Protocol

Low-dose Atropine for the Prevention of Myopia Progression in Danish Children (APP study)

A randomized, double-masked, multicenter, 36-month prospective 1:1:1 study of safety and efficacy of 0.1% atropine loading dose to single 0.01% atropine and placebo

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List of abbreviations

(Abbreviations are listed alphabetically)

AE:	Adverse event
AR:	Adverse reaction
BCVA:	Best-corrected visual acuity
ETDRS:	Early Treatment Diabetic Retinopathy study chart
CRF:	Case Report Form
ICH-GCP:	International Conference on Harmonization - Good Clinical Practice
IOP:	Intraocular pressure
logMAR:	Logarithm to the minimal angle of resolution
OCT:	Optical coherence tomography
SAE:	Serious adverse event
SAR:	Serious adverse reaction
UAR:	Unexpected adverse reaction
SUSAR:	Suspected unexpected serious adverse reaction

List of investigators, collaborators and research facilities

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The principle investigators (steering committee) of the study are:

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Research facilities

Clinical research facilities accustomed to GCP studies have been established at:

Research facility #1: Department of Ophthalmology, Rigshospitalet-Glostrup
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Research facility #2: Department of Ophthalmology, Aarhus University Hospital
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Contact person: Toke Bek (Principle investigator #2)

Research facility #3: Department of Ophthalmology, Vejle Hospital
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Purpose

Myopia (nearsightedness) is increasing in prevalence throughout the world. It is associated with a risk of potentially blinding complications such as retinal detachment and myopic maculopathy. There is a direct association between the degree of myopia and the risk of complications. Myopia develops in childhood and during adolescence. To prevent higher degrees of myopia, we need to halt disease progression in children and teenagers. Low-dose atropine eye drops have been shown to reduce myopia progression by 50% in Asian populations but its effect in non-Asian populations is unknown. The aim of this study is to investigate if low-dose atropine can reduce myopia progression in Danish children and teenagers. The study is an investigator initiated randomized clinical trial conducted as a collaboration between three Danish Eye Departments covering all of Denmark.

Introduction

Globally, myopia is a common cause of visual loss. (1,2) Myopia is the most common cause of moderate and severe visual impairment, (3,4) the second most common cause of blindness. (3,4) The prevalence of myopia is increasing. (1,2,5,6) In East Asia 80-90% of school-leavers are myopic (7) whereas Europeans are less affected, however still approximately 20% of 12-13 years children (8) and 47% of young adults (25-29 years) are myopic. (6) Myopia and especially high myopia (-6 diopters or more) increases the risk of sight-threatening eye diseases such as glaucoma, cataract, retinal detachment and myopic maculopathy. (9-11) Accordingly, myopia is now an immediate priority of the World Health Organization`s Global Initiative for the Elimination of Avoidable Blindness, and potential interventions to reduce myopia progression are warranted. (12)

Humans are born hypermetropic (farsighted) and during childhood the eye grows to reach adult size in a process termed emmetropization. In some children, eye growth and especially axial length elongation exceeds the normal growth rate and progress beyond normal adult length resulting in myopia. (13) In economically developed societies, most myopia appears during childhood (8-12 years), particularly during the school years. Since myopia typically develops during childhood it is relevant and necessary to investigate possible methods of halting the progression in children.

Myopia is the result of excessive elongation of the eyeball with light focusing in front of the retina causing a blurred image. It has yet to be established why this elongation develops but a number of theories have been proposed. Most researchers agree that both environmental and genetic factors contribute to the

development of myopia. (9,14) A small proportion of myopia is familial, generally early in onset and of high level (-6 diopters or more). The chromosomal locations characterized so far for high familial myopia do not seem to be relevant to school myopia. (15) Studies suggest that genetics are only accountable for a small proportion of myopia cases whereas the increasing prevalence is predominately the result of environmental factors. (9,15,16) Still, the exact environmental factors and the relative contribution of each factor remain elusive. Two major risk factors identified are intensive education, possibly by a link to near work stress, and limited time spent outdoors. (17) Near work is one of the most frequently cited risk factors for myopia. Near work causes convergence of the eyes and accommodation – both have been used to explain the progression of myopia (*use-abuse theory*) although an association has not been consistently observed. (17-19) In animal models, axial length and choroidal thickness may be controlled by retinal defocus. (18-20) Changes in the peripheral defocus by special contact lenses in human studies induces a prompt increase in choroidal thickness. (21) In the myopic human eye, the relative peripheral hyperopia is induced by the oval shaped eyeball, which may signal to further axial growth and progression of myopia possibly through signal pathways in the choroid. (22,23) In other words, in addition to genetic predisposition and near work a mismatch between image focusing in the central and peripheral retina have received theoretical and experimental support as likely causes for myopia development and progression. Thus, myopia is of diverse etiology.

Many studies have investigated possible preventive treatments of myopia. Time spent outdoors may reduce the odds of myopia onset by 2% per additional hour spent outside per week. (22) Orthokeratology contact lenses, which are rigid gas permeable contact lenses reshaping the corneal surface when worn nightly, have been shown to reduce axial elongation by 36-46%, (23-27) but may be associated with infectious keratitis. (28) In terms of relative peripheral hyperopia, the evidence is contradictory. Previous studies have shown that the peripheral defocus only have little influence on the risk of myopia onset, myopia progression and axial elongation. (29) Correspondingly, treatment strategies with novel spectacle lenses aimed at reducing the peripheral hyperopic defocus showed no statistically significant difference in the rates of myopia progression between the control and novel spectacle lens wearing eyes. (30) However, recent studies show that soft multifocal contact lenses slow myopia progression by a weighted average percent of 36.4% and axial elongation by a weighted average percent of 37.9%. (31)

Atropine, a non-selective muscarine acetylcholine receptor antagonist and pirenzepine, a selective muscarine (M1) receptor antagonist, reduces myopia progression by approximately 50% in Asian children. (32,33) The effect of pirenzepine was shown in 2 randomized clinical trials but the use of pirenzepine was

associated with side effects such as papillary conjunctivitis, photophobia and difficulties with near work. (34,35) Atropine has been shown in several animal (18,36,37) and human studies (38,39) to prevent axial elongation. However, the underlying basic mechanism for this effect in still unclear.

