being treated with atropine 0.01% or 0.025% for an unspecified duration, and had ≥0.50 progression in at least one eye in the previous 6 months. Treatment with HAL lenses was added and participants continued treatment with atropine 0.01% or 0.025%. The article reported a 75% reduction in SER change and 42% reduction in AL change at one year, presumably compared to the prior year on SVL plus atropine alone. The conclusion that combination therapy is more effective than atropine alone was

not based upon a comparison with children staying on the original therapy and thus should not be considered adequate evidence of efficacy.

1.3 Rationale for Present Study

Despite an increasing number of randomized trials evaluating strategies to slow myopia progression in children, evidence of effectiveness for any intervention in US populations is still lacking. Randomized trials of 0.01% atropine have shown little to no clinically meaningful effect.[19,21] Thus, there is a need to evaluate stronger atropine concentrations, balancing the anticipated increase in effectiveness due to greater potency with the possibility of increased side effects. For this reason, a 0.05% concentration was chosen for the present study rather than a stronger concentration.

While emerging data on HAL lenses in primarily Asian populations are compelling, studies in non-Asian populations are needed.[43] In addition, because there may be a combined benefit when using 0.01% or 0.02% atropine *and* HAL lenses simultaneously,[41,42] the study includes an exploratory combined treatment group of atropine 0.05% and HAL lenses to provide safety and tolerability data of the combination treatment in US children, and to provide an estimate of the effect of combined treatment that may be used in future study design.

1.4 Public Health Importance

Increasing prevalence of myopia and the unresolved problem of myopia progression pose significant healthcare concerns. Increasing axial length and high levels of myopia (>6.00D) are associated with serious ocular co-morbidities, (include retinal detachment, myopic maculopathy, glaucoma, and cataract), often resulting in visual impairment or even blindness.[44] While children with high myopia are at the greatest risk for these complications, both moderate and low myopes are at increased risk relative to persons with emmetropia.[45] Reduced myopic progression would allow many individuals to 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 many individuals progress to moderate myopia and, by doing so, are at increased risk for myopic co-morbidities compared with emmetropic individuals. The objective of slowing the progression of myopia is that the associated risks that come with higher myopia may be reduced for a large population.

Flitcroft has opined that it is important to slow progression even in the moderate range of -1.00 to -6.00D 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, there was a greater prevalence of myopic maculopathy for myopia -3.00 to -4.99D compared with emmetropia.[47] Tideman et al.[44] analyzed several population-based studies and found that visual impairment was increased in adults with higher axial lengths and higher spherical myopia, for example myopia -6.00 or less had a cumulative risk of vision impairment of 39% (SE 4.9%) at 75 years of age.

Treatment for myopia progression has proven effective; however, no treatment prevents myopia onset.[13] Low-concentration atropine treatment or HAL spectacle lenses potentially reduce the prevalence of high myopia and myopic progression among children with moderate myopia, thereby possibly reducing the incidence of undesirable sequelae associated with myopia. Additionally, Bullimore et al has suggested that slowing myopia by 1 diopter would reduce the likelihood of a patient developing myopic maculopathy by 40%.[48]

1.5 Potential Risks and Benefits of Study Treatment

1.5.1 Known Potential Risks of Atropine Eye Drops

Atropine use can be associated with photophobia, mydriasis, accommodative paralysis, allergic or hypersensitivity reactions, superficial keratitis and reduced lacrimation. As summarized in the Living Cochrane review,[13] adverse events related to atropine are concentration dependent and occurred with greater frequency in studies using high (≥0.5%) compared to moderate or low (<0.1%) concentrations of atropine.

In the Yam et al randomized trial[29] (Asian population), photochromic spectacles for light sensitivity were needed in 29 (31%) of 93 treated with 0.05% atropine over 1 year and 31 (33%) over 2 years. Progressive lenses for near blur were needed in only 1 (1%) over 2 years. In the same study, allergic conjunctivitis occurred in 2 (2%) of 93 over 1 year and 9 (10%) over 2 years. These rates were comparable to those in children treated with 0.01% and 0.025% concentrations.

In the MOSAIC2 extension study of a randomized trial[23] of 66 (mostly non-Asian) participants using one year of atropine 0.05% following two years of placebo treatment, blurred near vision was reported in 10 (15%; 3 of 10 opted to use varifocal lenses) and photophobia was reported in 5 (7.6%; none opted to use photochromic lenses). Overall, the rate of adverse events was higher in participants using 0.05% in the third year than in those using 0.01% atropine or placebo during that time.

Potential systemic side effects include dry skin and mouth, tachycardia, fever, flushing and irritability. Of these specific systemic effects, none have been reported in studies of 0.05% and lower atropine eyedrop concentrations[19-23,26,29] other than one occurrence of tachycardia with atropine 0.02% eyedrops.[21]

A rebound effect following cessation of atropine may occur, defined as the rate of progression of myopia being faster than natural history would suggest following treatment cessation (the myopia progression is simply delayed, not slowed). Per a recent review by Bullimore and Brennan,[49] the rebound effect was highest (≥0.14 mm) in red light therapy and atropine studies.

The table below summarizes potential side effects of low dose use of atropine for myopia progression.

Table 1: Summary of Side Effects Reported in Randomized Trials Evaluating Low Dose Atropine for Myopia Progression

Study	Ethnicity	Treatment Group	N	Blur/ Progressive lenses	Skin irritation	Allergy	Decreased VA	Photophobia/ glare	Photochromic lenses	Other
Repka[19] (PEDIG)	Non-Asian	Atropine 0.01%	125	17	NA	10*	6	32	0	Eye irritation (90) Ocular discomfort (8) Visual impairment (6) Eye pain (5) Blepharitis (6) Meibomian gland dysfunction (3) Any systemic adverse event (28)
Lee[20] (WA-ATOM)	Non-Asian	Atropine 0.01%	104	1	0	2*	0	0	0	Sore/heavy feeling eye (2) Visual floaters (1) Adnexal foreign body (1) Migraine (1) Asthma attack (1)
Zadnik[21] (CHAMP)	Non-Asian	Atropine 0.01%	164	2	0	3*	NA	4	NA	Eye irritation (1) Mydriasis (2) Eyelid swelling (3) Elevated heart rate (0)
		Atropine 0.02%	247	4	2	11*	NA	11	NA	Eye irritation (2) Mydriasis (4) Eyelid swelling (1) Elevated heart rate (2)
Loughman[22] (MOSAIC)	Non-Asian	Atropine 0.01%	167	1	2	NA	NA	0	NA	Eye discomfort (3) Temporary mydriasis (1)
Loughman[23] (MOSAIC2) *(Non-randomized extension)*	Non-Asian	Atropine 0.05%	66	10	0	NA	NA	5	0	Mydriasis (1) Discomfort with drops (1)
Yam[29] (LAMP) *2-year outcome*	Asian	Atropine 0.05%	93	1	NA	9*	NA	4	31	4 hospitalizations (reasons not specified)
		Atropine 0.025%	86	1	NA	10*	NA	3	28	6 hospitalizations (reasons not specified)
		Atropine 0.01%	91	2	NA	11*	NA	5	31	5 hospitalizations (reasons not specified)
Chia[26] (ATOM2)	Asian	Atropine 0.01%	71	1	0	0	11	0	NA	Ocular irritation (1) Acute gastric pain (1)

NA = not assessed or reported

*allergic conjunctivitis

1.5.2 Known Potential Risks of HAL Lens Wear

The potential risks related to HAL lens wear are expected to be minimal. Bao et al.[39] reported no adverse events in a 2-year study of HAL lens wear. Per a recent review by Bullimore and Brennan,[49] mean annualized rebound with optical corrections was -0.01 ± 0.03 mm.

It typically takes a short period of time to adapt to the glasses. During this time, study participants should use caution doing things that could potentially injure them, like riding a bike or skateboard, climbing walls, or playing sports.

1.6 Known Potential Benefits

The potential benefit of 0.05% atropine, HAL lenses or the two combined is to slow myopia progression.

1.7 Risk Assessment

The Sponsor (Jaeb Center for Health Research) has determined that the protocol's level of risk is consistent with 45 CFR 46.405 and 21 CFR 50.52 ISO 14971:2016, which indicates research involving greater than minimal risk but presenting the prospect of direct benefit to the individual child participating in the research; the risk is justified by the anticipated benefits; the relation of the anticipated benefit to the risk is at least as favorable to the participants as that presented by available alternative approaches; and adequate provisions will be made for soliciting the assent of the children and permission of their parents or guardians as instructed by the IRB.

Further, while the use of atropine will require an IND submission to the FDA, it is anticipated that the use of HAL lenses need only follow the abbreviated requirements of 21 CFR 812.2(b) as a non-significant risk device as it is not (1) intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject; (2) purported or represented to be for a use in supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject; (3) for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject; or (4) otherwise presenting a potential for serious risk to the health, safety, or welfare of a subject.

1.8 General Considerations

The study is being conducted in compliance with the policies described in the PEDIG network policies document, the ethical principles in the Declaration of Helsinki,[50] the protocol described herein, and the standards of Good Clinical Practice (GCP).[51]

When feasible, data will be directly entered in real-time in electronic case report forms that will be considered the source data.

Chapter 2: Study Enrollment and Screening

2.1 Participant Recruitment and Enrollment

The study plans to enroll up to 500 participants into the Run-In Phase for whom informed consent and assent will be obtained, such that approximately 348 participants will enter the Randomized Trial Phase.

Study participants will be recruited from PEDIG clinical centers in the United States. All eligible participants will be included regardless of gender, race, or ethnicity. There is no restriction on the number of participants to be enrolled by each site.

As the enrollment goal into the Randomized Trial Phase approaches 348 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 of participants for the Randomized Trial Phase might be exceeded. Enrollment into the Run-In Phase may be temporarily halted until it is determined how many participants will enter the Randomized Trial Phase.

2.2 Informed Consent and Authorization Procedures

A child is considered for the study after undergoing a routine eye examination (i.e., as part of standard of care) that identifies myopic refractive error appearing to meet the eligibility criteria. The study will be discussed with the child's parent(s) or guardian(s) (referred to subsequently as parent(s)). Parent(s) who express an interest in the study will be given a copy of the informed consent form to read. Written or electronic informed consent / assent must be obtained from a parent and child (the JCHR IRB requires assent for children 7 years of age and older) prior to performing any study-specific procedures that are not part of the child's routine care.

If a child turns 7 years of age after enrollment, then assent must be obtained before performing additional study-specific procedures, including data collection for the study. If assent cannot be obtained, then study procedures, including data collection, cannot continue and no data from the turning of age date can be used for the study.

If the participant and/or parent(s) are not fluent in written and spoken English, then the consent and/or assent forms, as well as all other participant/parent-facing materials (e.g., dosing instructions, questionnaires), must be translated into the language of fluency for the participant/parent(s). Further, a qualified interpreter must be available for the consent process and for all subsequent study-related interactions.

A child is considered enrolled when the informed consent form and assent form (as applicable) have been signed.

2.3 Participant Inclusion Criteria

Individuals must meet all the following inclusion criteria to be eligible:

1. Age 5 years to <12 years at time of enrollment. Children within 4 weeks of their 12th birthday are not eligible.
2. Refractive error meeting the following by cycloplegic autorefraction:

- Myopia of 0.75D to 6.00D SER and at least 0.75D in both principal meridians of each eye
- Astigmatism <2.50D both eyes
- Anisometropia <1.50D SER

3. Investigator has confirmed the following regarding best-corrected distance visual acuity (VA) in habitual spectacles or trial frames using the investigator's preferred VA testing method:
   - VA is age normal in both eyes[1,2]
     - 5-6 years: approximately 20/32 or better, ≤ 0.24 logMAR, ≥ 73 letters
     - 7-12 years: approximately 20/25 or better, ≤ 0.14 logMAR, ≥ 78 letters
   - Interocular difference ≤2 logMAR lines (0.2 logMAR) or ≤ 10 letters
4. Wearing spectacles by parent report ≥90% of waking hours ≥30 days duration before enrollment. For children who meet all other inclusion criteria but whose single-vision spectacles are broken or lost within the last 90 days, enrollment can proceed as long as the child was wearing their single-vision spectacles ≥90% of waking hours ≥30 days before the spectacles were broken or lost.
5. Gestational age ≥ 32 weeks.
6. Birth weight >1500 g.
7. Parent(s) and assenting child understand the study procedures and are willing to accept randomization to atropine 0.05%, HAL lenses, atropine combined with HAL lenses, or placebo (i.e., neither active treatment).
8. Parent is willing to participate in a 2- to 4-week run-in phase using nightly artificial tear eyedrops in both eyes.
9. Family can return in 2 to 4 weeks for possible randomization.
10. Child is willing to refrain from contact lenses for the duration of the study.
11. Parent has a phone (or access to a phone) and is willing to be contacted by the clinical site staff.
12. Relocation outside of the area of an active PEDIG site within the next 32 months is not anticipated.

