


BMJ Open Low-dose Atropine for Myopia Control in Children (AIM): protocol for a randomised, controlled, double-blind, multicentre, clinical trial with two parallel arms

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ABSTRACT

Introduction Myopia is a major cause of degenerative eye disease and increases the risk of secondary visual impairment. Mitigating its progression therefore has great potential of clinically relevant benefit as shown by using highly diluted atropine eye drops in children of Asian origin. However, limited evidence is available regarding the efficacy and safety of low-dose atropine therapy in non-Asian populations. Hence, the Low-dose Atropine for Myopia Control in Children (AIM) study will test the efficacy and safety of 0.02% atropine vs placebo in a German population.

Methods and analysis AIM is a national, multicentre, prospective, randomised, placebo-controlled, double-blind trial with two parallel arms. The primary objective is to assess the efficacy of atropine 0.02% eyedrops for myopia control in children of Caucasian origin. The primary outcome is the change in cycloplegic refraction after 1 year of treatment (D/year). Secondary and tertiary outcome measures comprise the change in axial length (mm/year) in children treated with 0.02% atropine compared with placebo, the myopic progression of participants treated with 0.01% compared with 0.02% atropine (D/year and mm/year), and the safety profile of both 0.02% and 0.01% atropine. Furthermore, the myopic progression 1 year after cessation of therapy with 0.02% atropine will be evaluated. Inclusion criteria are an age of 8–12 years and myopia of –1 D to –6 D with an estimated annual myopia progression of ≥ 0.5 D. After randomisation, patients will receive either atropine 0.02% (arm A) or placebo eye drops (arm B) in the first year of treatment. In the second year, they will continue to receive atropine 0.02% (arm A) or switch to atropine 0.01% (arm B). In the third year, they will switch to placebo (arm A) or continue with atropine 0.01% (arm B). To achieve a statistical power of 80%, the calculated sample size is 300. The trial has started

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ AIM is a double-blind, randomised, controlled trial with 3 years of total follow-up.
- ⇒ Only children of Caucasian heritage will be recruited to provide information on this population for which data on myopia control is limited.
- ⇒ Myopia progression is assessed by measuring both cycloplegic refraction and axial length.
- ⇒ The primary outcome is change in cycloplegic refraction after 1 year of treatment with atropine 0.02% compared with placebo.
- ⇒ For ethical reasons, the control group is treated with placebo for only 1 year, after which the therapy is continued with 0.01% atropine.

in October 2021 with a planned recruitment period of 18 months.

Ethics and dissemination AIM has been approved by the Central Ethics Committee of the University Medical Center Freiburg (21-1106), local ethics committees of each participating centre and the German Federal Institute for Drugs and Medical Devices (61-3910-4044659). It complies with the Declaration of Helsinki, local laws and ICH-GCP. Results and underlying data from this trial will be disseminated through peer-reviewed publications and conference presentations.

Trial registration number NCT03865160.

INTRODUCTION

Myopia (nearsightedness) is the most common developmental eye disorder.^{1–4} Its global prevalence is increasing at a staggering rate, however with high regional variance.^{3,5} East Asian countries have the highest

prevalence, while European countries are also reported to be increasingly affected.⁶ Although the notion of increasing myopia prevalence in the European population is controversial,^{5 7 8} its prevention is nevertheless of great importance.

Second only to age, myopia is the main risk factor for major degenerative eye diseases such as macular degeneration, retinal detachment, glaucoma and cataract.^{9 10} The risk for these conditions and subsequent visual impairment increases with the degree of myopia.¹¹ For example, a recent meta-analysis demonstrated that highly myopic eyes (≤ -6 D) have an approximately 60-fold increased OR for developing myopic maculopathy compared with eyes with low myopia (-0.5 – 3 D).¹¹ Hence, slowing the progression during childhood is expected to reduce the chances of visual impairment and blindness in later adulthood.

Myopia control can be achieved by topical low-dose atropine,¹² lifestyle changes (reduced near work and increased light exposure)¹³ and optical correction of the hyperopic, peripheral defocus through multifocal contact lenses,^{14 15} defocus incorporated multiple segment spectacle lenses^{16 17} or orthokeratology.^{18 19}

