CLINICAL TRIAL PROTOCOL
CP-NVK002-0001

CHILDHOOD ATROPINE FOR MYOPIA PROGRESSION (CHAMP): A 3-ARM RANDOMIZED, DOUBLE-MASKED, PLACEBO-CONTROLLED, PHASE 3 STUDY OF ATROPINE SULFATE OPHTHALMIC SOLUTION 0.01% AND 0.02%

EudraCT Number:	2018-001077-24
Study Phase:	Phase 3
Product Name:	Atropine Sulfate Ophthalmic Solution
Indication:	Slowing the progression of myopia in children
Sponsor:	Vyluma Inc., an affiliate of Nevakar Inc. NJ Center of Excellence 1019 Route 202/206, Bldg. K Bridgewater, NJ 08807
Original Protocol:	01 July 2017
Protocol Amendment (1):	05 September 2017
Protocol Amendment (2):	10 April 2018
Protocol Amendment (3):	12 August 2019
Protocol Amendment (4):	09 October 2020
Protocol Amendment (5):	14 June 2021

CONFIDENTIAL

SPONSOR SIGNATURE

Study Title	Childhood Atropine for Myopia Progression (CHAMP): A 3-Arm Randomized, Double-Masked, Placebo-Controlled, Phase 3 Study of Atropine Sulfate Ophthalmic Solution 0.01% and 0.02%
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Person authorized to sign the protocol and protocol amendment(s) for the Sponsor, Vyluma Inc., an affiliate of Nevakar Inc.:

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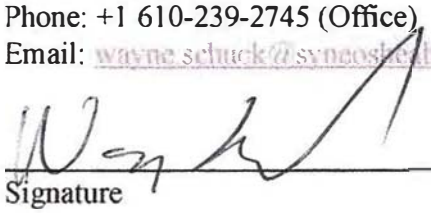

Signature 15 Jun 2021 Date

INVESTIGATOR'S AGREEMENT

Study Title	Childhood Atropine for Myopia Progression (CHAMP): A 3-Arm Randomized, Double-Masked, Placebo-Controlled, Phase 3 Study of Atropine Sulfate Ophthalmic Solution 0.01% and 0.02%
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I have fully discussed the objectives of this study and the content of this protocol with the sponsor's representative. I confirm that I have read and understood this protocol, the Investigator's Brochure and other product information provided for Atropine Sulfate Ophthalmic Solution.

I understand that information contained in or pertaining to this protocol is confidential and should not be disclosed, other than to those directly involved in the execution or the ethical review of the study, without written authorization from the sponsor. It is, however, permissible to provide information to a subject in order to obtain consent.

I agree to conduct this study according to this protocol and to comply with its requirements, subject to ethical and safety considerations and guidelines, and to conduct the study in accordance with the Declaration of Helsinki, International Council for Harmonisation guidelines on Good Clinical Practice (ICH E6 R2), and applicable regional regulatory requirements, including data protection laws and regulations, and the regulatory requirements for reporting serious adverse events defined in Section 9.9 of this protocol.

I agree to make available to Sponsor personnel, their representatives and relevant regulatory authorities, my subjects' study records in order to verify the data that I have entered into the Case Report Forms. I am aware of the responsibilities of a Principal Investigator as provided by the Sponsor.

I understand that the Sponsor may decide to suspend or prematurely terminate the study at any time for whatever reason; such a decision will be communicated to me in writing. Conversely, should I decide to withdraw from execution of the study, I will communicate my intention immediately in writing to the Sponsor.

_____

Printed Name of Investigator

_____

Signature of Investigator Date

PROCEDURES IN CASE OF EMERGENCY

Table 1: Emergency Contact Information

Role in Study	Name	Contact Information
Medical Monitor – NA	Dr. Michelle Bailey Syneos Health	Office : +1 919 745-2723 Mobile : +1 919 480-4169 Email : Michelle.bailey@syneoshealth.com
Medical Monitor – EU	Dr. Stanislava Glasnáková Syneos Health	Office : +420 241 040 971 Mobile : +420 608 336 944 Email : stanislava.glasnakova@syneoshealth.com

1. SYNOPSIS

Name of Sponsor/Company: Vyluma Inc., an affiliate of Nevakar Inc.	
Protocol Number: CP-NVK002-0001	
EudraCT Number: 2018-001077-24	
Name of Investigational Product: Atropine Sulfate Ophthalmic Solution	
Name of Active Ingredient: Atropine sulfate 0.01% and 0.02%	
Title of Study: Childhood Atropine for Myopia Progression (CHAMP): A 3-Arm Randomized, Double-Masked, Placebo-Controlled, Phase 3 Study of Atropine Sulfate Ophthalmic Solution 0.01% and 0.02%.	
Study Center(s): 15 – 30 centers in North America, Europe, and United Kingdom.	
Studied Period (Years): Estimated date first subject enrolled: November 2017 Estimated date completion BLEOS Month 36: August 2022 Estimated last subject completed Month 36- EOS Month 48: September 2023	**Phase of development:** 3
Objective: **Primary:** To evaluate the safety and efficacy of 2 concentrations of Atropine Sulfate Ophthalmic Solution (0.01% and 0.02%) compared to Vehicle (placebo) for slowing the progression of myopia in children over a 3-year treatment period. **Exploratory:** To observe safety and efficacy in subjects re-randomized to 1 year of treatment with Atropine Sulfate Ophthalmic Solution, 0.01% or 0.02%, or Vehicle following 3 years of treatment in children with progressive myopia.	
Study Rationale: Vyluma Inc., an affiliate of Nevakar Inc., hereinafter referred to as the Sponsor, is pursuing the development of Atropine Sulfate Ophthalmic Solution for slowing the progression of myopia in children. Ametropia in children is common, and if left uncorrected causes decreased vision, visual discomfort (eye strain), strabismus, and/or amblyopia (AAPOS 2013). The most common form of refractive error is myopia (nearsightedness), which has its onset in children 6 to 12 years of age (Zadnik 2015).	
Study Population: Study subjects will be children, male or female, aged 3 to ≤ 17.0 years at the time of enrollment, with myopia spherical equivalent refraction (SER) of at least -0.50 D and no greater than -6.00 D in each eye, astigmatism of no more than -1.50 D in each eye, and anisometropia (SER) of < 1.50 D as measured by cycloplegic autorefraction.	
Methodology: This will be a 3-arm randomized, multicenter, double-masked, placebo-controlled study conducted in 2 stages. Stage 1 is a safety and efficacy phase of 3 years (36 months) in duration, during which subjects will be allocated to 1 of 3 study medications. Stage 2 is a randomized cross-over phase of 1 year (12 months) in duration, during which subjects will be re-randomized to receive 1 of the 3 study medications with subjects initially randomized to Vehicle only eligible for randomization to	

0.01% or 0.02% atropine. Subjects (aged 3 to ≤ 17.0 years) will enter the study with myopia SER of at least -0.50 D and no greater than -6.00 D in each eye as measured by cycloplegic autorefraction.

At screening/baseline (Day 0), the site will obtain signed informed consent from the parent or legal guardian of the subject and assent from the subject (as applicable). The subject will then undergo a screening evaluation to determine eligibility for the study as per the inclusion and exclusion criteria defined in the protocol. Following confirmation of eligibility, the clinical site will access the Interactive Response Technology (IRT), which will assign the subject to 1 of the 3 treatment arms and assign the initial study medication kit to be dispensed to the parent/guardian following instruction on administration. The allocated study medication will be administered, one drop in each eye once daily (QD), at bedtime, for 3 years.

Treatment arms are:

- Atropine Sulfate Ophthalmic Solution, 0.01%
- Atropine Sulfate Ophthalmic Solution, 0.02%
- Vehicle (placebo)

Both eyes will be treated; myopia must be bilateral to qualify. If myopia is unilateral at screening or the child seems likely to cross the threshold for bilateral myopia of at least -0.50 SER, the subject can be asked to return while the enrollment period is still open to determine his or her eligibility.

Subjects will return to the clinical site at 6-month intervals for 3 years to undergo a series of safety and efficacy evaluations and at 3-month intervals throughout the study for update of concomitant medications and adverse event (AE) assessment. While it is preferred that the subject attend every visit, the parent/guardian may attend a 3-month visit without the subject if necessary; both the subject and their parent/guardian must be present for all 6-month visits. At each study visit, unopened/unused and used study medication materials will be returned, concomitant medications will be updated, AE assessment will be conducted, allocated study medication will be dispensed for the next 3-month study period, and treatment adherence assessment will be performed.

Site staff will also contact subjects or their parents/guardians by telephone at the end of Month 1 and Month 2 and then midway between office visits during the initial year of the study to collect information regarding AEs and treatment adherence. Telephone checks can be continued or reinstated at any time during the study to assist with maintaining protocol and treatment adherence.

After a subject completes all safety and efficacy assessments at Month 36 (the primary efficacy time point) the randomized cross-over stage (Stage 2) will commence, and each subject will be re randomized to receive 1 of the 3 study medications for the final year of the study. Subjects randomized to either 0.01% or 0.02% Atropine Sulfate Ophthalmic Solution during Stage 1 will be re randomized to treatment with Atropine Sulfate Ophthalmic Solution, 0.01%, Atropine Sulfate Ophthalmic Solution, 0.02%, or Vehicle, and subjects randomized to the Vehicle group in Stage 1 will be re-randomized to active treatment with Atropine Sulfate Ophthalmic Solution, 0.01% or Atropine Sulfate Ophthalmic Solution, 0.02%. In Stage 2, study medication will be administered one drop in each eye QD at bedtime, as before, for 1 year.

During Stage 2, the subject and their parents/guardians will again return at 6-month intervals for safety and efficacy evaluations and at 3-month intervals for update of concomitant medications and AE assessment. As in Stage 1, both the subject and their parent/guardian must be present for all 6-month visits, but the parent/guardian may attend a 3-month visit without the subject if necessary. At each study visit, unopened/unused and used study medication materials will be returned, concomitant medications will be updated, AE assessment will be conducted, study medication will be dispensed for the next 3-month study period, and treatment adherence assessment will be

performed. At Month 45, subjects will receive their final study medication kit and return at Month 48 for their final study visit assessments.

Subject or their parent/guardian will be encouraged to record their dosing on a daily basis, starting from the same evening after completing their Month 36 visit till the last visit (Stage 2 of the study) in an electronic patient diary (e-diary). The subject or their parent/guardian will be encouraged to use their cell phone to upload e-diary responses. At Month 36 visit, if subject or their parent/guardian do not have a cell phone or are unwilling to use their cell phone, a device will be provisioned by Medidata and provided to the subject. Once the instillation of the eye drops has been successfully completed, subject or their parent/guardian will log into the application to record dosing of the left eye and the right eye and complete diary submission daily. The diary can be completed between 6:00 PM and 11:45 PM. If the subject or their parent/guardian do **not** complete the e-diary within the allotted time, they will **not** be able to enter the missing data retroactively, as the purpose is to collect information on the actual date the study drops were instilled. Once data is submitted, this information will be automatically entered into the study's Medidata Rave database.

Inclusion of the Modified Amblyopia Treatment Index (ATI), quality of life (QoL) questionnaire

At Month 42 and Month 48, in addition to other assessments, the study staff will encourage participation in the Modified Amblyopia Treatment Index (ATI), quality of life (QoL) questionnaire which has been added to the study to be completed by the subject and their parent/guardian. Participation is voluntary and will be documented. The parent/guardian questionnaire should be completed prior to the subject's questionnaire. The questionnaires should be completed prior to the Investigator's examination of the subject.

All subjects are to be re-consented/re-assented at their next study visit, including subjects completing an End of Study (EOS) Visit (Stage 1 – Month 36, Month 39, Month 42, Month 45, and Month 48).

Number of Subjects (Planned): Subjects will be randomized in a 2:2:3 ratio of vehicle: Atropine Sulfate Ophthalmic Solution, 0.01%: Atropine Sulfate Ophthalmic Solution, 0.02%

The target number of subjects to be randomized into the 6- to 10-year age group (436), the primary efficacy population, will be:

- Vehicle (placebo): 125
- Atropine Sulfate Ophthalmic Solution, 0.01%: 125
- Atropine Sulfate Ophthalmic Solution, 0.02%: 186

Approximately 483 subjects over all eligible ages will be enrolled, resulting in the following numbers of subjects in each arm:

- Vehicle (placebo): 138
- Atropine Sulfate Ophthalmic Solution, 0.01%: 138
- Atropine Sulfate Ophthalmic Solution, 0.02%: 207

The Sponsor may conduct a sample size re-estimation based on a masked assessment of the primary endpoint response rate and/or the subject discontinuation rate.

The randomization will be stratified twice: (1) by age at randomization (subjects < 9 years; subjects ≥ 9 years) and (2) by refractive error (less myopic: SER -0.50 to -3.00 D; more myopic: one or more eyes with SER-3.01 to -6.00 D). The stratification is used to balance these characteristics across the 3 treatment groups. Enrollment will proceed until 436 subjects aged 6 to 10 years have been randomized and at least 483 subjects overall have been randomized. Enrollment may be closed

to subjects age ≥ 11 years following enrollment of 50 subjects into this age group to avoid over-enrollment into the study.

The drop-out rate over the 3 years of the safety and efficacy stage of the study (Stage 1) is estimated to be 27% (~10% per year). As long as this drop-out rate is not exceeded, then at least 150 subjects (300 eyes) receiving the higher concentration (0.02% atropine) will be available for the evaluation of safety.

Diagnosis and Main Criteria for Inclusion:

Inclusion Criteria

1. Children (male or female) aged 3 to ≤ 17.0 years.
2. Myopia SER of at least -0.50 D and no greater than -6.00 D myopia in each eye as measured by cycloplegic autorefraction.
3. If present, astigmatism of no more than -1.50 D in each eye as measured by cycloplegic autorefraction.
4. Anisometropia SER of < 1.50 D as measured by cycloplegic autorefraction.
5. Normal intraocular pressure of < 21 mm Hg in each eye.
6. Distance vision correctable to at least 0.1 logMAR or 20/25 Snellen equivalent in each eye.
7. Female subjects of childbearing potential (post menarche) must have a negative urine pregnancy test at screening.
8. Subject's parent or legal guardian must provide informed consent on behalf of the subject, and the subject should provide assent when applicable, per Institutional Review Board (IRB)/Ethics Committee (EC) guidelines. If a subject becomes an adult (depending on country regulations) during the study, they will need to sign an informed consent form to continue in the study.

Exclusion Criteria

1. Allergy to atropine or any of the excipients of the eye drops.
2. Current or history of amblyopia or manifest strabismus including intermittent tropia.
3. Heart rate is persistently (for more than 10 minutes) > 120 beats per minute at screening/baseline.
4. History of any disease or syndrome that predisposes the subject to severe myopia (e.g., Marfan syndrome, Stickler syndrome, retinopathy of prematurity).
5. History in either eye of abnormal ocular refractive anatomy (e.g., keratoconus, lenticonus, spherophakia).
6. History in either eye of previous intraocular or ocular laser/non-laser surgery.
7. Current or history of glaucoma; anatomic narrow anterior chamber angles.
8. Serious systemic illness that, in the Investigator's opinion, would render the subject ineligible.
9. Chronic use of any topical or systemic antimuscarinic/anticholinergic medications (e.g.,atropine, scopolamine, tropicamide) within 21 days prior to screening, and/or anticipated need for chronic use during the study period (i.e., more than 7 consecutive days in 1 month or more than 30 total days in 1 year). (Use of cycloplegic drops for dilated ocular exam are allowable.)
10. Chronic use (more than 3 days per week) of any topical ophthalmic medications (prescribed or over-the-counter) other than the assigned study medication. Use of artificial tears is allowed but may not be used within 2 hours of administration of study medication.
11. The anticipated need to use chronic ophthalmic or systemic oral corticosteroids during the study. Intranasal, inhaled, topical dermatologic, intra-articular, perianal steroids, and short-term oral steroids (i.e., < 2 weeks) are permitted.
12. Prior myopia control treatment including orthokeratology, bifocal contact lenses, or progressive addition spectacle lenses. The only allowable prior treatments are myopic correction in the form of single-vision eyeglasses and/or single-vision or toric soft contact lenses.
13. Preplanned hospitalization during the study period. (Note: The study period begins at the time of randomization.)
14. Unwilling or unable to complete study procedures or to be followed up for the 48-month duration of the study.
15. Participation in any other study of investigational therapy during the study period or within the last 30 days.
16. History of any substance abuse (excessive or habitual use of alcohol and/or drug including nicotine) and not willing to abstain from these substance(s) during the 4-year study period.
17. Female subjects who are pregnant, nursing, or plan to become pregnant at any time during the study.
18. Employees of the study site and their family members are not permitted to participate as subjects in the study. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted.
19. Current or history of significant or severe damage to the cornea.

Investigational Product, Dosage and Mode of Administration:

Atropine Sulfate Ophthalmic Solution, 0.01% or 0.02%, dosed QD by topical ocular administration into each eye, at bedtime.

Reference Therapy, Dosage and Mode of Administration:

Vehicle (placebo) ophthalmic solution, dosed QD by topical ocular administration into each eye, at bedtime.

Duration of Treatment:

The study will be conducted in 2 stages. Stage 1 is the primary safety and efficacy stage of the study and will be 3 years (36 months) in duration. Subjects will be randomized in a 2:2:3 ratio of Vehicle: Atropine Sulfate Ophthalmic Solution, 0.01%: Atropine Sulfate Ophthalmic Solution, 0.02%. On completion of 3 years of treatment, Stage 2, a randomized cross-over stage will commence, and all subjects will be re-randomized to 1 of the 3 study medications and will receive this treatment for 1 year (12 months). Subjects who were randomized to 0.01% or 0.02% Atropine Sulfate Ophthalmic Solution during Stage 1 will be re-randomized in a 1:1:1 ratio to one of the 3 treatment arms (Vehicle: Atropine Sulfate Ophthalmic Solution, 0.01%: Atropine Sulfate Ophthalmic Solution, 0.02%), and subjects who were randomized to Vehicle during Stage 1 will be re-randomized in a 1:1 ratio to active treatment (Atropine Sulfate Ophthalmic Solution, 0.01%: Atropine Sulfate Ophthalmic Solution, 0.02%).

Study Procedures:

Office Visits should occur within ± 2 weeks of the expected visit date.

Screening/Randomization/Baseline Visit (Day 0): Sites should complete screening/randomization/baseline procedures and enroll subjects within 30 days from signing the informed consent.

The clinical site will obtain signed informed consent from the parent or legal guardian of the subject and assent from the subject (as applicable). The subject will then undergo screening evaluations to determine eligibility for the study which will include review of medical/ocular and prior medication history, a urine pregnancy test for female subjects of childbearing potential, heart rate (HR), monocular Best-Corrected Visual Acuity (BCVA) measurement at distance and near, photopic pupil size measurement, slit-lamp examination (SLE) (check for narrow angles), tonometry, dilated fundus examination and cycloplegic autorefraction. Height and weight will also be assessed.

Following confirmation of eligibility, the clinical site will measure axial length and, if possible, crystalline lens thickness. The site will access the IRT, which will assign the subject to 1 of the 3 treatment arms and assign the initial study medication kit to be dispensed to the parent/guardian following instruction on administration.

One (1) drop of the study medication will be administered into each eye QD, at bedtime. Because AEs are to be collected beginning after signing of informed consent/assent, the site will document any events that may be volunteered spontaneously by the subject or parent/guardian that occur before the end of the visit.

If the subject requires initial or new spectacles/contact lenses (applicable if the refraction reveals at least -0.50 D myopic progression and/or if the eye care practitioner deems it clinically necessary to improve vision), the site will provide a refractive prescription and lenses/frames (if needed) or soft contact lenses.

All screening evaluations will serve as baseline measurements.

Stage 1 Telephone Checks – (Months 1, 2, 4.5, 7.5, and 10.5): Sites will contact the subject or their parent/guardian by telephone at the end of Month 1 and Month 2 and then midway between office visits during the initial year of the study to collect information regarding AEs and treatment adherence. Telephone checks can be continued or reinstated at any time during the study to assist with maintaining protocol and treatment adherence.

Stage 1 Three-Month Visits (Months 3, 9, 15, 21, 27, and 33)

At these visits, the subject and their parent/guardian will return to the study site with their randomized study medication for an evaluation of treatment adherence. While it is preferred that the subject attend every visit, the parent/guardian may attend a 3-month visit without the subject if necessary. Sites will update concomitant medications, conduct AE assessment, dispense study medication, and perform treatment adherence assessment (i.e., study medication accountability). (Note: Enrolled subjects approved by the sponsor to transfer from one site or a new site, who reside greater than 150 miles from the new research site, may not be required to attend 3-month interval visits. Alternate accommodations may be provided to the subject and subject's family in order to dispense study medication. Assessments may be obtained remotely via telephone and treatment adherence assessments completed at 6-Month interval visits).

Stage 1 Six-Month Visits (Months 6, 12, 18, 24, and 30)

At these visits, subject and their parent/guardian will return to the study site with their randomized study medication for an evaluation of treatment adherence. Subjects will undergo a measurement of height (yearly), weight (yearly), HR, BCVA measurement (distance and near), photopic pupil size measurement, SLE, tonometry, dilated fundus examination (yearly), cycloplegic autorefraction, axial length and, if possible, crystalline lens thickness. Sites will update concomitant medications, conduct AE assessment, dispense study medication, and perform treatment adherence assessment.

End of Stage 1/End of Study (EOS) Month 36 Primary Efficacy (BL-Month 36) and Evaluation/Commencement of Stage 2: Randomized Cross-Over (EOS Month 36)

At the Month 36 visit, End of Study (EOS) visit Stage 1, the subject and their parent/guardian will return to the study site for the EOS Month 36 study visit (Stage 1). The subject and their parent/guardian will return to the study site with their randomized study medication.

Subjects will undergo a measurement of height, weight, HR, BCVA measurement (distance and near), photopic pupil size measurement, SLE, tonometry, dilated fundus examination, cycloplegic autorefraction, axial length and, if possible, crystalline lens thickness. Subjects will then be re-randomized. Sites will update concomitant medications, conduct AE assessment, dispense randomized study medication for the randomized cross-over stage (Stage 2), and perform treatment adherence assessment. Additionally, the site staff will install an electronic diary application on subject's or their parent's/guardian's phone. Subject or their parent/guardian will be encouraged to record their dosing on a daily basis, starting from the same evening after completing their Month 36 visit. If the subject or their parent/guardian do not have a cell phone or are unwilling to use their cell phone, a device will be provisioned by Medidata and provided to the subject. Electronic diary training and Medidata patient cloud electronic clinical outcome assessments (eCOA) support will be provided.

Stage 2 Three-Month Visits (Months 39 and 45)

The subject and their parent/guardian will return to the study site with their randomized study medication for an evaluation of treatment adherence (as in Stage 1, it is preferred that the subject attend every visit, but the parent/guardian may attend a 3-month visit without the subject if necessary). Sites will update concomitant medications, conduct AE assessment, dispense study medication, review e-diary, and perform treatment adherence assessment. (Note: Enrolled subjects approved by the sponsor to transfer from one site or a new site, who reside greater than 150 miles from the new research site, may not be required to attend 3-month interval visits. Alternate accommodations may be provided to the subject and subject's family in order to dispense study medication. Assessments may be obtained remotely via telephone and treatment adherence assessments completed at 6-Month interval visits).

Stage 2 Six-Month Visit (Month 42)

At the Month 42 visit, the subject and their parent/guardian will return to the study site with their randomized study medication.

Information related to QoL (modified ATI) will be reviewed with the subject and their parent/guardian and they will be asked to participate in the QoL questionnaire. The site staff will confirm and document their willingness to participate in completing the questionnaire. Subjects can continue on to Stage 2 even if they elect not to participate in the completion of the QoL questionnaire.

The modified ATI will be completed by the parent/guardian and subject prior to the Investigator's examination of the subject. The parent/guardian QoL questionnaire should be completed prior to the subject questionnaire. Study staff will verify completion of the QoL questionnaires by both the parent/guardian and the subject.

Once the modified ATI has been completed, subjects will undergo a measurement of HR, BCVA measurement (distance and near), photopic pupil size measurement, SLE, tonometry, cycloplegic autorefraction, axial length, and, if possible, crystalline lens thickness. Sites will update concomitant medications, conduct AE assessment, dispense study medication, review e-diary, and perform treatment adherence assessment.

End of Stage 2/End of Study (Month 48)

At the Month 48/ end of study (EOS) visit Stage 2, the subject and their parent/guardian will return to the study site with their randomized study medication for an evaluation of treatment adherence. The modified ATI will be completed by the parent/guardian and subject prior to the Investigator's examination of the subject. The parent/guardian QoL questionnaire should be completed prior to the subject's questionnaire. Study staff will verify completion of the QoL questionnaires by both the parent/guardian and the subject.