2.4 Participant Exclusion Criteria

Individuals meeting any of the following exclusion criteria at baseline will be excluded from study participation:

1. Current or previous pharmacologic or light therapy used for myopia treatment.
2. Current or prior contact lens wear more than 7 days in the past 12 months
3. Current or previous use of bifocals, progressive-addition lenses, multi-focal contact lenses, or focus- or contrast-modifying spectacle lenses.
4. Current or previous use of orthokeratology, rigid gas permeable, or other contact lenses used to slow myopia progression.
5. Current or previous myopia control treatment or other uses of atropine, pirenzepine or other anti-muscarinic agents.
6. Known atropine allergy
7. Abnormality of the cornea, lens, central retina, iris, or ciliary body
8. Current constant or intermittent strabismus (phorias are acceptable)
9. Verified history of amblyopia or nystagmus.
10. Prior strabismus, intraocular, or refractive surgery
11. Down syndrome or cerebral palsy

12. Diseases known to affect accommodation, vergence, or ocular motility (e.g., multiple sclerosis, Graves' disease, myasthenia gravis, diabetes mellitus)
13. Any condition that, in the judgment of the investigator, could influence refractive error development.
14. Existing conditions in the opinion of the investigator 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, pre-diabetes).
15. Inability to comprehend and/or perform any study-related procedures.
16. Individuals who are pregnant, lactating, or intending to become pregnant within the next 30 months.
    a. A negative urine pregnancy test at randomization and the 6-, 12-, 18-, and 24-month follow-up visits will be required for individuals who have experienced menarche (at least one menstrual cycle).
17. Immediate family member (spouse, biological or legal guardian, child, sibling, parent) who is investigative site personnel directly affiliated with this study or who is an employee of the Jaeb Center for Health Research.
18. Sibling of, or living in the same household as, another child who is concurrently enrolled in the study.
19. Allergy to benzalkonium chloride (eyedrop preservative).

2.5 Screening/Enrollment Procedures

After informed consent is obtained (and written or verbal assent, if applicable), a potential participant will be evaluated for study eligibility by reviewing their medical history, along with data collection and testing as specified below.

2.5.1 Demographic & Historical Information

The following demographic and historical information will be collected: 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.

2.6 Testing at the Enrollment Visit

Refer to Chapter 6 herein and the MTS2 Site Manual of Procedures for a complete description of testing procedures, performed in the following order.

1. Drop Instillation for Testing Under Cycloplegia
   - 2 drops of cyclopentolate 1% 5 minutes apart
2. Cycloplegic Autorefraction
   - Taken 30 minutes ± 5 minutes after the second drop of 1% cyclopentolate is instilled
   - Sphere and cylinder will be recorded in 0.125D increments.
3. Axial Length with cycloplegia
4. Spectacle Prescription Determination with Cycloplegia (section 5.2.12)
   - A new spectacle prescription will be determined by cycloplegic refraction according to the investigator's usual method for all study participants. This may include retinoscopy, autorefraction, and/or subjective refinement.

2.7 Run-In Phase Refractive Correction

To complete the run-in phase without a change in spectacles, the participant must be *currently wearing* single vision spectacles that meet the following criteria:

- Myopia (by spherical equivalent) in both eyes corrected to within ±1.00D of the investigator's cycloplegic measurement of refractive error.
- Cylinder power in both eyes within ±1.00D of the investigator's cycloplegic measurement of refractive error.
- Cylinder axis for both eyes within ±20 degrees of the axis found on the investigator's cycloplegic measurement of refractive error when cylinder power is ≥ 1.00D or within ±30 degrees when the cylinder power is <1.00D.

If the participant's current refractive correction is within these tolerances, the participant will continue wearing their current spectacles during the run-in phase until new study spectacles are received after randomization.

If the participant meets all eligibility criteria for the run-in phase (see sections 2.3 and 2.4) but their current spectacle correction 1) is broken or lost or 2) does not meet the tolerances for refractive correction above, then new spectacles will be prescribed (paid for by the study) using the method described in section 2.7. These patients will start the run-in phase wearing their habitual correction or no spectacles (if spectacles are lost or broken) but will wear the study run-in phase spectacles once they are obtained prior to randomization. Participants who do not meet refractive error eligibility criteria at enrollment may be brought back at a later time for a subsequent chance to be enrolled.

2.8 Run-in Phase

All potential participants meeting study inclusion and exclusion criteria (sections 2.3 and 2.4) will be enrolled in the run-in phase to further determine eligibility for the RCT by assessing adherence with eyedrops.

2.9 Treatment in Run-In Phase

Artificial tears will be dispensed, and families will be instructed to instill 1 drop in each eye nightly for 2-4 weeks. Study personnel will demonstrate to the parent and participant how to instill a drop in each eye before the participant leaves the office. Parents and participants will be told that 90% adherence with artificial tears is required to be eligible for study randomization.
Participants will be instructed to wear their refractive correction full time (i.e. at least 10 hours per day). Families will be asked to complete an adherence calendar indicating Yes/No for spectacle wear and Yes/No for drop instillation each day. (The same calendar will be used to monitor adherence during the study.)

To promote and monitor adherence with artificial tears and with spectacles during the run-in phase:

- A calendar log will be provided to the parent, and the participant or parent will record whether the drop instillation was done each night in both eyes (yes/no) and whether the spectacles were worn at least 10 hours per day (yes/no).
- The parent and participant will be instructed to bring the calendar logs to the study randomization visit when they return in 2-4 weeks.
- The coordinator or investigator will assess adherence with drop instillation based on the calendar logs at the Randomization Visit.
- Note: If 90% eyedrop adherence is not verified, then the participant shall be withdrawn from the study.
- Participants who do not meet criteria for randomization (e.g., for adherence) cannot be brought back at a later time for a subsequent chance at randomization or enrollment.

Participants will be scheduled for a return visit for potential randomization in 2-4 weeks.

Chapter 3: Randomization

The participant should return to reassess study eligibility for randomization within 2-4 weeks of the Enrollment Visit and initiation of the run-in phase. If the participant cannot return for possible randomization within 6 weeks of enrollment (consent/assent) into the run-in phase, the participant will be withdrawn from the study.

3.1 Assessment of Adherence with Artificial Tears

Calendar logs will be reviewed to assess the level of adherence with the instillation of the artificial tear eyedrops during the run-in phase.

To be eligible for randomization, participants must have been at least 90% adherent with instilling the drops in both eyes, defined as the number of days the drops were instilled in both eyes divided by the total number of days since receiving the artificial tears determined by reviewing the adherence calendar log for the run-in phase.

Participants who are not able to 1) return the calendar log and 2) be at least 90% adherent with eyedrop instillation will be withdrawn from the study. Extension of the run-in phase or re-enrollment in the run-in phase to potentially meet the eyedrop adherence criteria is not allowed.

In addition, the parent (or participant) must demonstrate, to the investigator or study coordinator, the ability to instill an eyedrop in both eyes before being considered for randomization. Participants who cannot demonstrate successful eyedrop instillation (either by themselves or their parents) will be withdrawn from the study before randomization.

3.2 Assessment of Adherence with Refractive Correction Wear

Adherence with refractive correction will be collected during the run-in phase (using the same calendars that will be used throughout the study). However, adherence with glasses will not be used to determine eligibility for randomization because 1) adherence with glasses wear is an inclusion criterion that must be for at least 30 days in the 90 days prior to enrollment visit and 2) participants enrolling who have lost or broken glasses should not be penalized for apparent nonadherence while obtaining new pre-randomization glasses.

3.3 Testing at the Randomization Visit

Participants judged to be adherent with eyedrops will undergo the assessments outlined for the randomization visit, further described below.

Prior to any clinical testing, the participants' current spectacles (i.e. new prescribed at enrollment or pre-study spectacles that met tolerance criteria at enrollment/did not require updating) will need to meet the following criteria compared with the prescribed refractive correction at enrollment (Section 2.6) OR the participants are tested in trial frames with prescribed refractive correction at enrollment (Section 2.6):

- Myopia (by spherical equivalent) in both eyes corrected to within ±0.50D of the investigator's cycloplegic measurement of refractive error.
- Cylinder power in both eyes within ±0.50D of the investigator's cycloplegic measurement of refractive error.
- Cylinder axis for both eyes must be within ±5 degrees of the axis found on the investigator's

cycloplegic measurement of refractive error when the cylinder power is ≥ 1.00D or within ±15 degrees when the cylinder power is <1.00D

Refer to Chapter 6 herein and the MTS2 Site Manual of Procedures for a complete description of testing procedures, performed in the following order.

1. Automated Pupillometry
2. Monocular Distance Visual Acuity Testing
   a. Method: ATS-HOTV protocol if <7 years and E-ETDRS protocol if age 7 or older
   b. Refractive correction: habitual spectacles (which may be new spectacles prescribed at enrollment) in refractive correction determined at enrollment (spectacles or trial frame)
3. Binocular Near Visual Acuity Testing
4. Monocular Amplitude of Accommodation Right Eye Only

The following must be performed (i.e., repeated) only if the cycloplegic autorefraction and axial length measurements in the enrollment visit(s) were completed more than 4 weeks (>28 days) prior to the randomization visit (following the same instillation of cycloplegic eyedrop procedure as described for enrollment in section 2.6). If repeated, these will be considered the participant's "baseline" measurements and must meet the same eligibility criteria for enrollment (sections 2.3 and 2.4).

5. Cycloplegic Autorefraction *(only if >28 days since enrollment visit)*
6. Axial Length with cycloplegia *(only if >28 days since enrollment visit)*
7. Urine Pregnancy Test – *for individuals who have experienced menarche (at least one menstrual cycle)*
   - This test can be performed at any time during the visit.

If a participant is unable to complete the testing listed above in a single visit or does not meet visual acuity eligibility criteria, testing may be completed within 7 days.

3.4 Confirmation of Eligibility for Randomization

Randomization will occur at the end of the randomization visit after confirming the participant meets the following eligibility criteria:

1. Best-corrected distance visual acuity in habitual spectacles (which may be new spectacles prescribed at enrollment) meeting tolerances (section 3.3) or trial frames meeting the following criteria using the ATS-HOTV protocol if <7 and E-ETDRS protocol if age 7 or older:
   - If age 5-6 years: 20/32 or better by ATS-HOTV
   - If age 7-12 years: ≥ 78 letters by E-ETDRS
   - Interocular difference ≤2 logMAR lines (0.2 logMAR) or ≤ 10 letters
2. Refractive error meeting the following by cycloplegic autorefraction (performed at enrollment or the day of randomization, if repeat autorefraction required):
   - Myopia of 0.75D to 6.00D SER and at least 0.75 D in both principal meridians of each eye
   - Astigmatism <2.50D both eyes
   - Anisometropia <1.50D SER
3. At least 90% adherence with artificial tear eyedrops during the run-in phase

Participants who do not meet the adherence or refractive error eligibility criteria for randomization will be withdrawn from the study. If >28 days have elapsed since the enrollment visit, cycloplegic autorefraction and axial length measurements will need to be repeated (section 3.3).

Prior to randomization, the study requirements should be discussed again with the parent and child so there is reasonable assurance that the participant will adhere to the study requirements.

3.5 Randomization

Eligible participants will be randomly assigned 1:1:1:1 to the following groups:

- **ATROPINE GROUP:** atropine (0.05%) eyedrops + single vision lenses
- **PLACEBO GROUP:** placebo eyedrops + single vision lenses
- **HAL GROUP:** placebo eyedrops + HAL lenses
- **COMBINED GROUP:** atropine (0.05%) eyedrops + HAL lenses

A Master Randomization List using a permuted block design stratified by baseline age (5 to <9, 9 to <12), specifying the order of treatment group assignments, will be used for randomization.