The effect of atropine is dose dependent with high dose (1%) superior (≥0.50 diopter reduction in myopia/year) to other treatments. (33) However, the side effects of high dose treatment including photophobia related to pupil dilation, reading problems and headache together with the profound myopic rebound effect after treatment cessation make treatment unacceptable for standard care. (40) The Atropine for Treatment of Childhood Myopia (ATOM 2) study (41) compared the safety and efficacy of 3 lower doses of atropine (0.5%, 0.1% and 0.01%). The study was a 60-month doubled masked, randomized, controlled trial including 400 Asian children aged 6-12 years. A washout period of 12 months was included, and surprisingly atropine 0.01% was found superior in reducing myopia progression (-1.4 diopters less) compared to 0.5% and 0.1% after 60-months mainly because of less rebound effect in myopia progression when treatment was stopped. The side effects of atropine 0.01% and 0.1% were low. Pupil size under both photopic and mesopic conditions were only 1 and 3 millimeters, respectively, and accommodation amplitude decreased to 11.3 diopters and 3.8 diopters, respectively. Allergic conjunctivitis was seen in 4.5% of the children in the 0.1% group but in no children in the 0.01% group. (41)

Atropine appears to have the strongest clinical effect on reducing myopia progression of all reported modalities so far, and low-dose treatment seems favorable due to limited side effects and greater long-term effects because of the rebound catch-up myopia seen after treatment cessation with higher doses. However, these results are based on Asian studies, and it is unknown whether similar results can be replicated in Danish children, since environmental factors, heritability and genetics may influence the effect of the treatment.

Hypothesis

The main hypotheses tested in this study are:

- 0.01% atropine one drop nightly reduces the progression of childhood myopia in Danish children.
- 0.01% atropine one drop nightly is safe and with no significant side effects.
- A 6-month loading dose of 0.1% atropine followed by a 0.01% atropine maintenance dose is superior to single 0.01% atropine.
- 0.1% atropine one drop nightly is safe and has tolerable side effects.

- The rebound effect after stopping both atropine regimens is limited.
- Choroidal thickness is a predictor for the progression of childhood myopia.

Methods

Study design

The study is designed as a randomized, double-masked, multicenter, 36-month prospective, phase II 1:1:1 study of safety and efficacy of 0.1% atropine loading dose to single 0.01% atropine versus placebo. In phase 1 (treatment phase), the participants will be randomized in a 1:1:1 ratio to receive 0.1% atropine loading dose for 6 months followed by 0.01 % atropine for 18 months (n=50) versus 0.01% atropine (n=50) or placebo (n=50) for 24 months. The atropine is administered as one eye drop daily in each eye at bedtime. In phase 2 (washout phase), treatment will be stopped and the participants monitored for 12 months. A schematic presentation of the 3 interventional groups are shown in Figure 1.

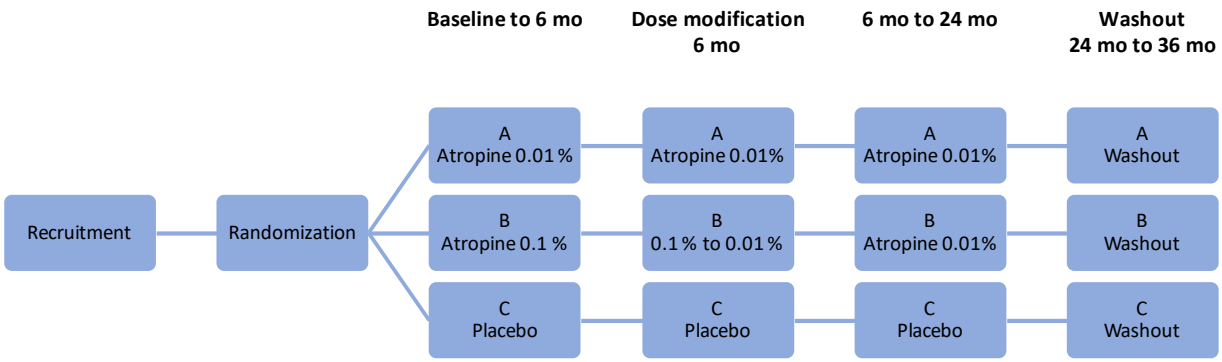

Figure 1: A schematic presentation of the 3 interventional groups.

Study period

The inclusion period began on January 1, 2019 and was completed at the end of April 2021. 124 potential candidates were screened, and 97 research participants were randomized for the intervention. Patients will receive 24 months treatment with atropine or placebo followed by a 12 months washout phase to allow for detection of a possible rebound effect. The last patient visit is scheduled to take place on April 30, 2024. Statistical evaluation of the study results and reporting of findings is scheduled to take approximately 8 months with an expected completion of the study on December 31, 2024. A rough time schedule is presented in Table 1. The authorities will be informed when the study has finished. If finished at the

planned date authorities will be informed within 90 days, if finished earlier authorities will be informed within 15 days.