Once the modified ATI is completed, subjects will undergo a measurement of height, weight, HR, BCVA measurement (distance and near), photopic pupil size measurement, SLE, tonometry, dilated fundus examination, cycloplegic autorefraction, axial length, and, if possible, crystalline lens thickness. Sites will update concomitant medications, conduct AE assessment, review e-diary, and perform treatment adherence assessment. The site staff will uninstall the Medidata eCOA application (installed on the cell phone) or retrieve the device provisioned by Medidata and provided to the subject.

Early Termination Visits

Every effort should be made to keep subjects in the study and conduct all study visits as scheduled. If a subject is discontinued from study medication before the Month 48 visit, then all Month 48 (EOS) procedures should be performed at the visit the subject is discontinued.

If a subject is off study medication and is being followed for safety assessments then an EOS Month 36 visit should be completed, as these subjects will not continue on to Stage 2.

Unscheduled visits

Unscheduled visits may occur at the Investigator's discretion to address any possible issues the subject may experience that are of concern to the subject or parent/guardian (e.g., blurry vision, pain, redness in one or both eyes).

Efficacy Assessments:

- SER error in each eye measured by cycloplegic autorefraction
- Axial length
- Crystalline lens thickness (exploratory efficacy measurement)

Treatment Adherence:

Treatment adherence will be measured by study medication accountability. Throughout treatment (efficacy/safety portion and randomized cross-over portion), the amount of unopened medication units will be recorded at each study visit.

Documentation of Mode of Administration:

At the EOS Month 36 and EOS Month 48, site will document mode of administration by asking the subject or their parent/guardian:

- Who administered the eyedrops to the subject during the study (i.e., self-administered or administered by parent/guardian)?
- Was there a transition in the dosing administrator?
- If yes, at what approximate age did the transition occur?

Safety Assessments:

- Heart Rate
- Monocular BCVA in each eye at distance and near
- Photopic pupil size
- Slit Lamp Exam
- Dilated fundus examination
- Adverse Events
- Tonometry

Data and Safety Monitoring Plan:

To minimize risk and ensure the immediate safety of study subjects, both local and systemic anticholinergic and other potential effects of study medication will be measured at each visit. Parameters such as heart rate, mydriasis, photophobia, blurred near vision, ocular and conjunctival inflammation and allergic reactions to study medication will be carefully and routinely monitored to assess both safety and tolerability.

All safety data will be collected and entered in the eCRF allowing for real-time review. Medical review will be performed concurrently with Data Management's review of data and issue of queries to sites. The aim of the medical review is to monitor eligibility issues, assess potential protocol deviations and identify safety issues.

In addition, the peer-reviewed and grey literature as well as global databases of AEs from other atropine products will be routinely and continually monitored.

Withdrawal of Subjects:

All subjects randomized into the study will be encouraged to complete all study assessments through the Month 48 Visit (End of Study), including subjects that cannot or do not wish to continue study treatment (withdraw consent/assent from study treatment but are willing to continue study visits).

The following are the criteria for considering withdrawal from the study (Study discontinuation prior to Visit Month 48):

- Withdrawal of subject consent/assent to continue with study visits.
- If the site and/or the overall study is terminated for any reason.
- The Investigator considers it is in the best interest for the subject to leave the study. This may include the development of damage to the cornea (Section 8.5 – Discontinuation of Study Medication).

If a subject withdraws from the study, the reason for the subject's withdrawal will be recorded in the electronic case report form (eCRF).

If a subject is discontinued from study medication before the Month 48 visit, then all Month 48 procedures should be performed at the visit the subject discontinues study medication. The subject should continue in the study off study medication. Subjects should be encouraged to return for the 6 Month interval visits; however, returning for the 12 Month interval visits is essential. Subjects discontinuing study medication prior to Month 36 would continue to be seen for scheduled visits (at 6 Month or 12 Month intervals as noted above) until they reach the Month 36 interval.

Criteria for Evaluation:

Safety:

The safety of 0.01% and 0.02% Atropine Sulfate Ophthalmic Solution will be compared to Vehicle (placebo) with analysis of safety variables including ophthalmic safety assessments (BCVA, photopic pupil size, SLE, dilated fundus examination, and tonometry), HR, and AEs.

Primary Efficacy Endpoint:

The primary efficacy endpoint is the between-treatment group (Atropine Sulfate Ophthalmic Solution, 0.02% versus Vehicle) difference in the proportion of subjects who show < -0.50 D myopia progression (SER) at the Month 36 visit.

The primary and all secondary endpoints comprise a fixed sequence set of endpoints to be tested in order. A 2-sided significance level of 0.05 will be adopted.

Secondary Efficacy Endpoints:

The secondary efficacy endpoints consist of:

1. Between-treatment group (Atropine Sulfate Ophthalmic Solution, 0.02% versus Vehicle) difference in the mean change from baseline in SER at the Month 36 visit.
2. Between-treatment group (Atropine Sulfate Ophthalmic Solution, 0.01% versus Vehicle) difference in the proportion of subjects who show < -0.50 D myopia progression (SER) from baseline at the Month 36 visit.
3. Between-treatment group (Atropine Sulfate Ophthalmic Solution, 0.01% versus Vehicle) difference in mean change from baseline in SER at the Month 36 visit.
4. Between-treatment group (Atropine Sulfate Ophthalmic Solution, 0.02% versus Vehicle) difference in the mean change from baseline in axial length at the Month 36 visit.
5. Between-treatment group (Atropine Sulfate Ophthalmic Solution, 0.01% versus Vehicle) difference in the mean change from baseline in axial length at the Month 36 visit.

Statistical Methods:

Analysis Sets:

Enrolled Set: All subjects enrolled.

Safety Set: All subjects who were administered at least one dose of study medication for a given stage.

Intent-to-treat (ITT) Set: All randomized subjects for a given stage.

Modified intent-to-treat (mITT) Set: All randomized subjects, for a given stage, aged 6 to 10 years at the time of randomization in Stage 1. This will be the population for the primary efficacy analyses.

Per Protocol Set (PPS): All subjects who remain in the study through end of stage and have no major or critical protocol violations (as defined in the SAP).

Modified Per Protocol Set (mPPS): All subjects in the PPS in each stage who were aged 6 to 10 years at the time of randomization in Stage 1.

Statistical Analyses:

The primary and secondary efficacy analyses will be performed using the mITT Set assuming data missing at random.

The primary analysis and any other analysis of binary response measures will be performed using a mixed-effects model based on the binomial distribution using a logit link function. The model will include subject, treatment group, visit, eye (left or right), and baseline age group (as randomized) and SER (as randomized) as independent variables and treatment group-by-visit interaction term included. Random intercepts for subject and eye within subject will be included using variance components and compound symmetry covariance structures, respectively. In addition, sensitivity analyses will be performed for the primary efficacy endpoint to assess the impact of missing data. These sensitivity analyses will be described in the statistical analysis plan.

For comparisons of mean change from baseline for continuous measures, the analysis will be performed using a mixed-effects model with a random intercept. The model will include treatment group, visit, eye (left or right), baseline age group (as randomized), and baseline SER group (as randomized) as independent variables and the treatment group-by-visit interaction. Will be included. The degrees of freedom will be determined using the Kenward-Roger approximation.

Random intercepts for subject and eye within subject will be included using unstructured covariance structures.

Statistical Analyses (cont'd):

Note, there will be 8 groups with different treatment histories tor Year 4:

Treatment Stage	Possible Treatment Histories		
Stage 1 (Years 1-3) Stage 2 (Year 4)	Atropine 0.01% Atropine 0.01%	Atropine 0.01% Atropine 0.02%	Atropine 0.01% Vehicle
Stage 1 (Years 1-3) Stage 2 (Year 4)	Atropine 0.02% Atropine 0.01%	Atropine 0.02% Atropine 0.02%	Atropine 0.02% Vehicle
Stage 1 (Years 1-3) Stage 2 (Year 4)	Vehicle Atropine 0.01%	Vehicle Atropine 0.02%	

For all subjects who respond in the Atropine Sulfate Ophthalmic Solution treatment groups at the Month 36 visit, summary statistics for the change in SER from Stage 2 baseline (Month 36 visit) will be presented at the Month 42 and Month 48 visits for each treatment history where subjects receive the same dose of Atropine Sulfate Ophthalmic Solution, a lower dose of Atropine Sulfate Ophthalmic Solution, or Vehicle.

Summary statistics will be presented for compliance collected in diaries, the frequency of switching from dosing by parent/guardian to dosing by subject, and the modified Amblyopia Treatment Index by visit and treatment group in Year 4.

Significance Level:

The 0.01% and 0.02% atropine response rates will be compared to the vehicle response rate. The primary and secondary efficacy endpoints will be tested at the 5% level of significance using a hierarchal testing procedure in the order listed.

Sample Size:

Atropine Sulfate Ophthalmic Solution, 0.02%:

A Fisher's exact test with a 0.05 two-sided significance level will have 95% power to detect the difference between an Atropine Sulfate Ophthalmic Solution, 0.02% responder proportion of 0.25 and a Vehicle responder proportion of 0.07 when the sample sizes are 136 and 91, respectively.

Atropine Sulfate Ophthalmic Solution, 0.01%:

A Fisher's exact test with a 0.05 two-sided significance level will have 90% power to detect the difference between an Atropine Sulfate Ophthalmic Solution, 0.01% responder proportion of 0.25 and a Vehicle responder proportion of 0.07 when the sample size in each group is 91.

Table 2: Schedule of Procedures

Assessment	Screening Baseline[a]	Treatment Stage 1 (Office Visits Every 3 Months and Telephone Checks[a] ± 2 Weeks)																	Treatment Stage 2 (Every 3 Months ± 2 Weeks)			
Visit Number	**1**	**T1**	**T2**	**2**	**T3**	**3**	**T4**	**4**	**T5**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**
Month	**0**	**1**	**2**	**3**	**4.5**	**6**	**7.5**	**9**	**10.5**	**12**	**15**	**18**	**21**	**24**	**27**	**30**	**33**	**36 (EOS)[b]**	**39**	**42**	**45**	**48 (EOS)[b]**
Informed consent/assent[c]	X																					
Demographics/medical/ocular history	X																					
Prior/concomitant medication	X																					
Urine pregnancy test[d]	X																					
Re-consent/re-assent[c]																		X	X	X	X	X
Modified ATI questionnaires (QoL)																				X[ef]		X[ef]
Height and weight	X									X				X				X				X
Heart rate	X					X				X		X		X		X		X		X		X
Best-corrected visual acuity[fg]	X					X				X		X		X		X		X		X		X
Pupil size measurement (photopic)	X					X				X		X		X		X		X		X		X
Slit-lamp examination	X					X				X		X		X		X		X		X		X
Intraocular pressure	X					X				X		X		X		X		X		X		X
Dilated fundus examination	X									X				X				X				X
Cycloplegic autorefraction	X					X				X		X		X		X		X		X		X
Inclusion/exclusion criteria assessment	X																					
Randomization/re-randomization (M 36)	X																	X				
Axial length	X					X				X		X		X		X		X		X		X
Crystalline lens thickness (where feasible)	X					X				X		X		X		X		X		X		X
Collect study medication materials				X		X		X		X	X	X	X	X	X	X	X	X	X	X	X	X

Assessment	Screening Baseline[a]	Treatment Stage 1 (Office Visits Every 3 Months and Telephone Checks[a] ± 2 Weeks)																	Treatment Stage 2 (Every 3 Months ± 2 Weeks)			
Visit Number	**1**	**T1**	**T2**	**2**	**T3**	**3**	**T4**	**4**	**T5**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**
Month	**0**	**1**	**2**	**3**	**4.5**	**6**	**7.5**	**9**	**10.5**	**12**	**15**	**18**	**21**	**24**	**27**	**30**	**33**	**36 (EOS)[b]**	**39**	**42**	**45**	**48 (EOS)[b]**
Concomitant medication review				X		X		X		X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse event assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense study medication (frames/lenses)[gh]	X			X		X		X		X	X	X	X	X	X	X	X	X	X	X	X	
Treatment adherence assessment[hi]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Electronic patient diary																		X[ij]	X[jk]	X[jk]	X[jk]	X[kl]

Abbreviations: ATI = amblyopia treatment index, eCOA = electronic clinical outcome assessments, EOS = end of study, QoL = quality of life.

[a] Assessments may be obtained remotely at the end of Month 1 and Month 2, followed by midway between visits during Year 1. Telephone checks can be continued as necessary to assist with protocol and treatment adherence. Note: Enrolled subjects approved by the sponsor to transfer from one site or a new site, who reside greater than 150 miles from the new research site, may not be required to attend 3-month interval visits. Alternate accommodations may be provided to the subject and subject's family in order to dispense study medication. Assessments may be obtained remotely via telephone and treatment adherence assessments completed at 6-Month interval visits.

[b] If a subject is discontinued from study medication before the Month 36 visit in Stage 1, then all Month 36 EOS procedures should be performed. If a subject is discontinued from medication before the Month 48 visit in Stage 2, , then all Month 48 EOS procedures should be performed at the visit the subject is discontinued.

[c] Sites should complete screening/randomization/baseline procedures and enroll subjects within 30 days from signing informed consent.

[d] Female subjects of childbearing potential (post menarche) only.

[e] All subjects are to be re-consented/re-assented at their next study visit if not done at earlier visits, including subjects completing an End of Study (EOS) Visit (Stage 1 – Month 36, Month 39, Month 42, Month 45, and Month 48).

[ef] At Month 42 and Month 48, the modified ATI will be completed by the parent/guardian and subject prior to the Investigator's examination of the subject. Prior to the examination, the site staff will ensure parent/guardian and subject understand the questions, by reading the questions. After each question, the site staff will proceed to read the choices. The parent/guardian and subject will pick the answer which comes closest to describing how they feel. The answer will be entered into the database by the site staff.

[fg] Measured at distance and near.

[gh] Medication dispensed by site. Dosing to be conducted at home each day at bedtime. Prescription for frames/lenses will be provided if necessary, per criteria defined in Section 6.1.

[hi] Treatment adherence will be verbally assessed during Telephone Check. Drug accountability and details regarding any incorrect dosing will be assessed every 3 months upon return of unused ampules.

[ij] Diary application uploaded to subject's or their parent's/guardian's phone or Medidata provisioned device (if required), e-diary training and Medidata eCOA support provided.

[jk] The site staff will review the electronic patient diary.

[kl] The site staff will uninstall the Medidata eCOA application (installed on the cell phone) or retrieve the device provisioned by Medidata and provided to the subject.

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3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations are used in this study protocol.

Table 3: Abbreviations

Abbreviation	Explanation
AE	Adverse Event
ATI	Amblyopia Treatment Index
ATOM2	Atropine Treatment of Myopia 2
BCVA	Best-Corrected Visual Acuity
CI	Confidence Interval
CRO	Contract Research Organization
e-diary	Electronic Patient Diary
EC	Ethics Committee
eCOA	Electronic Clinical Outcome Assessments
eCRF	Electronic Case Report Form
EOS	End of Study
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HR	Heart Rate
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IOP	Intraocular Pressure
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	Intent-To-Treat
mITT	Modified Intent-To-Treat
OTC	Over-The-Counter
PPS	Per Protocol Set
QD	Once Daily
QoL	Quality of Life
SAE	Serious Adverse Event

Abbreviation	**Explanation**
SAP	Statistical Analysis Plan
SER	Spherical Equivalent Refraction
SLE	Slit-Lamp Examination
SUSAR	Suspected Unexpected Serious Adverse Reaction
VA	Visual Acuity
w/v	Weight per Volume

4. INTRODUCTION

4.1. Background Information and Rationale for Development

Vyluma Inc., an affiliate of Nevakar Inc., hereinafter referred to as the Sponsor, is pursuing the development of Atropine Sulfate Ophthalmic Solution for slowing the progression of myopia in children.

Ametropia in children is common, and if left uncorrected causes decreased vision, visual discomfort (eye strain), strabismus, and/or amblyopia (AAPOS 2013). The most common form of refractive error is myopia (nearsightedness), which has its onset in children 6 to 12 years of age (Zadnik 2015). The American Association for Pediatric Ophthalmology and Strabismus (AAPOS) and American Academy of Ophthalmology (AAO) Joint Policy Statement in 2013 reports that it is important that myopia be addressed early in life because, in addition to correcting imperfect vision, good vision is essential for proper physical development and educational progress in growing children. If a growing child's eye does not provide a clear, focused image to the developing brain, irreversible loss of vision in one or both eyes may result (AAPOS 2013).

In addition, higher levels of myopia are associated with ocular complications such as glaucoma, cataracts, retinal detachment, and atrophy (Smith 2015). A recent meta-analysis estimated that the prevalence of both myopia (defined as -0.50 D [diopter] or more myopia) and high myopia (defined as -6.00 D or more myopia) are increasing and will continue to increase worldwide, potentially affecting as many as 49.8% (myopia) and 9.8% (high myopia) of the world population by the year 2050 (Holden 2016). The study further concludes that vision loss from high myopia is projected to increase seven-fold from 2000 to 2050.

There are currently no Food and Drug Administration (FDA)-approved drug products to treat the progression of myopia in children. Topical ophthalmic drugs such as 1% atropine and 2% pirenzepine (both antimuscarinic agents) have been shown to slow myopia progression (Brodstein 1984; Yen 1989; Chua 2006; Fan 2007; Yi 2015); however, pirenzepine is not FDA approved for ophthalmic use, and although 1% atropine is approved by the FDA for topical ocular use (cycloplegia, mydriasis, and penalization of the healthy eye in the treatment of amblyopia), it is not approved to slow the progression of myopia. Further, treatments such as orthokeratology and the use of multifocal lenses have been used as therapy to slow the progression of myopia in children, however, neither has shown efficacy equivalent to that of antimuscarinic agents (Walline 2011).

Recent reviews (Walline 2011; Huang 2016; Gong 2017) have concluded that antimuscarinic topical medication is an effective treatment to slow myopia progression. These reviews included studies investigating the use of atropine at concentrations of 1% and less and considered that the clinical use of 1% atropine may be limited by its side effect profile, including vision-related glare, photophobia, and near vision blur.

To avoid the side effects of this high concentration of atropine (1%), several studies in the United States (US) and Asia have investigated the use of lower concentrations of atropine (0.01% to 0.5%) for slowing myopic progression and have shown promising results with fewer adverse effects than higher concentrations (Chou 1997; Shih 1999; Lee 2006; Fang 2010; Wu

2011; Chia 2012; Cooper 2013; Clark 2015). Most notably, the Atropine Treatment of Myopia 2 (ATOM2) study investigated the use of 0.01%, 0.1% and 0.5% atropine to treat myopia in pediatric patients (Chia 2012; Chia 2014; and Chia 2016). In this 3-stage study, children 6 to 12 years of age were treated with atropine eye drops (0.01%, 0.1% or 0.5%) for 2 years. After the initial 2-year treatment, there was a washout period of 1 year and re-treatment with atropine if myopic progression during the washout period was determined to be ≥ 0.50 D/year. Results from this ATOM2 study showed that 0.01% atropine slowed myopic progression as well or better than either 0.1% or 0.5% atropine.

4.2. Justification for Dose, Regimen and Treatment Period

Atropine (1%) is widely approved (FDA and European Agencies) for use for cycloplegia, mydriasis, and penalization of the healthy eye in the treatment of amblyopia; however, its clinical use at a 1% concentration for the treatment of myopia is limited due to its side effects of vision-related glare, photophobia, and near vision blur.

Studies including the ATOM2 study have shown that concentrations of atropine as low as 0.01% are effective in treating myopia in children without any significant side effects and do not appear to be associated with the rebound progression of myopia seen at higher concentrations of atropine.

In order to further evaluate lower concentrations of atropine in myopic children in the US and Europe, the Sponsor has chosen to study 2 concentrations of atropine, 0.01% and 0.02%, compared to a Vehicle (placebo) control in this Phase 3 study. Evaluating 2 concentrations provides the ability to demonstrate a dose effect while also selecting a dose with optimal risk/benefit.

4.3. Good Clinical Practices Statement

This study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and in compliance with the ethical principles having their origin in the Declaration of Helsinki, International Council for Harmonisation (ICH) guidelines, consolidated Guideline E6 R2 for Good Clinical Practice (GCP) (CPMP/ICH/135/95), and applicable regulatory requirements:

- European Commission Directive (2001/20/EC Apr 2001);
- European Commission Directive (2005/28/EC Apr 2005);
- The Medicines for Human Use (Clinical Trials) Regulations (2006)
- Food and Drug Administration GCP Regulations: CFR Title 21, Parts 11, 50, 54, 56, and 312;
- EU General Data Protection Regulation (GDPR): 2016/679;
- The Health Insurance Portability and Accountability Act, as appropriate; and/or
- Other applicable local regulations.

4.4. Population to be Studied

Study subjects will be children, male or female, aged 3 to ≤ 17.0 years at the time of enrollment, with myopia spherical equivalent refraction (SER) of at least -0.50 D and no greater than -6.00 D in each eye, astigmatism of no more than -1.50 D in each eye, and anisometropia (SER) of < 1.50 D as measured by cycloplegic autorefraction. Because cases of corneal calcification have been reported very rarely in association with the use of phosphate-containing eye drops in some patients with significantly damaged corneas, subjects with a history of or current significant or severe damage to the cornea are excluded. See Section 7 for inclusion and exclusion criteria. Written informed consent from the parent/guardian and assent from the subject (when applicable) will be obtained prior to enrollment in the study.

4.5. Benefit/Risk Assessment

The benefits to study participants are largely unknown; however, prior research with low dose Atropine Sulfate 0.01% revealed a significant slowing (but not a reversal) of myopia progression in school-age children in Singapore (ATOM2). Non-medicinal benefits of participating include no-cost eye care and a stipend for new spectacles annually for 4 years.

There is a 5/7 chance for a given child to be randomized to active treatment in the first stage of the study; however, all children initially randomized to placebo will receive active treatment (0.01% or 0.02% atropine) in the second stage (final year) of the study.

Beyond the risk of receiving placebo, the child's myopia may continue to progress regardless of treatment. In addition, there is a small risk that side effects may occur while using very low dose (0.01% & 0.02%) Atropine Sulfate. For much higher doses of approved Atropine Sulfate eye drops (1%) used in both North America & the EU, side effects reported in previous studies of high-dose atropine eye drops include:

- Eye discomfort
- Glare
- Blurred near vision
- Light sensitivity
- Pain and stinging at time of drop
- Inflammation of the cornea (clear layer on the front of the eye)
- Dry eye
- Redness and swelling of the eye or eyelid
- Irritability
- Fast heartbeat
- Restlessness
- Dryness of skin, mouth, or throat

Other side effects reported:

- Seizures have been reported with both systemic and compounded use of Atropine. However, it is not clear what dose concentration was utilized in the eye drops.

While the risk of such side effects listed above are much less for the highly dilute Atropine (0.01% & 0.02%) eye drops being studied in this protocol, children may experience other risks or side effects of Atropine eye drops that are currently unknown. Allergic reactions and stinging, for example, can occur with any eye drop instilled into the eye.

Although studies by Cooper confirm the safety of highly dilute atropine (0.01% & 0.025%) eye drops, such as those used in this study, atropine eye drops may cause both blurry near vision and sensitivity to light (Cooper 2013).

5. STUDY OBJECTIVES AND PURPOSE

5.1. Primary Objective

To evaluate the safety and efficacy of 2 concentrations of Atropine Sulfate Ophthalmic Solution (0.01% and 0.02%) compared to Vehicle (placebo) for slowing the progression of myopia in children over a 3-year treatment period.

5.2. Exploratory Objective

To observe the safety and efficacy in subjects re-randomized to 1 year of treatment with Atropine Sulfate Ophthalmic Solution, 0.01% or 0.02%, or Vehicle following 3 years of treatment in children with progressive myopia.

6. INVESTIGATIONAL PLAN

6.1. Overall Study Design

This will be a 3-arm randomized, multicenter, double-masked, placebo-controlled study conducted in 2 stages. Stage 1 is a safety and efficacy phase of 3 years (36 months) in duration, during which subjects will be allocated 1 of 3 study medications. Stage 2 is a randomized cross-over phase of 1 year (12 months) in duration, during which subjects will be re-randomized to receive 1 of the 3 study medications with subjects initially randomized to Vehicle only eligible for randomization to 0.01% or 0.02% Atropine Sulfate Ophthalmic Solution. Subjects (aged 3 to ≤ 17.0 years) will enter the study with myopia SER of at least -0.50 D and no greater than -6.00 D myopia in each eye as measured by cycloplegic autorefraction, and following successful eligibility screening at the Screening/Baseline visit will be randomized to one of the following 3 treatment groups in a 2:2:3 ratio:

- Vehicle (placebo) (N = 138)
- Atropine Sulfate Ophthalmic Solution, 0.01% (N = 138)
- Atropine Sulfate Ophthalmic Solution, 0.02% (N = 207)

At the Screening/Baseline visit (Day 0), the site will obtain signed informed consent from the parent or legal guardian of the subject and assent from the subject (as applicable). The subject will then undergo screening evaluations to determine eligibility for the study which will include review of medical/ocular and prior medication history, a urine pregnancy test for female subjects of childbearing potential (post menarche), height, weight, heart rate (HR), monocular best-corrected visual acuity (BCVA) measurement in each eye at distance and near, photopic pupil size measurement, slit-lamp examination (SLE), tonometry, dilated fundus examination, and cycloplegic autorefraction.

