CHAMP UK

Low-dose atropine eye drops to reduce progression of myopia in children: a multi-centre placebo controlled randomised trial in the United Kingdom

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STATISTICAL ANALYSIS PLAN

2.0 Final 26/07/23

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This document and all preceding versions will be stored in the Trial Master File for this trial

Contents

ABBREVIATIONS

ABBREVIATION	DEFINITION
AE	Adverse Event
ANCOVA	Analysis of covariance
AR	Adverse Reaction
BCdVA	Best Corrected Distance Visual Acuity
CI	Confidence intervals
CRF	Case Report Form
CTU	Clinical Trials Unit
DMEC	Data Monitoring and Ethics Committee
ETDRS	Early Treatment Diabetic Retinopathy Study
EudraCT	European Clinical Trials Database
GEE	Generalised Estimating Equations
ISRCTN	International Standard Randomised Controlled Trial Number Register
ITT	Intention-to-treat
IQR	Inter-quartile range
LogMAR	Logarithm of the Minimum Angle of Resolution
MEMS	Medical Events Monitoring System
NICRF	Northern Ireland Clinical Research Facility
NICTU	Northern Ireland Clinical Trials Unit
NIHR	National Institute of Health Research
OCT	Optical Coherence Tomography
PI	Principal Investigator
PP	Per Protocol
RSI	Reference Safety Information
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SER	Spherical Equivalent Refractive Error
SD	Standard Deviation
SOPs	Standard Operating Procedures
SSAR	Suspected Serious Adverse Reaction
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
UAR	Unexpected Adverse Reaction
VA	Visual Acuity

1. BACKGROUND AND DESIGN

Atropine 1% is very effective in slowing myopia progression, but it is not popular because of its unwanted side effects of pupillary dilation and cycloplegia and possible rebound effect. Atropine eye drops at a concentration of 0.01% are expected to be safe and well tolerated. This is supported by evidence from other trials that have employed the same and other more potent anti-muscarinic agents (e.g. 1% atropine; pirenzepine), and the well-established safety profile of atropine use in ophthalmology.

This is a multicentre, randomised, double-masked, placebo-controlled, superiority trial, with 2:1 allocation of intervention and control (atropine: placebo).

1.1 Research Hypothesis

Our hypothesis is that low dose atropine eye drops will reduce myopia progression in children compared with placebo.

1.2 Study Aim

The aim of the study is to evaluate the efficacy and safety of low dose atropine (0.01%) eye drops to reduce progression of myopia in UK children.

1.3 Study Objectives

The primary objective is:

- To evaluate the efficacy of 0.01% atropine eye drops to reduce the progression of myopia in children after 24 months of treatment.

The secondary objectives are:

- To evaluate the safety and tolerability of low dose atropine eye drops in terms of difficulties with near vision and reading, local discomfort and stinging of eye drops, photophobia, and occurrence of allergic reactions.
- To determine the mechanism of action of atropine eye drops. Specifically, we will evaluate if atropine has an effect on central axial length of the eye, position of the lens, peripheral retinal defocus and use of spectacle correction.

The exploratory objectives are:

- To explore the influence of other factors in the progression of myopia, including accommodation, chorio-retinal thickness at the macula, peripheral axial length, hours of outdoor activity, iris colour, ethnicity, and family history.

1.4 Inclusion and Exclusion Criteria

Patients will be eligible to participate in the study if they fulfil the following criteria below. Eligibility will be confirmed by a medically qualified doctor and documented on the eligibility checklist form.

Inclusion Criteria

1. Age 6-12 years (at the time of consenting)
2. Myopia of -0.5D or greater (spherical equivalent refractive error) in both eyes
3. Best-corrected distance visual acuity (BCDVA) 0.20 logMAR or better in both eyes

Exclusion Criteria

1. Children with other ocular morbidities
2. Myopia of -10D or greater in either eye
3. Astigmatism of 2D or higher in either eye
4. Amblyopia
5. Significant health problems that can compromise the ability to attend research visits or complete the trial
6. Other factors that may compromise the ability to attend the research appointments
7. Parents or children with poor understanding of the English language
8. Children enrolled in other interventional trials*
9. Allergy or hypersensitivity to atropine or excipients
10. Previous use of atropine eye-drops, prior or current use of Ortho-K contact lenses or contact lenses with dual focus, multifocal or extended depth of focus lens design
11. Children or Parents / Guardians with latex allergy as the dropper used to administer the eye-drop contains latex

*Children enrolled in observational studies are potential candidates for CHAMP UK. Whether or not children enrolled in CHAMP UK are also involved in other observational studies is at the discretion of the CHAMP UK local Principal Investigator (PI) and should be considered when the burden on participants is not expected to be onerous. Co-enrolment with other studies should be documented in the Case Report Form (CRF).

Full details of the background to the trial and its design are presented in the protocol.

2. OUTCOME MEASURES

2.1 Primary outcome measure(s)

- The primary outcome is spherical equivalent refractive error (SER) (i.e. myopia severity) of both eyes after 24 months measured by autorefractor under cycloplegia, adjusted for baseline.

2.2 Secondary outcome measures

- Central axial length: measured using a laser biometer at central fixation conditions
- Best corrected distance visual acuity (BCdVA) (uniocular and binocular): assessed using the logMAR ETDRS chart. This is a standard letter chart used in research to ensure accuracy and validity of the acuity measurements and has been shown to be repeatable in children
- Near visual acuity (VA) (uniocular and binocular): tested using near logMAR ETDRS at 40 cm
- Reading speed: measured with the Wilkins Rate of Reading test
- Pupil diameter: measured using an autorefractor
- Spectacle correction
- Tolerability: using a 4-point scale to quantify, from the point of view of the participant, (1) local irritation/stinging associated with eye drop instillation;
  (2) photophobia; and
  (3) difficulties reading and writing
- Adverse event rates and allergic reactions rates
- Quality of Life: measured using the EQ-5D-Y

2.3 Exploratory Outcomes/Mechanistic Evaluations*

- Peripheral axial length: measured using a laser biometer at peripheral fixation conditions
- Peripheral retinal defocus: measured with the autorefractor at central and peripheral fixation conditions
- Anterior chamber depth: measured with a laser biometer
- Accommodation: using a near target and in accordance with the Clinical Assessment Guidelines
- Iris colour: measured using a visual grading scale of dark brown, light brown, blue, green, grey
- Height and weight to provide information about the links between the child's development and eye growth and potentially information about lifestyle
- Hours of outdoor activity: measured using an activities questionnaire
- Ciliary body biometry: measured using anterior-segment OCT (AS-OCT). This will enable changes in lens position and ciliary muscle changes resulting from atropine use to be compared with normal myopic growth
- Chorio-retinal thickness: measured using spectral domain OCT (SR-OCT). This will enable differences in choroidal thickness resulting from atropine use to be compared with normal myopic growth

*Only to be carried out in sites with the relevant equipment. If measurements for exploratory outcomes cannot be collected this will not be recorded as a protocol deviation.

3. DATA

3.1 CRF Forms and variables

Full details of data collection and timing are described in the trial protocol (Version 5.0 08/12/2020). A copy of the CRFs and questionnaires are presented in the Trial Master File (TMF).

3.2 Management of datasets

Below is the standard policy for management of data in the CTU as given in the CTU SOPs, at the time of analysis (including DMEC reports/Interim analysis (if required)):

- If the CTU is providing the Data Management for the study then the Data Manager in collaboration with the Study Statistician will extract data from MACRO following procedures as detailed in the SOP DM09 Database Closure/Lock and the corresponding study Data Management Plan (DMP).

The trial database will be stored in MACRO:

- DMEC reports: In collaboration with the Statistician, the Data Manager will create MACRO output files to support the analysis. This will act as the frozen dataset. It is the responsibility of the statistician to accurately record the date of freezing and ensure all data is retrieved. If there are no errors, the study database will be re-opened for further data entry.
- If there are errors, the Study Statistician will report these to the Data Manager. The Data Manager in consultation with the Study Statistician, Data Project Manager and Senior Statistician will resolve the errors and determine which of the database closure activities are required to be undertaken. The Data Manager will re-create the MACRO output files to support the analysis. Database closure & lock: The same process for DMEC reporting will be followed for database closure and lock, the only difference being when the MACRO output files are created and there are no errors found for final analysis, the database should be locked as per SOP DM09.