	2018				2019				2020				2021				2022				2023				2024			
Quarter	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
Application for Danish Medicines Agency	•	•																										
Application for National Committee on Health Research Ethics			•	•																								
Application for Data Protection Agency			•	•																								
Recruitment and follow-up					•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•		
Ph.D. courses					•	•	•	•	•	•	•	•	•	•	•	•			•	•	•	•	•	•	•	•		
Papers and theses																•	•	•	•	•	•	•	•	•	•	•	•	•

Table 1: Time schedule

Facilities

Clinical research facilities have been established at (1) Department of Ophthalmology, Rigshospitalet, (2) Department of Ophthalmology, Aarhus University Hospital and (3) Department of Ophthalmology, Vejle Hospital. All necessary equipment for the study as well as office facilities are already available at the facilities. All three institutions are well-trained in performing GCP clinical trials.

Randomization

Participants will be randomly assigned using a computer algorithm to 1 of the 3 interventional groups if the patient and his/her parents consent to participation in the study after the screening visit and after having received oral and written information on the study. Written informed consent will be obtained from parents and verbal assent will be obtained from children before randomization. Randomization will be done in 3 strata defined by research facility (i.e. (1) Department of Ophthalmology, Rigshospitalet, (2) Department of Ophthalmology, Aarhus University Hospital and (3) Department of Ophthalmology, Vejle Hospital). Randomization will be performed using a computer algorithm which is in-built in the electronic clinical report form (eCRF). The algorithm is based on a list of randomly created numbers that are each assigned to a specific treatment. The randomization list is stored by the sponsor-investigator so that each

randomization number is listed on a sealed envelope containing the specific treatment for that randomization number. All envelopes are stored together and in manner that is not accessible to other study investigators. In case of an emergency, the sealed envelope for the randomization code concerning a specific participant may be opened by the sponsor-investigator whereby sponsor-investigator will be unmasked to treatment status. If the code is broken, the sponsor-investigator will no longer take part in any of the directly participant related examinations, and the sponsor-investigator will not share this information with any other study investigators.

Blinding

Allocation concealment is performed by masking the investigators, additional study team performing the ocular measurements, parents and patients to randomization status throughout the entire study period. All statistical analyses will be performed masked to randomization status. A list linking participant study identification number to randomization status will be kept under lock in a designated space unavailable to study investigators. Trial medication will be prepackaged from external collaborator #1 so that bottles are pre-labeled according to the European rules on labelling of trial medicines (see *Appendix 1*) and of similar appearance.

If necessary, sponsor-investigator will be unblinded as to participants treatment status as described above. All statistical analyses will be performed in a masked fashion allowing sponsor-investigator to part of the analyses.

Participants

Criteria for inclusion

Preferably, children with a history of progression will be included in the study but since reliable refractive history can be difficult to obtain, the inclusion criteria are subdivided by age groups:

- Children aged ≥6-<9 years: myopia ≤-1 (spherical power) in at least one eye
- Children aged ≥9-≤12 years: myopia ≤-2 (spherical power) in at least one eye
- Cylinder less than 1.5 diopters

Criteria for exclusion

- Myopia related to retinal dystrophies
- Collagen syndroms (Ehlers-Danlos syndrome, Marfan syndrome and Stickler syndrome)

- Other ocular pathology (e.g., amblyopia, strabismus)
- Previous eye surgery
- Previous use of agents thought to affect myopia progression, e.g. atropine, pirenzepine or 7-methylxanthine (metabolite of caffeine and theobromine) and orthokeratology contact lenses
- Known allergy to atropine or any of the contents of the trial medication (active and in-active ingredients) used in the study
- Non-compliance to eye examinations
- Serious systemic health troubles (e.g., cardiac or respiratory illness) and developmental disorders and delays

Procedures for recruiting participants

Patients will be recruited from private practitioners in ophthalmology referring children to the 3 research centers at (1) Department of Ophthalmology, Rigshospitalet, (2) Department of Ophthalmology, Aarhus University Hospital and (3) Department of Ophthalmology, Vejle Hospital. In addition, patients can be referred to the research centers from optometrists/opticians, orthoptics or other health care professionals handling myopic children. Self-referral by patients and parents who have heard of the study from others will also be accepted.

The study will be announced to private practitioners in ophthalmology, optometrists/opticians and orthoptics at relevant ophthalmological conferences, meetings and magazines during spring, summer and autumn 2018. Ophthalmologist, optometrists/opticians and orthoptics who have expressed interest in in the study will be invited to informational meetings where the study, criteria for inclusion and study logistics will be presented in detail by the investigators. The written participant information describing the study in lay terms will be available for the ophthalmologist, optometrists/opticians and orthoptics to be distributed in their waiting rooms. A written parental authority will be attached to the participant information. Patients and parents who express an interest to participate in the study will be referred to the nearest research facility. Thus, the patient and parents will have ample time to read the information and consider if they want to participate before they are seen at the research facilities.

The written participant information for the parents, the written parental authority and a copy of subjects' rights in a health science research project are attached as appendices.

After referral, the patient and parents will be contacted by phone by an investigator and invited to a screening visit. At the screening visit, the patient and parents will receive oral and written information about the study and the patient will undergo a screening ophthalmological examination by the investigators. The screening ophthalmological examination will only be performed after the patient and parents have consented to study participation and a signed consent statement has been obtained from the parents. The patient and parents will be invited to bring a friend or relative to the screening visit. Patients who fulfill the inclusion criteria and none of the exclusion criteria will be offered participation in the study.

Informed consent

The patient and parents will receive oral and written information about the study at the screening visit. The screening visit takes place in a secluded room at one of the research facilities without disturbances or interruptions. The patient and parents will be offered at least a 24 hours reflection period and scheduled for a visit at a later time point to sign the consent form. Patients and parents who are offered reflection period may, on request, consent to study participation at the screening visit. Written informed consent will be obtained from the parents and verbal consent will be obtained from the patient.