Almost all clinical studies concerning atropine for myopia management have been performed in Asian populations.²⁰ The first milestone study, ATOM 2, compared topical 0.5%, 0.1% and 0.01% atropine in Singaporean children. Importantly, this study lacked a control group, and therefore data was compared with the historical control group of the ATOM 1 study. The authors concluded that 0.01% atropine was the most desirable concentration, as it reduced myopia progression by around 0.7 D (from 1.2 D in controls to 0.49 D in children treated with 0.01% atropine) while leading to fewer side effects compared with higher concentrations.^{21–23} Of note, 0.01% did not reduce axial elongation in the ATOM 2 study. Generally, the efficacy of 0.01% atropine in slowing axial elongation is somewhat disputed.²⁴ Therefore, a number of Asian studies, most notably the LAMP study from Hong Kong, examined the effects of atropine in the low-dose range.^{25–27} A recent meta-analysis found that atropine concentrations ranging from 0.01% to 1.0% show a good dose-effect and dose-side-effect relationship.²⁰ Taken together, these results support the notion that highly diluted atropine eye drops reliably attenuate myopia progression while minimising side effects.¹³ While the use of highly diluted atropine in Asian populations has been demonstrated in blinded, well-designed trials,^{28–30} only few randomised trials have been completed in Caucasian populations.^{28 29} Therefore, the cumulative evidence in Caucasian populations is not yet strong enough to prove the efficacy of atropine in these populations. This led to a number of randomised, controlled trials currently being conducted in Caucasian populations.^{31 32}

In a recent cohort study on the use of 0.05% and 0.01% atropine in children of Caucasian origin, we found that 0.05% atropine was associated with significant side effects including 3 mm of mydriasis and 4 D

of hypo-accommodation.³³ By contrast, Asian populations treated with the same dose have been reported to show only mild mydriasis of around 1 mm and hypo-accommodation of 2 D.²⁰ These data indicate ethnic differences in the (side-) effects of atropine.

Our current study, AIM, is an adequately powered randomised controlled trial (RCT) which will compare the efficacy of atropine 0.02% with placebo in children of Caucasian origin. We chose this concentration due to the following reasons: on the one hand, atropine doses of 0.05% and higher may lead to relevant side-effects in children of Caucasian heritage as described above. In line with this, it has been suggested that 0.02% may be the highest concentration that does not induce relevant side-effects.³⁴ On the other hand, the effect of very low-dose atropine such as 0.01%, especially on axial length, is disputed.²⁴

As a tertiary objective, we will also compare the efficacy of atropine 0.02% and atropine 0.01%. Our goals are to validate previous findings, to test whether this therapeutic concept holds its promise in a Caucasian population, thus to give validation to existing national recommendations for standard treatment³⁵ and to further advance finding of the optimal dosage of topical atropine in children of Caucasian origin.

Summary and aims

While low-dose atropine to slow the progression of childhood myopia has been extensively studied in Asian populations, there is far less evidence for this widely adopted therapy in children of Caucasian origin. AIM is an RCT, which will explore the efficacy and safety of unpreserved 0.02% and 0.01% atropine in a Caucasian population.

METHODS AND ANALYSIS

Our study protocol was designed following the Standard Protocol Items: Recommendations for Interventional Trials guidelines (SPIRIT guidelines; online supplemental material 1),³⁶ is registered on www.clinicaltrials.gov, www.germanctr.de (DRKS00023337) and the EudraCT Database (2020-001575-33).

Study design and setting

AIM is a prospective, multicentre, randomised, controlled, double-blind trial with two parallel arms. Patients will be randomised to either treatment arm A (interventional group, receiving atropine 0.02% (year 1+2)/placebo eye drops (year 3) or treatment arm B (control group receiving placebo (year 1)/atropine 0.01% eye drops (year 2+3)). Therefore, each participant will receive low-dose atropine treatment for 2 years.

A 1:1 allocation ratio will be applied to ensure equally sized treatment groups.

The trial sponsor is the Medical Center–University of Freiburg. Participating trial sites are the University Medical Centres in Bonn, Erlangen, Essen, Freiburg, Göttingen, Hamburg-Eppendorf, Hannover, Heidelberg,

Cologne, Leipzig, Magdeburg, Mainz, Munich (LMU), Münster, Oldenburg, Ulm and the eye centres in Ahaus and Rosenheim. Audits and inspections of these trial sites may be conducted by the sponsor or an independent external party.

Research question

To evaluate whether low-dose atropine treatment for myopia management is medically justifiable in children of Caucasian origin. For this purpose, we aim to determine the efficacy and safety of low-dose atropine 0.02% eye drops compared with placebo for myopia control in children of Caucasian origin in Germany.

Study population

Caucasian children aged 8–12 years with -1 D to -6 D of myopia and an estimated annual progression ≥ 0.5 D/year of myopia will be enrolled. Patients will be deemed eligible if they assent to participation, their parents/legal guardians provide written informed consent and the investigator has verified that they meet all of the inclusion criteria and none of the exclusion criteria (see next section). Patients of both genders will be enrolled.