3.3 Data completion schedule

Participants will be followed every six months for a total of five trial visits as outlined in accordance with the schedule of assessments as shown in Table 1:

Table 1: Schedule of Assessments for the CHAMP UK Study

	Baseline	6 months	12 months	18 months	24 months
Consent	✓				
Randomisation	✓				
Medical history (including height*, weight*, concomitant medications and spectacle correction)	✓	✓	✓	✓	✓
Severity of parental myopia (self-report)	✓				
Adverse events		✓	✓	✓	✓
Tolerability		✓	✓	✓	✓
EQ-5D-Y questionnaire	✓	✓	✓	✓	✓
Activities questionnaire- to be sent home with participant for completion	✓	✓	✓	✓	✓
Best corrected VA (logMAR ETDRS)	✓	✓	✓	✓	✓
Near VA (near logMAR ETDRS)	✓	✓	✓	✓	✓
Iris colour	✓				
Reading speed (Wilkins Rate of Reading Test)	✓	✓	✓	✓	✓
Pupil diameter prior to cycloplegia	✓	✓	✓	✓	✓
Accommodation (in accordance with guideline)*	✓	✓	✓	✓	✓
Peripheral retinal defocus (autorefractor)*	✓		✓		✓
Anterior chamber depth (laser biometer)*	✓		✓		✓
Cycloplegic refractive error (autorefractor)	✓	✓	✓	✓	✓
Ciliary body biometry (AS-OCT)*	✓		✓		✓
Central axial length (laser biometer)	✓	✓	✓	✓	✓
Peripheral axial length (laser biometer)*	✓		✓		✓
Chorio-retinal thickness (SD-OCT)*	✓	✓	✓	✓	✓
MEMS data		✓	✓	✓	✓
Study drug dispensing	✓	✓	✓	✓	

3.4 Data verification

Data verification, consistency and range checks will have been performed at the data entry stage by the CTU, as well as checks for missing data (copies can be found in the TMF) according to SOP DM04. Additional range, consistency and missing data checks will be performed, as appropriate, when the analysis is performed (and when the datasets for analysis are constructed). All variables will be examined for unusual, outlying, unlabelled or inconsistent values.

Given the thorough nature of our follow-up procedure we expect the issue of missing data to be relatively minimal. We anticipate high compliance with initial data collection as this is close to the time of patient registration.

If any clinical data is missing for the primary outcome at 24 months, imputation will be carried out by imputing extreme values of change within treatment arm (i.e. smallest and largest change from the previous time point to 24 months) in a sensitivity analysis. If the baseline primary outcome is missing, spectacle refraction will be used in the sensitivity analysis.

Study drug adherence will be self-reported and the event logs will be extracted from the MEMS during visits via a device connected to the computer to assess study drug adherence.

Any problems with trial data will be queried with the Trial Managers, Data Managers, or statisticians, as appropriate. If possible, data queries will be resolved, although it is accepted that due to administrative reasons and data availability a small number of problems will continue to exist. This will be minimised.

3.5 Data coding

The variable codings will be as specified on the CRF

4. DEFINITION OF TERMS

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a medicinal product has been administered including occurrences which are not necessarily caused by or related to that product.
Adverse Reaction (AR)	Any untoward and unintended response in a participant to an investigational medicinal product, which is related to any dose administered to that participant.
Unexpected Adverse Reaction (UAR)	An adverse reaction, the nature and severity of which is not consistent with the information about the medicinal product in question set out in: - The Summary of Product Characteristics (SPC) for that product (for products with a marketing authorisation) or - The Investigator's Brochure (IB) relating to the trial in question (for any other investigational product)
Serious Adverse Event (SAE)	An adverse event that: - results in death - is life-threatening - requires hospitalisation or prolongation of existing hospitalisation* - results in persistent or significant disability or incapacity - consists of a congenital anomaly or birth defect - is any other important medical event (s) that carries a real, not hypothetical, risk of one of the outcomes above.
Serious Adverse Reaction (SAR)	A SAR is an adverse reaction that is classed as serious and which is consistent with the information about the investigational medicinal product in question set out in the: - SPC in the case of a licensed product. - IB for any other investigational product.
Suspected Serious Adverse Reaction (SSAR)	Any adverse reaction that is classed in nature as serious and is consistent with the RSI.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A SUSAR is a serious adverse reaction which is unexpected i.e. the nature and severity of which is not consistent with the information about the medicinal product in question set out: - in the case of a product with a marketing authorisation, in the SPC for that product - in the case of any other investigational medicinal product, in the IB relating to the trial in question.
Per protocol Population	The per protocol population is defined as participants with overall study drug adherence of at least 80% using MEMs data.
Intention to treat	The intention to treat population is defined as all participants who are randomised regardless of what treatment they have received.

*Hospitalisation is defined as an inpatient admission regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisations for a pre-existing condition, including elective procedures that have not worsened, do not constitute an SAE.

5. SAMPLE SIZE CALCULATIONS

We anticipate that the effect of atropine eye drops in a UK population will be smaller than the reported effect in Chinese populations , but assuming that atropine reduces the progression of myopia by at least 40% in 24 months from a control mean of -0.8D7 (40% of 0.8 is equivalent to a mean difference of -0.32D between intervention and control group at 24 months), using SD=0.7D, a correlation (interclass correlation coefficient) between eyes of 0.9 and a variation inflation factor of 1.9, we will need 97 participants in each group. Considering a dropout rate of 15% and that 10% of the recruited children will be Chinese, we will need a total of 289 participants: 193 atropine, 96 placebo (152 atropine, 76 placebo inflated by a variance inflation factor of 1.9) to detect this difference in the non-Chinese population with 90% power.

Justification: In a study of 400 Chinese children evaluating the effect of 24 months of 1% atropine eye drops, myopia progression was -1.20 +/- 0.69 D in the placebo control group, and -0.28 +/- 0.92 D in the atropine group. We have assumed that progression of myopia and efficacy of atropine will be less in UK children than in Chinese children2.

Progression of myopia of untreated children was estimated from the control groups of randomized controlled trials for myopia. The following progression data have been reported:

- Katz 2003[4] (Chinese race): progression of -1.28D (SD 0.78) D after 2 years (control was spectacles)

- Edwards 2002[5] (Chinese race): progression of -1.26D (SD 0.74) D after 2 years (control was single vision lenses)

- Chua 2006[3], ATOM study (Chinese race): progression of -1.20D (SD 0.69) after 2 years (control was placebo drops)

- Hyman 2005[6], COMET trial (children of mixed races, with whites being the most common ethnicity): progression of 1.32D after 3 years (standard error 0.04) (control was single vision lenses)

- Breslin 2013[7], In an observational study from the UK, myopia progression was 1.14D after 3 years.

6. RANDOMISATION AND BLINDING

6.1 Randomisation

All participants who agree to join the study will be assigned a unique Participant Identification Number. Eligible participants will be randomised using a 2:1 allocation ration into the two groups (193 atropine: 96 placebo). Randomisation will use the remote automated computer randomisation application, Sealed Envelope, ensuring allocation concealment. Randomisation will be computer-allocated using a minimisation algorithm to ensure balanced allocation of participants across the two treatment groups. Minimisation will be by centre, ethnic background (white/non-white), and severity of myopia (less than -3D in either eye / -3D or greater in the eye with more severe myopia). The unit of randomisation will be the participant (not the eye).

6.2 Blinding and Allocation Concealment

The study will be conducted in a double-masked fashion. Study treatment assignment will be masked for both the investigators and the participant. The atropine and placebo eye drops will be packaged in identical bottles and labelled with a unique identification number so that the investigator and participants are unable to identify the contents.

To maintain the overall quality of the trial, unmasking (i.e. unblinding) should only occur in exceptional circumstances when knowledge of the group allocation is absolutely essential in a medical emergency for further management of the participant or where information is required for expedited reporting of a SUSAR. If time permits, the local PI should attempt to contact the Chief Investigator prior to unmasking. On the occurrence of any such event, the local Principal Investigator (PI) will request for the participant to be unmasked through the Sealed Envelope system. If they experience any difficulties the PI should contact the Northern Ireland Clinical Trials Unit (NICTU) to request emergency unmasking of the participant via the randomisation system (Sealed Envelope) during usual office hours. Where emergency unmasking is required out of hours, the local PI should contact the Chief Investigator and if they are unavailable, the BHSCT Pharmacy Oncall Service as detailed in the study unmasking guideline. In the event that unmasking occurs, the participant may discontinue the study drug but will remain on the trial unless they decide to withdraw or the local PI feels that this is necessary. Where unmasking has occurred, this should be fully documented by the site and the NICTU informed.

The randomisation list will be generated by Sealed Envelope and group allocation will only be visible to those with Administrator access in the Trial Management team in NICTU. The randomisation email generated by Sealed Envelope which is sent to the local researcher will provide the study drug kit number to be prescribed but will not reveal the group to which the participant has been assigned. The local researcher will access the automated randomisation system to obtain the kit number for each participant. Upon receipt of the randomisation email from Sealed Envelope, a prescription will be completed detailing the study drug kit number to be dispensed. A copy of the randomisation email will also be sent to the site pharmacist as a quality control check prior to dispensing.

7. ANALYSIS PRINCIPLES

Baseline characteristics and follow up measurements will be summarised as mean and standard deviation (SD), median and inter-quartile range (IQR) or numbers and frequencies (%) as appropriate, depending on the scale of measurement and distribution. Analysis will be based on both the intention to treat (ITT) principle and per protocol (PP) analysis. PP analysis will explore results in those who had at least 80% adherence to the study drug. A p-value <0.05 will be considered as statistically significant.

7.1 Primary outcome

The principal analysis will be based on complete case data without imputation for those who dropped out of the study before the end of the 24 months. The primary outcome (SER at month 24) results from both eyes will be used and adjusted for baseline SER. The atropine and control groups will be compared using generalised estimating equations (GEE) and 95% confidence intervals (CIs), to allow for the correlation between eyes within a participant. Secondary analysis of the primary outcome will be adjusted for baseline SER, minimisation variables (i.e. site and ethnicity), baseline age and history of parental myopia (at least one parent).

