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

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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.