Following confirmation of eligibility, the clinical site will measure baseline axial length and, if possible, the crystalline lens thickness. The site will then access the Interactive Response Technology (IRT), which will assign the subject to 1 of the 3 treatment arms and assign the initial study medication kit to be dispensed to the parent/guardian following instruction on administration. One (1) drop of the study medication will be administered in each eye once daily (QD), at bedtime. Because adverse events (AEs) are to be collected beginning after signing of informed consent/assent, the site will document any events that may be volunteered spontaneously by the subject or parent/guardian that occur before the end of the visit.

If the subject requires initial or new spectacles/contact lenses (applicable if the refraction reveals at least -0.50 D myopic progression and/or if the eye care practitioner deems it clinically necessary to improve vision), the site will provide a refractive prescription and lenses/frames (if needed) or soft contact lenses.

Both eyes will be treated; myopia must be bilateral to qualify. If myopia is unilateral at screening or the child seems likely to cross the threshold for bilateral myopia of at least -0.50 D SER, the child can be asked to return while the enrollment period is still open to determine his or her eligibility.

Subjects will return to the clinical site at 6-month intervals with their study medication materials for 3 years to undergo a series of safety and efficacy evaluations (height [yearly], weight [yearly], HR, BCVA measurement [distance and near], photopic pupil size measurement, SLE, tonometry, dilated fundus examination [yearly], cycloplegic autorefraction, axial length and, if possible, crystalline lens thickness, an update of concomitant medications, and AE assessment). The allocated study medication will be dispensed for the next 3-month study period, and treatment adherence assessment will be performed.

At 3-month intervals, unopened/unused and used study medication materials will be returned, concomitant medications will be updated, AE assessment will be conducted, allocated study medication will be dispensed for the next 3-month study period, and treatment adherence assessment will be performed. While it is preferred that the subject attend every visit, the parent/guardian may attend a 3-month visit without the subject if necessary; both the subject and their parent/guardian must be present for all 6-month visits.

After a subject completes all safety and efficacy assessments at the Month 36 visit, the randomized cross-over stage (Stage 2) will commence and each subject will be re-randomized to 1 of the 3 study medications and receive this treatment for the final year of the study. Subjects randomized to either 0.01% or 0.02% Atropine Sulfate Ophthalmic Solution during Stage 1 will be re-randomized to treatment with Atropine Sulfate Ophthalmic Solution, 0.01%, Atropine Sulfate Ophthalmic Solution, 0.02%, or Vehicle, and subjects randomized to the Vehicle group in Stage 1 will be re-randomized to active treatment with Atropine Sulfate Ophthalmic Solution, 0.01% or Atropine Sulfate Ophthalmic Solution, 0.02%. The site will dispense this study medication and conduct final treatment adherence assessment for Stage 1 of the study. Study medication during Stage 2 will be administered QD at bedtime as before, for 1 year.

During Stage 2, the subject and their parent/guardian will again return at 6-month intervals for safety and efficacy evaluations and treatment adherence assessment. Both the subject and their parent guardian must be present at all 6-month visits. At the Month 45 visit, they will receive their final study medication kit and return at Month 48 for their final study visit assessments.

Also during Stage 2, the subject and their parent/guardian will return to the site at 3-month intervals throughout the study with their unopened/unused and used study medication materials for update of concomitant medications, AE assessment, dispensing of allocated study medication for the next 3-month study period, and treatment adherence assessment. As in Stage 1, it is preferred that the subject attend every visit, but the parent/guardian may attend a 3-month visit without the subject if necessary.

Subject or their parent/guardian will be encouraged to record their dosing on a daily basis, starting from the same evening after completing their Month 36 visit till the last visit (Stage 2 of the study) in an e-diary. The subject or their parent/guardian will be encouraged to use their cell phone to upload e-dairy responses. At Month 36 visit, if the subject or their parent/guardian do not have a cell phone or are unwilling to use their cell phone, a device will be provisioned by Medidata and provided to the subject. Once the instillation of the eye drops has been successfully completed, the subject or their parent/guardian will log into the application to record dosing of the left eye and the right eye and complete diary submission daily. The diary can be completed between 6:00 PM and 11:45 PM. If the subject or their parent/guardian do not complete the e

diary within the allotted time, they will **not** be able to enter the missing data retroactively, as the purpose is to collect information on the actual date the study drops were instilled. Once data is submitted, this information will be automatically entered into the study's Medidata Rave database.

At Month 42 and Month 48, in addition to other assessments, the modified ATI, QoL questionnaire will be completed by the parent/guardian and subject prior to the Investigator's examination of the subject. The parent/guardian QoL questionnaire should be completed prior to the subject's questionnaire. Study staff will verify that the questionnaires are completed by both the parent/guardian and the subject.

During both Stage 1 and Stage 2, Office Visits are to occur within ± 2 weeks of the expected calendar date.

Telephone Checks: The sites will also contact subjects and/or their parent/guardian by telephone, at the end of Month 1 and Month 2 and then midway between office visits during the initial year of the study to collect information regarding AEs and treatment adherence. Telephone visits are to occur within ± 2 weeks of the expected calendar date. Telephone checks can be continued or reinstated at any time during the study to assist with maintaining protocol and treatment adherence.

6.2. Number of Subjects

Subjects will be randomized in a 2:2:3 ratio of Vehicle: Atropine Sulfate Ophthalmic Solution, 0.01%: Atropine Sulfate Ophthalmic Solution, 0.02%

The target number of subjects to be randomized into the 6- to 10-year age group (436), the primary efficacy population, will be:

- Vehicle (placebo): 125
- Atropine Sulfate Ophthalmic Solution, 0.01%: 125
- Atropine Sulfate Ophthalmic Solution, 0.02%: 186

Approximately 483 subjects over all ages will be randomized, resulting in the following numbers of subjects in each arm:

- Vehicle (placebo): 138
- Atropine Sulfate Ophthalmic Solution, 0.01%: 138
- Atropine Sulfate Ophthalmic Solution, 0.02%: 207

The Sponsor may conduct a sample size re-estimation based on a masked assessment of the primary endpoint response rate and/or the subject discontinuation rate.

The randomization will be stratified twice: (1) by age at randomization (subjects < 9 years; subjects ≥ 9 years) and by (2) refractive error (less myopic: SER -0.50 to -3.00 D; more myopic: one or more eyes with SER -3.01 to -6.00 D). The stratification is used to balance these characteristics across the 3 treatment groups. Enrollment will proceed until 436 subjects aged 6 to 10 years have been randomized and at least 483 subjects overall have been randomized.

Enrollment may be closed to subjects ≥ 11 years following enrollment of 50 subjects in this age group to avoid over-enrollment into the study of a sub-population which is the least likely to benefit.

The drop-out rate over the 3 years of the safety and efficacy stage of the study (Stage 1) is estimated to be 27% (~10% per year). As long as this drop-out rate is not exceeded, then at least 150 subjects (300 eyes) receiving the higher concentration (0.02% atropine) will be available for the evaluation of safety.

6.3. Criteria for Study Termination

The study may be terminated at any time by the Sponsor, Competent Authority, Government or Medical Research Ethics Committee following appropriate notification.

6.4. End of Study Definition

End of the study is the date of the last visit or last scheduled procedure shown in the Table 2 for the last subject.

7. SELECTION AND WITHDRAWAL OF SUBJECTS

7.1. Subject Inclusion Criteria

1. Children (female and male) aged 3 to ≤ 17.0 years.
2. Myopia SER of at least -0.50 D and no greater than -6.00 D myopia in each eye as measured by cycloplegic autorefraction.
3. If present, astigmatism of no more than -1.50 D in each eye as measured by cycloplegic autorefraction.
4. Anisometropia SER of < 1.50 D as measured by cycloplegic autorefraction.
5. Normal intraocular pressure of < 21 mm Hg in each eye.
6. Distance vision correctable to at least 0.1 logMAR or 20/25 Snellen equivalent in each eye.
7. Female subjects of childbearing potential (post menarche) must have a negative urine pregnancy test at screening.
8. Subject's parent or legal guardian must provide informed consent on behalf of the subject, and the subject should provide assent when applicable, per Institutional Review Board (IRB)/Ethics Committee (EC) guidelines. If a subject becomes an adult (depending on country regulations) during the study, they will need to sign an informed consent form (ICF) to continue in the study.

7.2. Subject Exclusion Criteria

1. Allergy to atropine or any of the excipients of the eye drops.
2. Current or history of amblyopia or manifest strabismus including intermittent tropia.
3. Heart rate is persistently (for more than 10 minutes) > 120 beats per minute at screening/baseline.
4. History of any disease or syndrome that predisposes the subject to severe myopia (e.g., Marfan syndrome, Stickler syndrome, retinopathy of prematurity).
5. History in either eye of abnormal ocular refractive anatomy (e.g., keratoconus, lenticonus, spherophakia).
6. History in either eye of previous intraocular or ocular laser/non-laser surgery.
7. Current or history of glaucoma; anatomic narrow anterior chamber angles.
8. Serious systemic illness that, in the Investigator's opinion, would render the subject ineligible.
9. Chronic use of any topical or systemic antimuscarinic/anticholinergic medications (e.g., atropine, scopolamine, tropicamide) within 21 days prior to screening and/or anticipated need for chronic use during the study period (i.e., more than 7 consecutive days in 1

month or more than 30 total days in 1 year). Use of cycloplegic drops for dilated ocular exam are allowable.

10. Chronic use (more than 3 days per week) of any topical ophthalmic medications (prescribed or over-the-counter [OTC]) other than the assigned study medication. Use of artificial tears is allowed but may not be used within 2 hours of administration of study medication.
11. The anticipated need to use chronic ophthalmic or systemic oral corticosteroids during the study. Intranasal, inhaled, topical dermatologic, intra-articular, perianal steroids, and short-term oral steroids (i.e., < 2 weeks) are permitted.
12. Prior myopia control treatment including orthokeratology, bifocal contact lenses, or progressive addition spectacle lenses. The only allowable prior treatments are myopic correction in the form of single-vision eyeglasses and/or single-vision or toric soft contact lenses.
13. Preplanned hospitalization during the study period. (Note: The study period begins at the time of randomization.)
14. Unwilling or unable to complete study procedures or to be followed up for the 48-month duration of the study.
15. Participation in any other study of investigational therapy during the study period or within the last 30 days.
16. History of any substance abuse (excessive or habitual use of alcohol and/or drug including nicotine) and not willing to abstain from these substance(s) during the 4-year study period.
17. Female subjects who are pregnant, nursing, or plan to become pregnant at any time during the study.
18. Employees of the study site and their family members are not permitted to participate as subjects in the study. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted.
19. Current or history of significant or severe damage to the cornea.

7.3. Subject Withdrawal Criteria

All subjects randomized into the study will be encouraged to complete all study assessments through the Month 48 Visit (end of study [EOS]), including subjects who cannot or do not wish to continue study treatment (withdraw consent/assent from study treatment but are willing to continue study visits).

The following are the criteria for considering withdrawal from the study (Study discontinuation prior to Month 48 Visit):

- Withdrawal of subject consent/assent to continue with study visits.
- If the site and/or the overall study is terminated for any reason.

- The Investigator considers it is in the best interest for the subject to leave the study.

If a subject withdraws from the study, the reason for the subject's withdrawal will be recorded in the electronic case report form (eCRF).

If a subject is discontinued from study medication before the Month 48 Visit, then all Month 48 procedures should be performed at the visit the subject discontinues study medication. The subject should continue in the study, off study medication. Subjects should be encouraged to return for the 6 Month interval visits; however, returning for the 12 Month interval visits is essential. Subjects discontinuing study medication prior to Month 36 would continue to be seen for scheduled visits (at 6 Month or 12 Month intervals as noted above) until they reach the Month 36 interval.

Ensure that due diligence (i.e., 3 attempts including a certified/registered letter) is completed for subjects that miss scheduled visits. Please see the Study Manual for additional guidance on handling out of window/missed Telephone Check-ins/on-site visits.

8. TREATMENT OF SUBJECTS

8.1. Description of Study Treatments

Atropine Sulfate Ophthalmic Solution and its Vehicle (placebo) are formulated for topical ocular delivery as aseptically prepared, sterile, preservative-free ophthalmic solutions and contain 0.01% weight per volume (w/v), 0.02% w/v or 0% w/v of the active ingredient, atropine sulfate, respectively. Both Atropine Sulfate Ophthalmic Solution (0.01% and 0.02%) and vehicle will be packaged in identical, unit dose ampules.

8.2. Randomization and Masking

8.2.1. Stage 1 Randomization and Masking

In Stage 1, subjects will be randomized in a 2:2:3 ratio of vehicle: Atropine Sulfate Ophthalmic Solution, 0.01%: Atropine Sulfate Ophthalmic Solution, 0.02%

The target number of subjects to be randomized into the 6- to 10-year age group (436), the primary efficacy population, will be:

- Vehicle (placebo): 125
- Atropine Sulfate Ophthalmic Solution, 0.01%: 125
- Atropine Sulfate Ophthalmic Solution, 0.02%: 186

Approximately 483 subjects over all eligible ages will be enrolled, resulting in the following numbers of subjects in each arm:

- Vehicle (placebo): 138
- Atropine Sulfate Ophthalmic Solution, 0.01%: 138
- Atropine Sulfate Ophthalmic Solution, 0.02%: 207

The randomization will be stratified twice: (1) by age at randomization (subjects < 9 years; subjects ≥ 9 years) and by (2) refractive error (less myopic: SER -0.50 to -3.00 D; more myopic: one or more eyes with SER -3.01 to -6.00 D). The stratification is used to balance these characteristics across the 3 treatment groups. Enrollment will proceed until 436 subjects aged 6 to 10 years have been randomized and at least 483 subjects overall have been randomized. Enrollment may be closed to subjects ≥ 11 years following enrollment of 50 subjects in this age group to avoid over-enrollment into the study.

The randomization list, a randomized block design, will be created by a biostatistician independent from the study team.

If subjects meet eligibility criteria (see Section 7) at the Screening/Baseline visit (Day 0), subjects will be randomly assigned to masked study medication. Study sites will utilize the IRT to assign kits to subjects. The treatment kit number will be recorded in the subject's eCRF. Study medication from the IRT-assigned kit will be dispensed to the subject/subject's parent or guardian for dosing that evening. Subjects will return to the study site at 3-month intervals to

return their study medication and their next assigned study medication kit will be dispensed. It is preferred that the subject attend every visit, but the parent/guardian may attend a 3-month visit without the subject if necessary. Both the subject and their parent/guardian must be present at all 6-month safety and efficacy visits.

The study will be double masked. The study medication will be provided in identical-appearing laminated pouches with no labeling indicating the identity of the study group or the contents of the unit dose ampules. The laminated pouches will contain identical-appearing unit dose ampules (see Section 8.1). Study subjects, Investigators and staff, and study management personnel will be masked to the identity of treatment until after the final database lock.

8.2.2. Stage 2 Randomization and Masking

At initiation of Stage 2 of the study, all subjects will be re-randomized to receive 1 of 3 study medications. Subjects who were randomized to 0.01% or 0.02% Atropine Sulfate Ophthalmic Solution during Stage 1 will be re-randomized in a 1:1:1 ratio to one of the 3 treatment arms (Vehicle: Atropine Sulfate Ophthalmic Solution, 0.01%: Atropine Sulfate Ophthalmic Solution, 0.02%), and subjects who were randomized to Vehicle during Stage 1 will be re-randomized in a 1:1 ratio to active treatment (Atropine Sulfate Ophthalmic Solution, 0.01%: Atropine Sulfate Ophthalmic Solution, 0.02%). The randomization list will be created by an independent biostatistician and sites will utilize the IRT to assign subject kits as per the procedures delineated for Stage 1. Study medication during Stage 2 will continue to be double masked.

8.2.3. Unmasking During the Study Period

Should it be necessary to unmask a subject's treatment assignment in case of emergency, the Investigator may obtain the treatment code for a given randomized subject from the IRT. The treatment code is to be obtained only if a medical emergency exists and knowledge of the medication being taken will influence the medical management of the subject.

The following procedure should be followed:

1. The Investigator should contact the Medical Monitor via phone immediately before unmasking a subject unless it is not possible to do so without risk to the subject.
2. If the subject is to be discontinued from study participation, then ALL procedures described in the Month 48 visit should be completed.
3. The Investigator should contact Syneos Health hereinafter referred to as the CRO (contract research organization) at Safetyeporting@syneoshealth.com within 24 hours with the subject number and details of the AE or SAE, any action taken, and whether the subject is continuing in the study.

8.3. Concomitant Medications

All concomitant medications (prescription, OTC, and for all indications [ophthalmic and other]) taken 2 months prior to the Screening/Baseline visit and/or throughout the course of the study will be recorded in the Concomitant Medications page of the eCRF. Information regarding the dates of first and last dose, route/site of dosing (e.g., right eye, left eye, both eyes, oral, topical,

inhaled), and the reason the concomitant medication is being taken must be recorded in the eCRF. When a concomitant medication has been taken at a stable dose for longer than 3 months, an estimation of the start date is adequate.

8.3.1. Permitted Medications and Treatments

Therapy considered necessary for the subject's welfare that will not interfere with the evaluation of the study medication may be given at the discretion of the Investigator. If there is any question as to whether the medication may interfere, the Investigator should contact the Medical Monitor or Sponsor. Whenever possible, medications should be administered in dosages that remain constant throughout the study duration.

8.3.2. Prohibited Medications

The Medical Monitor should be notified before prohibited medication or therapy is administered unless the safety of the subject requires immediate action. The decision to administer a prohibited medication or therapy should be done with the safety of the subject as the primary consideration. The Medical Monitor MUST be contacted to determine the permissibility of a specific medication or therapy and whether or not the subject should continue with study medication.

Prohibited ocular medications and therapies during the study include chronic use (more than 3 days per week) of any prescription or OTC topical ophthalmic medications other than the assigned study medication except for ocular medications and therapies for the treatment of seasonal allergic conjunctivitis. If ocular medications are required for the treatment of seasonal allergic conjunctivitis, they should be dosed at least 15 minutes before or after the administration of study medication. Please note, if the timing of the administration of the study drug and non-study drug will occur in close proximity, administer the non-study drug first, followed by the study medication at least 15 minutes later. If other chronic ocular medications are medically necessary during the course of the study, study medication should be interrupted, and the Medical Monitor called to discuss coadministration.

Chronic use of any topical antimuscarinic/anticholinergic medications (e.g., atropine, scopolamine, tropicamide) within 21 days prior to screening and throughout the study period is prohibited. Additionally, chronic use (i.e., more than 7 consecutive days in 1 month or more than 30 total days in 1 year) of any systemic antimuscarinic/anticholinergic medications (including but not limited to chlorpheniramine, diphenhydramine, oxitropium, tricyclic antidepressants, etc.) within 21 days of screening and throughout the study is prohibited. (Use of cycloplegic drops for dilated ocular examinations are allowable.)

Other prohibited medications are ophthalmic or systemic oral corticosteroids. Intranasal, inhaled, topical dermatologic, intra-articular, perianal steroids, and short-term oral steroids (i.e., < 2 weeks) are permitted.

8.4. Treatment Adherence

Treatment adherence will be monitored by study medication accountability. Throughout treatment, the amount of unopened medication returned at each study visit will be documented in

the IRT to provide an assessment of treatment adherence. In addition, the subject or their parent/guardian will be contacted by telephone at the end of Month 1 and Month 2 and then midway between office visits during the initial year of the study to collect information regarding treatment adherence. Telephone checks can be continued or reinstated at any time during the study to assist with maintaining protocol and treatment adherence.

Used medication ampules will be inserted into a study-provided receptacle immediately following drug administration. This container will be brought back to the study center for proper disposal.

The subject or their parent/guardian will be encouraged to record their dosing on a daily basis, starting from the same evening after completing the Month 36 visit till the last visit (Stage 2 of the study) in an e-diary.

Documentation of Mode of Administration:

At the EOS Month 36 and EOS Month 48 visit, site will document mode of administration by asking the subject or their parent/guardian:

- Who administered the eyedrops to the subject during the study (i.e., self-administered or administered by parent/guardian)?
- Was there a transition in the dosing administrator?
- If yes, at what approximate age did the transition occur?

8.5. Discontinuation of Study Medication

Subjects may be discontinued from study medication for any of the following reasons:

- The subject has a clinically significant or serious AE that would not be consistent with continuation in the study, as determined by the Investigator or Medical Monitor.
- Female subjects who become sexually active during the study who are not willing to use highly effective contraceptive measures. Note: Highly effective contraceptive measures: A method of contraception with a failure rate <1%. These methods of contraception are outlined in the note for guidance on non-clinical safety studies for the conduct of human trials for pharmaceuticals (CPMP/ICH286/95, modifications) and include the consistent and correct use of hormone containing implants and injectables, combined oral contraceptives, hormone containing intrauterine devices, surgical sterilization, sexual abstinence, and vasectomy of a male partner.
- Pregnancy.

Every effort should be made to keep subjects in the study and conduct all study visits as scheduled. If a subject is discontinued from study medication before the Month 48 visit, then all Month 48 (EOS) procedures should be performed at the visit the subject discontinues treatment (see Section 10.8).

8.6. Study Medication Materials and Management

8.6.1. Packaging and Labeling

Study medication will be packaged and labeled at a central packaging facility. Study sites will utilize the IRT to assign kits to subjects.

8.6.2. Storage

Study medication must be stored at room temperature 20°C to 25° C (68° F to 77° F) with excursions permitted. A room temperature log will be maintained at each study site. The subject or their parent/guardian should be instructed not to store or place the study medication where it can be exposed to extreme temperatures (e.g., leaving it in a hot car).

8.6.3. Administration and Dispensing

Site personnel will instruct the subject or their parent/guardian on the proper drop instillation technique at the Screening/Baseline visit using the provided artificial tear ampule. If the subject is deemed old enough to administer the drops, he or she should be allowed to administer the drops from the artificial tear ampule under site supervision, at which point the decision can be made as to whether the subject can self-administer study medication.

The key instruction points are as follows:

- Administer the drops in a supine or seated position.
- Twist the top off the ampule (the top can be discarded; the ampule will not be re-used).
- Tilt the head back, gently pull the lower eyelid down, and holding the ampule almost vertically, drop 1 full drop into the conjunctival cul-de-sac without touching the tip of the ampule to the eye.
- To avoid the potential of eye injury and contamination be careful not to touch the ampule tip to the eye or other surfaces.
- If a full drop is not instilled into the eye, the subject or caregiver (parent/guardian or trained individual) should wait approximately 10 to 15 seconds and administer a second drop.
- Keep the eyes gently closed for approximately 30 seconds after the drop is instilled.
- Place the open ampule and remaining contents in the provided receptacle that will be returned to the study center for proper disposal.

First Dose of Study Medication: The subject (or caregiver, if the subject is not able to self-administer the medication) will administer 1 full drop of the study medication into each eye from a single unit dose ampule at bedtime the evening of the randomization visit.

Each subsequent evening of dosing, the subject or caregiver will administer one full drop into each eye from a single new ampule and close the eyes gently for 30 seconds. The used ampule will be placed in the provided receptacle for return to the study site.

The subject and/or their parent/guardian should make every effort not to miss administering doses during the study. Should a subject miss a dose, then the subject should wait until the following evening and then continue with his/her regular dosing schedule. Subject should not administer more than 1 dose to each eye per day.

The subject or their parent/guardian will return all unopened/unused and used study medication materials at the next office visit. Site personnel will conduct treatment adherence assessment procedures for the last study period and dispense study medication for the next 3-month study period. At the Month 48 visit, final study drug accountability will be conducted. The Month 48 visit will mark the end of study treatment; no further study medication will be dispensed at this visit.

8.6.4. Study Medication Accountability

The Investigator or clinical site staff will maintain a full accountability record for the study medication and will be responsible for recording the receipt, dispensing, and return of all supplies of the study drug using the source and IRT. Each subject's kit will contain sufficient study medication for a 3-month period. At each 3-month study visit, the subject or their parent/guardian will return all unopened study medication to the study site for accountability assessment and will receive the next 3-month supply of study medication. In addition, the receptacle containing the used medication will be returned for proper destruction. Final study medication accountability will be conducted at the Month 48 visit.