Once the website randomization process is complete, a study participant is randomized. The participant will be included in that group for analysis regardless of whether the assigned treatment is received. Thus, the investigator must not randomize the participant unless convinced that the child is eligible, and the family will accept whichever treatment group is assigned through randomization.

Study spectacles and study medication will be dispensed at the 4-week Treatment InitiationVisit.

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 Treatment from 0 to 24 months

All participants will use study eyedrops and study spectacles as follows:

- Treatment with study eyedrops will be one drop in both eyes each night of either atropine 0.05% or placebo (based on randomized treatment group), including the night before study visits.

- Study spectacles with either single-vision lenses or HAL lenses should be worn full time (i.e. at least 10 hours per day).

No myopia control treatments other than the randomized assignments to study eyedrops and study spectacles can be used for the duration of the study. Only study spectacles are allowed.

4.1.1 Study Medication

A compounding pharmacy will package the study drug (0.05% atropine and placebo) in identical-appearing preservative free, multi-dose bottles (Novelia®). In addition to 0.05% atropine, the atropine eyedrops contain 99.95% buffered solution with inactive ingredients while the placebo eyedrops contain 100% buffered solution with inactive ingredients. Study drug will be shipped to a central pharmacy for labelling, to maintain masking. The central pharmacy will supply labelled medication to clinical sites which will dispense it to participants. Additional study medication details are summarized within a separate investigator brochure.

Eyedrops will be dispensed to participants concurrently with study spectacles at the Treatment Initiation Visit 4 weeks after randomization. Eyedrops will then be dispensed at each 6, 12, and 18-month office visit. At each semi-annual clinical visit and any other time the parent picks up eyedrops at the site, the previously dispensed eyedrop bottles (used or unused) will be retrieved and destroyed by the site. This is to avoid use of expired eyedrops or use of eyedrops when not prescribed later in the study.

4.1.2 Study Spectacles

Study spectacles with either single-vision lenses or HAL lenses will be prescribed at randomization and then new study spectacles at the end of every study visit thereafter at 6, 12, and 18, month visits; single vision spectacles will be prescribed to all participants at 24 months. New spectacles are prescribed regardless of any change in refractive correction every 6 months to ensure that the benefits of wear are not compromised by scratched lenses or bent frames.

The spectacle prescription is determined by cycloplegic refraction according to the investigator's usual method. This may include retinoscopy, autorefraction, and subjective refinement. Once the refractive error is determined under cycloplegic conditions, the spectacle prescription should match the cycloplegic refraction (i.e., "cutting" minus, cyl, etc. is not allowed).

Spectacles prescribed at randomization should be based on the cycloplegic refraction performed at the enrollment visit, unless the cycloplegic refraction had to be repeated at randomization (i.e. because it had been more than 4 weeks (>28 days) since the enrollment visit), in which case spectacles should be prescribed based on the cycloplegic refraction at randomization. Spectacles prescribed at follow up visits should be based on the cycloplegic refraction that occurs at the visit.

Once manufactured, two identical pairs of study spectacles will be sent to the study site where the Spectacles Fitter will verify each pair (primary and backup) using lensometry (section 4.7.1) and dispense one pair to the study participant (see sections 4.6 and 4.8) at the 4-Week Study Spectacle Fitting visit.

Staff responsible for receiving, verifying and dispensing the study spectacles will be informed about the study and instructed on the importance of not disclosing the type of lenses to the child or their family. Treatment with study spectacles will commence as soon as study spectacles are fit and dispensed. Eyedrops will be dispensed concurrently with study spectacles at the 4-Week Treatment Initiation Visit.

Participants will be instructed to wear their study spectacles full-time (i.e. at least 10 hours per day).

At each semi-annual visit, the previously dispensed spectacles will be retrieved and maintained at the site once new spectacles are given to the participant. This is to avoid wearing the outdated spectacles and because they are for investigational use only.

4.2 Treatment from 24 to 30 months

At the 24-month visit, study interventions will be discontinued. All participants will be prescribed single-vision-lens spectacles. The eyedrops will be returned to the site at the visit and the study spectacles will be exchanged at the spectacle fitting visit for the single vision spectacles prescribed. No myopia treatment should be prescribed from the 24- to the 30-month visit.

4.1 Telephone Calls

8 weeks following randomization (± 2 weeks), the site will contact parents to question the parent as to whether the child is experiencing any issues with treatment or have had any changes in medications.

At three months (±2 weeks) following randomization, the site will contact the participant's parents to encourage adherence to the randomized treatment and ask the parent if the participant is experiencing any issues with treatment

The site will make phone calls at 9, 15, 21, and 27 months (±2 weeks) after randomization, timepoints which are equidistant between the scheduled study visits). These calls will be conducted to maintain direct contact with participants' parents, develop and maintain rapport with participants and/or families, and assist with scheduling study visits if needed.

4.3 Adherence with Study Treatment

A calendar will be provided to promote adherence with eyedrops and study spectacles, on which the child/parent will record daily both whether an eyedrop was instilled into both eyes in the evening and whether the participant wore their study spectacles at least 10 hours.

At each office visit, an assessment of adherence will be recorded on the Follow-up Examination Form after a review of the calendars and an interview with the parent and child. Separately for eyedrops (whether received daily) and for spectacles (whether worn at least 10 hours per day), study personnel will describe the proportion of time that treatment that was used per protocol as excellent (76% to 100%), good (51% to 75%), fair (26% to 50%), or poor (≤ 25%).

Adherence will be encouraged at each visit and each phone call. If a participant does not adhere to the study treatment, parents and participants should be encouraged to continue trying their best to follow the study treatment plan.

4.4 Side Effects of Treatment

Reporting of adverse events is described in Chapter 6. Prior to deviating from the treatment protocol or prescribing non-protocol treatment, the situation should be discussed with and approved by a Protocol Co-chair.

If a participant is experiencing photophobia, the investigator may prescribe clip-on sunglasses.

If a participant reports blurry vision or difficulty seeing up close when doing schoolwork, reading, or other near activities, the investigator must call a Protocol Co-chair to discuss management.

If a participant has a confirmed allergic reaction to the eye drops, the investigator must call a Protocol Co-chair to discuss management and the child would need to stop the study eye drops and continue in the study.

If a participant's eyes feel dry after using study medication, artificial tears may be used 10 minutes after the study medication drop to moisturize the eyes.

4.5 Study Visits and Phone Calls in the Randomized Trial

Study visits and interactions will be timed from randomization unless otherwise specified and will occur at:

Follow Up Visits will occur at:

- 6 months ± 2 weeks
- 12 months ± 2 weeks
- 18 months ± 2 weeks
- 24 months ± 2 weeks: On-Treatment Primary Outcome – after which all eyedrops and study spectacles will be discontinued and SVLs will be prescribed for all.
- 30 months ± 2 weeks: Off-Treatment Secondary Outcome – six months following treatment discontinuation.

Treatment Initiation Visit (Spectacles Fitting and Eyedrop Dispensing) will occur at: 4 ± 2 weeks after randomization

Spectacle Fitting Visits will occur at:

- 4 ± 2 weeks after the 6-, 12, 18, and 24-month Clinical Follow Up Visits

Phone Calls will occur at:

- 8 weeks ± 2 weeks
- 3 months ± 2 weeks
- 9 months ± 2 weeks
- 15 months ± 2 weeks
- 21 months ± 2 weeks
- 27 months ± 2 weeks

Visit	Target Day	Target Window (around Target Day)	Allowable Window (around Target Day)
4-week treatment initiation visit (spectacle fitting and eyedrop dispensing)	Randomization + 28 days	± 2 weeks 26 to 42 days	± 2 weeks 26 to 42 days
8-week call	Randomization + 56 days	± 2 weeks 42 to 70 days	± 2 weeks 42 to 70 days
3-month call	Randomization + 91 days	±2 weeks 77 to 105 days	±2 weeks 77 to 105 days
6-month clinical visit	Randomization + 183 days	± 2 weeks 169 to 197 days	± 3 months 91 to 273 days
9-month call	Randomization + 273 days	± 2 weeks 259 to 287 days	± 2 weeks 259 to 287 days
12-month clinical visit*	Randomization + 365 days	± 2 weeks 335 to 379 days	± 3 months 273 to 454 days
15-month call	Randomization + 454 days	± 2 weeks 440 to 468 days	± 2 weeks 440 to 468 days
18-month clinical visit	Randomization + 548 days	± 2 weeks 534 to 562 days	± 3 months 454 to 838 days
21-month call	Randomization + 638 days	± 2 weeks 624 to 652 days	± 2 weeks 624 to 652 days
24-month clinical visit*	Randomization + 731 days	± 2 weeks 717 to 745 days	± 3 months 638 to N/A days
27-month call	Randomization + 821 days	± 2 weeks 807 to 835 days	± 2 weeks 624 to 652 days
30-month clinical visit*	Randomization + 913 days	± 2 weeks 899 to 927 days	± 3 months 821 to N/A
Additional study spectacle fittings after each clinical visit	Clinical follow up visits (6, 12, 18, and 24- months) + 28 days	± 2 weeks	± 2 weeks

**Denotes key study visits.*

The goal is for all participants to complete all scheduled visits. However, participants unable or unwilling to return for all follow-up visits will be permitted to return for key visits only as an alternative to withdrawal from the study. In such instances, a missed visit form will be entered for each missed visit with the reason specified as "Other" with comment that the parent/participant is unwilling to return except for key visits; these missed visits will not be recorded as protocol deviations.

4.6 Procedures at 4-Week Treatment Initiation Visit

At the 4-week Treatment Initiation Visit, participants will be seen by the Spectacles Fitter for fitting of the study spectacles (section 4.8) and by the site coordinator for dispensing of study medication; no clinical assessments will be performed.

The following procedures should be performed:

1. Lensometry (section 0) of primary spectacles and backup spectacles (if available)
2. Fit both primary and back up spectacles
3. Dispense primary spectacles to participant (Spectacles Fitter)
4. Retain backup spectacles at the site
5. Dispense study medication (Coordinator)
6. Provide treatment instructions sheets and compliance calendars (4-week visit only) (Coordinator)

4.7 Procedures at Follow Up Visits Between 6 and 30 Months

4.7.1 Lensometry

Prior to any clinical testing, the participants' current spectacles (primary or backup pair) will need to meet the following criteria compared with the last prescribed refractive correction OR the participants are tested in trial frames with the last prescribed refractive correction:

- Myopia (by spherical equivalent) in both eyes corrected to within ±0.50D of the investigator's cycloplegic measurement of refractive error.
- Cylinder power in both eyes within ±0.50D of the investigator's cycloplegic measurement of refractive error.
- Cylinder axis for both eyes must be within ±5 degrees of the axis found on the investigator's cycloplegic measurement of refractive error when the cylinder power is ≥ 1.00D or within ±15 degrees when the cylinder power is <1.00D.

If these criteria are not met, or the child did not bring their spectacles to the visit, testing must be done with the participant wearing their backup study spectacles; otherwise, in prescribed correction in trial frames.

4.7.2 Procedures at Clinical Follow Up Visits

Unless otherwise specified, the following procedures will be performed in the specified order at each visit with the participant wearing their study spectacles (primary or backup pair) or trial frames (see section 0), according to the description of procedures and assessments outlined in Chapter 5 and the MTS2 Site Manual of Procedures.