As a rule, only an investigator can obtain informed consent and sign the consent form. However, the sponsor-investigator request to waive from this requirement so that involved study staff (i.e. project nurses and optometrists) can obtain informed consent and sign the consent form as described in this section. The study staff in question is skilled within the pediatric ophthalmology from daily work life and trained in the study protocol and protocol specific procedures. If the nurse or optometrist wants further assessment or a parent wished to consult a medical doctor, an investigator is accessible. The assignment of obtaining consent is delegated to study staff (i.e. project nurses and optometrists) under the responsibility of the local principal investigator.

If both parents share the legal custody of the child, both parents must sign the consent statement. A written parental authority may be made from one parent to the other parent to give consent on behalf of both parents to study participation. The written parental authority will state what the purpose is (i.e., the child's participation in the study) and a duration of the parental authority of 1 month. The written parental authority will be included in the material distributed from the private practitioner in ophthalmology and requested completed at the screening visit if one parent is unable to participate in the screening visit. If only one parent holds the legal custody of the child, only this parent must sign the consent statement. In

that case, the investigator will ensure the necessary documentation for the legal custody, e.g. by asking the parent to provide an extract from the CPR registry or a copy of the child custody verdict.

During the screening visit, the patient and parents will receive a new copy of the written participant information for the parents and a copy of subjects' rights in a health science research project.

The study staff who informs the patient and parents will be aware of the pedagogical circumstances related to informing a child or young person of the relevant age group. However, the study staff does not have to hold a pedagogical education. The patient will be informed and involved in the discussions with the parents about the study, to the extent that the patient is capable of understanding the investigational situation. The information will therefore be adapted to the patient's intellectual level and mental capability. The patient's own desire to participate will be given importance when applicable and relevant. Protest also means resistance which is not formulated orally but which is expressed by the patient's attitude, body language or resistance to examination. This also applies to the entire trial period. A consent from the parents will never implies that study participation will be forced against the patient's own will. The patient will not be legal age during the course of the study period.

If the patient and parents consent to study participation the consent can be withdrawn at any time without any consequences to the child or family.

Patient and parents will not be offered any remuneration for participation in the study.

Access to patient records

At referral to the research facility, the healthcare professional involved will forward relevant information to the researchers involved in the trial. Only data concerning patients and parents who have shown interest in the study will be disclosed to the study. The information includes identification data, contact data and demographic data, such as gender and age, as well as racial background and health information relevant to the study, e.g. visual acuity, refraction, biometrics, retinal examinations and other ophthalmological and systemic diseases (e.g. cardiovascular disease, respiratory disease, rheumatologic disease, musculoskeletal disease, developmental disorders and delays).

At the time the patient and parents consent to study participation, they accept that the Danish Medicines Agency, sponsor (i.e. Line Kessel, sponsor-investigator), investigators (i.e. researchers at the Department of

Ophthalmology at Rigshospitalet; the Department of Ophthalmology at Aarhus University Hospital, and the Department of Ophthalmology at Vejle Hospital) and monitor (i.e. GCP units at Copenhagen University Hospital, Aalborg and Aarhus University Hospitals, and Odense University Hospital) may have direct access to obtaining relevant health information in the patient record including electronic records for quality control and monitoring.

Efforts to maximize adherence to treatment

If the patient and parents consent to study participation they will be offered to use artificial tear eye drops until the baseline visit to assess their ability to give the child eye drops each day throughout the 2-year treatment phase. The run-in phase will have an expected duration of approximately 1-4 weeks. The artificial tear eye drops will be distributed free of charge from the research facilities and is not regarded as trial medication. The summary of product characteristics of the artificial tear eye drops is available in the investigators brochure.

To assess the patient and parents' compliance level, the parents will receive written instructions at each planned visit for overview and checkmark of daily use of trial medication. The schedule will show which bottle (bottle number) the parents should use for each specific date interval. The written instruction works as a diary for trial medication use. For each week day in the date interval the parents can check mark that the eye drops have been (or not been) used as planned and make a optional comment. The written instruction filled out with check marks and notes comments by the parents as needed will be handed back to the researcher at each subsequent study-visit.

An example of the written instruction (*Dryppeskema til forsøgslægemidlet* in Danish) is attached as separate appendix.

At each visit during use of trial medication, the parents will additionally be asked how many days they have administered the trial medication as prescribed on an average week since last visit.

Patients and parents with a 75% compliance rate will be considered compliant.

Trial medicinations, procedures for receival and internal check-up

All trial medication (including placebo eye drops) will be manufactured and delivered from Skanderborg Apothecary (a simplified IMPD is provided in the investigators brochure). Upon receival of trial medication

(including placebo), medication will be registered, handled and stored according to local guidelines. Trial medication will be kept in a locked room with logging of temperature. Any person associated with the study and to whom the task of receiving and registering trial medications has been delegated will be able to receive and perform internal check-up of trial medication. Information regarding this will be kept in trial master file.

Sample size and data analysis

The primary endpoint of the present study is the mean change in axial length 36 months after baseline. Axial length is strongly related to the refraction of the eye and since we do not have valid data for axial length elongation in Danish myopic children, the power calculations have been performed using the refraction (in spherical equivalent) as a surrogate measure. A progression in untreated childhood myopia of -1.2 $\pm$ 0.69 diopters yearly has been shown in Asian children (ATOM1 study). (33) A similar myopia progression rate has been documented in untreated Danish school children. (42) Given a significance level (alpha) of 0.05 and a statistical power (type 2 error) of 80%, a study size of 21 patients in each interventional arm will be needed, assuming a difference in myopia progression of 50% after 36 months. In order to compensate for the study length and drop-out rates and unknown effect of low-dose atropine in non-Asian children, 50 patients will be included in each interventional arm.