Unused study medication will not be re-dispensed. The Investigator or clinical site staff will account for all received and returned study medication. The monitor will review dispensing and study medication accountability records during site visits and note any discrepancies. All investigational study medication must be stored in a temperature-monitored secure facility, with access limited to the Investigator and authorized staff.

9. STUDY ASSESSMENTS

Prior to entry into the study or initiation of any study-related procedures, the parent or legal guardian of the subject must read, sign, and date the current IRB/EC-approved version of the ICF. Assent from the subject, if applicable, must also be obtained. If subjects become and adult (depending on country regulations) during the study, they will need to sign an ICF to continue in the study. A full discussion of informed consent is presented in Section 13.3.

9.1. Demographic and Background Characteristics

9.1.1. Demographic Information: Baseline

Demographic information including date of birth, gender, race, ethnicity, iris color, and date of informed consent will be recorded. Note: Both the condition under study and the effectiveness of the treatment being studied are widely believed to vary based upon age, gender, race/ethnicity, and iris color.

9.1.2. Medical/Ocular History: Baseline

Clinically significant medical and ocular history will be documented and will include any previously diagnosed ophthalmic abnormalities and procedures.

9.1.3. Concomitant Medications History: Baseline and All Office Visits

All concomitant medications (prescription and OTC) taken at screening and for 2 months prior to screening and throughout the course of the study will be recorded in the Concomitant Medications page of the eCRF. Information regarding the dates of first and last dose, route/site of dosing (e.g., right eye, left eye, both eyes, oral, topical, inhaled), and the reason the concomitant medication is being taken must be recorded in the eCRF. When a concomitant medication has been taken at a stable dose for longer than 3 months, an estimation of the start date is adequate. Standard procedural medications will not go into the eCRF but are recorded on a standard procedural medication log provided by the CRO.

9.1.4. Urine Pregnancy Test: Subjects of Childbearing Potential Only

Female subjects who are of childbearing potential (post menarche) entering the study will have a urine pregnancy test performed at screening.

9.1.5. Heart Rate: Baseline and All Safety and Efficacy Office Visits (Every 6 Months)

Heart rate will be measured with a heart rate monitor after approximately 3 minutes of rest in the seated position.

9.1.6. Height and Weight: Baseline and at Yearly Visits

Height and body weight will be measured at baseline and yearly thereafter.

9.2. Efficacy Assessments

9.2.1. Cycloplegic Autorefraction: Baseline and All Safety and Efficacy Office Visits (Every 6 Months)

Cycloplegic refraction will be conducted with the autorefractor available at the site; once used at screening/baseline, this same autorefractor must be used for all refractions conducted during the entire study. (Note: Use of a different autorefractor may be acceptable in situations of equipment malfunction/breakage. In such a case, the Sponsor should be notified and the same make and model should be procured unless no longer produced by the manufacturer. The device should be calibrated according to the manufacturer's specifications.) If the Grand Seiko is available, this is the preferred model, but other autorefractors are acceptable provided the same autorefractor is used for all measurements for that given subject.

Autorefractors may produce obviously spurious readings that should be eliminated before the data are entered. Mis-readings can be identified as differing from the mode value (mode = most frequent value) for sphere by ±0.75 D or more, or by the mode value for cylinder by 0.75 D or more. Readings should be retained if there is any uncertainty about whether or not a value is spurious. It is recommended that additional readings be taken to keep the number of acceptable readings at 5.

Cycloplegic autorefraction will be conducted per the Study Manual with precise adherence to timing of cycloplegic drops and order of procedures.

9.2.2. Measurement of Axial Length: Baseline and All Safety and Efficacy Office Visits (Every 6 Months)

The Carl Zeiss Meditec IOLMaster®, the Haag Streit LENSTAR®, or appropriate instrument (see Study Manual) must be used to measure axial length. The instrument used at screening/baseline must be used for all subsequent measurements during the entire study. (Note: Use of a different instrument may be acceptable in situations of equipment malfunction/breakage. In such a case, the Sponsor should be notified and the same make and model should be procured unless no longer produced by the manufacturer. The device should be calibrated according to the manufacturer's specifications.) Measurements will be conducted per the Study Manual with precise adherence to timing and order of procedures and at intervals as specified on the Schedule of Procedures (Table 2).

9.2.3. Crystalline Lens Thickness: Baseline and All Safety and Efficacy Office Visits (Every 6 Months)

Crystalline lens thickness is an exploratory efficacy measurement and will be assessed if possible. The Haag Streit LENSTAR®, Carl Zeiss Meditec IOLMaster®, or Pentacam should be used for crystalline lens thickness measurement if available at the site. The instrument used at screening/baseline must be used for subsequent measurements conducted during the entire study. (Note: Use of a different instrument may be acceptable in situations of equipment malfunction/breakage. In such a case, the Sponsor should be notified and the same make and model should be procured unless no longer produced by the manufacturer. The device should be calibrated according to the manufacturer's specifications.)

9.3. The Modified Amblyopia Treatment Index (Modified ATI)

Quality of life questionnaires (called Modified ATI in this study) were modified from the ATI questionnaire developed by Felius et al., 2010, and will be used in the study after subjects have completed 6 months of treatment in Stage 2 of the CHAMP study. Participation is voluntary and will be documented. Subjects can continue in the study even if they elect not to participate. The questionnaires will be completed at Month 42 and at the completion of the trial at Month 48 prior to the Investigator's examination of the subject. The parent/guardian questionnaire should be completed prior to the subject's questionnaire. The questionnaires should be completed prior to the Investigator's examination of the subject.

The questionnaires will capture responses to evaluate QoL and burden of atropine treatment from the parent/guardian and subject's perspective. There are two versions of the modified ATI, the 'parent/guardian' version (Appendix C), and the 'subject' version (Appendix D). The two versions are on different response scales. Responses on the parent/guardian version are on a strength of agreement scale ("strongly agree" to "strongly disagree") whereas the responses on the subject version are on a frequency scale ("always" to "never"). This is because a frequency scale is believed to be easily understandable to children.

Re-consent/re-assent **will be obtained from all subjects, regardless** of their participation in the modified ATI, QoL questionnaire.

9.4. Recording Dosing in Electronic Patient Diary

Study data regarding subject's self-administration information has been recommended for the CP-NVK002-0001 CHAMP study, to support an eventual European filing. This information was not collected in the Stage 1 of the study. To collect this information, an e-diary has been added to the Stage 2 of the study. The Medidata eCOA application will support the e-diary data collection. Using a secure mobile online access, this technology will allow patients to complete the e-diary on a daily basis at pre-specified times.

The subject or their parent/guardian will be encouraged to use their cell phone to upload e-diary responses. At Month 36 visit, if the subject or their parent/guardian do not have a cell phone or are unwilling to use their cell phone, a device will be provisioned by Medidata and provided to the subject. Instructions to subject and their parent/guardian will be provided to allow them to complete responses within the application. The completion of the diary requires minimal effort and time. Once the instillation of the eye drops has been successfully completed, the subject or their parent/guardian will log into the application to record dosing of the left eye and the right eye and complete diary submission daily. The diary can be completed between 6:00 PM and 11:45 PM. If the subject or their parent/guardian do not complete the e-diary within the allotted time, they will **not** be able to enter the missing data retroactively, as the purpose is to collect information on the actual date the study drops were instilled. Once data is submitted, this information will be automatically entered into the study's Medidata Rave database. All study subjects should be encouraged to complete the e-diary as part of the study required assessments for the Stage 2 of the trial. The Medidata eCOA application will be installed on the subject's or their parent's/guardian's phone or provisioned device (if needed) at Month 36. At this time, instructions on usage and training will be provided. Any subject's or their parent's/guardian's questions with regard to the eCOA application will be addressed and supported by Medidata

Patient Cloud Patient Helpdesk support team. Subject's compliance of the use of the e-diary will be documented in the database.

The subject or their parent/guardian will be encouraged to record their dosing on a daily basis, starting from the same evening after completing the Month 36 visit till the last visit (Stage 2 of the study) in an e-diary. At the Month 36 visit, the subject or their parent/guardian will receive a device in the event they do not have a cell phone or are unwilling to use their cell phone. The participants will be provided with Medidata Patient Helpdesk contact information for guidance regarding data entry concerns.

The study site staff will review the e-diary at Month 39 visit, Month 42 visit, Month 45 visit, and Month 48 visit. Additionally, at Month 48 visit, the study site staff will uninstall the Medidata eCOA application (installed on the cell phone) or retrieve the device provisioned by Medidata and provided to the subject.

9.5. Safety Assessments

9.5.1. LogMAR Best-Corrected Visual Acuity: Baseline and All Safety and Efficacy Office Visits (Every 6 Months)

Best-corrected visual acuity measurements will be conducted using lighting as appropriate to the testing system used.

Children ≥7 years of age:

Distance BCVA:

Monocular BCVA at distance will be measured through the best refractive correction (if not current refractive correction then in a trial frame) using the site's visual acuity testing system at that system's appropriate test distance, e.g., the ETDRS visual acuity algorithm using the computerized Electronic Visual Acuity (EVA) tester or M&S® Vision Testing System, or any other acceptable method following the site's standard of care. The methodology used at screening/baseline must be used for subsequent measurements conducted during the entire study, except as described below. Record the 20/xx (Snellen equivalent) that the method generates for each eye. Note that the BCVA in each eye must be at least 20/25 for the child to be eligible to participate in the CHAMP Study.

Near BCVA:

Measurement of monocular best-corrected near VA in each eye will be conducted using either the Sloan Letter Near Vision Card or ETDRS Near Vision Card at 40 cm or another acceptable method viewed through the best refractive correction (if not current refractive correction then in a trial frame) or other acceptable method following the site's standard of care. The methodology used at screening/baseline must be used for subsequent measurements conducted during the entire study. Record the 20/xx (Snellen equivalent) that the method generates for each eye.

Children 3 to < 7 years of age:

Distance BCVA:

Monocular visual acuity will be measured through the best optical correction (if not current refractive correction then in a trial frame) using either 1) the HOTV visual acuity algorithm using the computerized Electronic Visual Acuity (EVA) tester or 2) HOTV letters or LEA Symbols® (either a single line presentation or single letters with crowding bars) at 10 feet (3 meters) or other acceptable method following the site's standard of care. Once a child turns 7 years old, a study-appropriate letter chart can be substituted for the HOTV, EVA, or LEA symbols. Record the 20/xx (Snellen equivalent) that the method generates for each eye. Note that the BCVA in each eye must be at least 20/25 for the child to be eligible to participate in the CHAMP Study.

Near BCVA:

Monocular near visual acuity will be measured through the best optical correction using LEA Symbols or HOTV optotypes at 40 cm or other acceptable method following the site's standard of care. Once a child turns 7 years old, a study-appropriate letter chart can be substituted for the HOTV, EVA, or LEA symbols. Record the 20/xx (Snellen equivalent) that the method generates for each eye.

9.5.2. Pupil Size Measurement: Baseline and All Safety and Efficacy Office Visits (Every 6 Months)

Pupils will be measured with a pupil diameter (PD) stick (i.e., small millimeter ruler) under photopic (i.e., room light) light conditions as subjects fixate at a distance equivalent to that used for the monocular BCVA (Section 9.5.1).

9.5.3. Slit-Lamp Examination: Baseline and All Safety and Efficacy Office Visits (Every 6 Months)

A routine slit-lamp examination will be performed to evaluate the anterior segment of the eye, including lids, cornea, conjunctiva, anterior chamber, iris, and lens, as specified in the Study Manual. Abnormalities will be documented.

9.5.4. Tonometry: Baseline and All Safety and Efficacy Office Visits (Every 6 Months)

Intraocular pressure should be measured as specified in the Study Manual (e.g., Tono-Pen, Icare tonometer, or Goldmann).

9.5.5. Dilated Fundus Examination: Baseline and Yearly

A dilated fundus exam consisting of the vitreous, optic nerve, macula, peripheral retina, retinal vasculature, and other will be conducted, and the structures will be graded as normal or abnormal, as specified in the Study Manual.

9.6. Adverse and Serious Adverse Events

9.6.1. Definition of Adverse Events

9.6.1.1. Adverse Event (AE)

An AE is any untoward medical occurrence in a patient or clinical study subject administered a study medication (pharmaceutical/biological product) whether or not the AE has a causal relationship to the study medication. An AE can therefore be any unfavorable and unintended sign (including abnormal laboratory findings), symptom, or disease temporally associated with the use of the study medication, whether or not related to the study medication. Study medication includes the investigational drug under evaluation and the comparator product or vehicle placebo that is given during any stage of the study.

Medical conditions/diseases present before starting the investigational treatment are only considered AEs if they worsen after starting the investigational treatment. Abnormal test results constitute AEs only if they induce clinical signs or symptoms, are considered clinically significant, or require therapy.

The occurrence of AEs should be sought by open-ended questioning of the subject and/or their parent/guardian at each visit during the study. At each clinic visit, study personnel should ask the following question: “How have you been feeling since your last visit?” AEs also may be detected when they are volunteered by the parent/guardian/subject during or between visits or through study assessments.

9.6.1.2. Serious Adverse Event (SAE)

An SAE is any untoward medical occurrence that at any dose:

- Results in death,
- Is life threatening?

Note: The term “life-threatening” under the definition of “serious” refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe (ICH E2A Guideline. Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, Oct 1994).

- Results in persistent or significant disability/incapacity (excluding progression/outcome of the disease under study);
- Is a congenital anomaly/birth defect,
- Requires inpatient hospitalization or prolongation of existing hospitalization, or
- Is medically significant; i.e., defined as an event that jeopardizes the health of the subject or may require medical or surgical intervention to prevent one of the outcomes listed above.

An event should be reported as an SAE if admission to the hospital or prolongation of hospitalization was a result of the AE. Emergency room visits that do not result in admission to

the hospital should be evaluated for one of the other serious outcomes (e.g., life threatening; required intervention to prevent permanent impairment or damage; other serious medically important event).

All SAEs that are ongoing at the time of completion or discontinuation from the study will be followed until stabilization (i.e., no other change in the condition is expected) or resolution of the event.

9.7. Relationship to Study Drug

The relationship of AEs to the study medication should be assessed by the Investigator using the definitions below.

Unrelated:	Clinical event with an incompatible time relationship to study drug administration, and that could be explained by underlying disease or other drugs or chemicals or is incontrovertibly not related to the study drug.
Unlikely:	Clinical event whose time relationship to study drug administration makes a causal connection improbable, but that could plausibly be explained by underlying disease or other drugs or chemicals.
Possible:	Clinical event with a reasonable time relationship to study drug administration, but that could also be explained by concurrent disease or other drugs or chemicals.
Probable:	Clinical event with a reasonable time relationship to study drug administration and is unlikely to be attributed to concurrent disease or other drugs or chemicals.
Very Likely/Certain:	Clinical event with plausible time relationship to study drug administration, and that cannot be explained by concurrent disease or other drugs or chemicals.

9.8. Recording Adverse Events

Adverse events spontaneously reported by the subject and/or in response to an open-ended question from the study personnel or revealed by observation, regardless of severity or potential association with the study medication or study procedures, will be recorded in the eCRF. Only clinically significant changes (increase or decrease) in heart rate should be reported as AEs. Ocular instillation of atropine has been associated with mild burning and stinging. Burning and stinging upon instillation should not be reported as an AE unless it is moderate or severe in intensity, and/or if the duration of burning/stinging is greater than 1 to 2 minutes, and/or if it led to discontinuation of the study medication or early termination of the subject. All AEs that occur after a subject has signed the ICF until the final study visit, Month 48, should be collected and recorded on the AE eCRF page. AEs that occur after informed consent is provided but before the first dose of study medication will be summarized separately from AEs that occur from the first dose of double-masked treatment on Day 0 to the Month 36 visit. Adverse events that occur

during the randomized cross-over stage of the study will also be summarized separately. Serious adverse events (SAEs) will be followed until the event is resolved or stabilized.

Medical conditions/diseases occurring before the first dose of study medication during screening/baseline (Day 0) should be collected on the medical/ocular history pages of the eCRF.

The AE term should be reported in standard medical terminology when possible. For each AE, the Investigator will evaluate and report the following:

- Onset (date and time);
- Resolution (date and time);
- Severity grade (mild, moderate, severe);
- Relationship to study medication (unlikely, possible, probable, very likely/certain);
- Action taken (none, study medication temporarily interrupted, study medication permanently discontinued; concomitant medication taken; hospitalization/prolonged hospitalization; other);
- Serious outcome (yes/no).

The severity grade should be determined by the Investigator using the definitions below.

- Mild: Discomfort noticed but no disruption of normal daily activity
- Moderate: Discomfort sufficient to cause interference with normal daily activity
- Severe: Incapacitating, with inability to perform normal activities

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity (as defined directly above) whereas seriousness is defined by the criteria under Section 9.6.1.2. An AE of severe intensity may not be considered serious.

9.9. Reporting Serious Adverse Events (SAEs)

All SAEs (related and unrelated) will be recorded from signing of informed consent until the final study visit, Month 48. Any SAEs "suspected" to be related to the investigational product and discovered by the Investigator at any time after the study should be reported to Safetyreporting@SyneosHealth.com.

Any SAE that occurs must be reported to the CRO (Syneos Health) within 24 hours of its occurrence or within 24 hours of learning of its occurrence. Recurrent episodes, complications, or progression of the initial SAE must be reported to the CRO as follow-up to the original episode within 24 hours of the Investigator receiving the information. Information about all SAEs will be collected and recorded on the SAE form. All pertinent medical records and information collected during the treatment and follow-up of the subject should be maintained at the site with a copy emailed to Safetyreporting@SyneosHealth.com. The Investigator must assess the SAE severity and relationship and sign the SAE form. The CRO may request additional information. Follow-up information (e.g., discharge summary) will be retained in the subject's chart and a copy will be emailed to Safetyreporting@SyneosHealth.com.

In addition, all SAEs should be recorded on the Adverse Event eCRF page with the serious question marked "Yes".

All subjects who experience an SAE should be followed clinically and undergo the appropriate diagnostic evaluations until stabilization or resolution of the event.

Any death occurring during the study period should be reported as an SAE. For any death occurring through the end of the study, regardless of the degree of relationship to study drug, the SAE resulting in the death must be reported to the CRO. A death occurring after completion of the study at Month 48 does not require completion of the SAE form.

9.10. Suspected Unexpected Serious Adverse Events (SUSARs)

Suspected unexpected serious adverse reactions (SUSARs) are serious events that are not listed in the IB and that the Investigator identifies as related to investigational product or procedure. United States 21 CFR 312.32 and European Union Clinical Trial Directive 2001/20/EC and the associated detailed guidances or national regulatory requirements in participating countries require the reporting of SUSARs. The CRO has procedures that will be followed for the identification, recording and expedited reporting of SUSARs that are consistent with global regulations and the associated detailed guidances.

Vyluma Inc., an affiliate of Nevakar Inc., or the CRO, will inform Investigators, IRBs/ECs, and regulatory authorities of any SUSARs occurring at other sites or within Vyluma Inc., an affiliate of Nevakar Inc. studies using the same investigational medicinal product, as appropriate and in line with local reporting requirements.

In the United States, upon receipt of the Sponsor's notification of SUSARs related to the investigational medicinal product, it is the Investigator's responsibility to inform the IRB per Sponsor's instruction (unless the Sponsor has stipulated otherwise).

In the European Economic Area, the Sponsor or designee will report SUSARs to all relevant competent authorities and ECs.

9.11. Exposure In-Utero During Clinical Studies

Vyluma Inc., an affiliate of Nevakar Inc., must be notified of any subject who becomes pregnant from the date of signing the informed consent form until EOS.

Although pregnancy is not technically an AE, all pregnancies must be followed to conclusion in order to determine outcome. This information is important for both drug safety and public health concerns. It is the responsibility of the Investigator, or designee, to report any pregnancy in a female subject using the pregnancy reporting form. The form is available on request from the study monitor and should be completed by the Investigator upon learning of a pregnancy. The Investigator should make every effort to follow the subject to completion of the pregnancy and complete the pregnancy reporting form with pregnancy outcome information, including normal delivery or induced abortion. Any adverse pregnancy outcome, either serious or non-serious, should be reported in accordance with study procedures. If the outcome of the pregnancy meets the criteria for immediate classification as a SAE (i.e., post-partum complications, spontaneous

or induced abortion, stillbirth, neonatal death, or congenital anomaly, including that in an aborted fetus), the Investigator should follow the procedures for reporting SAEs outlined in Section 9.9.

9.12. Data and Safety Monitoring Plan

To minimize risk and ensure the immediate safety of study subjects, both local and systemic anticholinergic and other potential effects of study medication will be measured at each visit. Parameters such as heart rate, mydriasis, photophobia, blurred near vision, ocular and conjunctival inflammation and allergic reactions to study medication will be carefully and routinely monitored to assess both safety and tolerability.

All safety data will be collected and entered in the eCRF allowing for real-time review. Medical review will be performed concurrently with Data Management's review of data and issue of queries to sites. The aim of the medical review is to monitor eligibility issues, assess potential protocol deviations and identify safety issues.

In addition, the peer-reviewed and grey literature as well as global databases of AEs from other atropine products will be routinely and continually monitored.

10. STUDY ACTIVITIES

All ophthalmic examinations are conducted in both eyes. An overview of the study and assessments to be completed at each visit is provided in Table 2, the Schedule of Procedures. The timing of each visit is relative to the day of randomization and assignment of study treatment (Day 0).

Office Visits should occur within ± 2 weeks of the expected calendar date. Telephone checks should occur within ± 2 weeks of the expected calendar date. If this is not possible then the visit should be scheduled as close to the interval as convenient for the parent/guardian and subject. Every effort should be made to maintain the subject on drug if the visit schedule is altered. If the visit scheduled is altered, the following study visits should be scheduled relative to the day of randomization.

10.1. Screening/Randomization/Baseline Visit (Day 0)

Sites should complete screening/randomization/baseline procedures and enroll subjects within 30 days from signing the informed consent. At the Screening/Baseline visit (Day 0), the parent or legal guardian will provide informed consent and subject assent, if applicable, will be obtained before any study-related procedures are conducted or screening procedures are initiated to establish eligibility for the study. All screening evaluations will serve as baseline measurements.

Subjects who meet eligibility criteria will be randomized to 1 of 3 treatment arms (Atropine Sulfate Ophthalmic Solution, 0.01%, Atropine Sulfate Ophthalmic Solution 0.02%, or Vehicle [placebo]) and the site will dispense the allocated randomized study medication which will be administered at home QD at bedtime. Because AEs are to be collected beginning after signing of informed consent/assent, the site will document any events that may be volunteered spontaneously by the subject or parent/guardian that occur before the end of the visit.

If the subject requires initial or new spectacles/contact lenses (applicable if the refraction reveals at least -0.50 D myopic progression and/or if the eye care practitioner deems if clinically necessary to improve vision), the site will provide a refractive prescription and lenses/frames (if needed) or soft contact lenses.

Screening/baseline procedures include:

- Informed consent/assent
- Demographics information
- Medical/ocular history
- Prior/concomitant medication review
- Urine pregnancy test (female subjects of childbearing potential only)
- Height and weight
- Heart Rate
- Monocular BCVA in each eye at distance and near

- Photopic pupil size measurement
- SLE (including assessment of anterior chamber angle)
- IOP measurement
- Instill first cycloplegic drop (cyclopentolate for subjects < 6 years at randomization and continuing throughout the study; 1% tropicamide for subjects ≥ 6 years at randomization and continuing throughout the study)
- Instill second cycloplegic drop approximately 5 minutes after instillation of the first drop
- Dilated fundus examination (at least 20 minutes after instillation of the second cycloplegic drop)
- Cycloplegic autorefraction (at least 30 minutes after instillation of the second drop)
- Review of inclusion/exclusion criteria
- Randomization of eligible subjects
- If eligible,
  - Axial length measurement
  - Crystalline lens thickness (if feasible)
  - Dispense and document dispensing of randomized study medication and provide instructions for administration to subject and their parent/guardian. One (1) drop of the study medication will be administered in each eye QD at home, at bedtime.
  - If initial or new spectacles/contact lenses are necessary as defined by the criteria (the refraction reveals at least -0.50 D myopic progression and/or the eye care practitioner deems it clinically necessary to improve vision), the site will provide a refractive prescription and lenses/frames (if needed) or soft contact lenses.

All screening evaluations will serve as baseline measurements.

10.2. Stage 1 and 2 Telephone Check-In Visits (Months 1, 2, 4.5, 7.5, and 10.5)

During Stage 1, sites will contact the subject or their parent/guardian by telephone at the end of Month 1 and Month 2 and then midway between office visits during the initial year of the study to collect information regarding AEs and treatment adherence. Telephone checks can be continued or be reinstated at any time during the study to assist with maintaining protocol and treatment adherence.