1. Lensometry (section 0)
2. Medical History
    - Including questioning about adverse events and concomitant medications.
3. Adherence to Eyedrop and Spectacles Treatment Assessment (*all visits except 30-month*)
4. Urine Pregnancy Test - *individuals who have experienced at least one menstrual cycle at all visits except 30-month*)
5. Treatment Impact Questionnaire (*parent and child at 6 and 24-month visit only; must be administered prior to clinical testing*)
6. Automated Pupillometry (for sites with equipment)

7. Monocular Distance Visual Acuity Testing
   a. Method: investigator discretion
   b. Refractive correction: habitual spectacles
8. Binocular Near Visual Acuity Testing
9. Monocular Amplitude of Accommodation in Right Eye Only
   - Measured once using the 20/30 Bernell line with the participant in their study spectacles or trial frames (see section 4.7.1).
10. Drop instillation for Testing Under Cycloplegia
11. Cycloplegic Autorefraction
12. Axial Length with cycloplegia
13. Refractive Error Determination with Cycloplegia
    - Refine refractive error (section 4.9)
14. If pre-cycloplegic monocular distance visual acuity in either eye was worse than 20/32 for children aged 5-6 years and 20/25 for children 7-12 years, retest monocular distance VA using phoropter or trial frames by same method used at randomization (ATS-HOTV or E-ETDRS).
15. Order Study Spectacles (all visits except 30-months, will be SVL for all at 24 months)
    - Participant selects frame from sample frame collection at site.
    - Site orders two identical pairs of study spectacles.
      - One pair will be dispensed to the participant at the Study Spectacles Visit.
      - The second pair will be sent to the site to serve as a backup in case the participant breaks or loses their spectacles, or to use for clinical testing if spectacles are not brought to the Clinical Follow Up Visit.
16. Manage study medication
    - Collect unused study medication (6, 12, 18, and 24 months)
    - Dispense supply of study medication (6, 12, and 18 months)
    - Provide treatment instructions sheets and compliance calendars

4.8 Procedures at Study Spectacle Fittings

At Spectacles Fitting Visits, participants will be seen by the Spectacles Fitter for fitting of the both pair of study spectacles (primary and backup); no clinical assessments will be performed.

- One pair of spectacles will be dispensed to the participant.
- The second pair will serve as a backup in case the participant breaks or loses their spectacles, or to use for clinical testing if spectacles are not brought to the Clinical Follow Up Visit.

The following procedures should be performed:

1. Lensometry (section 0) of primary spectacles and backup spectacles
2. Collect study spectacles being replaced
3. Fit both primary and backup spectacles
4. Dispense primary spectacles to participant (Spectacles Fitter)
5. Retain backup spectacles at the site

4.9 Management of Refractive Error

A new spectacle prescription will be determined by cycloplegic refraction according to the investigator's usual method of refinement for all study participants. This may include retinoscopy, autorefraction, and subjective refinement. Once the refractive error is determined under cycloplegic conditions, the spectacle prescription should match the cycloplegic refraction (i.e., "cutting" minus, cyl, etc. is not allowed).

The study spectacles will be updated even if there is no change in the refraction.

4.10 Non-Randomized Treatment

Non-randomized treatment for myopia other than study-specified eyedrops and spectacles is not permitted during the study. The investigator must call the Protocol Co-chair to discuss the case and obtain approval for an exception before starting any non-randomized treatment (including progressive lenses, sports spectacles, photochromic spectacles, orthokeratology, rigid gas permeable or other contact lenses). If sports spectacles are approved, they will be paid for by the study.

4.11 Text Message Contacts

Families will be offered the choice to opt-in to text messages to receive appointment reminders.

Chapter 5: Testing Procedures and Questionnaires

All reasonable efforts will be made to maintain masking for all study personnel and families throughout the study. After randomization, the investigator will not view a participant's pupils before dilation or any study spectacles. Participants and their families will be instructed not to discuss the appearance of the study spectacle lenses with the investigator. For the randomized trial, a certified tester who is not the investigator must perform lensometry and any procedures where the participant's study spectacles and/or undilated pupils could be observed (and for which it is not reasonable for the participant to wear stereo spectacles to prevent pupil observation). Measurement of cycloplegic autorefraction and biometry (primary outcome measures) must be performed by either the investigator or a separate biometry tester (BT), who is not also the certified tester (CT), coordinator (CO), or Spectacles Fitter (SF) for all visits after randomization.

5.1 Questionnaires

5.1.1 PEDIG Myopia Treatment Impact Questionnaire (Child and Parent)

At 6- and 24-month outcome exams, participants will complete a novel 24-item questionnaire assessing the impact of the child's eyedrop and spectacles treatment on the child. For participants requiring assistance, the questions should be read verbatim by study personnel (not the parent) and the participant's answers recorded.

A similar novel 21-item questionnaire will be completed by the parent to assess the impact of the child's treatment on the parent and family. Testing is anticipated to take 5-7 minutes for the child and 5-7 minutes for the parent.

5.2 Clinical Testing Procedures and Assessments

The following procedures will be performed at each visit. Refer to the *MTS2 Site Manual of Procedures* for additional details.

5.2.1 Lensometry

The current refractive correction (sphere, cylinder, and axis in each eye) will be verified using a lensometer at all visits. Lensometry must be performed by a certified tester who is not the investigator at 6-, 12-, 18-, and 24-month visits.

Testing time is approximately 3 minutes.

5.2.2 Medical History

The participant's medical history must be taken while they are wearing stereo spectacles (with or without their study spectacles) to prevent the investigator from observing the participant's pupils before dilation. The investigator will determine whether any adverse events occurred since the last study visit and update previously recorded adverse events. If an adverse event has occurred, any initiation, discontinuation, or dosage change in non-study medications concomitant to the adverse event will be recorded.

Completion time is approximately 5-15 minutes.

5.2.3 Adherence Assessment (all follow-up visits except 30-months)

Calendar logs (if brought to the visit) will be reviewed, and the level of nightly adherence with eyedrop administration and all-day study spectacle wear will be documented on the Follow-up Examination Form. If calendar logs are reviewed by the investigator, the participant must wear stereo spectacles to prevent the investigator from seeing the participant's pupils before dilation. If the calendars are not brought to the study visit, they should be mailed to the local site.

Completion time is approximately 5 minutes.

5.2.4 Urine pregnancy test

For individuals who have experienced menarche (at least one menstrual cycle), a dipstick-type urine pregnancy test will be required at enrollment and 6-, 12-, 18- and 24-month follow-up visits. If pregnancy testing is reviewed by the investigator, the participant must wear stereo spectacles to prevent the investigator from seeing the participant's pupils before dilation.

Testing time is approximately 7 minutes.

5.2.5 Automated Pupillometry

Pupil diameter will be measured using an automated method at sites with automated pupillometry equipment. The same method and lighting conditions are to be used throughout the study. This test must be performed by a certified tester who is not the investigator at the 6-, 12-, 18-, and 24-month visits.

Testing time is approximately 3 minutes.

5.2.6 Distance Visual Acuity Testing

Monocular distance visual acuity should be measured with the participant wearing most recent refractive correction in study spectacles (primary or backup) or trial frames; however, the testing method to be used varies by visit and purpose as follows:

- At the Enrollment Visit, monocular distance visual acuity should be tested in habitual refractive correction. The pre-cycloplegia method of visual acuity is at investigator discretion.

- At the Randomization Visit, children aged <7 years at the time of randomization will use the ATS-HOTV protocol on a study-certified VA device, and children 7 years and older will use E-ETDRS protocol on a study-certified VA device.

- At all visits after randomization, monocular distance visual acuity should be tested in habitual refractive correction. The pre-cycloplegia method of visual acuity is at investigator discretion. This test must be performed by a certified tester who is not the investigator at the 6-, 12-, 18-, 24-, and 30-month visits. If pre-cycloplegia visual acuity is less than age appropriate, monocular distance visual acuity should be repeated following cycloplegic refractive error determination using the EVA method that was conducted at Randomization.

Testing time is approximately 5 to 10 minutes.

5.2.7 Binocular Near Visual Acuity Testing

Binocular near visual acuity is measured using the ATS4 Near Acuity Test with the participant wearing optimal refractive correction (section 2.7) in study spectacles (primary or backup) or trial frames and without cycloplegia. This test must be performed by a certified tester who is not the investigator at the 6-, 12-, 18-, and 24-month visits.

Testing time is approximately 3 minutes.

5.2.8 Monocular Amplitude of Accommodation (right eye only)

Only the right eye is measured, and it is measured once using the 20/30 Bernell line with the participant wearing optimal refractive correction (section 2.7) in study spectacles (primary or backup) or trial frames without cycloplegia. This test must be performed by a certified tester who is not the investigator at the 6-, 12-, 18-, 24-month, and 30-month visits.

Testing time is approximately 3 minutes.

5.2.9 Drop Instillation for Testing Under Cycloplegia

Two drops of 1% cyclopentolate, separated by 5 minutes, will be administered to both eyes. The use of proparacaine prior to the cycloplegic drops is at investigator discretion. The cycloplegic autorefractions must be taken 30 minutes ± 5 minutes from the time the second drop of 1% cyclopentolate was instilled in the second eye. Biometry and refraction measurements should follow autorefraction. If eyes are not sufficiently dilated/cyclopleged or if the dilation/cycloplegia has worn off before all procedures requiring cycloplegia have been performed, a third drop of 1% cyclopentolate may be administered, followed by an additional 30-minute wait before testing. The drop installation cannot be performed by the investigator at the 6-, 12-, 18-, and 24-month visits.

Testing time is approximately 35 minutes.

5.2.10 Cycloplegic Autorefraction

Each participant must have their autorefraction measurements made using the same instrument for all study visits.

For each eye, 3 autorefraction measurements are taken. For each measurement, the autorefractor will yield a final reading (either an individual reading or the mean/median of several readings, depending on the autorefractor) consisting of sphere, cylinder, and axis (see *MTS2 Manual of Procedures*).

Testing time is approximately 2-4 minutes (after drop instillation and cycloplegia).

5.2.11 Axial Length Measurement

Axial length will be measured (with pupillary dilation with cycloplegia) 3 times in each eye using optical biometry (e.g., IOLMaster, LENSTAR, Pentacam, Myopia Expert 700).

Each participant must have their axial length measurements made using the same instrument for all study visits.

Testing time is approximately 5-10 minutes.

5.2.12 Spectacle Prescription Determination with Cycloplegia

Spectacle prescription is determined by cycloplegic refraction according to the investigator's usual method of refinement. This may include retinoscopy, autorefraction, and subjective refinement. Once the refractive error is determined under cycloplegic conditions, the spectacle prescription should match the cycloplegic refraction (i.e., "cutting" minus, cyl, etc. is not allowed).

Testing time is approximately 5-10 minutes.

Chapter 6: Unanticipated Problem / Adverse Event, and Device Issue Reporting

6.1 Unanticipated Problems

Site investigators will promptly report to the JCHR on an eCRF all unanticipated problems meeting the criteria below. Sites must report Unanticipated Problems to the IRB within seven (7) calendar days of recognition. For this protocol, an unanticipated problem is an incident, experience, or outcome that meets all the following criteria:

- Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied
- Related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research)
- Suggests that the research places participants or others at a greater risk of harm than was previously known or recognized (including physical, psychological, economic, or social harm)

The JCHR also will report to the JCHR IRB all unanticipated problems not directly involving a specific site, such as unanticipated problems that occur at the JCHR or another participating entity, such as a pharmacy or laboratory. These instances must be reported to the JCHR IRB within seven (7) calendar days of recognition. The Director of the Human Research Protection Program will report to the appropriate regulatory authorities if the JCHR IRB determines that the event indeed meets the criteria of an Unanticipated Problem that requires further reporting.

6.2 Adverse Events

6.2.1 Definitions

Adverse Event (AE): Any untoward medical occurrence in a study participant, irrespective of the relationship between the adverse event and the drug(s) and device under investigation.
To further clarify, an adverse event is any unintended disease or injury, or untoward clinically significant symptom or clinical sign (including abnormal laboratory findings) in a research participant that manifests while in the study if it was not present before enrolling in the study, or if it was present before enrolling, it has increased in severity, frequency or type since enrolling in the study. For this purpose, a participant is considered enrolled once the participant has signed the consent form. For clarity, abnormalities identified as part of study screening (e.g., laboratory abnormality, physical exam abnormality) are not considered AEs even though they may have been identified after consent was signed.

Serious Adverse Event (SAE): Any untoward medical 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 (e.g., sight threatening).

- Is a congenital anomaly or birth defect in the offspring of a participant.
- 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).

Unanticipated Adverse Device Effect (UADE): Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with a study device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of participants (21 CFR 812.3(s)).

Adverse Device Effect (ADE): An adverse event related to the use of a study investigational medical device. This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device. This definition includes any event resulting from use error or from intentional misuse of the investigational medical device. This includes comparator if the comparator is a comparable medical device to the investigational device. (Note that (1) ADE refers specifically to the study investigational device and not to any device used in the study and (2) an Adverse Event CRF is to be completed in addition to a Device Deficiency or Issue CRF for all ADEs.