7.2 Secondary outcomes

For the secondary outcome analyses, results will be used from both eyes to investigate if atropine has an effect on the following endpoints at month 24; central axial length, pupil diameter, uniocular BCdVA and uniocular near VA. Each of these endpoints will be compared between the atropine and placebo groups using GEE and 95% CIs and will be adjusted for the corresponding baseline secondary outcomes (if available).

For the following endpoints at month 24; binocular BCdVA, binocular near VA, reading speed, and quality of life (i.e. EQ-5D-Y VAS and Index) comparisons between the atropine and placebo groups will be performed using analysis of covariance (ANCOVA) and 95% CIs and will be adjusted for the corresponding baseline secondary outcome (if available). Tolerability at month 24 will be compared between the atropine and placebo groups using an independent samples t-test. Spectacle correction at month 24 will be compared between the atropine and placebo groups using the chi-square test (or Fisher's exact test if appropriate). N(%) of spectacle correction (all day and sometimes) will also be presented by treatment arm.

The number of AEs, ARs, SAE, SARs, SUSARs and number (%) of patients experiencing these events will be reported. The chi-square test (or Fisher's exact test if appropriate) will be used to check whether incidences of adverse events differ between the treatment groups. Risk ratio and 95% CIs will be reported.

7.3 Exploratory outcomes

For the exploratory outcome analyses, results for the following outcomes will be used from both eyes to investigate if atropine has an effect on the outcomes. At baseline, the exploratory outcomes will only be presented as mean (SD) by treatment arm. For the following endpoints, the results will be compared between the atropine and placebo groups at all available timepoints using GEE (repeated measures model) and 95% CIs and will be adjusted for the corresponding baseline exploratory outcomes (if available). This includes; anterior chamber depth, accommodative lag at 33, 25 and 20cm and chorio-retinal thickness. This also includes nasal and temporal results which will be looked at separately for each of the following outcomes; peripheral axial length (20°), ciliary body biometry, peripheral retinal defocus (20°) and peripheral retinal defocus (30°).

Descriptive statistics for height and weight will be presented by treatment arm at all available time points. Total hours of outdoor activity and binocular amplitude of accommodation will be compared between the atropine and placebo groups at all available time points using repeated measures

ANCOVA and 95% CI and will be adjusted for the corresponding baseline exploratory outcome (if available). For hours of outdoor activity, this will firstly be summed together based on the outdoor activity totals for each of the weeks across the study, to give the total hours of outdoor activity at each of the available time points.

7.4 Subgroup analyses

Exploratory subgroup analyses will be performed on the primary outcome using 99% CIs and interaction terms (treatment group by subgroup) for the following subgroups: age (6-9 and 10-12 years at start of trial), ethnic background (white versus non-white), severity of myopia (less than -3D in either eye versus -3D or greater myopia), iris colour (Dark brown and Other including; light brown, green, blue and grey) and gender (male/female). The subgroup analyses will be performed using GEE and adjusted for baseline SER. The global test for interaction will be used for the interaction term.

7.5 Additional analyses

Additional analyses will be performed on the primary and secondary outcomes to investigate any differences between atropine and placebo groups at all other available time points not previously analysed (i.e. 6, 12 and 18 months). The primary and secondary outcomes at baseline will only be presented by treatment arm in the PP analysis in this additional analyses, as the ITT baseline results are presented in the baseline characteristics table.

For the primary outcome SER, results will be used from both eyes and will be compared using GEE (repeated measures model) and 95% CIs and will be adjusted for baseline SER. Secondary analysis of the primary outcome will be adjusted for baseline SER and minimisation variables (i.e. site and ethnicity), baseline age and history of parental myopia (at least one parent).

For the secondary outcome analyses, results will be used from both eyes to investigate if atropine has an effect on the following endpoints; central axial length, pupil diameter, uniocular BCdVA and uniocular near VA. These endpoints will be compared between the two groups using GEE (repeated measures model) and 95% CIs and will be adjusted for the corresponding baseline secondary outcomes (if available). For the following endpoints; binocular BCdVA, binocular near VA, reading speed and quality of life (i.e. EQ-5D-Y VAS and Index) comparisons between the two groups will be performed using repeated measures ANCOVA and 95% CIs and will be adjusted for the corresponding baseline secondary outcome (if available).

Tolerability will be compared between the atropine and placebo groups using repeated measures ANOVA and 95% CI. Spectacle correction will be compared between the atropine and placebo groups using repeated measures generalised linear model. N(%) of spectacle correction (all day and sometimes) will also be presented by treatment arm.

7.6 Missing data

Sensitivity analyses will be undertaken to assess the impact of missing data for the primary outcome, by imputing extreme values of change within treatment arm (i.e. smallest and largest change from the previous time point to 24 months). Results between the atropine and placebo groups will be compared using GEE and 95% CIs and will be adjusted for baseline SER and also adjusted for baseline SER, minimisation variables (i.e site and ethnicity), baseline age and history of parental myopia (at least one parent). If the baseline primary outcome is missing, spectacle refraction based on the current prescription at baseline will be used in the sensitivity analysis.

7.7 Five-year follow up analysis

The change in SER measured by autorefractor will be compared at baseline to five years, as well as from 24 months to five years. If SER is not available at five years, spectacle refraction based on current prescription will be used.

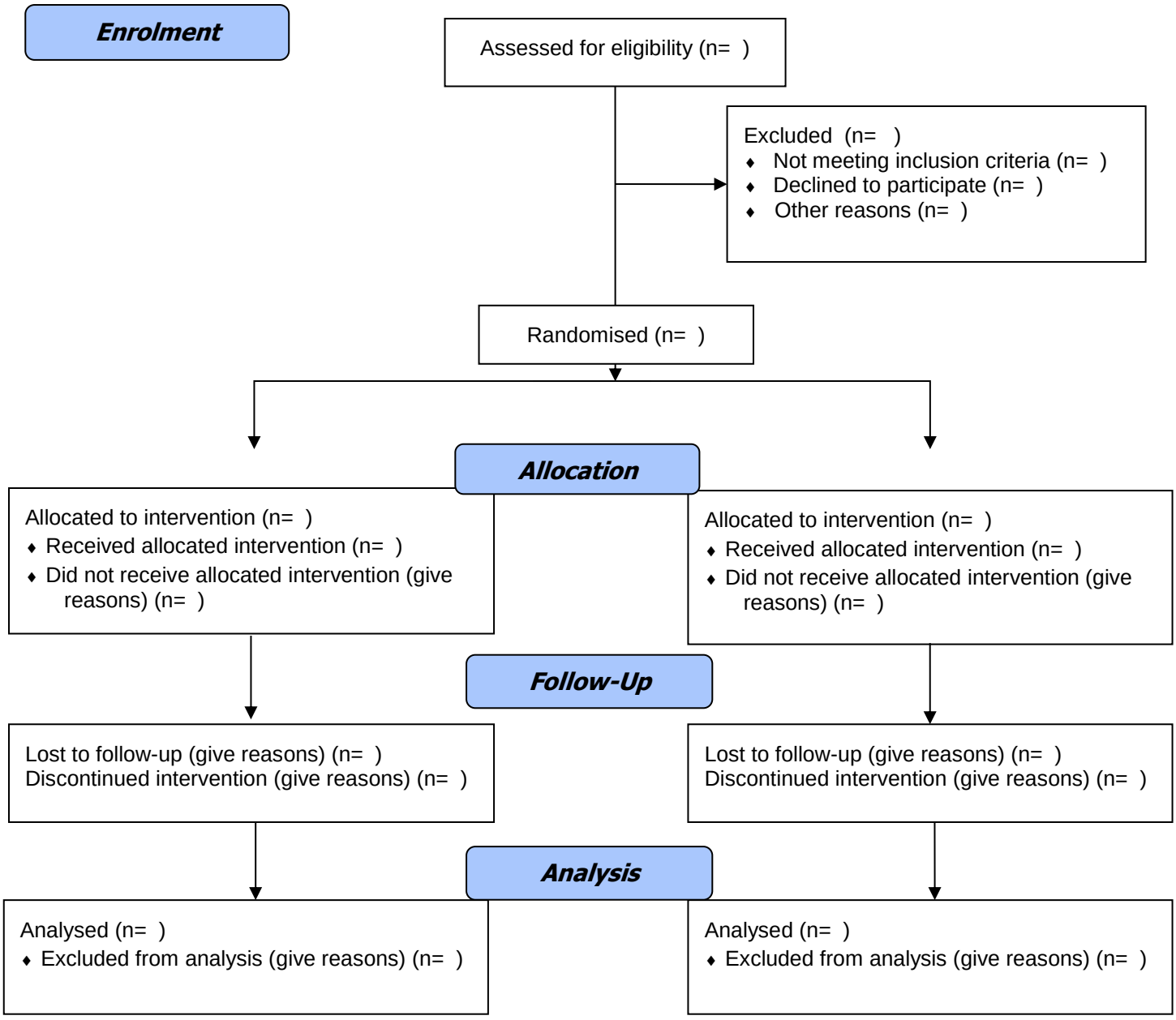
8. ANALYSIS DETAILS

The results of the analyses will be reported following the principles of the ICH E3 guidelines on the Structure and Content of Clinical Study Reports.