Procedures at these visits include:

- Friendly check-in
- Adverse event assessment

- Query how many ampules of study medication are remaining or how many doses were missed
- Query if the subject is receiving one drop in each eye at bedtime each evening
- Confirm date of first dose during M1 Telephone Check (to be reported on Treatment Adherence eCRF).

10.3. Stage 1 Three-Month Visits (Months 3, 9, 15, 21, 27, and 33)

The subject and their parent/guardian will return to the study site. It is preferred that the subject attend every visit, but the parent/guardian may attend a 3-month visit without the subject if necessary. When scheduling, site personnel should remind the parent/guardian to bring all unopened/unused and used study medication materials to the site for these visits. (Note: Enrolled subjects approved by the Sponsor to transfer from one site or a new site, who reside greater than 150 miles from the new research site, may not be required to attend 3-month interval visits. Alternate accommodations may be provided to the subject and subject's family in order to dispense study medication. Assessments may be obtained remotely via telephone and treatment adherence assessments completed at 6-Month interval visits).

Month 3, 9, 15, 21, 27, and 33 visit procedures include:

- Collect study medication materials
- Concomitant medication review
- AE assessment
- Dispense study medication for the following 3 months of the study
- Conduct treatment adherence assessment (i.e., study medication accountability)

10.4. Stage 1 Six-Month Visits (Months 6, 12, 18, 24, and 30)

At these visits, the subject and their parent/guardian will return to the study site. When scheduling, site personnel should remind the parent/guardian to bring all unopened/unused and used study medication materials to the site for these visits.

Month 6, 12, 18, 24, and 30 visit procedures include:

- Collect study medication materials
- Height and weight (yearly only)
- HR
- Monocular BCVA in each eye at distance and near
- Photopic pupil size
- SLE
- IOP measurement

- Instill first cycloplegic drop (cyclopentolate for subjects < 6 years at randomization and continuing throughout the study, 1% tropicamide for subjects ≥ 6 years at randomization and continuing throughout the study)
- Instill second cycloplegic drop approximately 5 minutes after instillation of the first drop
- Dilated fundus examination (at least 20 minutes after instillation of the second cycloplegic drop) (yearly only)
- Cycloplegic autorefraction (at least 30 minutes after instillation of the second drop)
- Axial length measurement
- Crystalline lens thickness (if feasible)
- Concomitant medication review
- AE assessment
- Dispense study medication for the following 3 months of the study
- If new lenses are necessary as defined by the criteria (the refraction reveals at least -0.50 D myopic progression and/or the eye care practitioner deems it clinically necessary to improve vision), the site will provide a refractive prescription and lenses
- Conduct study medication accountability

10.5. End of Stage 1/ End of Study (EOS) Month 36 Primary Efficacy (BL-Month 36) and Evaluation/Commencement of Stage 2: Randomized Cross-over (EOS Month 36)

At the Month 36 visit, End of Study (EOS) visit stage 1, the subjects and their parent/guardian will return to the study site for the EOS Month 36 study visit (Stage 1). The subject and their parent/guardian will return to the study site with their randomized study medication.

When scheduling the visit, site personnel should remind the parent/guardian to bring all unopened/unused and used study medication materials to the site.

Subjects will undergo measurement of HR, ophthalmic safety and efficacy evaluations, and the site will update concomitant medications, and conduct AE assessment.

Subjects will then be re-randomized, and sites will dispense randomized study medication to initiate the randomized cross-over stage (Stage 2).

EOS Month 36 visit procedures include:

- Collect study medication materials
- Mode of Administration (BL- EOS Month 36)
- Re-consent/re-assent (as applicable)
- Height and weight

- HR
- Monocular BCVA in each eye at distance and near
- Photopic pupil size
- SLE
- IOP measurement
- Instill first cycloplegic drop (cyclopentolate for subjects < 6 years at randomization and continuing throughout the study, 1% tropicamide for subjects ≥ 6 years at randomization and continuing throughout the study)
- Instill second cycloplegic drop approximately 5 minutes after instillation of the first drop
- Dilated fundus examination (at least 20 minutes after instillation of the second cycloplegic drop)
- Cycloplegic autorefraction (at least 30 minutes after instillation of the second drop)
- Axial length measurement
- Crystalline lens thickness (if feasible)
- Concomitant medication review
- AE assessment
- Re-randomization
- Dispense and document dispensing of re-randomized study medication
- If new lenses are necessary as defined by the criteria (the refraction reveals at least -0.50 D myopic progression and/or the eye care practitioner deems it clinically necessary to improve vision), the site will provide a refractive prescription and lenses
- Conduct treatment adherence assessment
- Upload e-diary application to subject's or their parent's/guardian's phone or Medidata provisioned device (if required). Subject or their parent/guardian will be encouraged to record their dosing on a daily basis, starting from the same evening after completing their Month 36 visit. If the subject or their parent/guardian do not have a cell phone or are unwilling to use their cell phone, a device will be provisioned by Medidata and provided to the subject. Additionally, e-diary training and Medidata eCOA support will be provided.

10.6. Stage 2 Three-Month Visits (Months 39 and 45)

The subject and their parent/guardian will return to the study site with their randomized study medication. It is preferred that the subject attend every visit, but the parent/guardian may attend a 3-month visit without the subject if necessary. When scheduling, site personnel should remind the parent/guardian to bring all unopened/unused and used study medication materials to the site

for these visits. (Note: Enrolled subjects approved by the Sponsor to transfer from one site or a new site, who reside greater than 150 miles from the new research site, may not be required to attend 3-month interval visits. Alternate accommodations may be provided to the subject and subject's family in order to dispense study medication. Assessments may be obtained remotely via telephone and treatment adherence assessments completed at 6-Month interval visits).

Month 39 and 45 visit procedures include:

- Collect study medication materials
- Re-consent/re-assent (as applicable) if not done at earlier visits
- Concomitant medication review
- AE assessment
- Review e-diary
- Dispense study medication for the following 3 months of the study
- Conduct treatment adherence assessment

10.7. Stage 2 Six-Month Visit (Month 42)

At this visit, the subject and their parent/guardian will return to the study site. When scheduling, site personnel should remind the parent/guardian to bring all unopened/unused and used study medication materials to the site for these visits.

Information related to QoL (modified ATI) will be reviewed with the subject and their parent/guardian and they will be asked to participate in the QoL questionnaire. The site staff will confirm and document their willingness to participate in completing the questionnaire. Subjects can continue on to Stage 2 even if they elect not to participate in the completion of the QoL questionnaire.

Month 42 visit procedures include:

- Collect study medication materials
- Re-consent/re-assent (as applicable) if not done at earlier visits
- Modified ATI will be completed by the parent/guardian and subject prior to the Investigator's examination of the subject. The parent/guardian QoL questionnaire should be completed prior to the subject's questionnaire. Study staff will verify that the questionnaires are completed by both the parent/guardian and the subject.
- HR
- Monocular BCVA in each eye at distance and near
- Photopic pupil size
- SLE
- IOP measurement

- Instill first cycloplegic drop (cyclopentolate for subjects < 6 years at randomization and continuing throughout the study, 1% tropicamide for subjects ≥ 6 years at randomization and continuing throughout the study)
- Instill second cycloplegic drop approximately 5 minutes after instillation of the first drop.
- Cycloplegic autorefraction (at least 30 minutes after instillation of the second drop)
- Axial length measurement
- Crystalline lens thickness (if feasible)
- Concomitant medication review
- AE assessment
- Review e-diary
- Dispense study medication for the following 3 months of the study
- If new lenses are necessary as defined by the criteria (the refraction reveals at least -0.50 D myopic progression and/or the eye care practitioner deems it clinically necessary to improve vision), the site will provide a refractive prescription and lenses
- Conduct treatment adherence assessment

10.8. End of Stage 2/End of Study (Month 48)

At the Month 48 (EOS) visit, the subject and their parent/guardian will return to the study site for the final study visit (Stage 2). When scheduling, site personnel should remind the parent/guardian to bring all unopened/unused and used study medication materials to the site for this visit.

Month 48 procedures include:

- Collect study medication materials
- Mode of Administration (Month 36-EOS Month 48)
- Re-consent/re-assent (as applicable) if not done at earlier visits
- Modified ATI will be completed by the parent/guardian and subject prior to the Investigator's examination of the subject. The parent/guardian QoL questionnaire should be completed prior to the subject's questionnaire. Study staff will verify that the questionnaires are completed by both the parent/guardian and the subject
- Height and weight
- HR
- Monocular BCVA in each eye at distance and near
- Photopic pupil size

- SLE
- IOP measurement
- Instill first cycloplegic drop (cyclopentolate for subjects < 6 years at randomization and continuing throughout the study, tropicamide for subjects ≥ 6 years at randomization and continuing throughout the study)
- Instill second cycloplegic drop approximately 5 minutes after instillation of the first drop.
- Dilated fundus examination (at least 20 minutes after instillation of the second cycloplegic drop)
- Cycloplegic autorefraction (at least 30 minutes after instillation of the second drop)
- Axial length measurement
- Crystalline lens thickness (if feasible)
- Concomitant medication review
- AE assessment
- Review e-diary
- Uninstall the Medidata eCOA application (installed on cell phone) or retrieve the device provisioned by Medidata and provided to the subject
- If new lenses are necessary as defined by the criteria (the refraction reveals at least -0.50 D myopic progression and/or the eye care practitioner deems it clinically necessary to improve vision), the site will provide a refractive prescription and lenses
- Conduct treatment adherence assessment

10.9. Early Termination Visits

Every effort should be made to keep subjects in the study and conduct all study visits as scheduled. If a subject is discontinued from study medication before the Month 48 visit, then all Month 48 (EOS) procedures should be performed at the visit the subject is discontinued (see Section 10.8).

If a subject is off study medication and is being followed for safety assessments then an EOS Month 36 visit should be completed, as these subjects will not continue on to Stage 2.

10.10. Unscheduled Visits

Unscheduled visits may occur at the Investigator's discretion to address any possible issues the subject may experience that are of concern to the subject or parent/guardian (e.g., blurry vision, pain, redness in one or both eyes).

11. STATISTICS

11.1. General Considerations

This will be a 3-arm randomized, multicenter, double-masked, placebo-controlled study of the safety and efficacy of Atropine Sulfate Ophthalmic Solution in 0.01% and 0.02% concentrations for slowing the progression of myopia in children. The study will be conducted in 2 stages. Stage 1 is a safety and efficacy phase of 3 years (36 months) in duration, during which subjects will be allocated to 1 of 3 study medications. Stage 2 is a randomized cross-over phase of 1 year (12 months) in duration, during which subjects will be re-randomized to receive 1 of the 3 study medications with subjects initially randomized to Vehicle only eligible for randomization to 0.01% or 0.02% atropine. Subjects (aged 3 to ≤ 17.0 years) will enter the study with myopia SER of at least -0.50 D and no greater than -6.00 D myopia in each eye as measured by cycloplegic autorefraction.

In Stage 1, subjects will be randomized in a 2:2:3 ratio of Vehicle: Atropine Sulfate Ophthalmic Solution, 0.01%: Atropine Sulfate Ophthalmic Solution, 0.02%.

The target number of subjects to be randomized into the 6- to 10-year age group (436), the primary efficacy population, will be:

- Vehicle (placebo): 125
- Atropine Sulfate Ophthalmic Solution, 0.01%: 125
- Atropine Sulfate Ophthalmic Solution, 0.02%: 186

Approximately 483 subjects over all ages will be randomized, resulting in the following numbers of subjects in each arm:

- Vehicle (placebo): 138
- Atropine Sulfate Ophthalmic Solution, 0.01%: 138
- Atropine Sulfate Ophthalmic Solution, 0.02%: 207

The Sponsor may conduct a sample size re-estimation based on a masked assessment of the primary endpoint response rate and/or the subject discontinuation rate.

The randomization will be stratified twice: (1) by age at randomization (subjects < 9 years; subjects ≥ 9 years) and by (2) refractive error (less myopic: SER -0.50 to -3.00 D; more myopic: one or more eyes with SER -3.01 to -6.00 D). The stratification is used to balance these characteristics across the 3 treatment groups. Enrollment will proceed until 436 subjects aged 6 to 10 years have been randomized and at least 483 subjects overall have been randomized. Enrollment may be closed to subjects ≥ 11 years following enrollment of 50 subjects in this age group to avoid over-enrollment into the study.

To initiate Stage 2, all subjects will be re-randomized to receive 1 of 3 study medications. Subjects who were randomized to 0.01% or 0.02% Atropine Sulfate Ophthalmic Solution during Stage 1 will be re-randomized in a 1:1:1 ratio to one of the 3 treatment arms (Vehicle: Atropine Sulfate Ophthalmic Solution, 0.01%: Atropine Sulfate Ophthalmic Solution, 0.02%). Subjects

who were randomized to Vehicle during Stage 1 will be re-randomized in a 1:1 ratio to active treatment (Atropine Sulfate Ophthalmic Solution, 0.01%: Atropine Sulfate Ophthalmic Solution, 0.02%).

The drop-out rate over the 3 years of the safety and efficacy stage of the study (Stage 1) is estimated to be 27% (~10% per year). As long as this drop-out rate is not exceeded, then at least 150 subjects (300 eyes) receiving the higher concentration (0.02% atropine) will be available for the evaluation of safety.

A biostatistician will perform statistical analyses as agreed with the Sponsor according to the Statistical Analysis Plan. Any additional or supplemental data analysis performed independently by an Investigator shall be submitted to the Sponsor for review.

Efficacy analysis will be conducted on the Intent-to-Treat (ITT) Set, the Modified Intent-to-Treat (mITT) Set, the Per Protocol Set (PPS), and the Modified Per Protocol Set (mPPS). Safety analyses will be performed using the Safety Set. Definitions for all the analysis populations can be found in Section 11.4.

11.2. Handling of Missing Data

Use of mixed-effects models require only that data are missing at random so that no other method will be employed to deal with missing data.

Various sensitivity analyses will be performed for the primary efficacy analysis to assess the impact of missing data

11.3. Determination of Sample Size

Significance Level:

The 0.01% and 0.02% atropine response rates will be compared to the vehicle response rate. The primary and secondary efficacy endpoints will be tested at the 5% level of significance using a hierarchal testing procedure in the order listed.

Atropine Sulfate Ophthalmic Solution, 0.02%:

A Fisher's exact test with a 0.05 two-sided significance level will have 95% power to detect the difference between an Atropine Sulfate Ophthalmic Solution, 0.02% responder proportion of 0.25 and a Vehicle responder proportion of 0.07 when the sample sizes are 136 and 91, respectively.

Atropine Sulfate Ophthalmic Solution, 0.01%:

A Fisher's exact test with a 0.05 two-sided significance level will have 90% power to detect the difference between an Atropine Sulfate Ophthalmic Solution, 0.01% responder proportion of 0.25 and a Vehicle responder proportion of 0.07 when the sample size in each group is 91.

11.4. Analysis Populations

11.4.1. Populations for Efficacy Analysis

11.4.1.1. Enrolled Set

The Enrolled Set will include all subjects enrolled.

11.4.1.2. Intent-to-Treat (ITT) Set

The ITT Set will include all randomized subjects for a given stage.

11.4.1.3. Modified Intent-to-Treat (mITT) Set

The mITT Set will include all randomized subjects, for a given stage, aged 6 to 10 years at the time of randomization in Stage 1. This will be the population for the primary efficacy analysis.

11.4.1.4. Per Protocol Set (PPS)

The PPS will include all subjects who remain in the study through the end of the stage and have no major or critical protocol violations (as defined in SAP).

11.4.1.5. Modified Per Protocol Set (mPPS)

The mPPS will include all subjects in the PPS Set in each stage who were aged 6 to 10 years at the time of randomization in Stage 1.

11.4.2. Safety Set

The Safety Set will include all subjects who were administered at least one dose of study medication for a given stage.

11.5. Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized for the Safety Set by actual treatment and overall and for the ITT Set, mITT Set, PPS, and mPPS by randomized treatment group and overall. Summary statistics and by-subject listings will be provided. The summary will be repeated for all subjects who enter Stage 2.

11.6. Efficacy Analyses

The primary and secondary efficacy analyses will be performed using the mITT Set assuming data missing at random.

The primary analysis and any other analysis of binary response measures will be performed using a mixed-effects model based on the binomial distribution using a logit link function. The model will include subject, treatment group, visit, eye (left or right), and baseline age group (as randomized) and SER (as randomized) as independent variables and treatment group-by-visit interaction term included. Random intercepts for subject and eye within subject will be included using variance components and compound symmetry covariance structures, respectively. . In

addition, sensitivity analyses will be performed for the primary efficacy endpoint to assess the impact of missing data. These sensitivity analyses will be described in the statistical analysis plan.

For comparisons of mean change from baseline for continuous measures, the analysis will be performed using a mixed-effects model with a random intercept. The model will include treatment group, visit, eye (left or right), baseline age group (as randomized), and baseline SER group (as randomized) as independent variables and the treatment group-by-visit interaction. Will be included. The degrees of freedom will be determined using the Kenward-Roger approximation. Random intercepts for subject and eye within subject will be included using unstructured covariance structures.

Note, there will be 8 groups with different treatment histories for Year 4:

Treatment Allocation	**Possible Treatment Histories**		
Stage 1 (Years 1-3) Stage 2 (Year 4)	Atropine 0.01% Atropine 0.01%	Atropine 0.01% Atropine 0.02%	Atropine 0.01% Vehicle
Stage 1 (Years 1-3) Stage 2 (Year 4)	Atropine 0.02% Atropine 0.01%	Atropine 0.02% Atropine 0.02%:	Atropine 0.02% Vehicle
Stage 1 (Years 1-3) Stage 2 (Year 4)	Vehicle Atropine 0.01%	Vehicle Atropine 0.02%	

For all subjects who respond in the Atropine Sulfate Ophthalmic Solution treatment groups at the Month 36 visit, summary statistics for the change in SER from Stage 2 baseline (Month 36 visit) will be presented at the Month 42 and Month 48 visits for each treatment history where subjects receive the same dose of Atropine Sulfate Ophthalmic Solution, a lower dose of Atropine Sulfate Ophthalmic Solution, or Vehicle.

Summary statistics will be presented for compliance collected in diaries, the frequency of switching from dosing by parent/guardian to dosing by subject, and the modified Amblyopia Treatment Index by visit and treatment group in Year 4.

The planned sample sizes and estimated sample sizes, accounting for a drop-out rate of approximately 10% per year, are shown in Table 4.

For details on the various analyses planned, for both Stage 1 and Stage 2 of the study, please refer to the statistical analysis plan.

Table 4: Planned Sample Sizes and Estimated Sample Sizes After Accounting for Drop-Out Rate

Strata and Study Periods	**Stage 1**	**Stage 2**		**Stage 1**		**Stage 2**		**Stage 1**		**Stage 2**	
6-10 Years Old	**Vehicle**	**0.01%**	**0.02%**	**0.01%**	**0.01%**	**0.02%**	**Vehicle**	**0.02%**	**0.01%**	**0.02%**	**Vehicle**
Start Year 1	125			125				186			
End Year 1	113			113				168			
End Year 2	101			101				151			
End Year 3	91			91				136			
Start Year 4	91	46	46	91	30	30	30	136	45	45	45
End Year 4		41	41		27	27	27		41	41	41
All Ages											
Start Year 1	138			138				207			
End Year 1	124			124				186			
End Year 2	111			111				168			
End Year 3	100			100				151			
Start Year 4	100	50	50	100	33	33	33	151	50	50	50
End Year 4		45	45		30	30	30		45	45	45

0.01% = Atropine Sulfate Ophthalmic Solution, 0.01%; 0.02% = Atropine Sulfate Ophthalmic Solution, 0.02%

11.6.1. Primary Efficacy Endpoint

The primary efficacy endpoint is the between-treatment group (Atropine Sulfate Ophthalmic Solution, 0.02% versus Vehicle) difference in the proportion of subjects who show < -0.50 D myopia progression (SER) at the Month 36 visit.

The primary and all secondary endpoints comprise a fixed sequence set of endpoints to be tested in order. A 2-sided significance level of 0.05 will be adopted.

11.6.2. Secondary Efficacy Endpoints

The secondary efficacy endpoints consist of:

1. Between-treatment group (Atropine Sulfate Ophthalmic Solution, 0.02% versus Vehicle) difference in the mean change from baseline in SER at the Month 36 visit.
2. Between-treatment group (Atropine Sulfate Ophthalmic Solution, 0.01% versus Vehicle) difference in the proportion of subjects who show < -0.50 D myopia progression (SER) from baseline at the Month 36 visit.
3. Between-treatment group (Atropine Sulfate Ophthalmic Solution, 0.01% versus Vehicle) difference in mean change from baseline in SER at the Month 36 visit.
4. Between-treatment group (Atropine Sulfate Ophthalmic Solution, 0.02% versus Vehicle) difference in the mean change from baseline in axial length at the Month 36 visit.
5. Between-treatment group (Atropine Sulfate Ophthalmic Solution, 0.01% versus Vehicle) difference in the mean change from baseline in axial length at the Month 36visit.

11.7. Safety Analyses

The safety of 0.01% and 0.02% Atropine Sulfate Ophthalmic Solution will be compared to Vehicle (placebo) with analysis of safety variables including ophthalmic safety assessments (BCVA, photopic pupil size, SLE, dilated fundus examination, and tonometry), HR, and AEs.

Safety and tolerability data will be presented in tables of descriptive statistics and frequency distribution. All summary tables will be supported with individual subject data listings.

12. QUALITY CONTROL, ETHICS AND REGULATORY COMPLIANCE

The Sponsor, the CRO, and/or their contracted agents utilize standard operating procedures (SOPs) designed to ensure that research procedures and documentation are consistently conducted/prepared to the highest quality standards. These SOPs require compliance with FDA regulations and the ICH GCP guidance.

The study will be monitored by the CRO to verify that the rights and well-being of human subjects are being protected, the reported data are accurate, complete, and verifiable, and that the conduct of the study is in compliance with the currently approved protocol, the ethical principles that have their origin in the Declaration of Helsinki, ICH guidelines, consolidated Guideline E6 R2 for GCP, and applicable regulatory requirements:

- European Commission Directive (2001/20/EC Apr 2001);
- European Commission Directive (2005/28/EC Apr 2005);
- The Medicines for Human Use (Clinical Trials) Regulations (2006)
- Food and Drug Administration GCP Regulations: CFR Title 21, Parts 11, 50, 54, 56, and 312;
- EU General Data Protection Regulation (GDPR): 2016/679;
- The Health Insurance Portability and Accountability Act, as appropriate; and/or
- Other applicable local regulations.

To ensure compliance with GCP and all applicable regulatory requirements, the Sponsor or its agent may conduct a quality assurance audit at any time during or after completion of a study. The Investigator will be given adequate notice if he/she is selected for an audit. The audit will include but is not limited to: a review of all ICFs, medical records, and regulatory documentation; an assessment of study conduct and protocol compliance; and a review of the investigational drug product receipt, storage, and administration. At the conclusion of an audit, the auditor will conduct a brief meeting with the Investigator to review the findings of the audit.

13. ADMINISTRATIVE CONSIDERATIONS

13.1. Institutional Review Board (IRB) and Ethics Committee (EC)

The EC/IRB must review, approve, and provide continuing review of the clinical study protocol, protocol amendments, the informed consent documents, subject recruitment advertisements, and any other written information to be provided to the subjects. Initial EC and IRB approval is an affirmative decision that the clinical study has been reviewed and may be conducted at the study site within the constraints set forth by the EC and IRB, the Declaration of Helsinki, ICH guidelines, consolidated Guideline E6 R2 for GCP, and applicable local regulatory requirements. A copy of EC and/or IRB approval letters for the protocol, the informed consent, the intended advertising, and any written material to be provided to the subject must be submitted to the CRO prior to release of investigational supplies to the study site. Progress reports and notifications of serious adverse drug reactions will be provided to the EC and IRB according to local regulations and guidelines. The EC and IRB must be notified of completion or termination of the study. The study site and the CRO must maintain an accurate and complete record of all reports, documents, and other submissions made to the EC and IRB concerning this protocol.

13.2. Ethical Conduct of the Study

The study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and in compliance with the ethical principles that have their origin in the Declaration of Helsinki, ICH guidelines consolidated Guideline E6 R2 for GCP (CPMP/ICH/135/95), and applicable regulatory requirement(s):

- European Commission Directive (2001/20/EC Apr 2001);
- European Commission Directive (2005/28/EC Apr 2005);
- Food and Drug Administration GCP Regulations: CFR Title 21, parts 11, 50, 54, 56 and 312;
- EU General Data Protection Regulation (GDPR): 2016/679;
- The Health Insurance Portability and Accountability Act as appropriate; and/or
- Other applicable local regulations.