Comparator: Medical device, therapy (e.g., active treatment, normal clinical practice), placebo or no treatment, used in the control group in a clinical investigation. (ISO 14155:2020)

Device Complaints and Malfunctions: A device complication or complaint is something that happens to a study device or related to study device performance, whereas an adverse event happens to a participant. A device complaint may occur independently from an AE, or along with an AE. An AE may occur without a device complaint or there may be an AE related to a device complaint. A device malfunction is any failure of a device to meet its performance specifications or otherwise perform as intended. Performance specifications include all claims made in the labeling for the device. For cleared devices, the intended performance of a device refers to the intended use for which the device is labeled or marketed (21 CFR 803.3). Note: for reporting purposes, sites will not be asked to distinguish between device complaints and malfunctions.

Use Error: User action or lack of user action while using the medical device that leads to a different result than that intended by the manufacturer or expected by the user. Includes the inability of the user to complete a task. Use errors can result from a mismatch between the characteristics of the user, user interface, task or use environment. Users might be aware or unaware that a use error has occurred. An unexpected physiological response of the patient is not by itself considered a use error. A malfunction of a medical device that causes an unexpected result is not considered a use error. (ISO 14155:2020)

6.3 Reportable Adverse Events

For this protocol, any events between enrollment and randomization will be entered as prior medical conditions.

During the randomized trial, the following are reportable adverse events:

- Ocular symptoms and signs meeting the definition of an adverse event (section 0)
- Systemic symptoms and signs meeting the definition of an adverse event (section 0) and

occurring within one hour of drop administration.

- Events meeting the definition of serious adverse events (section 0).
- Events meeting the definition of adverse device effects (section 0)

All reportable Adverse Events and Adverse Device Effects, whether volunteered by the participant's parents, discovered by study personnel during questioning, or detected through physical examination, laboratory testing, or other means, will be reported online on an adverse event form. The Medical Monitor will review each adverse event form to verify the coding.

6.4 Relationship of Adverse Event to Study Drug, Device or Procedure

The study investigator will assess the relationship of each adverse event to be *related* or *unrelated* to the study treatment or procedure by deciding if there is a reasonable possibility that the adverse event may have been caused by the treatment or study procedure. The Medical Monitor also will make this assessment, which may or may not agree with that of the site investigator. Reporting requirements will be based on the Medical Monitor's assessment. The investigator brochure that will be developed will list potential adverse events that may be expected.

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.

6.5 Severity (Intensity) of Adverse Event

The severity (intensity) of an adverse event will be rated by the site investigator and Medical Monitor. A severity assessment is a clinical determination of the maximum intensity of the adverse event. 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.

- MILD: Usually transient, requires no special treatment, and does not interfere with the participant's daily activities.

- MODERATE: Usually causes a low level of inconvenience, discomfort, or concern to the participant and may interfere with daily activities, but is usually ameliorated by simple therapeutic measures, and the participant is able to continue in the study.

- SEVERE: Interrupts a participant's usual daily activities, causes severe discomfort, may cause discontinuation of study drug, and generally requires systemic drug therapy or other treatment.

6.6 Expectedness

For a serious adverse event that is considered possibly related to the study treatment, the Medical Monitor will classify the event as unexpected if the nature, severity, or frequency is inconsistent with the risk information previously described in the background section.

6.7 Coding of Adverse Events

Adverse events will be coded using the MedDRA dictionary. To facilitate coding, the site will enter a preliminary event descriptor code, which the Medical Monitor may accept or change (the Medical Monitor's coding will be used for all reporting and the site's preliminary coding will not be updated or used in reporting).

The Medical Monitor will review the investigator's assessments of causality and severity and may agree or disagree. For causality, the Medical Monitor will only attempt to reconcile differences for causality when one party's coding is no/unlikely and the other party's coding is possible/probable/definite. For severity, the Medical Monitor will only attempt to reconcile differences when one party codes as severe and the other party as mild/moderate. The investigator's and Medical Monitor's assessments do not need to agree. For reporting purposes, the Medical Monitor will make the final determination with respect to causality as well as whether an event is classified as a serious adverse event and/or an unanticipated adverse device effect. However, both the investigator's and the Medical Monitor's coding will be recorded.

6.8 Outcome of Adverse Event

The outcome of each reportable adverse event will be classified by the investigator as follows:

- RECOVERED/RESOLVED: The participant recovered from the AE/SAE without sequelae. Record the AE/SAE stop date.
- RECOVERED/RESOLVED WITH SEQUELAE: The event persisted and stabilized without change in the event anticipated. Record the AE/SAE stop date.
- FATAL: A fatal outcome is defined as an SAE that results in death. Only the event that was the cause of death should be reported as fatal. AEs/SAEs that were ongoing at the time of death, but were not the cause of death, will be recorded as "resolved" at the time of death. Primary and secondary (if applicable) causes of death will be recorded.
- NOT RECOVERED/NOT RESOLVED (ONGOING): An ongoing AE/SAE is defined as a still ongoing event with an undetermined outcome.
  - An unresolved outcome will require follow up by the site to determine the final outcome of the AE/SAE.
    The outcome of an ongoing event at the time of death that was not the cause of death will be updated and recorded as "resolved," with the date of death recorded as the stop date.
- UNKNOWN: An unknown outcome is defined as an inability to contact the participant or access the participant's records to determine the outcome (for example, a participant lost to follow-up).

If any reported adverse events are ongoing when a participant completes the study (or withdraws), adverse events classified as suspected, unexpected serious adverse reactions (SUSARs) will be followed until they are either resolved or have no prospect of improvement or change, even after the participant has completed all study visits/contacts. For all other adverse events, data collection will

end when the participant completes the study. Note: participants should continue to receive appropriate medical care for an unresolved adverse event after their participation in the study ends.

6.9 Reportable Device (Spectacles) Issues

All UADEs and ADEs as defined in section 0 will be reported on both a Device Issue CRF and AE CRF.

Study device complaints and device malfunctions will be reported except in the following circumstances. These occurrences are expected and will not be reported on a Device Issue CRF assuming criteria for a UADE or ADE have not been met.

6.10 Timing of Event Reporting

Serious or unexpected adverse events must be reported to the JCHR within 24 hours by completing the online adverse event form.

Other reportable adverse events will be reported within three (3) days of the site staff becoming aware of the event by completion of an electronic case report form.

Each principal investigator is responsible for reporting study-related events and abiding by any other reporting requirements specific to his/her local Institutional Review Board or Ethics Committee. As the JCHR IRB is the overseeing IRB, sites must also report all serious adverse events that they have determined to be unexpected and are probably, possibly, or definitely related to the study to the JCHR IRB within seven (7) calendar days.

The JCHR will be responsible for notifying the FDA and all participating investigators of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible, but in no case later than seven (7) calendar days after initial receipt of the information. In addition, the JCHR will notify FDA and all participating investigators in an Investigational New Drug (IND) safety report of potential serious risks, from clinical trials or any other source, as soon as possible, but in no case later than fifteen (15) calendar days after the sponsor determines that the information qualifies for reporting.

6.11 Safety Oversight

The Medical Monitor will review all adverse events that are reported during the study. SAEs typically will be reviewed within twenty-four (24) hours of reporting. Other AEs typically will be reviewed on a weekly basis.

A Data and Safety Monitoring Committee (DSMC) will review compiled safety data at periodic intervals, with a frequency of no less than twice a year. The DSMC can request modifications to the study protocol, suspension, or outright stoppage of the study if deemed necessary based on the safety data available. Details regarding the DSMC review will be documented in a separate DSMC charter.

The objective of the DSMC review is to determine whether the study (or the treatment for an individual or study cohort) should continue as planned, proceed with caution, undergo further investigation, be discontinued, or be modified before continuing. Suspension of enrollment (for a particular group, a particular study site, or for the entire study) is a potential outcome of a DSMC safety review.

6.12 Criteria for Suspending or Stopping Study

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

The study may also be suspended or discontinued if the Medical Monitor deems it necessary based on the totality of safety data available or if the manufacturer of any constituent study medication or device requires stoppage of use for safety reasons (e.g., drug or product recall).

6.13 Participant Discontinuation of Study Treatment

Rules for discontinuing study treatment (spectacles and/or eyedrops) use are:

1. The investigator believes it is unsafe for the participant to continue to receive the treatment.
2. The participant requests that the treatment be stopped.
3. Eyedrop discontinuation in case of participant pregnancy

Even if the study treatment is discontinued, the participant will be encouraged to remain in the study and complete all remaining study visits. For each specific treatment discontinued, the CRF treatment prescribed form at each subsequent visit will record that the specified treatment was discontinued (spectacles, medication) and the reason.

Participants who discontinue the study will be included in the primary analysis of all randomized patients who complete the 24-month visit.

Chapter 7: Miscellaneous Considerations

7.1 Contacts by the Jaeb Center for Health Research and Sites

The Jaeb Center is the Sponsor and also serves as the PEDIG Coordinating Center. The Jaeb Center will be provided with the parent's contact information. The Jaeb Center may contact the parents of the participants. Permission for such contacts will be included in the Informed Consent Form. The principal purpose of the contacts will be to develop and maintain rapport with the participant and family and to help coordinate the scheduling of the outcome examinations.

7.2 Pregnancy Reporting

If pregnancy occurs, eyedrops will be discontinued, but the participant will continue wearing the randomized spectacle lenses,and remain in the study. and will contribute to the primary analysis.. The occurrence of pregnancy will be reported to the JCHR via the study database, and to the JCHR IRB via the Unanticipated Problem xForm in IRBManager, within seven (7) days of the site learning of the pregnancy.

7.3 Prohibited Medications, Treatments, and Procedures

As previously described, participants are prohibited from using other myopia-control treatments and contact lens wear during the study.

7.4 Precautionary Medications, Treatments, and Procedures

There are no precautionary medications, treatments, or procedures.

7.5 Participant Compensation

Participant compensation will be specified in the informed consent form.

7.6 Participant Withdrawal

Participation in the study is voluntary, and a participant may withdraw at any time. For participants who withdraw, their data will be used up until the time of withdrawal.

7.7 Confidentiality

For security and confidentiality purposes, participants will be assigned an identifier that will be used instead of their name. Protected health information gathered for this study will be shared with the Jaeb Center for Health Research in Tampa, FL as specified in the consent forms. De-identified participant information may also be provided to research sites involved in the study, also as specified in the consent forms.

Chapter 8: Statistical Considerations

8.1 Statistical and Analytical Plans

The approaches to sample size and statistical analyses are summarized below.

8.2 Statistical Hypotheses

A test of superiority will be used to evaluate two hypotheses for the change in axial length from baseline at the 24-month visit (primary outcome):

- Between spectacles with single vision lenses + nightly placebo eye drops (hereafter **PLACEBO** group) and spectacles with HAL lenses + nightly placebo eye drop (hereafter **HAL** group)

  AND

- Between **PLACEBO** group and spectacles with single vision lenses + nightly atropine 0.05% eye drop (hereafter **ATROPINE** group)

Since two treatments with different mechanisms of action are being compared to a shared control group, no adjustment for multiplicity is necessary (see Section 8.15).

8.2.1 ATROPINE Versus PLACEBO

The 0.05% atropine versus placebo eyedrops hypothesis is evaluated in the cohort using single-vision lenses.

- Null Hypothesis (H_0): There is *no difference* in the primary outcome between the PLACEBO group and the ATROPINE group.

- Alternative Hypothesis (H_a): There *is a difference* in the primary outcome between the PLACEBO group and the ATROPINE group.

8.2.2 HAL Versus PLACEBO

The HAL vs. single vision lenses hypothesis is evaluated in the cohort using placebo eye drops.

- Null Hypothesis (H_0): There is *no difference* in the primary outcome between the PLACEBO group and the HAL group.

- Alternative Hypothesis (H_a): There *is a difference* in the primary outcome between the PLACEBO group and the HAL group.

8.3 Sample Size

8.3.1 Estimate of Effect with PLACEBO

Data from the MTS1 randomized trial of 0.01% atropine eyedrops vs. placebo eyedrops were used to estimate the effect of PLACEBO in the current study.[19] Among participants in MTS1 who were aged 5 to <12 years at enrollment and randomized to spectacles with single vision lenses and daily placebo eye drop, 53 completed 24 months of follow-up. The mean change in axial length from baseline after 24 months was 0.43 mm (95% CI: 0.35 to 0.51 mm), and the standard deviation was

0.28 mm (95% CI: 0.23 to 0.32 mm). The standard deviation adjusted for baseline axial length and age was 0.24 mm (95% CI: 0.17 to 0.29 mm).