8.1 Recruitment and follow-up patterns

- Screening, patient enrolment, treatment allocation, withdrawals, follow-up and inclusion in primary analysis will be reported using CONSORT diagram.
- Recruitment will be reported by site.

8.2 CONSORT Flow Diagram



8.3 Baseline Characteristics

- Minimisation factors, n (%) by treatment arm and total
- Gender, n (%) by treatment arm and total
- Age (years), mean (SD) by treatment arm and total
- Weight (kg), mean (SD) by treatment arm and total
- Height (cm), mean (SD) by treatment arm and total
- Ethnicity, no. (%) by treatment arm and total
- Parental myopia, no. (%) by treatment arm and total
- SER in both eyes, mean (SD) by treatment arm and total
- SER in left eye, mean (SD) by treatment arm and total
- SER in right eye, mean (SD) by treatment arm and total
- Central axial length in both eyes, mean (SD) by treatment arm and total
- Central axial length in left eye, mean (SD) by treatment arm and total
- Central axial length in right eye, mean (SD) by treatment arm and total
- EQ5D-Y- Visual Analogue Scale, mean (SD) by treatment arm and total
- EQ5D-Y- index score, mean (SD) by treatment arm and total
- Uniocular BCdVA in both eyes, mean (SD) by treatment arm and total
- Uniocular BCdVA in left eye, mean (SD) by treatment arm and total
- Uniocular BCdVA in right eye, mean (SD) by treatment arm and total
- Binocular BCdVA, mean (SD) by treatment arm and total
- Uniocular near VA in both eyes, mean (SD) by treatment arm and total
- Uniocular near VA in left eye, mean (SD) by treatment arm and total
- Uniocular near VA in right eye, mean (SD) by treatment arm and total
- Binocular near VA, mean (SD) by treatment arm and total
- Reading speed, mean (SD) by treatment arm and total
- Pupil diameter in both eyes, mean (SD) by treatment arm and total
- Pupil diameter in left eye, mean (SD) by treatment arm and total
- Pupil diameter in right eye, mean (SD) by treatment arm and total
- Spectacle correction, no. (%) by treatment arm and total
- Frequency of spectacle correction; all day and sometimes, no. (%) by treatment arm and total
- Contact lens use, no. (%) by treatment arm and total
- Frequency of contact lens use; all day and sometimes, no. (%) by treatment arm and total

8.4 Trial treatment

- Time from randomisation to start of study drug, mean (sd) by treatment arm
- Medical Events Monitoring System (MEMS): Average adherence (%), average drug holidays and average overdosing over total study time period, mean (sd) by treatment arm
- Reasons for termination of study drug: number (%) by treatment arm for study drug related AE, study drug related SAE, study drug expiry date, patient request, clinicians request and other
- Protocol deviations/violations: number (%) by treatment arm for eligibility, study drug administration (participant reported), study drug administration (MEMS data), safety reporting (AE/SAE), visit outside schedule OR missed visit, assessment not done and other
- Premature withdrawals: number (%) by treatment arm for adverse event, serious adverse event, protocol deviation, lost to follow up, withdrawal of patient consent, death, withdrawal at clinician's request and other
- Did not receive allocated treatment (which includes those who received no treatment), number (%) by treatment arm
- Received treatment of other group, number (%) by treatment arm

8.5 Trial Outcomes

Primary efficacy outcome:

- SER at month 24: mean (SD) by treatment arm, difference in means with 95% CI, p-value from GEE model, adjusted for baseline SER in ITT analysis and PP analysis.

Secondary analysis of the primary efficacy outcome:

- SER at month 24: mean (SD) by treatment arm, difference in means with 95% CI, p-value from GEE model, adjusted for baseline SER, minimisation variables (i.e. site and ethnicity), baseline age and history of parental myopia (at least one parent), in ITT analysis and PP analysis.
- Uniocular (BCdVA) at month 24: mean (SD) by treatment arm, difference in means with 95% CI, p-value from GEE, adjusted for baseline uniocular BCdVA in ITT and PP analysis.
- Binocular BCdVA at month 24: mean (SD) by treatment arm, difference in means with 95% CI, p-value from ANCOVA, adjusted for baseline BCdVA in ITT and PP analysis.
- Central axial length at month 24: mean (SD) by treatment arm, difference in means with 95% CI, p-value from GEE, adjusted for baseline central axial length in ITT and PP analysis.
- Uniocular near VA at month 24: mean (SD) by treatment arm, difference in means with 95% CI, p-value from GEE, adjusted for baseline uniocular near VA in ITT and PP analysis.
- Binocular near VA at month 24: mean (SD) by treatment arm, difference in means with 95% CI, p-value from ANCOVA, adjusted for baseline binocular near VA in in ITT and PP analysis..
- Pupil diameter at month 24: mean (SD) by treatment arm, difference in means with 95% CI, p-value from GEE, adjusted for baseline pupil diameter in ITT and PP analysis.
- Spectacle correction at month 24: no. (%) by treatment arm, risk difference and p-value from from chi-square test in ITT and PP analysis.
- Frequency of spectacle correction at month 24 (all day and sometimes): no. (%) by treatment arm in ITT and PP analysis.
- EQ-5D-Y VAS at month 24: mean (SD) by treatment arm, difference in means with 95% CI, p-value from ANCOVA, adjusted for baseline EQ-5D-Y VAS in intention to treat analysis and per protocol analysis.
- EQ-5D-Y Index score at month 24: mean (SD) by treatment arm, difference in means with 95% CI, p-value from ANCOVA, adjusted for baseline EQ-5D-Y index in ITT and PP analysis.
- Tolerability eye feels at month 24: mean (SD) by treatment arm, difference in means with 95% CI, p-value from independent t-test, in ITT and PP analysis.
- Tolerability stingy at month 24: mean (SD) by treatment arm, difference in means with 95% CI, p-value from independent t-test, in ITT and PP analysis.
- Tolerability itchiness at month 24: mean (SD) by treatment arm, difference in means with 95% CI, p-value from independent t-test, in ITT and PP analysis.
- Tolerability blurry vision at month 24: mean (SD) by treatment arm, difference in means with 95% CI, p-value from independent t-test, in ITT and PP analysis.
- Tolerability sore eyes at month 24: mean (SD) by treatment arm, difference in means with 95% CI, p-value from independent t-test, in ITT and PP analysis.
- Tolerability difficult to read/write at month 24: mean (SD) by treatment arm, difference in means with 95% CI, p-value from independent t-test, in ITT and PP analysis.

8.6 Sensitivity analyses

- SER at month 24: mean (SD) by treatment arm, difference in means with 95% CI, p-value from GEE model, adjusted for baseline SER in ITT and PP analysis.
- SER at month 24: mean (SD) by treatment arm, difference in means with 95% CI, p-value from GEE model, adjusted for baseline SER and minimisation variables (i.e. site and ethnicity), baseline age and history of parental myopia (at least one parent), in ITT and PP analysis.

8.7 Subgroup analyses

- SER at month 24 according to age group (6-9 and 10-12): mean (SD) by treatment arm, difference in means with 95% CI, p-value from GEE model, adjusted for baseline SER in ITT and PP analysis.
- SER at month 24 according to ethnicity group (white and non-white): mean (SD) by treatment arm, difference in means with 95% CI, p-value from GEE model, adjusted for baseline SER in ITT and PP analysis.

- SER at month 24 according to severity of myopia (less than -3D and -3D or greater): mean (SD) by treatment arm, difference in means with 95% CI, p-value from GEE model, adjusted for baseline SER in ITT and PP analysis.
- SER at month 24 according to iris colour (Dark brown and Other including; light brown, green, blue and grey): mean (SD) by treatment arm, difference in means with 95% CI, p-value from GEE model, adjusted for baseline SER in ITT and PP analysis.
- SER at month 24 according to gender (male/female): mean (SD) by treatment arm, difference in means with 95% CI, p-value from GEE model, adjusted for baseline SER in ITT and PP analysis.

8.8 Additional analyses

Primary outcome:

- SER at baseline, mean (SD) by treatment arm in PP analysis.
- SER at months 6, 12 and 18, mean (SD) by treatment arm, difference in means with 95% CI, p-value from GEE (repeated measures model), adjusted for baseline SER, in ITT and PP analysis.
- SER at months 6, 12 and 18, mean (SD) by treatment arm, difference in means with 95% CI, p-value from GEE (repeated measures model), adjusted for baseline SER, minimisation variables (i.e. site and ethnicity), baseline age and history of parental myopia, in ITT analysis and PP analysis.