13.3. Written Informed Consent/Assent

A sample ICF containing the required elements of informed consent will be provided by the CRO. Sample minor assent form(s) will be provided as required by IRB and EC guidelines. Any changes made to these samples must be reviewed by the CRO prior to submission to the IRB. After review by the CRO, the informed consent and minor assent form must be submitted to and approved by the IRB or relevant ECs. The informed consent will be submitted to the IRB/ECs of the participating countries in the country local language(s).

It is the responsibility of the Investigator to inform each subject of the purpose of this clinical study, including possible risks and benefits, and to document the informed consent/assent process.

In obtaining and documenting informed consent, the Investigator should comply with all applicable regulatory requirements, and should adhere to GCP and ethical principles outlined above.

Prior to undergoing any study-related procedures, the subject must read, sign, and date the current IRB/EC-approved version of the ICF. For minor subjects, the assent form must be signed and dated per IRB/EC guidelines. If a subject becomes an adult (depending on country regulations) during the study, they will need to sign an ICF to continue in the study. The original informed consent/assent form is to be retained by the study site, and copies are to be given to the subject.

13.4. Subject Confidentiality and Confidentiality of Data

The Investigator and Sponsor will preserve the confidentiality of all subjects taking part in the study, in accordance with GCP, applicable data protections laws, and local regulations.

Data generated for the study should be stored in a limited-access file area and be accessible only to representatives of the study site, the Sponsor, the CRO, the ECs, the IRB, and FDA/relevant regulatory agencies. Medical information resulting from a subject's participation in this study may be given to the subject's personal physician or to the appropriate medical personnel responsible for the subject's welfare. No information that can be related to a specific individual subject will be released or used in any fashion without the signed written consent of that subject. All reports and communications relating to study subjects will identify subjects only by initials and subject identification number. Complete subject identification will be kept by the Investigator for purposes of long-term follow-up, if needed. This information will be treated with strict adherence to professional standards of confidentiality.

13.5. Study Monitoring

The study will be monitored by the CRO on behalf of the Sponsor in accordance with current GCP, applicable data protection laws, and local regulations to assure compliance with the study protocol and the quality of the data collected. Monitoring visits will occur as required and could include a study initiation visit, a monitoring visit, and a study close-out visit. Training will be provided for key investigative personnel in all aspects of study conduct. The Investigator will be responsible for making sure that clinical site personnel are provided adequate training on conducting their designated tasks. Documentation of site personnel training will be maintained at the site.

This study will utilize electronic data capture. Monitors will review source data (initial entry is considered the source) and overall study data onsite and remotely and query discrepancies based upon eCRF entries. During this monitoring, data are reviewed as entered by the site, and the monitors will flag any abnormalities, trends, or safety signals for Medical Monitor review and monitor follow-up onsite, if necessary.

During visits to the study site, the monitor may review the source documents including but not limited to signed ICFs, study medication accountability and storage, and the reporting of AEs and SAEs. All data generated during this study and the medical records/documents from which they originated are subject to inspection by the study Sponsor, the CRO, the FDA, and other

regulatory agencies. The Investigator must notify the Sponsor and the CRO promptly of any inspections scheduled by regulatory authorities.

Upon completion of the study, the clinical monitor will conduct a final visit (closeout) to the site. The objectives of this visit are to ascertain that all regulatory records and reports are complete, verify that the study drug and other supplies have been accounted for, and ensure that the Investigators are aware of their responsibilities once the study ends.

The Investigator is responsible for permitting the CRO direct access to any study documents for monitoring and auditing purposes, for providing adequate space for monitoring, and for addressing any questions or issues that might be raised by the monitor or auditor on a timely basis.

13.6. Case Report Forms and Study Records

All data relating to study procedures will be entered by site personnel onto eCRFs provided by the CRO.

The first place the study data are recorded will be considered the source document. Paper source documents, when generated, will be retained at the study site.

13.6.1. Electronic Patient Diary

Subject or their parent/guardian will be encouraged to record their dosing on a daily basis, starting from the same evening after completing their Month 36 visit till the last visit (Stage 2 of the study) in an e-diary. The e-diary will be considered a source document.

At their last study visit, site staff will uninstall the Medidata eCOA application (installed on the cell phone) or retrieve the device provisioned by Medidata and provided to the subject.

13.7. Protocol Deviations

The Investigator should conduct the study in compliance with the protocol agreed to by the Sponsor and, if required, by the regulatory authorities, and which was given approval/favorable opinion by the IRB/EC.

A deviation to any protocol procedure or waiver to any stated criteria will not be allowed in this study except where it is necessary in order to eliminate immediate hazard(s) to subject(s).

The Sponsor must be notified of all intended or unintended deviations to the protocol (e.g., inclusion/exclusion criteria) on an expedited basis.

The Investigator, or person designated by the Investigator, should document, and explain any deviation from the approved protocol.

If a subject was ineligible or received the incorrect dose of investigational treatment, and had at least one administration of investigational medicinal product, then this data should be collected for safety purposes and reported as a deviation.

The Investigator should notify the EC or IRB of any deviations from the protocol in accordance with local procedures.

All changes to the protocol made by the Sponsor/CRO or designee which are assessed as being substantial shall be submitted to and approved by the FDA and approved by the IRB and to the relevant European regulatory authorities and ECs prior to implementation unless there is an imminent safety risk to the subjects.

Definitions of major protocol violations will be provided in the SAP.

13.8. Access to Source Documentation

A study-related monitoring audit, review by the ECs, IRB, and/or regulatory inspection may be conducted at any time during or after completion of a study (Section 12). The Investigator will be given adequate notice if he/she is selected for an audit and must provide direct access to study documentation. The audit may include, but is not limited to, a review of all ICFs; a review of medical records; a review of regulatory documentation; an assessment of study conduct and protocol compliance; and a review of the investigational drug product receipt, storage, and administration.

13.9. Data Generation and Analysis

Management of data and the production of the clinical study report will be the responsibility of the CRO or its designee.

During the course of the study, data queries will be generated for data items that are potentially erroneous and require appropriate clarification or correction. Such clarifications and corrections will be discussed with and approved by study site personnel and appropriately documented. Prior to database lock, data listings will be generated, and anomalous values investigated.

13.9.1. Retention of Data

Investigators should retain study-related records at the site for 25 years (Source documentation will be retained in accordance with local legislation). The Investigator will not discard any records without notifying the Sponsor. If the Principal Investigator moves from the current clinical site, the Sponsor should be notified of the name of the person who will assume responsibility for maintenance of the records at the clinical site or the new address at which the records will be stored. The Investigator will notify the Sponsor as soon as possible in the event of accidental loss or destruction of any study documentation. If it becomes necessary for the Sponsor, the CRO, or the FDA or relevant regulatory authorities to review any documentation relating to the study, the Investigator must permit access to such records.

13.10. Publication and Disclosure Policy

All information concerning Atropine Sulfate Ophthalmic Solution and the operations of Vyluma Inc., an affiliate of Nevakar Inc., such as patent applications, formulas, manufacturing processes, basic scientific data, or formulation information not previously published, are considered CONFIDENTIAL and shall remain the sole property of Vyluma Inc., an affiliate of Nevakar Inc. The Sponsor herby grants to the institution and/or the Investigator a limited right to use the study data for scientific publication purposes. The institution and the Investigator undertake and agree that they will not publish, communicate, or otherwise disclose in whatever manner or through

any vehicle any information derived from the study or the study data for the whole duration of the study, before the study report is notified to the competent authorities and for a period of 18 months after the end of the study, unless otherwise agreed to by the Sponsor.

The rights are detailed in a separate agreement. The publication policy is addressed in a separate agreement.

14. LIST OF REFERENCES

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15. APPENDICES

APPENDIX A. PROTOCOL AMENDMENT SUMMARY

Overview of Protocol CP-NVK002-0001, Amendment (5)

Protocol CP-NVK002-0001, Childhood Atropine for Myopia Progression (CHAMP): A 3-Arm Randomized, Double-Masked, Placebo-Controlled, Phase 3 Study of Atropine Sulfate Ophthalmic Solution 0.01% and 0.02%, has been amended a fifth time. The new protocol is indicated as CP-NVK002-0001(5) and will be used to conduct the study in place of any preceding version of the protocol.

The overall changes and rationale for the changes made to this protocol are described in the following table:

Amendment Summary for Protocol CP-NVK002-0001, Amendment (5)

Section # and Name	Description of Change	Brief Rationale
Global Change	"Vyluma Inc., an affiliate of Nevakar Inc." has been added to replace "Nevakar Inc." at all applicable places throughout the document	Updated Sponsor name as per current change
Title page and Sponsor signature page	Added protocol amendment 5 details	Aligned with the current numbering
Investigator's agreement page	Added protocol amendment 5 details. Also, modified Section 9.5 to Section 9.9 for reporting serious adverse events.	Aligned with the current section no.
Synopsis – Study Centers	Added - United Kingdom	QoL questionnaire will include the subjects from UK
Synopsis – Studied Period (Years)	Revised text: Estimated date completion BL-EOS Month 36: August 2022 Estimated last subject completed Month 36- EOS Month 48: September 2023	Updated per current projections
Global change	Section numbers modified throughout the document (as a new Section 9.3 of "The modified Amblyopia Treatment Index (modified ATI)" has been added. This section has been introduced to cover a quality of life questionnaire (QoL) which is added to the Stage 2 of the CHAMP study.	Aligned all section numbers as applicable
Section 3: List of Abbreviations and Definitions of Terms	Abbreviation for Amblyopia Treatment Index (ATI) and Quality of Life (QoL) has been added to the table	New abbreviations have been added
Section 4.3 Good Clinical Practices Statement Section 12. Quality Control, Ethics and Regulatory Compliance	Added text: • The Medicines for Human Use (Clinical Trials) Regulations (2006)	Added text to cover UK regulation as QoL questionnaire will include the subjects from UK

Synopsis- Methodology	Added text: **Inclusion of the Modified Amblyopia Treatment Index (ATI), quality of life (QoL) questionnaire** At Month 42 and Month 48, in addition to other assessments, the study staff will encourage participation in the Modified Amblyopia Treatment Index (ATI), quality of life (QoL) questionnaire which has been added to the study to be completed by the subject and their parent/guardian. Participation is voluntary and will be documented. The parent/guardian questionnaire should be completed prior to the subject's questionnaire. The questionnaires should be completed prior to the Investigator's examination of the subject. All subjects are to be re-consented/re-assented at their next study visit, including subjects completing an End of Study (EOS) Visit (Stage 1 – Month 36, Month 39, Month 42, Month 45, and Month 48).	Added text for re-consent/re-assent to be obtained from all subjects regardless of participation in the modified ATI, QoL questionnaire. The QoL questionnaire has been added to the Stage 2 of the CHAMP study (randomized cross-over stage).
4.5 Benefit/Risk Assessment	Added text: Other side effects reported: • Seizures have been reported with both systemic and compounded use of Atropine. However, it is not clear what dose concentration was utilized in the eye drops.	Added side effect of seizure reported from the current study
6.1 Overall Study Design	Added text: Methodology and Schedules of Procedure: At Month 42 and Month 48, in addition to other assessments, the modified ATI, QoL questionnaire will be completed by the parent/guardian and subject prior to the Investigator's examination of the subject. The parent/guardian QoL questionnaire should be completed prior to the subject's questionnaire. Study staff will verify that the questionnaires are completed by both the parent/guardian and the subject.	Quality of life questionnaires have been added to the Stage 2 of the CHAMP study (randomized cross-over stage), which commences at Month 36. This QoL questionnaires will support an eventual European filing and will be used to evaluate the burden and benefit of myopia treatment in children and parent.

Synopsis: Study Procedures End of Stage 1/End of Study (EOS) Month 36 Primary Efficacy (BL-Month 36) and Evaluation/Commencement of Stage 2: Randomized Cross-Over (EOS Month 36)	Study Procedures: Revised text. At the Month 36 visit, End of Study (EOS) visit Stage 1, the subjects and their parent/guardian will return to the study site for the EOS Month 36 study visit (Stage 1). The subject and their parent/guardian will return to the study site with their randomized study medication.	Added QoL relevant text for consent at Month 36
Synopsis: Study Procedures Stage 2 Six-Month Visit (Month 42):	**Stage 2 Six-Month Visit (Month 42)** …Information related to QoL (modified ATI) will be reviewed with the subject and their parent/guardian and they will be asked to participate in the QoL questionnaire. The site staff will confirm and document their willingness to participate in completing the questionnaire. Subjects can continue on to Stage 2 even if they elect not to participate in the completion of the QoL questionnaire. The modified ATI will be completed by the parent/guardian and subject prior to the Investigator's examination of the subject. The parent/guardian QoL questionnaire should be completed prior to the subject questionnaire. Study staff will verify completion of the QoL questionnaires by both the parent/guardian and the subject. Once the modified ATI has been completed, subjects will undergo a measurement of HR, BCVA measurement (distance and near), photopic pupil size measurement, SLE, tonometry, cycloplegic autorefraction, axial length, and, if possible, crystalline lens thickness.	Added QoL relevant text for Month 42

Synopsis: Study Procedures End of Stage 2/End of Study (Month 48)	**End of Stage 2/ End of Study (Month 48)** … At the Month 48/ end of study (EOS) visit Stage 2, the subject and their parent/guardian will return to the study site with their randomized study medication for an evaluation of treatment adherence. The modified ATI will be completed by the parent/guardian and subject prior to the Investigator's examination of the subject. The parent/guardian QoL questionnaire should be completed prior to the subject's questionnaire. Study staff will verify completion of the QoL questionnaires by both the parent/guardian and the subject. Once the modified ATI is completed, subjects will undergo a measurement of height, weight, HR, BCVA measurement (distance and near), photopic pupil size measurement, SLE, tonometry, dilated fundus examination, cycloplegic autorefraction, axial length, and, if possible, crystalline lens thickness.	Added QoL relevant text for Month 48
Table 2, Schedule of Procedures	Added footnote "e": All subjects are to be re-consented/re-assented at their next study visit if not done at earlier visits, including subjects completing an End of Study (EOS) Visit (Stage 1 – Month 36, Month 39, Month 42, Month 45, and Month 48). Added footnote "f": At Month 42 and Month 48, the modified ATI, QoL questionnaire, will be completed by the parent/guardian and subject prior to the Investigator's examination of the subject. Prior to the examination, the site staff will ensure parent/guardian and subject understand the questions, by reading the questions. After each question, the site staff will proceed to read the choices. The parent/guardian and subject will pick the answer which comes closest to describing how they feel. The answer will be entered into the database by the site staff.	Added modified ATI assessment and its applicable footnote

Synopsis, Methodology	Moved text: Site staff will also contact the subject or their parent/guardian by telephone at the end of Month 1 and Month 2 and then midway between office visits during the initial year of the study to collect information regarding AEs and treatment adherence. Telephone checks can be continued or reinstated at any time during the study to assist with maintaining protocol and treatment adherence.	Moved text for better flow (from end of methodology section to in between the methodology section)
Synopsis, Treatment Adherence 8.4 Treatment Adherence	Added text: Documentation of Mode of Administration: At the EOS Month 36 and EOS Month 48 visit, site will document mode of administration by asking the subject or their parent/guardian: • Who administered the eyedrops to the subject during the study (i.e., self-administered or administered by parent/guardian)? • Was there a transition in the dosing administrator? • If yes, at what approximate age did the transition occur?	Added Mode of Administration for treatment adherence to add more clarity.

Synopsis: Methodology 9.3 The Modified Amblyopia Treatment Index (Modified ATI)	Added text: Quality of life questionnaires (called Modified ATI in this study) were modified from the ATI questionnaire developed by Felius et al., 2010, and will be used in the study after subjects have completed 6 months of treatment in the Stage 2 of CHAMP study. Participation is voluntary and will be documented. Subjects can continue in the study even if they elect not to participate. The questionnaires will be completed at Month 42 and at the completion of the trial at Month 48 prior to the Investigator's examination of the subject. The parent/guardian questionnaire should be completed prior to the subject's questionnaire. The questionnaires should be completed prior to the Investigator's examination of the subject. The questionnaires will capture responses to evaluate QoL and burden of atropine treatment from the parent/guardian and subject's perspective. There are two versions of the modified ATI, the 'parent/guardian' version (Appendix C), and the 'subject' version (Appendix D). The two versions are on different response scales. Responses on the parent/guardian version are on a strength of agreement scale ("strongly agree" to "strongly disagree") whereas the responses on the subject version are on a frequency scale ("always" to "never"). This is because a frequency scale is believed to be easily understandable to children. Re-consent/re-assent will be obtained from all subjects, regardless of their participation in the modified ATI, QoL questionnaire.	Quality of life questionnaires have been added to the Stage 2 of the CHAMP study (randomized cross-over stage), which commences at Month 36. This QoL questionnaires will support an eventual European filing and will be used to evaluate the burden and benefit of myopia treatment in children and parent.

10. STUDY ACTIVITIES 10.5. End of Stage 1/ End of Study (EOS) Month 36 Primary Efficacy (BL-Month 36) and Evaluation/Commencement of Stage 2: Randomized Cross-over (EOS Month 36) 10.6. Stage 2 Three-Month Visits (Months 39 and 45) 10.7. Stage 2 Six-Month Visit (Month 42) 10.8. End of Stage 2/ End of Study (Month 48)	Added text: **Section 10.5:** • Mode of Administration (BL- EOS Month 36) • Re-consent/re-assent (as applicable). **Section 10.6:** • Re-consent/re-assent (as applicable) if not done at earlier visits. **Section 10.7:** • Re-consent/re-assent (as applicable) if not done at earlier visits. Information related to QoL (modified ATI) will be reviewed with the subject and their parent/guardian and they will be asked to participate in the QoL questionnaire. The site staff will confirm and document their willingness to participate in completing the questionnaire. Subjects can continue on to Stage 2 even if they elect not to participate in the completion of the QoL questionnaire. Modified ATI will be completed by the parent/guardian and subject prior to the Investigator's examination of the subject. The parent/guardian QoL questionnaire should be completed prior to the subject's questionnaire. Study staff will verify that the questionnaires are completed by both the parent/guardian and the subject. **Section 10.8:** • **Mode of Administration (BL- EOS Month 36)** • Re-consent/re-assent (as applicable) if not done at earlier visits Modified ATI, QoL questionnaire, will be completed by the parent/guardian and subject prior to the Investigator's examination of the subject. The parent/guardian QoL questionnaire should be completed prior to the subject's questionnaire. Study staff will	Added details for modified ATI assessment, re-consent/re-assent, and mode of administration.

	verify that the questionnaires are completed by both the parent/guardian and the subject.	
Section 10.9 Early Termination Visits	Added text: If a subject is off study medication and is being followed for safety assessments then an EOS Month 36 visit should be completed, as these subjects will not continue on to Stage 2.	Clarified for subjects who are off study medication and who are not to continue to Stage 2, then an EOS visit should be completed at Month 36.
Section 11.1 General Considerations	Modified text: Original text: Efficacy analysis will be conducted on the intent-to-treat (ITT) population, the modified intent to-treat (mITT) population, the per protocol (PP) population, and the modified per protocol (mPP) population. Safety analyses will be performed using the safety analysis population. New text: Efficacy analysis will be conducted on the Intent-to-Treat (ITT) Set, the Modified Intent to-Treat (mITT) set, the Per Protocol Set (PPS), and the Modified Per Protocol Set (mPPS). Safety analyses will be performed using the Safety Set.	Changed analysis population nomenclature
Section 11.2 Handling Missing data	Added text: Various sensitivity analyses will be performed for the primary efficacy analysis to assess the impact of missing data Deleted text: Generalized estimating equation methods however require that data are missing completely at random. It may be necessary to test whether this assumption applies to the data set. If more than 5% of data for an endpoint in the testing hierarchy are missing, multiple imputation will be performed. In addition, for the analysis of responder endpoints, a tipping point sensitivity analysis may be performed.	Added sensitivity analysis for the primary efficacy analysis to assess the impact of missing data.

Synopsis, Section 11.3 Determination of Sample Size	The primary and secondary efficacy endpoints will be tested at the 5% level of significance using a hierarchal testing procedure in the order listed	Clarified that the efficacy endpoints will be tested at the 5% level of significance using a hierarchal testing procedure
Section 11.4.1 Population for Efficacy Analysis	Added text: Section 11.4.1 1 Enrolled Set The Enrolled Set will include all subjects enrolled. Modified text: Section 11.4.1.2 Modified nomenclature for ITT Population to ITT Set, and will include all randomized subjects for a given stage. Section 11.4.1.3 Modified nomenclature for mITT Population to mITT Set, and will include all randomized subjects, for a given stage, aged 6 to 10 years at the time of randomization in Stage 1. Section 11.4.1.4 Modified nomenclature for PP Population to PPS and will include all subjects who remain in the study through the end of the stage and have no major or critical protocol violation. Section 11.4.1.5 Modified nomenclature for mPP Population to mPPS and will include all subjects in each stage who were aged 6 to 10 years at the time of randomization in Stage 1. Section 11.4.1.5 Modified nomenclature for Safety Population to Safety Set, and will include all subjects who were administered at least one dose of study medication for a given stage.	Changed population nomenclature and clarified with respect to stage in the analysis population description

Section 11.5 Demographic and Baseline Characteristics	Added text: Demographic and baseline characteristics will be summarized for the Safety Set by actual treatment and overall and for the ITT Set, mITT Set, PPS, and mPPS by randomized treatment group and overall. Summary statistics and by-subject listings will be provided. The summary will be repeated for all subjects who enter Stage 2. Deleted text: however, should there be a reasonable difference in the size of the ITT and safety analysis populations, demographic and baseline characteristics will be summarized for both. The comparability of groups used in comparison analyses will be characterized in tables of demographic data. Summary tables will be supported with individual subject data listings.	Aligned the text for analysis population nomenclature and removed the criteria of having a reasonable size difference in the size of the ITT and safety population.
Section 11.6 Efficacy Analysis	Added text: The primary and secondary efficacy analyses will be performed using the mITT Set assuming data missing at random. For all subjects who respond in the Atropine Sulfate Ophthalmic Solution treatment groups at the Month 36 visit, summary statistics for the change in SER from Stage 2 baseline (Month 36 visit) will be presented at the Month 42 and Month 48 visits for each treatment history where subjects receive the same dose of Atropine Sulfate Ophthalmic Solution, a lower dose of Atropine Sulfate Ophthalmic Solution, or Vehicle. Summary statistics will be presented for compliance collected in diaries, the frequency of switching from dosing by parent/guardian to dosing by subject, and the modified Amblyopia Treatment Index by visit and treatment group in Year 4. For details on the various analyses planned, for both Stage 1 and Stage 2 of the study, please refer to the statistical analysis plan.	Details of endpoints will be added in SAP. SAP will be available as a separate standalone document. Clarified the primary analysis and any other analysis of binary response measures will be performed using a mixed-effects model based on the binomial distribution using use a logit link function. Clarified that the comparisons of mean change from baseline for continuous measures, the analysis will be performed using a mixed-effects model with a random intercept

Section 11.6.1 Primary Efficacy Endpoint	Modified text: Modified from overall between-group difference from baseline in the proportion of subjects who show < -0.50 D myopia progression (SER) at the Month 36 visit to between-treatment group difference in the proportion of subjects who show < -0.50 D myopia progression (SER) at the Month 36 visit	Clarified between-treatment group difference in the proportion of subjects will be analyzed for the primary efficacy endpoint.
Synopsis, Section 11.6.2 Secondary Efficacy Endpoint	Modified text for endpoints #1 to #5 Deleted text: 6. Between-group (Atropine Sulfate Ophthalmic Solution, 0.01% versus Vehicle) difference in the proportion of subjects who show < -0.75 D myopia progression (SER) at the Month 36 visit. 7. Between-group (Atropine Sulfate Ophthalmic Solution, 0.01% versus Vehicle) median time to change in myopia of -0.75 D SER. 8. Between-group (Atropine Sulfate Ophthalmic Solution, 0.01% versus Vehicle) mean change from baseline in SER at the Month 36, Month 24, and Month 12 visits. 9. Between-group (Atropine Sulfate Ophthalmic Solution, 0.02% versus Vehicle) comparison of the mean number of new prescriptions given after the start of treatment due to progression, at Month 36. 10. Between-group (Atropine Sulfate Ophthalmic Solution, 0.01% versus Vehicle) comparison of the mean number of new prescriptions given after the start of treatment due to progression, at Month 36. 11. Between-group (Atropine Sulfate Ophthalmic Solution, 0.02% versus Vehicle) comparison of the proportion of subjects who progressed to high myopia (SER -6.00 D or more myopic) at Month 36. 12. Between-group (Atropine Sulfate Ophthalmic Solution, 0.01% versus Vehicle) comparison of the proportion of subjects who progressed to high myopia (SER -6.00 D or more myopic) at Month 36.	Details of endpoints will be added in SAP. SAP will be available as a separate standalone document.