Examinations

All examinations are non-contact methods that are used in daily clinical routine on children. A schematic presentation of the examinations during the study is shown in Figure 2 (see below). Expected duration of the different examinations is indicated in parentheses in the following.

Examination at screening visit (approx. 1 hour 30 min to 2 hours):

- Best corrected (using “push plus” refraction principle) visual acuity using the HOTV chart that is based on the same principle as the Early Treatment Diabetic Retinopathy study (ETDRS) chart.
- Cycloplegic auto-refraction performed at least 30 minutes after the last of two drops of Minims® (Bausch & Lomb, Chauvin Pharmaceuticals Ltd., UK) cyclopentolate 1% separated 5 minutes apart. A minimum of 5 readings are made. In situations of unstable fixation, readings are eliminated if cylinder values deviate more than 1 diopter from values obtained during stable fixation and/or obvious incorrect readings.

- Intraocular pressure (Icare® TA01i, tonometer, Icare Finland Oy, Vantaa, Finland) with a minimum of 5 readings.
- Axial length measurements (IOLMaster® 700, Carl Zeiss Meditec AG, Jena, Germany). Separate measurements are recorded until 5 readings variating less ≤ 0.05 mm are obtained.
- Anterior Eye Segment Tomography by Scheimpflug imaging (Pentacam®, OCULUS Optikgeräte GmbH, Wetzlar, Germany).
- Pupil diameter measurements under different light intensities.

NB! If the screening visit and baseline visit take place less than 1 month in between, examinations performed at the screening visit will not be repeated at the baseline visit.

Standard examinations at baseline and month 3, 6, 12, 18, 24, 30 and 36 (approx. 2 hours):

- Best corrected (using "push plus" refraction principle) visual acuity using the HOTV chart that is based on the same principle as the ETDRS chart.
- Cycloplegic auto-refraction performed 30 minutes after the last of two drops of Minims® (Bausch & Lomb, Chauvin Pharmaceuticals Ltd., UK) cyclopentolate 1% separated 5 minutes apart. A minimum of 5 readings are made. In situations of unstable fixation, readings are eliminated if cylinder values deviate more than 1 diopter from values obtained during stable fixation and/or obvious incorrect readings. In situations of more than 5 valid readings, the number is reduced by eliminating readings from the beginning alternating with the end of the set of measurements until 5 readings remain.
- Intraocular pressure (Icare® TAO1i, tonometer, Icare Finland Oy, Vantaa, Finland) with a minimum of 5 readings.
- Axial length measurements (IOLMaster® 700, Carl Zeiss AG, Oberkochen, Germany). Separate measurements are recorded until 5 readings variating less ≤ 0.05 mm are obtained.
- Anterior Eye Segment Tomography by Scheimpflug imaging (Pentacam®, OCULUS Optikgeräte GmbH, Wetzlar, Germany).
- Pupil diameter measurements under different light intensities.
- Swept Source Optical Coherence Tomography chorio-retinal images (DRI OCT Triton, Topcon, Hasunuma-cho, Itabashi-ku, Tokyo, Japan) at baseline and month 6,12,18,24,30 and 36.
- Near visual acuity assessed using best-corrected distance spectacle correction with a reduced logarithm of the minimum angle of resolution (logMAR) reading chart placed at 40 cm under well-lit conditions.

- Near point of accommodation measured using a Royal Air Force near point rule using best-corrected distance spectacle correction. Accommodation amplitude is calculated as the inverse of near point of accommodation.

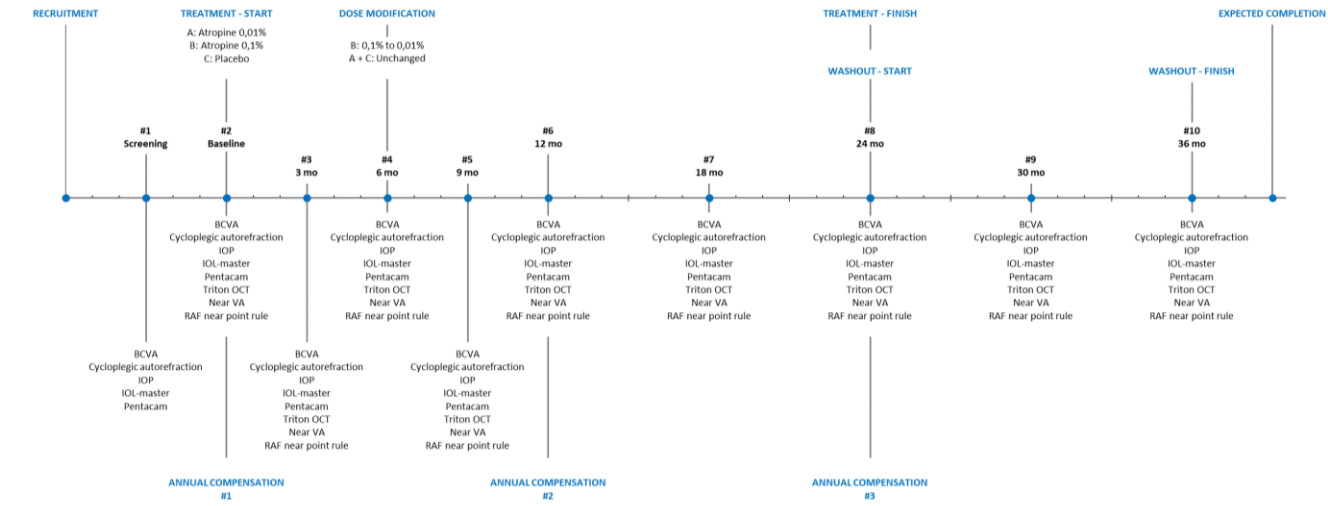

Figure 2: Time schedule of the study.