Secondary outcomes:

- Reading speed at baseline, mean (SD) by treatment arm in PP analysis.
- Reading speed at months 6, 12 and 18: mean (SD) by treatment arm, difference in means with 95% CI, p-value from repeated measures ANCOVA, adjusted for baseline reading speed in ITT and PP analysis.
- Uniocular BCdVA at baseline, mean (SD) by treatment arm in PP analysis.
- Uniocular BCdVA at months 6, 12 and 18: mean (SD) by treatment arm, difference in means with 95% CI, p-value from GEE (repeated measures model), adjusted for baseline uniocular BCdVA in ITT and PP analysis.
- Binocular BCdVA at baseline, mean (SD) by treatment arm in PP analysis.
- Binocular BCdVA at months 6, 12 and 18: mean (SD) by treatment arm, difference in means with 95% CI, p-value from repeated measures ANCOVA, adjusted for baseline BCdVA in ITT and PP analysis.
- Central axial length at baseline, mean (SD) by treatment arm in PP analysis.
- Central axial length at months 6, 12 and 18 mean (SD) by treatment arm, difference in means with 95% CI, p-value from GEE (repeated measures model), adjusted for baseline central axial length in ITT and PP analysis.
- Uniocular near VA at baseline, meam (SD) by treatment arm in PP analysis.
- Uniocular near VA at months 6, 12 and 18: mean (SD) by treatment arm, difference in means with 95% CI, p-value from GEE (repeated measures model), adjusted for baseline uniocular near VA in ITT and PP analysis.
- Binocular near VA at baseline, mean (SD) by treatment arm in PP analysis.
- Binocular near VA at months 6, 12 and 18: mean (SD) by treatment arm, difference in means with 95% CI, p-value from repeated measures ANCOVA, adjusted for baseline binocular near VA in ITT and PP analysis.
- Pupil diameter at baseline, mean (SD) by treatment arm in PP analysis.
- Pupil diameter at months 6, 12 and 18: mean (SD) by treatment arm, difference in means with 95% CI, p-value from GEE (repeated measures model), adjusted for baseline pupil diameter in ITT and PP analysis.
- Spectacle correction at baseline, no. (%) by treatment arm in PP analysis.
- Spectacle correction at months, 6, 12 and 18: no. (%) by treatment arm, risk difference and p value from repeated measures generalized linear model in ITT and PP analysis.
- Frequency of spectacle correction at baseline (all day and sometimes), no. (%) by treatment arm in PP analysis.
- Frequency of spectacle correction at months 6, 12 and 18 (all day and sometimes): no. (%) by treatment arm in ITT and PP analysis.

- EQ-5D-Y VAS at baseline, mean (SD) by treatment arm in PP analysis.
- EQ-5D-Y VAS at months 6, 12 and 18: mean (SD) by treatment arm, difference in means with 95% CI, p-value from repeated measures ANCOVA, adjusted for baseline EQ-5D-Y VAS in ITT and PP analysis.
- EQ-5D-Y Index score at baseline, mean (SD) by treatment arm in PP analysis.
- EQ-5D-Y Index score at months 6, 12 and 18: mean (SD) by treatment arm, difference in means with 95% CI, p-value from repeated measures ANCOVA, adjusted for baseline EQ-5D-Y Index in ITT and PP analysis.
- Tolerability eye feels at months 6, 12 and 18: mean (SD) by treatment arm, difference in means with 95% CI, p-value from ANOVA, in ITT and PP analysis.
- Tolerability stingy at months 6, 12 and 18: mean (SD) by treatment arm, difference in means with 95% CI, p-value from ANOVA, in ITT and PP analysis.
- Tolerability itchiness at months 6, 12 and 18: mean (SD) by treatment arm, difference in means with 95% CI, p-value from ANOVA, in ITT and PP analysis.
- Tolerability blurry vision at months 6, 12 and 18: mean (SD) by treatment arm, difference in means with 95% CI, p-value from ANOVA, in ITT and PP analysis.
- Tolerability sore eyes at months 6, 12 and 18: mean (SD) by treatment arm, difference in means with 95% CI, p-value from ANOVA, in ITT and PP analysis.
- Tolerability difficult to read/write at months 6, 12 and 18: mean (SD) by treatment arm, difference in means with 95% CI, p-value from ANOVA, in ITT and PP analysis.

8.9 SWAT analyses

Data from medication event monitoring systems (MEMs) are used to measure adherence to medication. For this study, AARDEX software is used to store medication adherence data from MEMs, whilst bottle weight data is measured separately and routinely.

This study within a study (SWAT) will investigate if the inexpensive and pragmatic measure of bottle weight measurements, is as effective as MEMs for measuring compliance to medication in individual patients, and in groups of patients.

For individual patients, MEMs and difference in bottle weight values will be explored, and discrepancies between datasets measured. Summary statistics for differences in bottle weight will be measured according to good (>= 80%), moderate (50% - 79%) and bad (<50%) MEMs adherence. Summary statistics will include mean, min, max, standard deviation, median and interquartile range. Pearson's correlation will be used to measure the relationship between MEMs data and difference in bottle weight data.

Summary statistics including mean and standard deviation will also be calculated for groups of patients. These statistics will be used to examine if bottle weight provides a sufficient approximation of adherence to medication for a group of people in a trial.

8.10 Toxicity/ Symptoms

- AEs, no.events (%) by treatment arm, no. patients(%) by treatment arm, Risk ratio with 95% CI and p value
- ARs, no.events (%) by treatment arm, no. patients(%) by treatment arm, Risk ratio with 95% CI and p value
- SARs, no. events (%) by treatment arm, no. patients (%) by treatment arm, Risk ratio with 95% CI and p value
- UARs, no. events (%) by treatment arm, no. patients (%) by treatment arm, Risk ratio with 95% CI and p value
- SAEs, no. events (%) by treatment arm, no. patients (%) by treatment arm, Risk ratio with 95% CI and p value
- SUSARs, no. events (%) by treatment arm, no. patients (%) by treatment arm, Risk ratio with 95% CI and p value

- Fatal AEs/SAEs, no. events (%) by treatment arm, no. patients (%) by treatment arm, Risk ratio with 95% CI and p value

AEs, ARs, SAEs, SARs, UARs and SUSARs will also be presented by system organ class.

9. ADDITIONAL INFORMATION

9.1 Trial Steering Committee (TSC)

The conduct of the trial will be overseen by a TSC. The TSC is a group that act as the oversight body for the trial on behalf of the Sponsor and Funder. Throughout the trial, the TSC will take responsibility for monitoring and guiding overall progress, scientific standards, operational delivery and protecting the rights and safety of trial participants.

The TSC will include an independent Chair, at least two independent clinicians or trialists, at least one patient representative and the CI. Representatives of the Sponsor/Funder and the NICTU may attend TSC meetings as observers and at the discretion of the Chair. The TSC Charter will outline the terms of reference of the TSC including roles and responsibilities, membership, organisation of meetings, reporting, decision making and the relationship with the other trial committees. As the frequency of DMC meetings will be dependent on recruitment rates, TSC meetings will be arranged to coincide with these and will be convened to discuss issues and recommendations raised by the DMC.

9.2 Data Monitoring and Ethics Committee (DMEC)

A DMC has been appointed with responsibility for safeguarding the interests of trial participants. The DMC will monitor the main outcome measures including safety and efficacy and assist and advise the TSC to protect the validity and credibility of the trial. The DMC will include two clinicians and a statistician who are independent of the trial. The DMC Charter will outline the terms of reference of the DMC including roles and responsibilities, membership, organisation of meetings, reporting, decision making (including stopping rules if applicable) and the relationship with the other trial committees. In the light of interim data and other relevant evidence, the DMC will inform the TSC if, in its view, there is proof beyond reasonable doubt that the data indicate that the trial should be terminated. A joint TSC and DMC inaugural meeting will be held prior to recruitment commencing. Subsequent meetings will be scheduled at regular intervals. The Trial Statistician will produce reports for the DMC and TSC which may include recruitment, baseline data, adverse events, compliance and outcome data to enable them to monitor the trial and guide overall progress.

9.3 User involvement or any other relevant committees

The participant information sheets (PIS) have been reviewed by the NIHR Medicines for Children Research Network and parent representatives. In addition, two parent representatives sit on the TSC.

10. REFERENCES

1. Manny R, Huessein M, Gwiazda J and Marsh-Tootle W. Repeatability of ETDRS Visual Acuity in Children Investigative Ophthalmol Visual Sci. 2003;44:3294-300.

2. Li SM, Wu SS, Kang MT, Liu Y, Jia SM, Li SY, Zhan SY, Liu LR, Li H, Chen W, Yang Z, Sun YY, Wang N, Millodot M. Atropine slows myopia progression more in Asian than white children by meta-analysis. Optom Vis Sci. 2014;91:342-50.

3. Chua WH, Balakrishnan V, Chan YH, et al. Atropine for the treatment of childhood myopia. Ophthalmol. 2006;113:2285–91.

4. Katz J, Schein OD, Levy B, Cruiscullo T, Saw SM, Rajan U, Chan TK, Yew Khoo C, Chew SJ. A randomized trial of rigid gas permeable contact lenses to reduce progression of children's myopia. Am J Ophthalmol. 2003;136:82-90.

5. Edwards MH, Li RW, Lam CS, Lew JK, Yu BS. The Hong Kong progressive lens myopia control study: study design and main findings. Invest Ophthalmol Vis Sci. 2002;43:2852-8.

6. Hyman L, Gwiazda J, Hussein M, Norton TT, Wang Y, Marsh-Tootle W, Everett D. Relationship of age, sex, and ethnicity with myopia progression and axial elongation in the correction of myopia evaluation trial. Arch Ophthalmol. 2005;123:977-87.

7. Breslin KM, O'Donoghue L, Saunders KJ. A prospective study of spherical refractive error and ocular components among Northern Irish schoolchildren (the NICER study). Invest Ophthalmol Vis Sci. 2013;54:4843-50.