Synopsis, Section 11.6.3 Exploratory Efficacy Endpoint	Deleted text: Exploratory Efficacy Endpoints 1. Between-group comparison of proportion of subjects with higher myopia (SER at least 3.00 D) at baseline who progressed at least -0.75 D at 36 months. 2. Between-group comparison of the change in axial length between baseline and Month 36. 3. Between-group comparison of the change in crystalline lens thickness between baseline and Month 36. 4. Interaction between demographic variables and slowing progression of myopia (age 6 – 8 years versus 9 – 10 years; baseline SER -0.50 to -3.00 D versus more myopic than -3.00 D SER; Asian versus non-Asian; dark irides versus light irides) and SER.	Details of endpoints will be added in SAP. SAP will be available as a separate standalone document.
Section 11.8: Stage 1 Analysis	Deleted text: Stage 1 is a safety and efficacy phase of 3 years in duration. When data from subjects who have completed Stage 1 have been obtained, a snapshot of the database will occur with subsequent analyses of Stage 1 data. Results from Stage 1 will then be reported in a clinical study report. The Stage 1 analyses will be conducted to ensure that important 3-year safety and efficacy results are made available for review to the scientific community in a timely manner. Unblinding details are specified in the unblinding plan section of the statistical analysis plan or a separate unblinding plan document.	Deleted text as details will be provided in SAP
14. LIST OF REFERENCES	Added reference: Felius J, Chandler DL, Holmes JM, Chu RH, Cole SR, Hill M, et al. Evaluating the burden of amblyopia treatment from the parent and child's perspective. Journal of American Association for Pediatric Ophthalmology and Strabismus. 2010 Oct 1; 14 (5):389-95.	Since a myopia specific quality of life instrument has not been identified, we have used a modified version of the Amblyopia Treatment Index developed by Felius et al., 2010.
15 APPENDICES	Added: Appendix C: Modified ATI Questionnaire for Parent/Guardian	Added modified ATI questionnaire for parent/guardian
15 APPENDICES	Added: Appendix D: Modified ATI Questionnaire for Subject	Added modified ATI questionnaire for subject

APPENDIX B. REVISED PROTOCOL SECTIONS

Note:	Deletions have been identified by ~~strikethroughs~~. Additions have been identified by the use of underscore.

INVESTIGATOR'S AGREEMENT

Study Title	Childhood Atropine for Myopia Progression (CHAMP): A 3-Arm Randomized, Double-Masked, Placebo-Controlled, Phase 3 Study of Atropine Sulfate Ophthalmic Solution 0.01% and 0.02%
Study Number	CP-NVK002-0001
Original Protocol	01 July 2017
Protocol Amendment 1	05 September 2017
Protocol Amendment 2	10 April 2018
Protocol Amendment 3	12 August 2019
Protocol Amendment 4	09 October 2020
Protocol Amendment 5	14 June 2021

….

I agree to conduct this study according to this protocol and to comply with its requirements, subject to ethical and safety considerations and guidelines, and to conduct the study in accordance with the Declaration of Helsinki, International Council for Harmonisation guidelines on Good Clinical Practice (ICH E6 R2), and applicable regional regulatory requirements, including data protection laws and regulations, and the regulatory requirements for reporting serious adverse events defined in Section ~~9.5~~ 9.9 of this protocol.

1. SYNOPSIS

…

Study Center(s): 15 – 30 centers in North America, ~~and~~ Europe, and United Kingdom

Studied Period (Years):

Estimated date completion BL-EOS Month 36: August 2022

Estimated last subject completed Month 36- EOS Month 48: September 2023

Methodology:

…

Inclusion of the Modified Amblyopia Treatment Index (ATI), quality of life (QoL) questionnaire

At Month 42 and Month 48, in addition to other assessments, the study staff will encourage participation in the Modified Amblyopia Treatment Index (ATI), quality of life (QoL) questionnaire which has been added to the study to be completed by the subject and their parent/guardian. Participation is voluntary and will be documented. The parent/guardian questionnaire should be completed prior to the subject's questionnaire. The questionnaires should be completed prior to the Investigator's examination of the subject.

All subjects are to be re-consented/re-assented at their next study visit, including subjects completing an End of Study (EOS) Visit (Stage 1 – Month 36, Month 39, Month 42, Month 45, and Month 48).

Study Procedures

…

End of Stage 1/ End of Study (EOS) Month 36 Primary Efficacy (BL-Month 36) and Evaluation/Commencement of Stage 2: Randomized Cross-Over (EOS Month 36)

…

At the Month 36 visit, End of Study (EOS) visit Stage 1, the subjects and their parent/guardian will return to the study site for the EOS Month 36 study visit (Stage 1). The subject and their parent/guardian will return to the study site with their randomized study medication. ~~for an evaluation of treatment adherence~~.

Subjects will undergo a measurement of height, weight, HR, BCVA measurement (distance and near), photopic pupil size measurement, SLE, tonometry, dilated fundus examination, cycloplegic autorefraction, axial length and, if possible, crystalline lens thickness

…

Stage 2 Six-Month Visit (Month 42)

At the Month 42 visit, the subject and their parent/guardian will return to the study site with their randomized study medication.

Information related to QoL (modified ATI) will be reviewed with the subject and their parent/guardian and they will be asked to participate in the QoL questionnaire. The site staff will confirm and document their willingness to participate in completing the questionnaire. Subjects can continue on to Stage 2 even if they elect not to participate in the completion of the QoL questionnaire.

The modified ATI will be completed by the parent/guardian and subject prior to the Investigator's examination of the subject. The parent/guardian QoL questionnaire should be completed prior to the

subject questionnaire. Study staff will verify completion of the QoL questionnaires by both the parent/guardian and the subject.

Once the modified ATI has been completed, subjects will undergo a measurement of HR, BCVA measurement (distance and near), photopic pupil size measurement, SLE, tonometry, cycloplegic autorefraction, axial length, and, if possible, crystalline lens thickness. Sites will update concomitant medications, conduct AE assessment, dispense study medication, review e-diary, and perform treatment adherence assessment.

End of Stage 2/ ~~Final Study Visit~~ End of Study (Month 48)

At the Month 48/ end of study (EOS) visit Stage 2, the subject and their parent/guardian will return to the study site with their randomized study medication for an evaluation of treatment adherence.

The modified ATI will be completed by the parent/guardian and subject prior to the Investigator's examination of the subject. The parent/guardian QoL questionnaire should be completed prior to the subject questionnaire. Study staff will verify completion of the QoL questionnaires by both the parent/guardian and the subject.

Once the modified ATI has been completed, subjects will undergo a measurement of height, weight, HR, BCVA measurement (distance and near), photopic pupil size measurement, SLE, tonometry, dilated fundus examination, cycloplegic autorefraction, axial length, and, if possible, crystalline lens thickness. Sites will update concomitant medications, conduct AE assessment, review e-diary, and perform treatment adherence assessment. The site staff will uninstall the Medidata eCOA application (installed on the cell phone) or retrieve the device provisioned by Medidata and provided to the subject.

Early Termination Visits

..

If a subject is off study medication and is being followed for safety assessments than an EOS Month 36 visit should be completed, as these subjects will not continue on to Stage 2.

Treatment Adherence

…

Documentation of Mode of Administration:

At the EOS Month 36 and EOS Month 48, site will document mode of administration by asking the subject or their parent/guardian:

- Who administered the eyedrops to the subject during the study (i.e., self-administered or administered by parent/guardian)?
- Was there a transition in the dosing administrator?
- If yes, at what approximate age did the transition occur?

Criteria for Evaluation:

Primary Efficacy Endpoint

The primary efficacy endpoint is the ~~overall~~ between- treatment group (Atropine Sulfate Ophthalmic Solution, 0.02% versus Vehicle) difference ~~from baseline~~ in the proportion of subjects who show < -0.50 D myopia progression (SER) at the Month 36 visit.

The primary and all secondary endpoints comprise a fixed sequence set of endpoints to be tested in order. A 2-sided significance level of 0.05 will be adopted.

Secondary Efficacy Endpoints:

The secondary efficacy endpoints consist of:

1. Between-treatment group (Atropine Sulfate Ophthalmic Solution, 0.02% versus Vehicle) difference in the mean change from baseline in ~~proportion of subjects who show < -0.50 D myopia progression (~~SER~~)~~ at the Month 36 ~~24 and Month 12 visits~~.
2. Between-treatment group (Atropine Sulfate Ophthalmic Solution, 0.01~~2~~% versus Vehicle) difference in the proportion of subjects who show < -0.75 D myopia progression (SER) from baseline at the Month 36 visit.
3. Between-treatment group (Atropine Sulfate Ophthalmic Solution, 0.01~~2~~% versus Vehicle) difference in mean change from baseline in ~~median time to change in myopia of -0.75 D~~ SER at the Month 36 visit.
4. Between-treatment group (Atropine Sulfate Ophthalmic Solution, 0.02% versus Vehicle) difference in the mean change from baseline in axial length ~~SER~~ at the Month 36 visit.~~, Month 24, and Month 12 visits~~
5. Between-treatment group (Atropine Sulfate Ophthalmic Solution, 0.01% versus Vehicle) difference in the mean change from baseline in axial length ~~proportion of subjects who show < -0.50 D myopia progression (SER)~~ at the Month 36~~, Month 24, and Month 12~~ visits.
6. ~~Between-group (Atropine Sulfate Ophthalmic Solution, 0.01% versus Vehicle) difference in the proportion of subjects who show < -0.75 D myopia progression (SER) at the Month 36 visit.~~
7. ~~Between-group (Atropine Sulfate Ophthalmic Solution, 0.01% versus Vehicle) median time to change in myopia of -0.75 D SER.~~
8. ~~Between-group (Atropine Sulfate Ophthalmic Solution, 0.01% versus Vehicle) mean change from baseline in SER at the Month 36, Month 24, and Month 12 visits.~~
9. ~~Between-group (Atropine Sulfate Ophthalmic Solution, 0.02% versus Vehicle) comparison of the mean number of new prescriptions given after the start of treatment due to progression, at Month 36.~~
10. ~~Between-group (Atropine Sulfate Ophthalmic Solution, 0.01% versus Vehicle) comparison of the mean number of new prescriptions given after the start of treatment due to progression, at Month 36.~~
11. ~~Between-group (Atropine Sulfate Ophthalmic Solution, 0.02% versus Vehicle) comparison of the proportion of subjects who progressed to high myopia (SER -6.00 D or more myopic) at Month 36.~~
12. ~~Between-group (Atropine Sulfate Ophthalmic Solution, 0.01% versus Vehicle) comparison of the proportion of subjects who progressed to high myopia (SER -6.00 D or more myopic) at Month 36.~~

~~**Exploratory Efficacy Endpoints**~~

1. ~~Between-group comparison of proportion of subjects with higher myopia (SER at least -3.00 D) at baseline who progressed at least -0.75 D at 36 months.~~
2. ~~Between-group comparison of the change in axial length between baseline and Month 36.~~
3. ~~Between-group comparison of the change in crystalline lens thickness between baseline and Month 36.~~
4. ~~Interaction between demographic variables and slowing progression of myopia (age 6 – 8 years versus 9 – 10 years; baseline SER -0.50 to -3.00 D versus more myopic than -3.00 D SER; Asian versus non-Asian; dark irides versus light irides) and SER.~~

Statistical Methods:
Analysis Sets~~Populations~~:

Enrolled Set: All subjects enrolled.
Safety Set: All subjects who were administered at least one dose of study medication for a given stage.
Intent-to-treat (ITT) Set: All randomized subjects for a given stage.
Modified intent-to-treat (mITT) Set: All randomized subjects, for a given stage, aged 6 to 10 years at the time of randomization in Stage 1. This will be the population for the primary efficacy analyses.
Per ~~p~~Protocol Set (PPS): All ~~ITT~~ subjects who remain in the study through end of stage ~~Month 36~~ and have no major or critical protocol violations (as defined in the SAP).
Modified ~~p~~Per ~~p~~Protocol Set (mPPS): All subjects in the PPS ~~analysis population~~ in each stage who were aged 6 to 10 years at the time of randomization in Stage 1.
~~Safety: All subjects who received at least one dose of study medication.~~

Statistical Analyses:

The primary and secondary efficacy analyses will be performed using the mITT Set assuming data missing at random.
The primary analysis and any other analysis of binary response measures will be performed using a mixed-effects model based on the binomial distribution using ~~use~~ a logit link function. The model will include subject, treatment group, visit, eye (left or right), and baseline age group (as randomized) and SER (as randomized) as independent variables and treatment group-by-visit interaction term included. Random intercepts for subject and eye within subject will be included using variance components and compound symmetry covariance structures, respectively. ~~and treatment group as main effect, and baseline age and SER as covariables. To account for correlation between the eyes, the data are analyzed using a Generalized Estimating Equations model with an unstructured correlation matrix (SAS® Proc GENMOD). The difference in the estimated response rates between the treatment groups and all visits and by visit and its 95% confidence interval (CI) will be provided.~~ In addition, sensitivity analyses will be performed for the primary efficacy endpoint to assess the impact of missing data. These sensitivity analyses will be described in the statistical analysis plan.

For comparisons of mean change from baseline for continuous measures, the analysis will be performed using a mixed-effects model with a random intercept. The model will include treatment group, visit, eye (left or right), baseline age group (as randomized), and baseline SER group (as randomized) as independent variables and the treatment group-by-visit interaction. will be included. The degrees of freedom will be determined using the Kenward-Roger approximation. Random intercepts for subject and eye within subject will be included using unstructured covariance structures. ~~the adjusted estimate of difference between groups at each post-baseline visit will be obtained from a restricted maximum likelihood repeated measures mixed model on change from baseline values with baseline age and SER as covariates, treatment group, visit and the interaction of treatment group and visit as fixed factors and observations from both eyes and visit and its interaction with treatment group as repeated measures using an unstructured covariance structure. The adjusted estimate of difference between groups, *P*-value and its adjusted 95% CI will be tabulated.~~

~~The SER will be summarized by the observed value and change from baseline value at all visits. Cross tabulations will be prepared that display the distribution of the degree of change by 0.50 D increments at Year 3 and Year 4 (one year after re-randomization).~~

For all subjects who respond in the Atropine Sulfate Ophthalmic Solution treatment groups at the Month 36 visit, summary statistics for the change in SER from Stage 2 baseline (Month 36 visit) will be

presented at the Month 42 and Month 48 visits for each treatment history where subjects receive the same dose of Atropine Sulfate Ophthalmic Solution, a lower dose of Atropine Sulfate Ophthalmic Solution, or Vehicle.

Summary statistics will be presented for compliance collected in diaries, the frequency of switching from dosing by parent/guardian to dosing by subject, and the modified Amblyopia Treatment Index by visit and treatment group in Year 4.

Significance Level:

The 0.01% and 0.02% atropine response rates will be compared to the vehicle response rate. The primary and secondary efficacy endpoints will be tested at the 5% level of significance using a hierarchal testing procedure in the order listed. ~~It is desired to claim statistical significance if either or both atropine groups are different from Vehicle. Therefore, the significance level of 0.025 will be used to keep the overall Type I error rate at 0.05.~~

Table 2: Schedule of Procedures

Assessment	Screening Baseline[a]	Treatment Stage 1 (Office Visits Every 3 Months and Telephone Checks[a] ± 2 Weeks)																	Treatment Stage 2 (Every 3 Months ± 2 Weeks)			
Visit Number	**1**	**T1**	**T2**	**2**	**T3**	**3**	**T4**	**4**	**T5**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**
Month	**0**	**1**	**2**	**3**	**4.5**	**6**	**7.5**	**9**	**10.5**	**12**	**15**	**18**	**21**	**24**	**27**	**30**	**33**	**36**	**39**	**42**	**45**	**48 (EOS)[b]**
Informed consent/assent[c]	X																					
Demographics/medical/ocular history	X																					
Prior/concomitant medication	X																					
Urine pregnancy test[d]	X																					
Re-consent/re-assent[c]																		X	X	X	X	X
Modified ATI questionnaires (QoL)																				X[e]		X[e]
Height and weight	X									X				X				X				X
Heart rate	X					X				X		X		X		X		X		X		X
Best-corrected visual acuity[ef]	X					X				X		X		X		X		X		X		X
Pupil size measurement (photopic)	X					X				X		X		X		X		X		X		X
Slit-lamp examination	X					X				X		X		X		X		X		X		X
Intraocular pressure	X					X				X		X		X		X		X		X		X
Dilated fundus examination	X									X				X				X				X
Cycloplegic autorefraction	X					X				X		X		X		X		X		X		X
Inclusion/exclusion criteria assessment	X																					
Randomization/re-randomization (M 36)	X																	X				
Axial length	X					X				X		X		X		X		X		X		X
Crystalline lens thickness (where feasible)	X					X				X		X		X		X		X		X		X
Collect study medication materials				X		X		X		X	X	X	X	X	X	X	X	X	X	X	X	X

Assessment	Screening Baseline[a]	Treatment Stage 1 (Office Visits Every 3 Months and Telephone Checks[a] ± 2 Weeks)																	Treatment Stage 2 (Every 3 Months ± 2 Weeks)			
Visit Number	**1**	**T1**	**T2**	**2**	**T3**	**3**	**T4**	**4**	**T5**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**
Month	**0**	**1**	**2**	**3**	**4.5**	**6**	**7.5**	**9**	**10.5**	**12**	**15**	**18**	**21**	**24**	**27**	**30**	**33**	**36**	**39**	**42**	**45**	**48 (EOS)[b]**
Concomitant medication review				X		X		X		X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse event assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense study medication (frames/lenses)[efg]	X			X		X		X		X	X	X	X	X	X	X	X	X	X	X	X	
Treatment adherence assessment[ghi]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Electronic patient diary																		X[hij]	X[ijk]	X[ijk]	X[ijk]	X[jkl]

Abbreviations: ATI = amblyopia treatment index, eCOA= electronic clinical outcome assessments, EOS = end of study, QoL = quality of life.

[a] Assessments may be obtained remotely at the end of Month 1 and Month 2, followed by midway between visits during Year 1. Telephone checks can be continued as necessary to assist with protocol and treatment adherence. Note: Enrolled subjects approved by the sponsor to transfer from one site or a new site, who reside greater than 150 miles from the new research site, may not be required to attend 3-month interval visits. Alternate accommodations may be provided to the subject and subject's family in order to dispense study medication. Assessments may be obtained remotely via telephone and treatment adherence assessments completed at 6-Month interval visits.

[b] If a subject is discontinued from study medication before the Month 48 visit, then all Month 48 EOS procedures should be performed at the visit the subject is discontinued.

[c] Sites should complete screening/randomization/baseline procedures and enroll subjects within 30 days from signing informed consent.

[d] Female subjects of childbearing potential (post menarche) only.

[c] All subjects are to be re-consented/re-assented at their next study visit if not done at earlier visits, including subjects completing an End of Study (EOS) Visit (Stage 1 – Month 36, Month 39, Month 42, Month 45, and Month 48).

[ef] At Month 42 and Month 48, the modified ATI will be completed by the parent/guardian and subject prior to the Investigator's examination of the subject. Prior to the examination, the site staff will ensure parent/guardian and subject understand the questions, by reading the questions. After each question, the site staff will proceed to read the choices. The parent/guardian and subject will pick the answer which comes closest to describing how they feel. The answer will be entered into the database by the site staff.

[efg] Measured at distance and near.

[fgh] Medication dispensed by site. Dosing to be conducted at home each day at bedtime. Prescription for frames/lenses will be provided if necessary, per criteria defined in Section 6.1.

[ghi] Treatment adherence will be verbally assessed during Telephone Check. Drug accountability and details regarding any incorrect dosing will be assessed every 3 months upon return of unused ampules.

[hij] Diary application uploaded to subject's or their parent's/guardian's phone or Medidata provisioned device (if required), e-diary training and Medidata eCOA support provided.

[ijk] The site staff will review the electronic patient diary.

[jkl] The site staff will ensure uninstall the Medidata eCOA application (installed on the cell phone) or retrieve the device provisioned by Medidata and provided to the subject.

3.0 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ATI	Amblyopia Treatment Index
PPS	Per Protocol Set
QoL	Quality of Life

4.3 Good Clinical Practices Statement

This study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and in compliance with the ethical principles having their origin in the Declaration of Helsinki, International Council for Harmonisation (ICH) guidelines, consolidated Guideline E6 R2 for Good Clinical Practice (GCP) (CPMP/ICH/135/95), and applicable regulatory requirements:

- European Commission Directive (2001/20/EC Apr 2001);
- European Commission Directive (2005/28/EC Apr 2005);
- The Medicines for Human Use (Clinical Trials) Regulations (2006)
- Food and Drug Administration GCP Regulations: CFR Title 21, Parts 11, 50, 54, 56, and 312;
- EU General Data Protection Regulation (GDPR): 2016/679;
- The Health Insurance Portability and Accountability Act, as appropriate; and/or
- Other applicable local regulations

4.5 Benefit/Risk Assessment

…

Other side effects reported:

- Seizures have been reported with both systemic and compounded use of Atropine. However, it is not clear what dose concentration was utilized in the eye drops.

6.1. Overall Study Design

…

Subject or their parent/guardian will be encouraged to record their dosing on a daily basis, starting from the same evening after completing their Month 36 visit till the last visit (Stage 2 of the study) in an e-diary. The subject or their parent/guardian will be encouraged to use their cell phone to upload e-diary responses. At Month 36 visit, if the subject or their parent/guardian do not have a cell phone or are unwilling to use their cell phone, a device will be provisioned by Medidata and provided to the subject. Once the instillation of the eye drops has been successfully

completed, the subject or their parent/guardian will log into the application to record dosing of the left eye and the right eye and complete diary submission daily. The diary can be completed between 6:00 PM and 11:45 PM. If the subject or their parent/guardian do not complete the e diary within the allotted time, they will **not** be able to enter the missing data retroactively, as the purpose is to collect information on the actual date the study drops were instilled. Once data is submitted, this information will be automatically entered into the study's Medidata Rave database.

At Month 42 and Month 48, in addition to other assessments, the modified ATI, QoL questionnaire will be completed by the parent/guardian and subject prior to the Investigator's examination of the subject. The parent/guardian QoL questionnaire should be completed prior to the subject's questionnaire. Study staff will verify that the questionnaires are completed by both the parent/guardian and the subject.

8.4 Treatment Adherence

…

Documentation of Mode of Administration:

At the EOS Month 36 and EOS Month 48, site will document mode of administration by asking the subject or their parent/guardian:

- Who administered the eyedrops to the subject during the course of the study (i.e., self-administered or administered by parent/guardian)?
- Was there a transition in the dosing administrator?
- If yes, at what approximate age did the transition occur?

…

9.3 The Modified Amblyopia Treatment Index (Modified ATI)

Quality of life questionnaires (called Modified ATI in this study) were modified from the ATI questionnaire developed by Felius et al., 2010, and will be used in the study after subjects have completed 6 months of treatment in the Stage 2 of CHAMP study. Participation is voluntary and will be documented. Subjects can continue in the study even if they elect not to participate. The questionnaires will be completed at Month 42 and at the completion of the trial at Month 48 prior to the Investigator's examination of the subject. The parent/guardian questionnaire should be completed prior to the subject's questionnaire. The questionnaires should be completed prior to the Investigator's examination of the subject

The questionnaires will capture responses to evaluate QoL and burden of atropine treatment from the parent/guardian and subject's perspective. There are two versions of the modified ATI, the 'parent/guardian' version (Appendix C), and the 'subject' version (Appendix D). The two versions are on different response scales. Responses on the parent/guardian version are on a strength of agreement scale ("strongly agree" to "strongly disagree") whereas the responses on the subject version are on a frequency scale ("always" to "never"). This is because a frequency scale is believed to be easily understandable to children.

Re-consent/re-assent **will be obtained from all subjects, regardless** of their participation in the modified ATI, QoL questionnaire.

10. STUDY ACTIVITIES

10.5. End of Stage 1/ End of Study (EOS) Month 36 Primary Efficacy (BL-Month 36) and Evaluation/Commencement of Stage 2: Randomized Cross-over (EOS Month 36)

At the Month 36 visit, End of Study (EOS) visit Stage 1, the subjects and their parent/guardian will return to the study site for the EOS Month 36 study visit (Stage 1). The subject and their parent/guardian will return to the study site with their randomized study medication.

When scheduling the visit, site personnel should remind the parent/guardian to bring all unopened/unused and used study medication materials to the site.

Subjects will undergo measurement of HR, ophthalmic safety and efficacy evaluations, and the site will update concomitant medications, and conduct AE assessment.