The mean change in spherical equivalent refractive error (SER) after 24 months was -0.77 D (95% CI: -0.94 to -0.60 D), and the standard deviation was 0.60 D (95% CI: 0.47 to 0.71 D). The standard deviation adjusted for baseline SER and age was 0.56 D (95% CI: 0.42 to 0.66 D).

8.3.2 Estimate of Effect with ATROPINE and with HAL

Prior studies in Asian populations have demonstrated a reduction in SER and axial length greater than 50% with nightly 0.05% atropine eye drops and spectacles with HAL lenses (Table 1); however, no published data exist for either treatment modality in North American populations.

In this study for both ATROPINE and HAL treatment groups, the study will be powered to detect a treatment effect versus PLACEBO, assuming that the true treatment effect is a 40% reduction in myopic progression in SER and axial length change after 24 months. Because studies conducted in Asian populations saw a larger effect (50% reduction), this choice of 40% is a conservative estimate.[30,39]

Table 1. Prior Studies of Daily Atropine 0.05% and of Spectacles with HAL Lenses for Myopia Treatment in Asian Populations

Study	Treatment Studied	Treatment Effect (Follow-up – Baseline)				Percentage Reduction in Myopia Progression over 24 Months (Active Treatment vs. Placebo)	
		Mean change in axial length (mm) at 24 months (Standard Deviation)		Mean change in SER (D) at 24 months (Standard Deviation)		Axial Length	SER
		Placebo	Active Treatment	Placebo	Active Treatment		
Zhu et al[30]	**Atropine 0.05%**	N=70 0.76 (0.62)	N=72 0.26 (0.30)	N=70 -1.72 (1.12)	N=72 -0.46 (0.30)	66%	73%
Bao et al[39]*	**HAL Spectacles**	N=50 0.69 (0.28)	N=54 0.34 (0.22)	N=50 -1.46 (0.64)	N=54 -0.66 (0.66)	51%	55%

*Standard deviations calculated from reported standard errors multiplied by the square root of the sample size.

8.3.3 Required Sample Size for Current Study

Tables 2 and 3 below show the total required sample size to evaluate two independent two-group comparisons (PLACEBO vs HAL and PLACEBO vs ATROPINE; 3 groups total), each with 90% power and 5% type 1 error rate for 24-month change in axial length and SER, respectively.

Table 2. Sample Size per Group Required for Change in Axial Length at 24 Months for Two Independent Hypothesis Tests

Standard Deviation, mm	Mean Difference, mm				
	0.14	0.155	0.17	0.185	0.20
0.17	32	27	23	19	17
0.205	47	38	32	27	24
0.24	63	52	43	37	32
0.265	77	63	53	45	38
0.29	92	75	63	53	46

Table 3. Sample Size per Group Required for Change in Spherical Equivalent Refractive Error at 24 Months for Two Independent Hypothesis Tests

Standard Deviation, D	Mean Difference, D				
	0.24	0.275	0.31	0.345	0.38
0.49	89	68	54	44	36
0.56	116	89	70	57	47
0.59	128	98	78	63	52
0.60	133	102	80	65	54
0.66	160	123	97	78	65

Although change in axial length is the primary outcome of this trial, change in SER is considered a key secondary outcome. Therefore, the sample size will be based on the change in SER, given that it requires a larger sample size than the change in axial length.

If the true mean difference in change in SER is 0.31 D (i.e., a 40% reduction in progression relative to similarly aged MTS1 control group participants) and the adjusted standard deviation for change in SER is 0.59 D, then the sample size required per group for two independent 2-group comparisons is 78 participants for a total of 234 across 3 groups (PLACEBO, HAL, and ATROPINE).

Adjusting for 10% loss to follow-up results in a per group sample size of 87 participants per group for a total of 261 participants. This sample size for the secondary SER outcome results in an anticipated power for the axial length primary outcome of 99%, assuming the mean difference in change in axial length is 0.17 mm (i.e., 40% reduction in progression relative to similarly aged MTS1 control group participants) and the adjusted standard deviation for change in axial length is 0.24 mm. Assuming the same mean difference and sample size, power will still be greater than or equal to 90% for axial length if the adjusted standard deviation is 0.325 mm or lower.

8.3.3.1 COMBINED Treatment

An additional 87 participants will be enrolled into a fourth treatment group to explore the effect of COMBINED treatment with 0.05% atropine eyedrops and HAL spectacles, for a total sample size of 348 participants (87 in each of the four treatment groups). For comparison with PLACEBO, power is expected to be 90% or greater assuming the treatment effect is as large or larger than HAL or ATROPINE alone and the standard deviation is the same. For other scenarios, Tables 4 and 5 present anticipated power for various mean differences and standard deviations. Assuming the adjusted standard deviation for change in axial length is 0.24 mm, the study will have 80% power to detect a difference as small as 0.11 mm. Assuming the adjusted standard deviation for change in SER is 0.59 D, the study will have 80% power to detect a difference as small as 0.27 D.

Table 4. Power for comparison of COMBINED with PLACEBO, HAL, or ATROPINE given various mean differences and standard deviations for change in axial length (N=78 per group)

Standard Deviation, mm	Mean Difference, mm				
	0.08	0.11	0.14	0.17	0.20
0.17	83%	98%	>99%	>99%	>99%
0.205	68%	91%	99%	>99%	>99%
0.24	54%	81%	95%	99%	>99%
0.265	47%	73%	91%	98%	>99%
0.29	40%	65%	85%	95%	99%

Table 5. Power for comparison of COMBINED with PLACEBO, HAL, or ATROPINE given various mean differences and standard deviations for change in SER (N=78 per group)

Standard Deviation, D	Mean Difference, D				
	0.10	0.17	0.24	0.31	0.38
0.49	24%	58%	86%	98%	>99%
0.56	20%	47%	76%	93%	99%
0.59	18%	43%	71%	90%	98%
0.60	18%	42%	70%	89%	98%
0.66	16%	36%	62%	83%	95%

8.4 Outcome Measures

8.4.1 Primary Efficacy Outcome

- Change in axial length from baseline at 24 months

8.4.2 Secondary Efficacy Outcomes

- Change in spherical equivalent refractive error (SER) from baseline at 24 months
- Change in axial length from baseline at 30 months
- Change in SER from baseline at 30 months
- Change in axial length from baseline at 18 months
- Change in SER from baseline at 18 months
- Change in axial length from baseline at 12 months
- Change in SER from baseline at 12 months
- Change in axial length from baseline at 6 months
- Change in SER from baseline at 6 months

8.4.3 Exploratory Outcomes

- Change in monocular amplitude of accommodation from baseline at 6, 12, and 24 months
- Change in pupil size from baseline at 6, 12, and 24 months
- Change in flat corneal radius from baseline at 24 and 30 months
- Change in anterior chamber depth from baseline at 24 and 30 months
- Change in lens thickness from baseline at 24 and 30 months
- Change in axial length over 24 months (area under the curve)
- Change in axial length from 12 to 24 months
- Change in axial length from 24 to 30 months

- Change in SER from 12 to 24 months
- Change in SER from 24 to 30 months
- Change in axial length over 24 months (area under the curve)
- Child and parent Treatment Impact Questionnaire scores at 6 months and 24 months.

8.5 Analysis Cohorts

- Intention-To-Treat (ITT) Analysis Cohort: all randomized participants, irrespective of treatment received, will be analyzed according to treatment assignment.
- Safety Analysis Cohort: participants who receive at least one dose of the randomly assigned study medication (placebo or 0.05% atropine) or wear either of the randomly assigned spectacles (HAL or SVL) for any amount of time.

The primary analysis will follow the ITT principle. It will include all randomized participants. The data from the ITT cohort will be analyzed according to the group to which the participants were assigned through randomization, regardless of treatment received.

8.6 Analysis of the Primary Efficacy Outcome

The average of three separate axial length measurements visits will be calculated for each eye at baseline and all follow-up visits. If fewer than three measurements are available for an eye at a timepoint, the mean of available measurements will be used to calculate the mean axial length for each eye. The mean of the right and left eyes will be used for analysis. The change in mean axial length from baseline to the 24-month visit will be used as the primary outcome.

The primary analysis will be a treatment group comparison of change in axial length from baseline at 24-month visit, using a longitudinal discrete time mixed effects model using axial length at randomization, 6, 12, 18, and 24 months as dependent variable and adjusting for age to account for confounding due to potential imbalances between groups and to increase statistical power. The treatment group difference (active treatment – placebo) for change in mean axial length from baseline to 24 months, 95% confidence interval, and P value for the null hypothesis of no difference will be calculated based on the model estimates at 24 months.

The model assumption for the mixed model will be assessed, including the linearity of the adjustment covariates (baseline axial length and age), and normality and homoscedasticity of the residuals.

Only data from visits completed within the analysis windows (±3 months from the expected visit date) will be included in the analysis. There will be no explicit imputation of outcome data for exams not completed or completed outside of the analysis window, as the mixed model will produce an unbiased estimate of treatment effect via direct maximum likelihood as long as the missing outcome data are missing at random (MAR).

Sensitivity analyses evaluating the robustness of the primary analysis will be outlined in the statistical analysis plan.

8.7 Analysis of the Secondary Outcomes

8.7.1 Change in Spherical Equivalent Refractive Error from Baseline at 24 Months

The mean SER of each eye at baseline and all follow-up visits, measured by the masked examiner using cycloplegic autorefraction, will be calculated as the average of the three separate readings from autorefraction. If fewer than three readings are available, the average of available readings will be used. The mean of the right and left eyes will be used for analysis. A longitudinal discrete time mixed effects model will be used for treatment group comparison of change in SER from baseline at the 24-month visit using SER at randomization, 6, 12, 18, and 24 months as dependent variables and adjusting for age. The other aspects of the analysis are the same as outlined in the primary analyses (Section 8.6).

8.7.2 Change in Axial Length from Baseline at 30 Months

The same method described for the primary outcome (Section 8.6) will be used, but data from 6, 12, 18, 24, and 30 months will be included in the model.

8.7.3 Change in Spherical Equivalent Refractive Error from Baseline at 30 Months

The same method as described in Section 0 will be used but with data from 6, 12, 18, 24, and 30 months included in the model.

8.7.4 Changes in Axial Length and SER at 6, 12, and 18 Months

The same methods described in Sections 8.6 and 0 will be used.

8.8 Analyses of Exploratory Outcomes

8.8.1 Change in Monocular Amplitude of Accommodation at 6, 12, and 24 Months

Change in the monocular amplitude of accommodation will be analyzed using a discrete time longitudinal mixed effects model adjusted for age similar to the primary outcome (Section 8.6).

8.8.2 Change in Additional Ocular Parameters

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 and age similar to the primary outcome

8.8.3 Change in Pupil Size at 6, 12, and 24 Months

Change in pupil will be analyzed using a discrete-time longitudinal mixed effects model adjusted for age similar to the primary outcome (Section 8.6).

8.8.4 Change in Axial Length Over 24 Months (Area Under the Curve)

The change in axial length over 24 months (area under the curve) will be calculated and compared between treatment groups using the same discrete-time longitudinal mixed effects model used for the analyses of the primary outcome (Section 8.6). The area under the curve can be interpreted as a weighted average of the change in axial length at each visit with weights proportional to the time between visits.

AUC will be calculated by linear combination of model estimates using the trapezoidal rule and the following formula:

$$AUC = \sum_{i=1}^{n} \left(\frac{X_i + X_{i+1}}{2} \times m \right)$$

Where X_i is the axial length measured at the i^{th} visit, m is the number of months between visits i and $i+1$, and n is the number of outcome visits included in the analysis. In this analysis there are $n = 5$ visits total: 0, 6, 12, 18, and 24 months. For presentation, AUC will be divided by the number of months between baseline and the n^{th} visit (i.e., 24) so that the value shown will have units of millimeters rather than millimeter·months.

8.8.5 Change in Axial Length from 12 to 24 Months

The change in axial length from 12 to 24 months will be calculated and compared between treatment groups using the same discrete-time longitudinal mixed effects model used for the analyses of the primary outcome (Section 8.6).

8.8.6 Change in Axial Length from 24 to 30 Months

The change in axial length from 24 to 30 months will be calculated and compared between treatment groups using the same discrete-time longitudinal mixed effects model used for the analyses of the secondary outcome in axial length (Section 8.7.2).