11. SIGNATURES OF APPROVAL

Date: 26/07/2023
Version: 2.0 Final
This document has completed a final review and is understood and approved by the following:

See attached email

Augusto Azuara-Blanco

Chief Investigator Name	*Chief Investigator Signature*	Date dd/mm/yyyy
Cliona McDowell	See attached email	

Senior Statistician or designee Name	*Senior Statistician or designee Signature*	Date dd/mm/yyyy
Cliona McDowell	See attached email	

Study Statistician Name	*Study Statistician Signature*	Date dd/mm/yyyy

APPENDIX 1: SUMMARY TABLES

Table XXX: Characteristics at Study Entry

Baseline Characteristics	Treatment Group		Total
	Atropine sulfate	Placebo	
	n=<n>	n=<n>	n=<n>
Minimisation Factors			
White	n(%)	n(%)	n(%)
Non-white	n(%)	n(%)	n(%)
Severity of Myopia			
≥ -3D	n(%)	n(%)	n(%)
< -3D	n(%)	n(%)	n(%)
Gender Male	n(%)	n(%)	n(%)
Female	n(%)	n(%)	n(%)
Age (years)	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x ± xx.x n=
Weight (kg)	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x ± xx.x n=
Height (cm)	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x ± xx.x n=
Ethnicity			
White	n(%)	n(%)	n(%)
Irish Traveler	n(%)	n(%)	n(%)
Mixed/Multiple Ethnic Groups	n(%)	n(%)	n(%)
Asian/Asian British(excluding Chinese)	n(%)	n(%)	n(%)
Black/African/Caribbean/Black British	n(%)	n(%)	n(%)
Chinese	n(%)	n(%)	n(%)
Other	n(%)	n(%)	n(%)
Parental myopia			
Yes	n (%)	n (%)	n (%)
No	n (%)	n (%)	n (%)
Unknown	n (%)	n (%)	n (%)
Spherical equivalent refractive error[a]	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x ± xx.x n=
Left eye	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x ± xx.x n=
Right eye	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x ± xx.x n=
Central Axial Length[a]	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x ± xx.x n=
Left eye	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x ± xx.x n=
Right eye	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x ± xx.x n=
EQ5D-Y- Visual Analogue Scale[b]	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x ± xx.x n=
EQ5D-Y-index score	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x ± xx.x n=
Uniocular BCdVA (0.20 logMAR)	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x ± xx.x n=
Left eye	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x ± xx.x n=
Right eye	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x ± xx.x n=
Binocular BCdVA (0.20 logMAR)	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x ± xx.x n=
Uniocular near VA	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x ± xx.x n=
Left eye	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x ± xx.x n=
Right eye	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x ± xx.x n=
Binocular near VA	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x ± xx.x n=
Reading speed	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x ± xx.x n=

Baseline Characteristics	Treatment Group		Total
	Atropine sulfate	Placebo	
	n=<n>	n=<n>	n=<n>
Pupil diameter[a]	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x ± xx.x n=
Left eye	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x ± xx.x n=
Right eye	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x ± xx.x n=
Spectacle correction			
Yes	n(%)	n(%)	n(%)
No	n(%)	n(%)	n(%)
Frequency of spectacle correction			
All day	n(%)	n(%)	n(%)
Sometimes	n(%)	n(%)	n(%)
Contact lens use			
Yes	n(%)	n(%)	n(%)
No	n(%)	n(%)	n(%)
Frequency of contact lens use			
All day	n(%)	n(%)	n(%)
Sometimes	n(%)	n(%)	n(%)

Reported as frequency (percentage), mean ± SD, or median (p25 to p75) based on the distribution of the data. [a]Mean of two eyes, [b]not weighted.

Table XXX: Treatment after trial entry

	Atropine sulfate N=	**Placebo N=**
Time from randomisation to start of study drug	xx.x (xx.x)	xx.x (xx.x)
MEMS data[a]		
Adherence	xx.x (xx.x)	xx.x (xx.x)
Drug holidays	xx.x (xx.x)	xx.x (xx.x)
Over dosing	xx.x (xx.x)	xx.x (xx.x)
Reasons for termination of study drug		
Study Drug related AE	n (xx.x%)	n (xx.x%)
Study Drug related SAE	n (xx.x%)	n (xx.x%)
Study Drug Expiry Date	n (xx.x%)	n (xx.x%)
Patient Request	n (xx.x%)	n (xx.x%)
Clinician's Request	n (xx.x%)	n (xx.x%)
Other	n (xx.x%)	n (xx.x%)
Protocol deviations/ violations		
Eligibility	n (xx.x%)	n (xx.x%)
Study Drug Administration (Participant reported)[b]	n (xx.x%)	n (xx.x%)
Study Drug Adminstration (MEMS data)[b]	n (xx.x%)	n (xx.x%)
Safety reporting (AE/SAE)	n (xx.x%)	n (xx.x%)
Visit outside schedule OR missed visit	n (xx.x%)	n (xx.x%)
Assessment not done	n (xx.x%)	n (xx.x%)
Other	n (xx.x%)	n (xx.x%)
Premature Withdrawals		
Adverse Event	n (xx.x%)	n (xx.x%)
Serious Adverse Event	n (xx.x%)	n (xx.x%)
Protocol deviation	n (xx.x%)	n (xx.x%)
Lost to Follow Up	n (xx.x%)	n (xx.x%)
Withdrawal of patient consent	n (xx.x%)	n (xx.x%)
Death	n (xx.x%)	n (xx.x%)
Other	n (xx.x%)	n (xx.x%)
Did not receive allocated treatment (which includes those who received no treatment)	n (xx.x%)	n (xx.x%)
Received treatment of other group	n (xx.x%)	n (xx.x%)

[a] MEMs data averaged over the total study time period. [b]If the drops are missed 20% or more.

Table XXX: Main Clinical Outcomes

Variables		Treatment Group		Unadjusted		Adjusted [a]		Adjusted [b]	
		Atropine sulfate N=	**Placebo N=**	**Mean difference (95% CI)**	**P value**	**Mean difference (95% CI)**	**P value**	**Mean difference (95% CI)**	**P value**
Primary Outcome: Spherical equivalent refractive error at 24 months									
Intention to treat (ITT) [c]		xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx
Per protocol (PP) [c]		xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx
Secondary Outcomes at 24 months									
Reading speed [d]	ITT	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx		
	PP	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx		
Uniocular BCdVA [c]	ITT	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx		
	PP	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx		
Binocular BCdVA [d]	ITT	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx		
	PP	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx		
Central axial length [c]	ITT	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx		
	PP	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx		
Uniocular near VA [c]	ITT	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx		
	PP	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx		
Binocular near VA [d]	ITT	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx		
	PP	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx		
Pupil diameter [c]	ITT	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx		
	PP	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx		
Spectacle correction [e]	ITT	n (%)	n (%)	xx.x (x.x, x.x)	x.xx				
	PP	n (%)	n (%)	xx.x (x.x, x.x)	x.xx				
Frequency of spectacle	ITT	n (%)	n (%)						
	PP	n (%)	n (%)						

correction (all day)[e]									
Frequency of spectacle correction (sometimes) [e]	ITT	n (%)	n (%)						
	PP	n (%)	n (%)						
EQ-5D-Y VAS [d]	ITT	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx		
	PP	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx		
EQ-5D-Y Index score [d]	ITT	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx		
	PP	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx		
Tolerability									
Eye feels [f]	ITT	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx				
	PP	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx				
Stingy [f]	ITT	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx				
	PP	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx				
Itchiness [f]	ITT	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx				
	PP	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx				
Blurry vision [f]	ITT	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx				
	PP	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx				
Sore eyes [f]	ITT	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx				
	PP	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx				
Difficult to read/write [f]	ITT	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx				
	PP	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx				

[a] Adjusted for baseline SER. [b] Adjusted for baseline SER, minimisation variables (i.e. site and ethnicity), age and history of parental myopia (at least one parent). [c] Mean(SD) was calculated with data from both eyes. Mean difference estimate and p value from GEE. [d] Mean difference estimate and p value from ANCOVA. [e] Frequency (%) presented for categorical variables and risk difference and p value from the chi-square test (or fishers exact test if applicable).[f] Mean(SD) and p value from independent samples t-test, no adjustment as tolerability not measured at baseline.

Table XXX: Sensitivity analysis of primary outcome

Primary Outcome		Treatment Group		Unadjusted		Adjusted[a]		Adjusted [b]	
		Atropine sulfate N=	**Placebo N=**	**Mean difference (95% CI)**	**P value**	**Mean difference (95% CI)**	**P value**	**Mean difference (95% CI)**	**P value**
Intention to treat									
Spherical equivalent refractive error at 24 months [c]	Smallest change	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx	x.xx	x.xx
	Largest change	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx	x.xx	x.xx
Per Protocol									
Spherical equivalent refractive error at 24 months [c]	Smallest change	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx	x.xx	x.xx
	Largest change	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx	x.xx	x.xx

[a] Adjusted for baseline SER. [b] Adjusted for baseline SER and minimisation variables (i.e. site and ethnicity), baseline age and history of parental myopia (at least one parent). [c]Mean(sd) was calculated with data from both eyes. Mean difference estimate and p value from GEE.