Subjects will then be re-randomized and sites will dispense randomized study medication to initiate the randomized cross-over stage (Stage 2)~~, and perform treatment adherence assessment~~.

EOS Month 36 visit procedures include:

- Collect study medication materials
- Mode of Administration (BL- EOS Month 36)
- Re-consent/re-assent (as applicable).
- Height and weight
- HR
- Monocular BCVA in each eye at distance and near
- Photopic pupil size
- SLE
- IOP measurement
- Instill first cycloplegic drop (cyclopentolate for subjects < 6 years at randomization and continuing throughout the study, 1% tropicamide for subjects ≥ 6 years at randomization and continuing throughout the study)
- Instill second cycloplegic drop approximately 5 minutes after instillation of the first drop
- Dilated fundus examination (at least 20 minutes after instillation of the second cycloplegic drop)
- Cycloplegic autorefraction (at least 30 minutes after instillation of the second drop)

- Axial length measurement
- Crystalline lens thickness (if feasible)
- Concomitant medication review
- AE assessment
- Re-randomization
- Dispense and document dispensing of re-randomized study medication
- If new lenses are necessary as defined by the criteria (the refraction reveals at least -0.50 D myopic progression and/or the eye care practitioner deems it clinically necessary to improve vision), the site will provide a refractive prescription and lenses
- Conduct treatment adherence assessment
- Upload e-diary application to subject's or their parent's/guardian's phone or Medidata provisioned device (if required). Subject or their parent/guardian will be encouraged to record their dosing on a daily basis, starting from the same evening after completing their Month 36 visit. If the subject or their parent/guardian do not have a cell phone or are unwilling to use their cell phone, a device will be provisioned by Medidata and provided to the subject. Additionally, e-diary training and Medidata eCOA support will be provided.

10.6 Stage 2 Three-Month Visits (Months 39 and 45)

Month 39 and 45 visit procedures include:

- Collect study medication materials
- Re-consent/re-assent (as applicable) if not done at earlier visits
- Concomitant medication review
- AE assessment
- Review e-diary
- Dispense study medication for the following 3 months of the study
- Conduct treatment adherence assessment

10.7 Stage 2 Six-Month Visit (Month 42)

At this visit, the subjects and their parent/guardian will return to the study site. When scheduling, site personnel should remind the parent/guardian to bring all unopened/unused and used study medication materials to the site for these visits.

Information related to QoL (modified ATI) will be reviewed with the subject and their parent/guardian and they will be asked to participate in the QoL questionnaire. The site staff will confirm and document their willingness to participate in completing the questionnaire. Subjects

can continue on to Stage 2 even if they elect not to participate in the completion of the QoL questionnaire.

Month 42 visit procedures include:

- Collect study medication materials
- Re-consent/re-assent (as applicable) if not done at earlier visits.
- Modified ATI will be completed by the parent/guardian and subject prior to the Investigator's examination of the subject. The parent/guardian QoL questionnaire should be completed prior to the subject's questionnaire. Study staff will verify that the questionnaires are completed by both the parent/guardian and the subject.
- HR
- Monocular BCVA in each eye at distance and near
- Photopic pupil size
- SLE
- IOP measurement
- Instill first cycloplegic drop (cyclopentolate for subjects < 6 years at randomization and continuing throughout the study, 1% tropicamide for subjects ≥ 6 years at randomization and continuing throughout the study)
- Instill second cycloplegic drop approximately 5 minutes after instillation of the first drop.
- Cycloplegic autorefraction (at least 30 minutes after instillation of the second drop)
- Axial length measurement
- Crystalline lens thickness (if feasible)
- Concomitant medication review
- AE assessment
- Review e-diary
- Dispense study medication for the following 3 months of the study
- If new lenses are necessary as defined by the criteria (the refraction reveals at least -0.50 D myopic progression and/or the eye care practitioner deems it clinically necessary to improve vision), the site will provide a refractive prescription and lenses
- Conduct treatment adherence assessment

10.8 End of Stage 2/~~Final Study Visit~~ End of Study (Month 48)

…

Month 48 procedures include:

- Collect study medication materials
- Mode of Administration (Month 36-EOS Month 48)
- Re-consent/re-assent (as applicable) if not done at earlier visits
- Modified ATI will be completed by the parent/guardian and subject prior to the Investigator's examination of the subject. The parent/guardian QoL questionnaire should be completed prior to the subject's questionnaire. Study staff will verify that the questionnaires are completed by both the parent/guardian and the subject.
- Height and weight
- HR
- Monocular BCVA in each eye at distance and near
- Photopic pupil size
- SLE
- IOP measurement
- Instill first cycloplegic drop (cyclopentolate for subjects < 6 years at randomization and continuing throughout the study, tropicamide for subjects ≥ 6 years at randomization and continuing throughout the study)
- Instill second cycloplegic drop approximately 5 minutes after instillation of the first drop.
- Dilated fundus examination (at least 20 minutes after instillation of the second cycloplegic drop)
- Cycloplegic autorefraction (at least 30 minutes after instillation of the second drop)
- Axial length measurement
- Crystalline lens thickness (if feasible)
- Concomitant medication review
- AE assessment
- Review e-diary
- Uninstall the Medidata eCOA application (installed on cell phone) or retrieve the device provisioned by Medidata provided to the subject
- If new lenses are necessary as defined by the criteria (the refraction reveals at least -0.50 D myopic progression and/or the eye care practitioner deems it clinically necessary to improve vision), the site will provide a refractive prescription and lenses
- Conduct treatment adherence assessment

10.9 Early Termination Visits

…

If a subject is off study medication and is being followed for safety assessments then an EOS Month 36 visit should be completed, as these subjects will not continue on to Stage 2.

11.1 General Considerations

Efficacy analysis will be conducted on the ~~i~~Intent-to-~~t~~Treat (ITT) Set~~population~~, the ~~m~~Modified ~~i~~Intent-to-~~t~~Treat (mITT) Set~~population~~, the ~~p~~Per ~~p~~Protocol Set (PPS)~~population~~, and the ~~m~~Modified ~~p~~Per ~~p~~Protocol Set (mPPS) ~~population~~. Safety analyses will be performed using the S~~s~~afety Set ~~analysis population.~~

11.2 Handling of Missing Data

Use of ~~a repeated measures~~ mixed-effects models ~~approach~~ requires only that data are missing at random so that no other method will be employed to deal with missing data. ~~Generalized estimating equation methods however require that data are missing completely at random. It may be necessary to test whether this assumption applies to the data set.~~

Various sensitivity analyses will be performed for the primary efficacy analysis to assess the impact of missing data. ~~If more than 5% of data for an endpoint in the testing hierarchy are missing, multiple imputation will be performed. In addition, for the analysis of responder endpoints, a tipping point sensitivity analysis may be performed.~~

11.3 Determination of Sample Size

Significance Level:

The 0.01% and 0.02% atropine response rates will be compared to the vehicle response rate. The primary and secondary efficacy endpoints will be tested at the 5% level of significance using a hierarchal testing procedure in the order listed.

11.4.1 Population for Efficacy Analysis

11.4.1.1 Enrolled Set

The Enrolled Set will include all subjects enrolled.

~~11.4.1.1~~ 11.4.1.2 Intent-to-Treat ~~Population~~ (ITT) Set

The ITT Set ~~population~~ will include all randomized subjects for a given stage.

~~11.4.1.2~~ 11.4.1.3 Modified Intent-to-Treat (mITT) Set

The mITT Set ~~population~~ will include all randomized subjects, for a given stage, aged 6 to 10 years at the time of randomization in Stage 1. This will be the population for the primary efficacy analyse~~i~~s.

~~11.4.1.3~~ 11.4.1.4 Per Protocol Set ~~Population~~ (PPS)

The PPS ~~population~~ will include all ~~ITT~~ subjects who remain in the study through the end of the stage ~~Month 36~~ and have no major or critical protocol violations (as defined in SAP).

~~11.4.1.4~~ 11.4.1.5 Modified Per Protocol ~~Population~~ Set(mPPS)

The mPPS ~~population~~ will include all subjects in the PPS Set~~analysis population~~ in each stage who were aged 6 to 10 years at the time of randomization in Stage 1.

11.4.2 Safety Set~~Analysis Population~~

The ~~s~~Safety Set~~population~~ will include all subjects who were administered ~~received~~ at least one dose of study medication for a given stage.

11.5 Demographics and Baseline Characteristics

~~Subject d~~Demographic and baseline characteristics will be summarized for the Safety Set by actual treatment and overall and for the ITT Set, mITT Set, PPS, and mPPS by randomized treatment group and overall. Summary statistics and by-subject listings will be provided. The summary will be repeated for all subjects who enter Stage 2.~~analysis population; however, should there be a reasonable difference in the size of the ITT and safety analysis populations, demographic and baseline characteristics will be summarized for both. The comparability of groups used in comparison analyses will be characterized in tables of demographic data. Summary tables will be supported with individual subject data listings.~~

11.6 Efficacy Analyses

The primary and secondary efficacy analyses will be performed using the mITT Set assuming data missing at random.

The primary analysis and any other analysis of binary response measures will be performed using a mixed-effects model based on the binomial distribution using ~~use~~ a logit link function. The model will include subject, treatment group, visit, eye (left or right), and baseline age group (as randomized) and SER (as randomized) as independent variables and treatment group-by-visit interaction term included. Random intercepts for subject and eye within subject will be included using variance components and compound symmetry covariance structures, respectively. ~~and treatment group as main effect, and baseline age and SER as covariables. To account for correlation between the eyes, the data are analyzed using a Generalized Estimating Equations model with an unstructured correlation matrix (SAS® Proc GENMOD). The difference in the estimated response rates between the treatment groups and all visits and by visit and its 95% confidence interval (CI) will be provided.~~ In addition, sensitivity analyses will be performed for the primary efficacy endpoint to assess the impact of missing data. These sensitivity analyses will be described in the statistical analysis plan.

For comparisons of mean change from baseline for continuous measures, the analysis will be performed using a mixed-effects model with a random intercept. The model will include treatment group, visit, eye (left or right), baseline age group (as randomized), and baseline SER group (as randomized) as independent variables and the treatment group-by-visit interaction. will be included. The degrees of freedom will be determined using the Kenward-Roger approximation. Random intercepts for subject and eye within subject will be included using unstructured covariance structures. ~~the adjusted estimate of difference between groups at each~~

~~post-baseline visit will be obtained from a restricted maximum likelihood repeated measures mixed model on change from baseline values with baseline age and SER as covariates, treatment group, visit and the interaction of treatment group and visit as fixed factors and observations from both eyes and visit and its interaction with treatment group as repeated measures using an unstructured covariance structure. The adjusted estimate of difference between groups, *P*-value and its adjusted 95% CI will be tabulated.~~

~~The SER will be summarized by the observed value and change from baseline value at all visits. Cross tabulations will be prepared that display the distribution of the degree of change by 0.50 D increments at Year 3 and Year 4 (one year after re-randomization).~~

…

For all subjects who respond in the Atropine Sulfate Ophthalmic Solution treatment groups at the Month 36 visit, summary statistics for the change in SER from Stage 2 baseline (Month 36 visit) will be presented at the Month 42 and Month 48 visits for each treatment history where subjects receive the same dose of Atropine Sulfate Ophthalmic Solution, a lower dose of Atropine Sulfate Ophthalmic Solution, or Vehicle.

Summary statistics will be presented for compliance collected in diaries, the frequency of switching from dosing by parent/guardian to dosing by subject, and the modified Amblyopia Treatment Index by visit and treatment group in Year 4.

For details on the various analyses planned, for both Stage 1 and Stage 2 of the study, please refer to the statistical analysis plan.

11.6.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the ~~overall~~ between- treatment group (Atropine Sulfate Ophthalmic Solution, 0.02% versus Vehicle) difference ~~from baseline~~ in the proportion of subjects who show < -0.50 D myopia progression (SER) at the Month 36 visit.
The primary and all secondary endpoints comprise a fixed sequence set of endpoints to be tested in order. A 2-sided significance level of 0.05 will be adopted.

11.6.2 Secondary Efficacy Endpoints:

The secondary efficacy endpoints consist of:

1. Between-treatment group (Atropine Sulfate Ophthalmic Solution, 0.02% versus Vehicle) difference in the mean change from baseline in ~~proportion of subjects who show < -0.50 D myopia progression (~~SER~~)~~ at the Month 36 ~~24 and Month 12~~ visits~~.~~
2. Between-treatment group (Atropine Sulfate Ophthalmic Solution, 0.01~~2~~% versus Vehicle) difference in the proportion of subjects who show < -0.75 D myopia progression (SER) from baseline at the Month 36 visit.
3. Between-treatment group (Atropine Sulfate Ophthalmic Solution, 0.01~~2~~% versus Vehicle) difference in mean change from baseline in ~~median time to change in myopia of -0.75 D~~ SER at the Month 36 visit.
4. Between-treatment group (Atropine Sulfate Ophthalmic Solution, 0.02% versus Vehicle) difference in the mean change from baseline in axial length ~~SER~~ at the Month 36 visit.~~,~~ ~~Month 24, and Month 12 visits~~

5. Between-treatment group (Atropine Sulfate Ophthalmic Solution, 0.01% versus Vehicle) difference in the mean change from baseline in axial length ~~proportion of subjects who show < -0.50 D myopia progression (SER)~~ at the Month 36~~, Month 24, and Month 12~~ visits.
6. ~~Between-group (Atropine Sulfate Ophthalmic Solution, 0.01% versus Vehicle) difference in the proportion of subjects who show < -0.75 D myopia progression (SER) at the Month 36 visit.~~
7. ~~Between-group (Atropine Sulfate Ophthalmic Solution, 0.01% versus Vehicle) median time to change in myopia of -0.75 D SER.~~
8. ~~Between-group (Atropine Sulfate Ophthalmic Solution, 0.01% versus Vehicle) mean change from baseline in SER at the Month 36, Month 24, and Month 12 visits.~~
9. ~~Between-group (Atropine Sulfate Ophthalmic Solution, 0.02% versus Vehicle) comparison of the mean number of new prescriptions given after the start of treatment due to progression, at Month 36.~~
10. ~~Between-group (Atropine Sulfate Ophthalmic Solution, 0.01% versus Vehicle) comparison of the mean number of new prescriptions given after the start of treatment due to progression, at Month 36.~~
11. ~~Between-group (Atropine Sulfate Ophthalmic Solution, 0.02% versus Vehicle) comparison of the proportion of subjects who progressed to high myopia (SER -6.00 D or more myopic) at Month 36.~~
12. ~~Between-group (Atropine Sulfate Ophthalmic Solution, 0.01% versus Vehicle) comparison of the proportion of subjects who progressed to high myopia (SER -6.00 D or more myopic) at Month 36.~~

~~11.6.3 Exploratory Efficacy Endpoints~~

1. ~~Between-group comparison of proportion of subjects with higher myopia (SER at least -3.00 D) at baseline who progressed at least -0.75 D at 36 months.~~
2. ~~Between-group comparison of the change in axial length between baseline and Month 36.~~
3. ~~Between-group comparison of the change in crystalline lens thickness between baseline and Month 36.~~
4. ~~Interaction between demographic variables and slowing progression of myopia (age 6 – 8 years versus 9 – 10 years; baseline SER -0.50 to -3.00 D versus more myopic than -3.00 D SER; Asian versus non-Asian; dark irides versus light irides) and SER.~~

~~11.8 Stage 1 Analysis~~

~~Stage 1 is a safety and efficacy phase of 3 years in duration. When data from subjects who have completed Stage 1 have been obtained, a snapshot of the database will occur with subsequent analyses of Stage 1 data. Results from Stage 1 will then be reported in a clinical study report. The Stage 1 analyses will be conducted to ensure that important 3-year safety and efficacy results are made available for review to the scientific community in a timely manner.~~

~~Unblinding details are specified in the unblinding plan section of the statistical analysis plan or a separate unblinding plan document.~~

12 Quality Control, Ethics and Regulatory Compliance

The study will be monitored by the CRO to verify that the rights and well-being of human subjects are being protected, the reported data are accurate, complete, and verifiable, and that the conduct of the study is in compliance with the currently approved protocol, the ethical principles that have their origin in the Declaration of Helsinki, ICH guidelines, consolidated Guideline E6 R2 for GCP, and applicable regulatory requirements:

- European Commission Directive (2001/20/EC Apr 2001);
- European Commission Directive (2005/28/EC Apr 2005);
- The Medicines for Human Use (Clinical Trials) Regulations (2006)
- Food and Drug Administration GCP Regulations: CFR Title 21, Parts 11, 50, 54, 56, and 312;
- EU General Data Protection Regulation (GDPR): 2016/679;The Health Insurance Portability and Accountability Act, as appropriate; and/or
- Other applicable local regulations.

To ~~insure~~ ensure compliance with GCP and all applicable regulatory requirements, the Sponsor or its agent may conduct a quality assurance audit at any time during or after completion of a study.

APPENDIX C. MODIFIED ATI QUESTIONNAIRE FOR PARENT/GUARDIAN

Patient ID# [PtID] Namecode [Namecode] ATI Parent/Guardian Questionnaire for [M42 visit and M48 visit]

INSTRUCTIONS FOR PARENT/GUARDIAN QUESTIONNAIRE

Instructions to clinic staff:

1. The questionnaire should be completed PRIOR to the Investigator's examination of the subject.
2. The parent/guardian questionnaire should be completed prior to the subject questionnaire.
3. The study staff will start by saying: “I am now going to start the questions. I will read the questions. After each question, I will read the answer choices.” “Please pick the answer which comes closest to describing how you feel.” “Please tell me if you don’t understand any of the questions.”

Patient ID# [PtID] Namecode [Namecode] ATI Parent/Guardian Questionnaire for [M42 visit and M48 visit]

INSTRUCTIONS FOR PARENT/GUARDIAN QUESTIONNAIRE

Instructions to Parent/Guardian:

1. This questionnaire asks you for your feelings about your child's vision and your difficulties in treating your child with the eyedrops. There are no right or wrong answers. The information you provide will be kept strictly confidential.
2. This questionnaire is meant for the child's parent/guardian who is responsible for putting the eyedrops in. If you are not the parent/guardian, you do not need to complete the questionnaire. If you are not sure, please ask the clinic staff if you should complete this questionnaire.
3. If you have put the eyedrops in at any time during the second stage of the study (Month 36 through 48), we ask that you complete the questionnaire.
4. Please answer every question. If a question does not apply to you or your child, mark the "not applicable" choice.
5. Please ask the clinic staff if you have any questions.
6. Once you have completed the responses to the questionnaire, the responses will be entered into the CHAMP study database by the study coordinator.
7. The questions ask you to describe your feelings. While you may not find an answer which exactly states your feelings, please mark the answer which comes closest to describing how you feel. Your first reaction to each question should be your answer.

Patient ID# [PtID] Namecode [Namecode] ATI Parent/Guardian Questionnaire for [, M42 visit and M48 visit]

INITIAL QUESTIONS FOR PARENT/GUARDIAN QUESTIONNAIRE

For completion by parent/guardian

Date Form Completed __ __ / __ __ /__ __

mm/dd/yy

1. What is your relationship with the child? *Circle one*

Mother Father Other: _____

2. Who is the person in your family who is <u>most</u> responsible for putting the eyedrops in? *Circle one*

Mother Father Other: _____

3. How often are you the one who puts the eyedrops in? *Circle one*

All of the time	Most of the time	About 1/2 of the time	Some, but less than 1/2 of the time	None of the time

If you answered "Some, but less than ½ of the time" or "None of the time," you can stop the questionnaire here.

Patient ID# [PtID] Namecode [Namecode] ATI Parent/Guardian Questionnaire for [M42 visit and M48 visit]

PARENT/GUARDIAN QUESTIONNAIRE

For completion by parent/guardian

Please answer every question. If a question does not apply to you or your child, mark the "not applicable" choice.

The questions ask you to describe your feelings. While you may not find an answer which exactly states your feelings, please mark the answer which comes closest to describing how you feel. Your first reaction to each question should be your answer

		Strongly Agree	Agree	Neither Agree nor Disagree	Disagree	Strongly Disagree	Not Applicable
1.	My child does not seem to mind using the drops.	☐	☐	☐	☐	☐	☐
2.	I worry that by using the drops, my child may miss out on fun activities (such as games, sports, and parties).	☐	☐	☐	☐	☐	☐
3.	Using the drops affects my child's learning.	☐	☐	☐	☐	☐	☐
4.	Using the drops makes it hard for my child to play outside, such as riding a bike.	☐	☐	☐	☐	☐	☐
5.	I have trouble putting the drops in my child's eye.	☐	☐	☐	☐	☐	☐
6	Using the drops is a source of tension or conflict in my relationship with my child	☐	☐	☐	☐	☐	☐
7.	Using the drops makes it difficult for my child to read or write.	☐	☐	☐	☐	☐	☐

		Strongly Agree	Agree	Neither Agree nor Disagree	Disagree	Strongly Disagree	Not Applicable
8.	I worry that my child will become injured when using the drops.	☐	☐	☐	☐	☐	☐
9.	My child can see well when using the drops.	☐	☐	☐	☐	☐	☐
10.	My child complains when it is time to put in the drops.	☐	☐	☐	☐	☐	☐
11.	Using the drops makes my child's eye or eyelids red or irritated.	☐	☐	☐	☐	☐	☐
12.	I worry that my child does not get the drops often enough.	☐	☐	☐	☐	☐	☐
13.	My child is more clumsy and uncoordinated than usual when using the drops.	☐	☐	☐	☐	☐	☐
14.	I believe that using the drops will improve my child's vision.	☐	☐	☐	☐	☐	☐
15.	Using the drops makes it difficult for my child to play with small toys or handheld videogames.	☐	☐	☐	☐	☐	☐
16.	I sometimes forget to put the drops in my child's eye.	☐	☐	☐	☐	☐	☐

***** study staff should verify questionnaire is complete and no data is missing *****

APPENDIX D. MODIFIED ATI QUESTIONNAIRE FOR SUBJECT

Patient ID# [PtID] Namecode [Namecode] ATI Subject Questionnaire for [M42 visit and M48 visit]

INSTRUCTIONS FOR SUBJECT QUESTIONNAIRE

Instructions to clinic staff:

1. The questionnaire should be completed PRIOR to the Investigator's examination of the subject.
2. The parent/guardian questionnaire should be completed prior to the subject questionnaire.
3. The parent/guardian should be present during the completion of the subject questionnaire.
4. Please read the instructions below aloud to the subject.
5. After the instructions have been read, begin the questionnaire. There are 15 questions with answer choices, and 1 section for additional subject comments. For each question:
   - **a.** Read the statement aloud to the subject exactly as written, followed by the 6 answer choices.
   - **b.** You may explain the statement if the subject does not understand, but then reread all possible answer choices.
   - **c.** Do not steer the subject toward any answer.

Instructions for clinic staff to read to the subject:

1. I am now going to start the questions. I will read questions that ask you to describe your feelings. After each question, I will read the answer choices. Please pick the answer which comes closest to describing how you feel. Your first answer to each question should be the answer you give.
2. Please tell me if you don’t understand any of the questions.

SUBJECT QUESTIONNAIRE

For completion by clinic staff

Date Form Completed __ __ / __ __ /__ __

mm/dd/yy

		Always	A lot	Sometimes	A little	Never	Not Applicable
1.	It bothers me to use the drops.	☐	☐	☐	☐	☐	☐
2.	I can't do fun things (such as games and sports) because of the drops.	☐	☐	☐	☐	☐	☐
3.	The drops make my school work harder.	☐	☐	☐	☐	☐	☐
4.	The drops make it hard for me to play outside.	☐	☐	☐	☐	☐	☐
5.	It's hard to get drops put in my eye.	☐	☐	☐	☐	☐	☐
6.	The drops make it hard to read and write.	☐	☐	☐	☐	☐	☐
7.	I worry that I will run into things because of the drops.	☐	☐	☐	☐	☐	☐
8.	I can see well when the drops are in.	☐	☐	☐	☐	☐	☐

Patient ID# [PtID] Namecode [Namecode] ATI Subject Questionnaire for [M42 visit andM48 visit]

		Always	A lot	Sometimes	A little	Never	Not Applicable
9.	I don't like it when it's time for the drops.	☐	☐	☐	☐	☐	☐
10	The drops make my eyes or eyelids red.	☐	☐	☐	☐	☐	☐
11.	I worry that I don't get enough drops.	☐	☐	☐	☐	☐	☐
12.	The drops make me clumsy.	☐	☐	☐	☐	☐	☐
13.	I think the drops will help me see better.	☐	☐	☐	☐	☐	☐
14.	The drops make it hard to play with small toys or handheld videogames.	☐	☐	☐	☐	☐	☐
15.	My parents forget to put the drops in.	☐	☐	☐	☐	☐	☐

***** study staff should verify questionnaire is complete and no data is missing *****