8.8.7 Change in Spherical Equivalent Refractive Error from 12 to 24 Months

The change in SER from 12 to 24 months will be calculated and compared between treatment groups using the same discrete-time longitudinal mixed effects model used for the analyses of the secondary outcome in SER (Section 8.7.1).

8.8.8 Change in Spherical Equivalent Refractive Error from 24 to 30 Months

The change in SER from 24 to 30 months will be calculated and compared between treatment groups using the same discrete-time longitudinal mixed effects model used for the analyses of the secondary outcome in SER (Section 8.7.3).

8.8.9 Change in Spherical Equivalent Refractive Error Over 24 Months

The change in SER over 24 months (area under the curve) will be calculated and compared between treatment groups using the same discrete-time longitudinal mixed effects model used for the analyses of the primary outcome (Section 8.6). The area under the curve can be interpreted as a weighted average of the change in SER at each visit with weights proportional to the time between visits.

AUC will be calculated by linear combination of model estimates using the trapezoidal rule and the following formula:

$$AUC = \sum_{i=1}^{n} \left(\frac{X_i + X_{i+1}}{2} \times m \right)$$

Where X_i is the SER measured at the i^{th} visit, m is the number of months between visits i and $i+1$, and n is the number of outcome visits included in the analysis. In this analysis there are $n = 5$ visits total: 0, 6, 12, 18, and 24 months. For presentation, AUC will be divided by the number of months between baseline and the n^{th} visit (i.e., 24) so that the value shown will have units of diopters rather than diopters·months.

8.8.10 Treatment Impact Questionnaire

The Treatment Impact Questionnaire (TIQ) will be used as a quantitative measure to evaluate opinions regarding the burdens and impact of the randomized treatment at 6 months and 24 months (as questions for the child – the Child TIQ and the parent themselves – the Parent TIQ).

The Child-TIQ and Parent-TIQ will undergo separate factor analysis to determine the number of domains for each TIQ. Each domain will be refined through the evaluation of misfitting items and will then be Rasch scored.

Note that because the TIQ is not administered at baseline (because treatment has not been started), there will be no adjustment for baseline score in any analysis.

Additional methods to score and analyze the Treatment Impact Questionnaire will be detailed in a separate SAP.

8.9 Safety Analyses

Safety analyses will be performed in the safety analysis cohort (section 8.5**Error! Reference source not found.**). Adverse events will be coded and tabulated based on the Medical Dictionary of Regulatory Activities (MedDRA) by treatment group. The severity, frequency, and relationship to study treatment will also be tabulated. There will be no formal statistical comparison of adverse events.

The proportion of participants with loss of ≥ 2 logMAR lines of binocular near visual acuity at any visit after randomization will be tabulated for each group and compared using Fisher's Exact Test.

The proportion of participants with loss of ≥ 2 logMAR lines of monocular distance visual acuity in best correction at any visit after randomization will be tabulated for each group and compared using Fisher's Exact Test.

8.10 Intervention Adherence

Adherence to study eyedrops (atropine and placebo eyedrop) and spectacles (SVL and HAL lenses) based on calendars brought to each follow-up visit will be tabulated in each treatment group.

8.11 Protocol Adherence and Retention

Protocol deviations and visit completion rates (excluding participant deaths) will be tabulated for each treatment group.

8.12 Baseline Descriptive Statistics

The following baseline characteristics will be tabulated according to treatment group:

- Age
- Sex
- Race
- Ethnicity
- Iris color
- Number of biological parents with myopia
- Distance visual acuity in habitual refractive correction

8.13 Planned Interim Analyses

There are no formal planned interim analyses for this study. The Data and Safety Monitoring Committee will review safety and efficacy data approximately every 6 months; they have the authority to recommend stopping the trial if deemed necessary.

8.14 Subgroup Analyses

Subgroup analyses will be considered exploratory. The treatment group difference for change in axial length and change in SER from baseline to 24 within the following subgroups will be estimated with a 95% confidence interval:

- Sex
- Race/Ethnicity
- Brown iris vs. non-brown iris
- Age (continuous)
- Axial Length (continuous)
- SER (continuous)

These planned subgroup analyses will modify the primary and secondary analyses by including the baseline factor and the baseline factor by treatment interaction. In general, statistical power will be low for detecting 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.

8.15 Multiple Comparison/Multiplicity

For the primary outcome of axial length, two tests of superiority will be conducted: ATROPINE vs PLACEBO and HAL vs PLACEBO. The tests will be performed independently, and each will be conducted with an alpha level of 0.05.

Although two pairwise comparisons are being evaluated, there will be no formal adjustment to the familywise error rate. Because the primary objective of this trial is to compare each of two active treatments (atropine eye drops and HAL lenses), which likely have different mechanisms of action, with a shared PLACEBO control group (not with one another), a multiplicity adjustment is not needed.[52-54] The risk of a false positive finding with this approach is lower than if the two hypotheses were evaluated in two studies with different control groups.[52] The same logic applies to secondary, exploratory, safety, and subgroup analyses.

For the secondary outcomes (Section 8.4.2), the familywise error rate will be controlled with a hierarchical (i.e., fixed sequence) approach. If the null hypothesis for the primary outcome (axial length) is rejected (for either HAL vs PLACEBO or ATROPINE vs PLACBO), then the first secondary outcome (change in SER at 24 months) will be compared without further adjustment to the type 1 error rate.[55] If the primary outcome null hypothesis is not rejected, then the comparison of the change in SER at 24 months will be considered exploratory; a 95% confidence interval (without adjustment for multiplicity) will be presented, and a *p*-value will not be presented. Subsequent secondary outcomes will be tested in the order listed in Section 8.4.2.

No formal adjustments for multiple exploratory outcomes will be made, and P values will not be presented for exploratory outcome analyses (Section 8.8). However, for changes in monocular amplitude of accommodation (Section 8.8.2), additional ocular parameters (Section 0), and pupil

size (Section 8.8.4), the adaptive false discovery rate[56] procedure will be used to adjust the 95% confidence intervals for the analysis of multiple time points (i.e., one adjustment for the 3 amplitude comparisons and a separate adjustment for the 3 pupil size comparisons).

There will be no formal adjustment for safety analyses because type 2 errors (false negatives) are of greater concern than type 1 errors (false positives).

The adaptive false discovery rate will be used to adjust for multiple subgroup analyses. Both interaction P values and within-group 95% confidence intervals will be adjusted. P values for interactions will only be presented if the overall analysis indicates a significant effect.

8.16 Additional Tabulations and Analyses

- A flow chart accounting for all participants for all visits and phone calls will be developed.
- Visit and phone contact completion rates for each follow-up visit will be tabulated.
- Proportion of participants with a change in myopia of ≥ 0.50 D and ≥ 1.0 D from baseline to 12, 24, and 30 months.
- Proportion of participants with a change in axial length ≥ 0.25 mm and ≥ 0.50 mm from baseline to 12, 24, and 30 months.

8.17 Exploratory Analyses in COMBINED Atropine + HAL Lenses Group

Exploratory comparisons between the COMBINED group and the ATROPINE, HAL, and PLACEBO groups will parallel the analyses conducted for the ATROPINE vs PLACEBO and HAL vs PLACEBO comparisons. An exploratory analysis pooling across cells in the factorial design will be conducted if prespecified criteria suggesting absence of an interaction are met. Details will be provided in the SAP.

Chapter 9: Data Collection and Monitoring

9.1 Case Report Forms and Other Data Collection

The main study data are collected on electronic case report forms (eCRFs). When data are directly collected in real-time in electronic case report forms, this will be considered the source data. For any data points for which the eCRF is not considered source (e.g., lab results that are transcribed from a printed report into the eCRF; other data that are not directly entered in real-time), the original source documentation must be maintained in the participant's study chart or medical record. This source must be readily verifiable against the values entered into eCRF. Even where all study data are directly entered into the eCRFs at office visits, evidence of interaction with a live participant must be recorded (e.g., office note, visit record, etc.).

Electronic device data files are obtained from the study software and individual hardware components. These electronic device files are considered the primary source documentation. 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.

9.2 Study Records Retention

Study documents should be retained for a minimum of three (3) years after completion of the final grant reporting, or for two (2) years after a marketing application is approved for the investigational product(s); or, if an application is not approved, until two (2) years after shipment and delivery of the product for investigational use is discontinued and the FDA has been so notified. These documents should be retained for a longer period, however, if required by local regulations or institutional requirements. No records will be destroyed without the written consent of the sponsor. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

9.3 Quality Assurance and Monitoring

Designated personnel from the JCHR 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 adhering to Good Clinical Practice (GCP) and the applicable regulatory requirements, as well as to ensure that the rights and wellbeing of trial participants are protected and that the reported trial data are accurate, complete, and verifiable. Adverse events will be prioritized for monitoring.

A risk-based monitoring (RBM) plan will be developed and revised as needed during the study, consistent with the FDA's "Guidance for Industry Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring" (August 2013). This plan describes in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of monitoring reports.

The data of most importance for monitoring at the site are informed consent/assent, participant eligibility, and adverse events. Therefore, the RBM plan will focus on these areas. Whenever possible, remote monitoring will be conducted in real-time supplemented by on-site monitoring to evaluate the accuracy and completeness of the key study 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
- Agent/Device accountability
- Communications with site staff
- Patient retention and visit completion
- Quality control reports
- Management of noncompliance
- Documenting monitoring activities
- Adverse event reporting and monitoring

JCHR representatives or their designees may visit the study facilities at any time 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. The investigational site will provide direct access to all trial related sites, source data/documents, and reports for monitoring and auditing by the sponsor and inspection by local and regulatory authorities.

9.4 Protocol Deviations

A protocol deviation is noncompliance with the clinical trial protocol, GCP, or clinical procedure requirements. Noncompliance may be on the part of the participant, the investigator, or the study site staff. As a result of deviations, the site must develop and implement corrective actions promptly.

The site PI and study staff are responsible for knowing and adhering to their local requirements. Further details about the handling of protocol deviations will be included in the Monitoring Plan.

Chapter 10: Ethics/Protection of Human Participants

10.1 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.

10.2 Institutional Review Boards

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

10.3 Informed Consent, Assent, and HIPAA Authorization Process

10.3.1 Procedures and Documentation

Informed consent is a process that is initiated prior to the individual's agreeing to participate, or allowing their child to participate, in the study and continues throughout study participation. Assent is the process by which a child is informed of the study and has the right and requirement to provide affirmative agreement to participate (verbally or in writing as required by the overseeing IRB). HIPAA Authorization is the process by which the parent/participant provides their approval to allow their protection health information to be collected and shared as specified in a similarly named document, or within the applicable section of the consent form. Extensive discussion of risks and possible benefits of participation will be provided to the participants and their parent(s). Consent, assent and HIPAA forms will be IRB-approved and the parent(s)/participant will be asked to read and review the document(s) as applicable. The investigator will explain the research study to the parent(s)/participant and answer any questions that may arise. All parents/participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Parents/participants will have the opportunity to carefully review the written form(s) and ask questions prior to signing.

The parents/participants should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The parent(s)/participant will sign the applicable forms prior to any procedures being done or data being collected for the study. The parents/participants may withdraw consent, assent or HIPAA Authorization at any time throughout the course of the study. A copy of the forms will be given to the parents/participants for their records. The rights and welfare of the participants will be protected by emphasizing that the quality of their medical care and benefits to which they are otherwise entitled will not be adversely affected if they decline to participate in this study or withdraw at a later date.

10.3.2 Participant and Data Confidentiality

Parent/participant confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. This confidentiality is extended to include testing of biological samples and genetic tests in addition to the clinical information relating to participants. 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 from the study will be released to any unauthorized third party without prior written approval of the sponsor.

The study monitor, other authorized representatives of the sponsor, representatives of the IRB, regulatory agencies, or company supplying the study product 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 remain in a secure location for as long as dictated by the reviewing IRB, institutional policies, or sponsor requirements.

Study participant research data for statistical analysis and scientific reporting will be transmitted to and stored at the Jaeb Center for Health Research. This will not include the participant's contact or identifying information. Instead, individual participants and their research data will be identified by a unique study identification number. The study data entry and management systems used by clinical sites and Jaeb Center for Health 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.