Table XXX: Primary Outcome Subgroup Analyses

Primary Outcome Subgroup Analysis	Treatment Group		Adjusted [a]	
	Atropine sulfate	Placebo	Mean difference (99% CI)	Interaction Term [b]
Intention to treat analysis				
Age (years old at start of trial)				
6-9	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx
10-12	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	
Ethnicity				
White	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx
Non-white	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	
Severity of myopia				
Less than -3D	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx
-3D or greater	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	
Iris Colour				
Dark brown	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx
Other [c]	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	
Gender				
Male	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx
Female	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	
Per Protocol analysis				
Age (years old at start of trial)				
6-9	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx
10-12	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	
Ethnicity				
White	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx
Non-white	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	
Severity of myopia				
Less than -3D	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx
-3D or greater	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	
Iris Colour				
Dark brown	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx

Other [c]	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	
Gender				
Male	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx
Female	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	

[a]Adjusted for baseline SER. [b] Mean difference estimate from GEE and Interaction term p-value is from a global test for interaction. [c]Includes; light brown, green, blue and grey.

Table XXX: Exploratory outcomes / Mechanistic evaluations

Variables		Treatment Group		Unadjusted		Adjusted [a]	
		Atropine sulfate N=	**Placebo N=**	**Mean difference (95% CI)**	**P value**	**Mean difference (95% CI)**	**P value**
Nasal peripheral axial length (20°)[b]							
ITT	Baseline	xx.x ± xx.x n=	xx.x ± xx.x n=				
	12 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx
	24 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx
PP	Baseline	xx.x ± xx.x n=	xx.x ± xx.x n=				
	12 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx
	24 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx
Temporal peripheral axial length (20°) [b]							
ITT	Baseline	xx.x ± xx.x n=	xx.x ± xx.x n=				
	12 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx
	24 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx
PP	Baseline	xx.x ± xx.x n=	xx.x ± xx.x n=				
	12 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx
	24 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx
Nasal peripheral retinal defocus (30°) [b]							
ITT	Baseline	xx.x ± xx.x n=	xx.x ± xx.x n=				
	12 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx
	24 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx
PP	Baseline	xx.x ± xx.x n=	xx.x ± xx.x n=				
	12 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx
	24 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx
Temporal peripheral retinal defocus (30°) [b]							
ITT	Baseline	xx.x ± xx.x n=	xx.x ± xx.x n=				

	12 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx
	24 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx
PP	Baseline	xx.x ± xx.x n=	xx.x ± xx.x n=				
	12 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx
	24 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx
Nasal peripheral retinal defocus (20°) [b]							
ITT	Baseline	xx.x ± xx.x n=	xx.x ± xx.x n=				
	12 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx
	24 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx
PP	Baseline	xx.x ± xx.x n=	xx.x ± xx.x n=				
	12 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx
	24 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx
Temporal peripheral retinal defocus (20°) [b]							
ITT	Baseline	xx.x ± xx.x n=	xx.x ± xx.x n=				
	12 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx
	24 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx
PP	Baseline	xx.x ± xx.x n=	xx.x ± xx.x n=				
	12 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx
	24 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx
Anterior chamber depth [b]							
ITT	Baseline	xx.x ± xx.x n=	xx.x ± xx.x n=				
	12 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx
	24 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx
PP	Baseline	xx.x ± xx.x n=	xx.x ± xx.x n=				
	12 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx
	24 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx
Binocular amplitude of accommodation [c]							
ITT	Baseline	xx.x ± xx.x n=	xx.x ± xx.x n=				
	6 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx
	12 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx

	18 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx
	24 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx
PP	Baseline	xx.x ± xx.x n=	xx.x ± xx.x n=				
	6 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx
	12 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx
	18 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx
	24 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx
Accomodative lag (33cm) [b]							
ITT	Baseline	xx.x ± xx.x n=	xx.x ± xx.x n=				
	6 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx
	12 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx
	18 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx
	24 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx
PP	Baseline	xx.x ± xx.x n=	xx.x ± xx.x n=				
	6 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx
	12 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx
	18 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx
	24 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx
Accomodative lag (25cm) [b]							
ITT	Baseline	xx.x ± xx.x n=	xx.x ± xx.x n=				
	6 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx
	12 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx
	18 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx
	24 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx
PP	Baseline	xx.x ± xx.x n=	xx.x ± xx.x n=				
	6 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx
	12 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx
	18 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx
	24 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx
Accomodative lag (20cm) [b]							

ITT	Baseline	xx.x ± xx.x n=	xx.x ± xx.x n=				
	6 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx
	12 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx
	18 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx
	24 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx
PP	Baseline	xx.x ± xx.x n=	xx.x ± xx.x n=				
	6 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx
	12 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx
	18 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx
	24 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx
Total hours of outdoor activity [c]							
ITT	Baseline	xx.x ± xx.x n=	xx.x ± xx.x n=				
	6 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx
	12 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx
	18 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx
	24 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx
PP	Baseline	xx.x ± xx.x n=	xx.x ± xx.x n=				
	6 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx
	12 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx
	18 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx
	24 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx
Nasal ciliary body biometry [b]							
ITT	Baseline	xx.x ± xx.x n=	xx.x ± xx.x n=				
	12 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx
	24 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx
PP	Baseline	xx.x ± xx.x n=	xx.x ± xx.x n=				
	12 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx
	24 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx
Temporal ciliary body biometry [b]							
ITT	Baseline	xx.x ± xx.x n=	xx.x ± xx.x n=				

	12 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx
	24 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx
PP	Baseline	xx.x ± xx.x n=	xx.x ± xx.x n=				
	12 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx
	24 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx
Chorio-retinal thickness [b]							
ITT	Baseline	xx.x ± xx.x n=	xx.x ± xx.x n=				
	6 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx
	12 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx
	18 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx
	24 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx
PP	Baseline	xx.x ± xx.x n=	xx.x ± xx.x n=				
	6 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx
	12 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx
	18 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx
	24 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx
Height [d]							
ITT	Baseline	xx.x ± xx.x n=	xx.x ± xx.x n=				
	6 months	xx.x ± xx.x n=	xx.x ± xx.x n=				
	12 months	xx.x ± xx.x n=	xx.x ± xx.x n=				
	18 months	xx.x ± xx.x n=	xx.x ± xx.x n=				
	24 months	xx.x ± xx.x n=	xx.x ± xx.x n=				
PP	Baseline	xx.x ± xx.x n=	xx.x ± xx.x n=				
	6 months	xx.x ± xx.x n=	xx.x ± xx.x n=				
	12 months	xx.x ± xx.x n=	xx.x ± xx.x n=				
	18 months	xx.x ± xx.x n=	xx.x ± xx.x n=				
	24 months	xx.x ± xx.x n=	xx.x ± xx.x n=				
Weight [d]							
ITT	Baseline	xx.x ± xx.x n=	xx.x ± xx.x n=				
	6 months	xx.x ± xx.x n=	xx.x ± xx.x n=				

	12 months	xx.x ± xx.x n=	xx.x ± xx.x n=				
	18 months	xx.x ± xx.x n=	xx.x ± xx.x n=				
	24 months	xx.x ± xx.x n=	xx.x ± xx.x n=				
PP	Baseline	xx.x ± xx.x n=	xx.x ± xx.x n=				
	6 months	xx.x ± xx.x n=	xx.x ± xx.x n=				
	12 months	xx.x ± xx.x n=	xx.x ± xx.x n=				
	18 months	xx.x ± xx.x n=	xx.x ± xx.x n=				
	24 months	xx.x ± xx.x n=	xx.x ± xx.x n=				

[a]Adjusted for baseline exploratory outcome where applicable. [b]Mean (sd) was calculated with data from both eyes. Mean difference estimate and p value from GEE.
[c]Mean difference estimate and p value from ANCOVA. [d]Mean(SD) presented by treatment arm.