Monofocal spectacle and soft contact lenses

Several recent studies and reports conclude that undercorrection of myopia is associated with higher rate of myopic progression in children. (28,43-46) Hence, the patients will be provided full correction of their refractive error during the entire trial period. The parents will receive a maximum annual compensation of 1000 DKK at baseline visit, 12 months visit and 24 months visit designated the acquisition of full refractive correction. The patient and parents decide if spectacles, contact lenses or both are preferred as refractive correction but only monofocal refraction may be purchased. At baseline visit, 12 months visit and 24 months visit, the patient and parents will receive a refractive prescription to show the optician when acquiring new refractive correction. The parents will be instructed to submit documentation for each purchase by email within one month. For each new acquisition of refractive correction, only the purchased amount up to a maximum of 1000 DKK will be compensated. The compensation will be transferred to desired bank account appointed by the parents when submitting the documentation of purchase.

If a patient experiences glare or their parents are worried of excessive light exposure as a result of trial medication, the patient will be offered photochromatic spectacles (that darken on exposure to ultraviolet light). If a patient experiences difficulty with near vision as a result of trial medication, the patient will be offered reading add as bifocal spectacles. In both cases, the investigator will decide upon clinical

assessment if photochromatic or bifocal spectacles are indicated. If deemed relevant, the parents will be instructed in the acquisition and compensated the full amount of purchase. The purchase of photochromatic or bifocal spectacles will not be compensated if the investigator finds it irrelevant or if the investigator is not consulted before the purchase.

Endpoints

Primary endpoints

- Axial length elongation at 36 months
- Change in spherical equivalent at 36 months

Secondary endpoints

- Adverse effects and reactions
- Change in choroidal thickness
- Change in ocular biometry (i.e. keratometry, anterior chamber depth, lens thickness, vitreous axial distance)
- Change in higher-order aberrations

Risks, side effects and inconveniences

The use of atropine 1% eye drops has been approved for cycloplegia, mydriasis and penalization of the healthy eye in the treatment of amblyopia. The most frequently reported side effects of atropine 1% eye drops include photophobia, blurred vision, decreased lacrimation and allergic reactions such as papillary conjunctivitis, contact dermatitis and lid edema. Systemic side effects rarely occur but include anticholinergic effects such as dryness of skin, mouth and throat from decreased secretion from mucus membranes, flushing, gastrointestinal symptoms, urinary retention and tachycardia. Systemic absorption may be reduced by gently compressing the lacrimal sac at the medial canthus for a minute during and following the instillation of the drops. This blocks the passage of the drops via the naso-lacrimal duct to the wide absorptive area of the nasal and pharyngeal mucosa.

The use of low-dose atropine has not yet been approved for the treatment of myopia and is not yet commercially available. In the ATOM 2 study, the reported side effects of atropine 0.01% and 0.1% were low. The pupil size under both photopic and mesopic conditions increased only 1 and 3 millimeters,

respectively, in the 0.01% and 0.1% group. (32) Accommodation amplitude in the 0.01% group was reduced to only 11.3 diopters (from 16.2 diopters) compared with a reduction to 3.8 diopters (from 16.7 diopters) in the 0.1% group. The mean reduction in accommodation amplitude over 2 years treatment was 4.6 diopters and 10.1 diopters in the atropine 0.01% and 0.1% group, respectively. (32) In functional terms, the changes in accommodation meant that near visual acuity was not significantly impaired in the 0.01% group, whereas deficiencies were noted in the 0.1% group. (32) Mean distant best-corrected visual acuity (BCVA) was not affected by low-dose atropine, although 13% in both groups reported mild distance blur. (32) Regarding adverse reactions attributable to atropine, allergic reactions were most frequent in the ATOM 2 study with 3.2% experiencing allergic conjunctivitis and 0.8% experiencing an allergy-associated dermatitis, all of which were in the 0.1% and 0.5% group. From a total of 400 children, 6 children had other eye symptoms, 5 of which could be attributed to atropine treatment, including 1 case of ocular irritation and 1 case of blur in the atropine 0.01% group, and 2 cases of ocular irritation and 1 case of intolerable glare in the atropine 0.5% group. All reported side effects were reversible on stopping medication. No adverse events were deemed to be related to the use of atropine at any concentration. (32)

Patients who experience adverse effects during the study will provide data for the study to determine the rate of complications. Since the sample size calculation was made to account for dropout, additional inclusion of participants to replace excluded participants is not intended.

Registration of adverse events

At all trial visits, patients are checked for adverse events to the investigational medicinal product. All visits include measuring distant BCVA, IOP, pupil size and accommodation. The patients and parents will also be asked for subjective complaints and symptoms related to the investigational medicinal product. The number of trial visits is illustrated in Figure 2. Patient and parents will be instructed to contact the investigators immediately if vision gets worse, the eye or eye surroundings turns red and/or painful or they become sensitive to light, or experience halos around light sources. If the patient experiences an adverse event or reaction within the trial period, the patient will be monitored and/or treated for as long as it is relevant given the circumstances. Principle investigators will make the decision.

Adverse events and reactions

Adverse event (AE): Any untoward event regarding a participant in the clinical trial treated with an investigational medicinal product, not necessarily linked to the treatment.

Adverse reaction (AR): Any harmful and untoward reaction to an investigational medicinal product with no regards to the dose.

Unexpected adverse reaction (UAR): An adverse reaction of which the character or severity does not match the description of adverse reactions in the summary product characteristics for the given investigational medicinal product.