To further protect the privacy of study participants, a Certificate of Confidentiality is provided from the NIH. This certificate protects identifiable research information from forced disclosure. It allows the investigator and others who have access to research records to refuse to disclose identifying information on research participation in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. By protecting researchers and institutions from being compelled to disclose information that would identify research participants, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by helping assure confidentiality and privacy to participants.

10.3.3 Future Use of Data

Data collected for this study will be analyzed and stored at the Jaeb Center for Health Research. After the study is completed, the de-identified, archived data will be made available to the public as specified in the consent form(s).

Chapter 11: References

1. Drover JR, Felius J, Cheng CS, Morale SE, Wyatt L, Birch EE. Normative pediatric visual acuity using single surrounded HOTV optotypes on the Electronic Visual Acuity Tester following the Amblyopia Treatment Study protocol. *J AAPOS*. 2008;12(2):145-9.
2. Pan Y, Tarczy-Hornoch K, Cotter SA, et al. Visual acuity norms in pre-school children: the Multi-Ethnic Pediatric Eye Disease Study. *Optom Vis Sci*. 2009;86(6):607-12.
3. Pan CW, Ramamurthy D, Saw SM. Worldwide prevalence and risk factors for myopia. *Ophthalmic & Physiological Optics*. 2012;32(1):3-16.
4. Foster PJ, Jiang Y. Epidemiology of myopia. *Eye (Lond)*. 2014;28(2):202-208.
5. French AN, Morgan IG, Burlutsky G, Mitchell P, Rose KA. Prevalence and 5- to 6-year incidence and progression of myopia and hyperopia in Australian schoolchildren. *Ophthalmology*. 2013;120(7):1482-1491.
6. Giordano L, Friedman DS, Repka MX, et al. Prevalence of refractive error among preschool children in an urban population: the Baltimore Pediatric Eye Disease Study. *Ophthalmology*. 2009;116(4):739-46, 746 e1-4.
7. Multi-Ethnic Pediatric Eye Disease Study Group. Prevalence of myopia, hyperopia, and astigmatism in non-Hispanic white and Asian children: multi-ethnic pediatric eye disease study. *Ophthalmology*. 2013;120(10):2109-2116.
8. Multi-Ethnic Pediatric Eye Disease Study Group. Prevalence of myopia and hyperopia in 6- to 72-month-old african american and Hispanic children: the multi-ethnic pediatric eye disease study. *Ophthalmology*. 2010;117(1):140-147 e3.
9. Theophanous C, Modjtahedi BS, Batech M, Marlin DS, Luong TQ, Fong DS. Myopia prevalence and risk factors in children. *Clin Ophthalmol*. 2018;12:(doi)(eCollection 2018.):1581-1587.
10. Vitale S, Sperduto RD, Ferris FL, 3rd. Increased prevalence of myopia in the United States between 1971-1972 and 1999-2004. *Arch Ophthalmol*. 2009;127(12):1632-1639.
11. Holden BA, Fricke TR, Wilson DA, et al. Global prevalence of myopia and high myopia and temporal trends from 2000 through 2050. *Ophthalmology*. 2016;123(5):1036-42.
12. Liang J, Pu Y, Chen J, et al. Global prevalence, trend and projection of myopia in children and adolescents from 1990 to 2050: a comprehensive systematic review and meta-analysis. *Br J Ophthalmol*. 2024;
13. Lawrenson JG, Shah R, Huntjens B, et al. Interventions for myopia control in children: a living systematic review and network meta-analysis. *Cochrane Database Syst Rev*. 2023;2(2):Cd014758.
14. Grodum K, Heijl A, Bengtsson B. Refractive error and glaucoma. *Acta Ophthalmol Scand*. 2001;79(6):560-566.
15. Tano Y. Pathologic myopia: where are we now? *Am J Ophthalmol*. 2002;134(5):645-660.
16. Willis JR, Vitale S, Morse L, et al. The Prevalence of Myopic Choroidal Neovascularization in the United States: Analysis of the IRIS((R)) Data Registry and NHANES. *Ophthalmology*. 2016;123(8):1771-82.
17. Huang J, Wen D, Wang Q, et al. Efficacy comparison of 16 interventions for myopia control in children: a network meta-analysis. *Ophthalmology*. 2016;123(4):697-708.
18. National Academies of Sciences E, Medicine, Division of B, et al. The National Academies Collection: Reports funded by National Institutes of Health. *Myopia: Causes, Prevention, and Treatment of an Increasingly Common Disease*. National Academies Press (US)

19. Repka MX, Weise KK, Chandler DL, et al. Low-dose 0.01% atropine eye drops vs placebo for myopia control: A randomized clinical trial. *JAMA Ophthalmol*. 2023;141(8):756-765.
20. Lee SS, Lingham G, Blaszkowska M, et al. Low-concentration atropine eyedrops for myopia control in a multi-racial cohort of Australian children: A randomised clinical trial. *Clin Exp Ophthalmol*. 2022;
21. Zadnik K, Schulman E, Flitcroft I, et al. Efficacy and Safety of 0.01% and 0.02% Atropine for the Treatment of Pediatric Myopia Progression Over 3 Years: A Randomized Clinical Trial. *JAMA Ophthalmol*. 2023;141(10):990-999.
22. Loughman J, Kobia-Acquah E, Lingham G, et al. Myopia outcome study of atropine in children: Two-year result of daily 0.01% atropine in a European population. *Acta Ophthalmol*. 2023;11(10):15761.
23. Loughman J, Lingham G, Nkansah EK, Kobia-Acquah E, Flitcroft DI. Efficacy and Safety of Different Atropine Regimens for the Treatment of Myopia in Children: Three-Year Results of the MOSAIC Randomized Clinical Trial. *JAMA Ophthalmol*. 2025;143(2):134-144.
24. Shih YF, Chen CH, Chou AC, Ho TC, Lin LL, Hung PT. Effects of different concentrations of atropine on controlling myopia in myopic children. *J Ocul Pharmacol Ther*. 1999;15(1):85-90.
25. Shih YF, Hsiao CK, Chen CJ, Chang CW, Hung PT, Lin LL. An intervention trial on efficacy of atropine and multi-focal glasses in controlling myopic progression. *Acta Ophthalmol Scand*. 2001;79(3):233-236.
26. Chia A, Chua WH, Cheung YB, et al. Atropine for the treatment of childhood myopia: safety and efficacy of 0.5%, 0.1%, and 0.01% doses (Atropine for the Treatment of Myopia 2). *Ophthalmology*. 2012;119(2):347-354.
27. Chua WH, Balakrishnan V, Chan YH, et al. Atropine for the treatment of childhood myopia. *Ophthalmology*. 2006;113(12):2285-91.
28. Yam JC, Jiang Y, Tang SM, et al. Low-concentration Atropine for Myopia Progression (LAMP) study: A Randomized, double-blinded, placebo-controlled trial of 0.05%, 0.025%, and 0.01% atropine eye drops in myopia control. *Ophthalmology*. 2019;126(1):113-124.
29. Yam JC, Li FF, Zhang X, et al. Two-year clinical trial of the Low-concentration Atropine for Myopia Progression (LAMP) study: Phase 2 report. *Ophthalmology*. 2020;127(7):910-919.
30. Zhu Q, Tang GY, Hua ZJ, et al. 0.05% atropine on control of myopia progression in Chinese school children: a randomized 3-year clinical trial. *Int J Ophthalmol*. 2023;16(6)(eCollection 2023):939-946. .
31. Li FF, Kam KW, Zhang Y, et al. Differential effects on ocular biometrics by 0.05%, 0.025%, and 0.01% atropine: Low-concentration atropine for myopia progression study. *Ophthalmology*. 2020;127(12):1603-1611
32. Schaeffel F, Glasser A, Howland HC. Accommodation, refractive error and eye growth in chickens. *Vision Res*. 1988;28(5):639-57.
33. Troilo D, Smith EL, 3rd, Nickla DL, et al. IMI - Report on Experimental Models of Emmetropization and Myopia. *Invest Ophthalmol Vis Sci*. 2019;60(3):M31-M88.
34. Smith EL, 3rd, Hung LF, Huang J. Relative peripheral hyperopic defocus alters central refractive development in infant monkeys. *Vision Res*. 2009;49(19):2386-92.
35. Tse DY, Lam CS, Guggenheim JA, et al. Simultaneous defocus integration during refractive development. *Invest Ophthalmol Vis Sci*. 2007;48(12):5352-9.
36. Woods J, Guthrie SE, Keir N, et al. Inhibition of defocus-induced myopia in chickens. *Invest Ophthalmol Vis Sci*. 2013;54(4):2662-8.
37. Irving EL, Yakobchuk-Stanger C. Myopia progression control lens reverses induced myopia in chicks. *Ophthalmic & Physiological Optics*. 2017;37(5):576-584.
38. Bao J, Yang A, Huang Y, et al. One-year myopia control efficacy of spectacle lenses with aspherical lenslets. *Br J Ophthalmol*. 2022;106(8):1171-1176.

39. Bao J, Huang Y, Li X, et al. Spectacle lenses with aspherical lenslets for myopia control vs single-vision spectacle lenses: A randomized clinical trial. *JAMA Ophthalmol*. 2022;140(5):472-478.
40. Sankaridurg P, Weng R, Tran H, et al. Spectacle Lenses With Highly Aspherical Lenslets for Slowing Myopia: A Randomized, Double-Blind, Cross-Over Clinical Trial. *Am J Ophthalmol*. 2023;247:18-24.
41. Vagge A, Frattolillo A, Nucci P, et al. Highly Aspherical Lenslet Target (HALT) technology in combination with low-dose atropine to control myopia progression. *Invest Ophalmol Vis Sci*. 2024;65(7):2739-2739.
42. Sim B. Combining the Essilor® Stellest® lens with atropine – Q&A with Dr Bryan Sim. MyopiaProfile. 2024. https://www.myopiaprofile.com/articles/Combining-Essilor-Etellest-with-Atropine-Bryan-Sim
43. Li SM, Wu SS, Kang MT, et al. Atropine slows myopia progression more in Asian than white children by meta-analysis. *Optom Vis Sci*. 2014;91(3):342-350.
44. Tideman JW, Snabel MC, Tedja MS, et al. Association of axial length with risk of uncorrectable visual impairment for Europeans with myopia. *JAMA Ophthalmol*. 2016;134(12):1355-1363.
45. Haarman AEG, Enthoven CA, Tideman JWL, Tedja MS, Verhoeven VJM, Klaver CCW. The complications of myopia: A review and meta-analysis. *Invest Ophthalmol Vis Sci*. 2020;61(4):49.
46. Flitcroft DI. The complex interactions of retinal, optical and environmental factors in myopia aetiology. *Prog Retin Eye Res*. 2012;31(6):622-60.
47. Vongphanit J, Mitchell P, Wang JJ. Prevalence and progression of myopic retinopathy in an older population. *Ophthalmology*. 2002;109(4):704-11.
48. Bullimore MA, Brennan NA. Myopia control: Why each diopter matters. *Optom Vis Sci*. 2019;96(6):463-465.
49. Bullimore MA, Brennan NA. Efficacy in myopia control-The impact of rebound. *Ophthalmic & Physiological Optics*. 2024;
50. World Medical Association. World Medical Association Declaration of Helsinki: Ethical principles for medical research involving human subjects. *JAMA*. 2013;310(20):2191-2194.
51. Food and Drug Administration. FDA Regulations Relating to Good Clinical Practice and Clinical Trials. 2021.
52. Howard DR, Brown JM, Todd S, Gregory WM. Recommendations on multiple testing adjustment in multi-arm trials with a shared control group. *Stat Methods Med Res*. 2018;27(5):1513-1530.
53. Juszczak E, Altman DG, Hopewell S, Schulz K. Reporting of Multi-Arm Parallel-Group Randomized Trials: Extension of the CONSORT 2010 Statement. *JAMA*. 2019;321(16):1610-1620.
54. Parker RA, Weir CJ. Non-adjustment for multiple testing in multi-arm trials of distinct treatments: Rationale and justification. *Clin Trials*. 2020;17(5):562-566.
55. Dmitrienko A, D'Agostino RB, Sr. Multiplicity Considerations in Clinical Trials. *New England Journal of Medicine*. 2018;378(22):2115-2122.
56. Benjamini Y, Krieger AM, Yekutieli D. Adaptive linear step-up procedures that control the false discovery rate. *Biometrika*. 2006;93(3):491-507.