Table XXX: Additional analysis – Primary and secondary outcomes at other time points

Variables		Treatment Group		Unadjusted		Adjusted [a]		Adjusted [b]	
		Atropine sulfate N=	**Placebo N=**	**Mean difference (95% CI)**	**P value**	**Mean difference (95% CI)**	**P value**	**Mean difference (95% CI)**	**P value**
Primary Outcome: Spherical equivalent refractive error									
SER ITT [c]	6 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx
	12 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx
	18 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx
SER PP [c]	Baseline	xx.x ± xx.x n=	xx.x ± xx.x n=						
	6 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx
	12 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx
	18 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx
Secondary Outcomes									
Reading speed ITT [d]	6 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx		
	12 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx		
	18 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx		
Reading speed PP [d]	Baseline	xx.x ± xx.x n=	xx.x ± xx.x n=						
	6 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx		
	12 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx		
	18 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx		
Uniocular BCdVA ITT [c]	6 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx		
	12 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx		
	18 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx		
Uniocular BCdVA PP [c]	Baseline	xx.x ± xx.x n=	xx.x ± xx.x n=						
	6 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx		
	12 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx		
	18 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx		
	6 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx		

Binocular BCdVA ITT [d]	12 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx		
	18 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx		
Binocular BCdVA PP [d]	Baseline	xx.x ± xx.x n=	xx.x ± xx.x n=						
	6 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx		
	12 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx		
	18 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx		
Central axial length ITT [c]	6 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx		
	12 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx		
	18 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx		
Central axial length PP [c]	Baseline	xx.x ± xx.x n=	xx.x ± xx.x n=						
	6 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx		
	12 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx		
	18 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx		
Uniocular near VA ITT[c]	6 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx		
	12 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx		
	18 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx		
Uniocular near VA PP[c]	Baseline	xx.x ± xx.x n=	xx.x ± xx.x n=						
	6 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx		
	12 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx		
	18 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx		
Binocular near VA ITT [d]	6 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx		
	12 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx		
	18 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx		
Binocular near VA PP [d]	Baseline	xx.x ± xx.x n=	xx.x ± xx.x n=						
	6 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx		
	12 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx		
	18 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx		
Pupil diameter ITT [c]	6 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx		
	12 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx		
	18 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx		
	Baseline	xx.x ± xx.x n=	xx.x ± xx.x n=						

Pupil diameter PP [c]	6 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx		
	12 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx		
	18 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx		
Spectacle correction ITT [e]	6 months	n (%)	n (%)	xx.x (x.x, x.x)	x.xx				
	12 months	n (%)	n (%)	xx.x (x.x, x.x)	x.xx				
	18 months	n (%)	n (%)	xx.x (x.x, x.x)	x.xx				
Spectacle correction PP [e]	Baseline	n (%)	n (%)	xx.x (x.x, x.x)	x.xx				
	6 months	n (%)	n (%)	xx.x (x.x, x.x)	x.xx				
	12 months	n (%)	n (%)	xx.x (x.x, x.x)	x.xx				
	18 months	n (%)	n (%)	xx.x (x.x, x.x)	x.xx				
Frequency of spectacle correction (all day) ITT [e]	6 months	n (%)	n (%)						
	12 months	n (%)	n (%)						
	18 months	n (%)	n (%)						
Frequency of spectacle correction (all day) PP [e]	Baseline	n (%)	n (%)						
	6 months	n (%)	n (%)						
	12 months	n (%)	n (%)						
	18 months	n (%)	n (%)						
Frequency of spectacle correction (sometimes) ITT [e]	6 months	n (%)	n (%)						
	12 months	n (%)	n (%)						
	18 months	n (%)	n (%)						
Frequency of spectacle correction (sometimes) PP [e]	Baseline	n (%)	n (%)						
	6 months	n (%)	n (%)						
	12 months	n (%)	n (%)						
	18 months	n (%)	n (%)						
EQ-5D-Y VAS ITT [d]	6 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx		
	12 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx		
	18 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx		
EQ-5D-Y VAS PP [d]	Baseline	xx.x ± xx.x n=	xx.x ± xx.x n=						
	6 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx		

	12 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx		
	18 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx		
EQ-5D-Y Index score ITT [d]	6 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx		
	12 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx		
	18 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx		
EQ-5D-Y Index score PP [d]	Baseline	xx.x ± xx.x n=	xx.x ± xx.x n=						
	6 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx		
	12 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx		
	18 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx	xx.x (x.x, x.x)	x.xx		
Tolerability									
Eye feels ITT [f]	6 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx				
	12 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx				
	18 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx				
Eye feels PP [f]	6 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx				
	12 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx				
	18 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx				
Stingy ITT [f]	6 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx				
	12 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx				
	18 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx				
Stingy PP [f]	6 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx				
	12 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx				
	18 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx				
Itchiness ITT [f]	6 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx				
	12 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx				
	18 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx				
Itchiness PP [f]	6 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx				
	12 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx				
	18 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx				
Blurry Vision ITT [f]	6 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx				
	12 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx				
	18 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx				
Blurry Vision PP [f]	6 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx				
	12 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx				
	18 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx				

Eyes sore ITT [f]	6 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx				
	12 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx				
	18 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx				
Eyes sore PP [f]	6 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx				
	12 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx				
	18 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx				
Difficult to read/write ITT [f]	6 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx				
	12 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx				
	18 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx				
Difficult to read/write PP [f]	6 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx				
	12 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx				
	18 months	xx.x ± xx.x n=	xx.x ± xx.x n=	xx.x (x.x, x.x)	x.xx				

[a] Adjusted for baseline SER. [b] Adjusted for baseline SER, minimisation variables (i.e. site and ethnicity), age and history of parental myopia (at least one parent). [c] Mean(SD) was calculated with data from both eyes. Mean difference estimate and p value from GEE. [d] Mean difference estimate and p value from ANCOVA. [e] Frequency (%) presented for categorical variables and risk difference and p value from the chi-square test (or fishers exact test if applicable).[f] Mean(SD) and p value from independent samples t-test, no adjustment as tolerability not measured at baseline.

Table XXX: Safety Outcomes by treatment group

	Number of Events			Number of Patients				
	Total N=	**Atropine sulfate N=**	**Placebo N=**	**Total N=**	**Atropine sulfate N=**	**Placebo N=**	**Risk Ratio (95% CI)**	**p-value**
Adverse Events	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	xx.x (x.x to x.x)	x.xx
Adverse Reactions	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	xx.x (x.x to x.x)	x.xx
Unexpected Adverse Reactions	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	xx.x (x.x to x.x)	x.xx
Serious Adverse Events	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	xx.x (x.x to x.x)	x.xx
Serious Adverse Reactions	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	xx.x (x.x to x.x)	x.xx
Suspected Unexpected Serious Adverse Reactions	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	xx.x (x.x to x.x)	x.xx
Fatal Serious Adverse Events	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	xx.x (x.x to x.x)	x.xx

Table XXX: Safety outcomes by system organ class and treatment group

		Number of Events			Number of Patients				
		Total	**Atropine sulfate**	**Placebo**	**Total N=**	**Atropine sulfate N=**	**Placebo N=**	**RR (95%CI)**	**p-value**
AEs	Blood and lymphatic system disorders	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	xx.x (x.x to x.x)	x.xx
	Cardiac disorders	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	xx.x (x.x to x.x)	x.xx
	Gastrointestinal disorders	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	xx.x (x.x to x.x)	x.xx
	Hepatobiliary disorders	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	xx.x (x.x to x.x)	x.xx
	Respiratory, thoracic and mediastinal disorders	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	xx.x (x.x to x.x)	x.xx
	……	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	xx.x (x.x to x.x)	x.xx
ARs	Blood and lymphatic system disorders	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	xx.x (x.x to x.x)	x.xx
	Cardiac disorders	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	xx.x (x.x to x.x)	x.xx
	Gastrointestinal disorders	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	xx.x (x.x to x.x)	x.xx
	Hepatobiliary disorders	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	xx.x (x.x to x.x)	x.xx
	Respiratory, thoracic and mediastinal disorders	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	xx.x (x.x to x.x)	x.xx
	……	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	xx.x (x.x to x.x)	x.xx
UARs	Blood and lymphatic system disorders	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	xx.x (x.x to x.x)	x.xx
	Cardiac disorders	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	xx.x (x.x to x.x)	x.xx
	Gastrointestinal disorders	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	xx.x (x.x to x.x)	x.xx

		Number of Events			Number of Patients				
		Total	Atropine sulfate	Placebo	Total N=	Atropine sulfate N=	Placebo N=	RR (95%CI)	p-value
	Hepatobiliary disorders	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	xx.x (x.x to x.x)	x.xx
	Respiratory, thoracic and mediastinal disorders	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	xx.x (x.x to x.x)	x.xx
	……	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	xx.x (x.x to x.x)	x.xx
SAEs	Blood and lymphatic system disorders	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	xx.x (x.x to x.x)	x.xx
	Cardiac disorders	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	xx.x (x.x to x.x)	x.xx
	Gastrointestinal disorders	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	xx.x (x.x to x.x)	x.xx
	Hepatobiliary disorders	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	xx.x (x.x to x.x)	x.xx
	Respiratory, thoracic and mediastinal disorders	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	xx.x (x.x to x.x)	x.xx
	……	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	xx.x (x.x to x.x)	x.xx
SARs	Blood and lymphatic system disorders	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	xx.x (x.x to x.x)	x.xx
	Cardiac disorders	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	xx.x (x.x to x.x)	x.xx
	Gastrointestinal disorders	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	xx.x (x.x to x.x)	x.xx
	Hepatobiliary disorders	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	xx.x (x.x to x.x)	x.xx
	Respiratory, thoracic and mediastinal disorders	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	xx.x (x.x to x.x)	x.xx
	……	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	xx.x (x.x to x.x)	x.xx

		Number of Events			Number of Patients				
		Total	**Atropine sulfate**	**Placebo**	**Total N=**	**Atropine sulfate N=**	**Placebo N=**	**RR (95%CI)**	**p-value**
SUSARs	Blood and lymphatic system disorders	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	xx.x (x.x to x.x)	x.xx
	Cardiac disorders	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	xx.x (x.x to x.x)	x.xx
	Gastrointestinal disorders	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	xx.x (x.x to x.x)	x.xx
	Hepatobiliary disorders	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	xx.x (x.x to x.x)	x.xx
	Respiratory, thoracic and mediastinal disorders	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	xx.x (x.x to x.x)	x.xx
	……	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	xx.x (x.x to x.x)	x.xx