Serious adverse event (SAE) or serious adverse reaction (SAR): An adverse event or reaction that, regardless of dose, results in death, is life-threatening, causes hospitalization, results in significant or sustained incapacity, or leads to a congenital anomaly or malformation.

Suspected unexpected serious adverse reaction (SUSAR): A suspected unexpected serious adverse reaction which was not expected.

Reporting adverse effects to the authorities

As a rule, all adverse events will be registered in a clinical trial on medicinal drugs. However, due to the age, level of activity and healthy nature of the patients involved as well as the duration and logistic possibilities of the study considered, the sponsor-investigator request to waive from this requirement.

Therefore, adverse events and reactions that are considered normal reactions to an eye examination (including stinging when applying eye drops for the examinations and short-term photophobia and blurred vision following eye examination) will not be considered an AE/AR. The sponsor-investigator request that only the following organ-specific symptoms or any likely related symptoms will be reported during the study as AE/AR: visual symptoms (e.g. photophobia, blurred vision and difficulties reading and focusing on text on short distance); eye-related symptoms (e.g. red eye, dry eye, itching eye, stinging or painful eye, changes in lacrimation, allergic reactions such as papillary conjunctivitis, contact dermatitis and lid edema); symptoms of the eye surroundings (e.g. skin changes (i.e. itching, stinging, swelling, redness and dryness); systemic anticholinergic effects (e.g. dryness of skin, mouth and throat from decreased secretion from mucus membranes, flushing, gastrointestinal symptoms, urinary retention and tachycardia). At baseline, patients and parents will be asked to report if the patient has any known tendency within the listed symptoms, e.g. constipation, urinary problems or skin-related problems such as dry or eczematoid skin. For

example, if a patient is reported to have a tendency to constipation at baseline, the registration and reporting of AE/AE during study participation will be based upon changes in existing symptoms at baseline.

Due to the requested deviation from the usual procedure regarding registration and reporting of AE/AR, examples of adverse events that are exempted from registration and reporting includes conditions that are common to normal child development and child life (e.g. growth, menarche, common colds, a skin abrasion after falling in the schoolyard, a plantar wart, a superficial cut in the finger after the scout camp, tenderness in the shoulder after travel vaccination. However, if an investigator has the least suspicion that e.g. the superficial cut in the finger is related to difficulties in accommodation the event will be registered and reported as an adverse event.

Sponsor-investigator will report any serious adverse event and reaction (SAE/SAR) as well as suspected unexpected serious adverse reaction (SUSAR) to the Danish Medicines Agency and the Committees on Health Research Ethics for the Capital Region of Denmark. All SAE/SAR will be reported to the sponsor-investigator by email. All SAE/SAR will be reported to the sponsor-investigator within 24 hours of recognition of the investigator. SAEs will be included in the final report of the study. SARs and SUSARs will be included in an annual report to the Danish Medicines Agency and the Committees on Health Research Ethics for the Capital Region of Denmark. All reports will include a report on the safety of participants and a comment on the consequences for the ongoing trial.

SUSARs that are mortal or life-threatening will be reported by sponsor-investigator as soon as possible and within 7 days from recognition of the sponsor-investigator. All relevant information on follow-up will be reported within 8 days from the initial report. All other SUSARs will be reported within 15 days from recognition.

Since atropine 0.01% and 0.1% eye drops are not yet commercially available, no summary of product characteristics is assessable. As a result, the summary of product characteristics from Minims® (Bausch & Lomb, Chauvin Pharmaceuticals Ltd., UK) Atropine Sulphate 1% will serve as reference document. Due to no available summary of product characteristics for the investigational medicinal product the sponsor-investigator has decided that all SARs will be reported as SUSARs.

When the study has completed all results, adverse events and adverse reactions will be entered in the EudraCT within 1 year. The Danish Medicines Agency will be informed within 90 days from termination of the study.

Criteria for aborting the study

The entire study will be aborted if one or more of the interventional groups experience a significant worse outcome than the other interventional groups regarding unexpected complications.
Interim analyses will be performed when all included patients have completed the first six months, year 1 and year 2.
In case of adverse effect to the trial medication, the participants will be treated according to standard procedures at our research facilities.

Ethical considerations

The study has the potential to determine if low-dose atropine reduces the progression of myopia in Danish children and pose a treatment for final reduction in myopia and accordingly fewer ocular sight threatening complications such as retinal detachment, glaucoma and myopic maculopathy. Reducing the final myopia may benefit both patients and society in terms of reduced inconvenience, reduced sight threatening consequences of myopia and overall reduced costs. The investigators of the study therefore find that the potential advantages outweigh the inconveniences and risks related to participation in the study. We do not expect that the treatment will be associated with significant adverse events or harms. The children will receive a thorough eye examination and their refraction will be corrected annually which is thought to reduce myopia progression thus giving all children an advantage of participation. It may be considered a disadvantage that the patients and parents will have to spent a lot of time on the examinations, however, the benefits of participation (especially the expected reduced myopia progression and financial support for refractive correction) greatly outweighs the disadvantages of participation.

The study relies on testing the effect on myopia progression of atropine in children. Pharmaceutical testing in children should always be minimized. When it comes to myopia, the disease only progress in children and teenagers and in order to halt disease progression to reduce the risk associated with excessive myopia we need to treat children. For each individual child participating in the study, the life term benefits of a

reduced end degree of myopia outweigh the ethical concerns of pharmaceutical testing in children, especially since we do not expect any serious side effects of the treatment.

The participants in the study are, as participants in a health science study, covered by the patient insurance.

Quality assurance

The study is monitored by the GCP-units at Copenhagen University Hospital, Aalborg and Aarhus University Hospitals, and Odense University Hospital. The GCP units and the Danish Health Authority will be allowed direct access to source data during monitoring, auditing and/or inspection. Any information about participants is protected according to the Danish Data Protection Act. The study has been approved by the Danish Medicines Agency (reference number 2018040088), the Committees on Health Research Ethics for the Capital Region of Denmark and the Danish Data Protection Agency. The study will be registered in the EudraCT- and www.clinicaltrials.gov databases. The study will be conducted per protocol and applicable laws, and in accordance with the principle of the Declaration of Helsinki and in compliance with International Conference on Harmonization - Good Clinical Practice (ICH-GCP).

Data storage after the study has completed

The data will be stored for 5 years after the study has completed. Electronical Case Report Form (eCRF) will be handled in REDCap. Logging and monitoring is performed by CIMT (Center for IT, Medico og Telefoni) RegionH.

Economy

This is an investigator-initiated study and we declare no conflicts of interests. We have applied for funding from independent funds and received a total of 7,453,500 DKK to cover the costs with preparing and initiating the study in 2018 and 2019. We intend to continue applying for funding through independent funds. The parents of the patient and the Committees on Health Research Ethics for the Capital Region of Denmark will be informed if additional funding is obtained. The budget of the study is presented in Table 2.

Expenses	Version: v9_24APR2022							Grants	
Article	2019	2020	2021	2022	2023	2024	Total amount	Article	Total amount
Salary, Ph.D. student (A)	600.000 DKK	600.000 DKK	625.000 DKK	495.000 DKK			2.320.000 DKK	Fight for Sight Denmark 2017	304.399 DKK
Salary, Ph.D. student (N)			110.000 DKK	535.000 DKK	535.000 DKK	575.000 DKK	1.755.000 DKK	The Danish Eye Research Foundation 2018	265.000 DKK
Salary, optician (Vejle)	120.000 DKK	240.000 DKK	240.000 DKK	240.000 DKK	240.000 DKK	100.000 DKK	1.180.000 DKK	Fight for Sight Denmark 2018	1.000.000 DKK
Salary, optician (Aarhus)		100.000 DKK	100.000 DKK	100.000 DKK	100.000 DKK	45.000 DKK	445.000 DKK	Synoptik-Fonden 2018	100.000 DKK
Salary, TAP (All)	60.000 DKK	60.000 DKK	60.000 DKK	60.000 DKK	60.000 DKK	kr. 25.000,00	325.000 DKK	The Danish Eye Research Foundation 2019	360.000 DKK
Transportation	10.000 DKK	10.000 DKK	10.000 DKK	10.000 DKK	10.000 DKK	10.000 DKK	60.000 DKK	Synoptik-Fonden 2019	100.000 DKK
Congresses (All)				50.000 DKK	50.000 DKK	50.000 DKK	150.000 DKK	Danish Regions	529.101 DKK
Statistical assistance			25.000 DKK	50.000 DKK		50.000 DKK	125.000 DKK	Fight for Sight Denmark 2019	250.000 DKK
Publications			25.000 DKK	75.000 DKK	50.000 DKK	100.000 DKK	250.000 DKK	"Fonden for Faglig Udvikling af Speciallægepraksis"	720.000 DKK
Glasses and lenses	45.000 DKK	50.000 DKK	95.000 DKK	95.000 DKK			285.000 DKK	A.P. Møller Fonden (Lægefonden)	55.000 DKK
Trial medication	200.000 DKK		195.000 DKK				395.000 DKK	Synoptik-Fonden 2020	50.000 DKK
Ophtha, viscous eye drops	8.500 DKK						8.500 DKK	The Danish Eye Research Foundation 2020	240.000 DKK
Offices (e.g. computer)	10.000 DKK	10.000 DKK	10.000 DKK	20.000 DKK	15.000 DKK	15.000 DKK	80.000 DKK	Synoptik-Fonden 2020	50.000 DKK
Tuition fee (A+N)		50.000 DKK	50.000 DKK	100.000 DKK	50.000 DKK	50.000 DKK	300.000 DKK	Fight for Sight Denmark 2020	350.000 DKK
Administration	25.000 DKK	25.000 DKK	25.000 DKK	25.000 DKK	25.000 DKK	25.000 DKK	150.000 DKK	"Fonden for Faglig Udvikling af Speciallægepraksis"	720.000 DKK
								Gangstedfonden 2021	500.000 DKK
								Reimbursement from regional COVID-19 funds	240.000 DKK
								Synoptik-Fonden 2021	75.000 DKK
								Aase og Ejnar Danielsens Fond	100.000 DKK
								Synoptik-Fonden 2021	100.000 DKK
								Fight for Sight Denmark 2021	625.000 DKK
								"Fonden for Faglig Udvikling af Speciallægepraksis"	720.000 DKK
Total amount	1.078.500 DKK	1.145.000 DKK	1.570.000 DKK	1.855.000 DKK	1.135.000 DKK	1.045.000 DKK	7.828.500 DKK	Total amount	7.453.500 DKK

Table 2: Budget

Dissemination of findings

Both positive, negative and inconclusive results of the study will be published in international peer-reviewed scientific journals and presented at international and national meetings. The study is conducted as a multicenter study. Study management is ensured by a steering committee (Principle investigator #1-3, see *Investigators*, page 7) with representatives from each of the three departments. Authorship will follow Vancouver guidelines.

Perspectives

Myopia has been named a global health care concern by the WHO because of the rising prevalence and the risk of blinding complications to especially high degrees of myopia. Reducing the end degree of myopia is of paramount importance in ensuring lifelong healthy eyes and good vision. The present study has the potential to pave the way for reducing end degree myopia in Danish children and teenagers with an enormous potential in term of saving sight.

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