Inclusion and exclusion criteria

Inclusion criteria

1. Male or female patients aged 8–12 years (up to the day before the 13th birthday)
2. Myopia of -1 D to -6 D with reported or documented annual progression ≥ 0.5 D of myopia
3. Patient assent as well as written informed consent obtained from parents or legal guardians according to international guidelines and local laws
4. Ability to understand the nature of the trial and the trial related procedures and to comply with them

Exclusion criteria

1. Asian or African origin
2. Abnormal binocular vision
3. Manifest strabismus
4. Astigmatism > 1.5 D
5. Anisometropia > 1.5 D
6. History of amblyopia
7. Corrected visual acuity in any eye < 0.63 decimal
8. Any acquired or developmental organic eye disease
9. Premature birth
10. Any known systemic metabolic disease or chromosomal anomaly
11. Previous use of any kind of contact lenses
12. Previous use of atropine eye drops
13. Epilepsy
14. Known hypersensitivity to the active substances or any of the excipients
15. Participation in any other interventional clinical trial within the last 30 days before the start of this trial
16. Simultaneous participation in other interventional trials which could interfere with this trial; simultaneous participation in registries and diagnostic trials is allowed

17. Contraindications according to the Summary of Product Characteristics (SmPC): increased intraocular pressure (primary forms of glaucoma or narrow angle glaucoma), chronic rhinitis sicca
18. Caution and paediatric counselling shall be assured if any of the following conditions are present according to the SmPC: cardiac insufficiency, arrhythmia, coronary stenosis, hyperthyroidism, stomach or bowel stenosis, bowel paralysis, megacolon, muscle weakness, lung oedema, hypersensitivity to atropine, spastic paralysis
19. Parents or children with poor understanding of the German language
20. Person who is in a relationship of dependence/employment with the sponsor or the investigator.

At the time of study design, the new defocus incorporated multiple segment spectacle lenses for myopia control were not yet available. Therefore, the use of such spectacles has not been listed as a formal exclusion criterion. However, in the meantime, each participating centre was informed that patients who currently or previously used such spectacles should not be enrolled. Participants who have already been enrolled are informed not to wear such spectacles throughout the duration of the study.

Treatment

The trial medication is atropine sulfate, a non-specific, competitive muscarinic receptor antagonist. Dosages administered are 0.01% w/v (weight (g)/volume (100 mL)) solution and 0.02% w/v solution. The placebo solution is identical to the atropine formulation but without the active ingredient atropine. The release specification for the pH value of atropine and placebo eye drops is 4.2–5.2.

Active, unpreserved drug/placebo will be supplied as eye drops solution in single-dose containers. One drop per eye will be administered daily at bedtime. The total duration of follow-up per patient is 3 years. Discontinuation may occur due to intolerable adverse events, withdrawal of consent, death or termination of the trial.

Experimental intervention arm (arm A)

Treatment phase 1: Atropine 0.02% for 12 months
 Treatment phase 2: Atropine 0.02% for 12 months
 Treatment phase 3: Placebo for 12 months

Control intervention arm (Arm B)

Treatment phase 1: Placebo for 12 months
 Treatment phase 2: Atropine 0.01% for 12 months
 Treatment phase 3: atropine 0.01% for 12 months

Objectives and outcome measures

Table 1 summarises the objectives and measures.

Visit schedule

At the baseline visit, eligibility of each participant will be confirmed, informed assent/consent will be provided by the participant and the parents/legal guardian(s) and baseline examinations are performed. After the baseline

Table 1 Objectives and outcome measures

	Objective	Outcome measure
Primary	The primary objective is to demonstrate superiority of low-dose atropine 0.02% eye drops compared with placebo for myopia control in children of Caucasian origin.	Change in cycloplegic refraction (ie, myopia progression) (dioptre (D)/year) after 1 year of treatment. The mean value of both eyes will be analysed.
Secondary	To assess axial eye length growth under low-dose atropine 0.02% in comparison to placebo.	Change in axial length (mm/year) after 1 year of treatment. The mean value of both eyes will be analysed.
	To assess the categorised rate of change in refraction of low-dose atropine 0.02% compared with placebo.	Percentage of patients progressing <0.25 D, 0.25 D–0.75 D and >0.75 D after 1 year of treatment.
Tertiary	To assess the rebound of myopia progression after cessation of atropine 0.02% treatment.	Change in refraction and axial length in year 3, to be determined only in the intervention group.
	Comparison of change in refraction and axial length in the interventional group receiving atropine 0.02% during years 1 and 2 with the control group receiving atropine 0.01% during years 2 and 3.	Change in refraction (D/year) and axial length (mm/year) after 2 years of treatment (after year 2 in the interventional group and after year 3 in the control group).
Safety	To assess the safety of topical preservative-free atropine in comparison to placebo with regard to adverse events, pupil size, near vision, accommodation and pulse rate will be measured.	<ul style="list-style-type: none"> ▶ (Serious) adverse events ▶ Pupil diameter ▶ Near visual acuity ▶ Accommodative amplitude ▶ Pulse rate

visit, study visits will be conducted at 2, 26, 52, 54, 78, 104, 130 and 156 weeks. At the end of study (EOS), a phone call will be made 30 days after end of treatment (EOT), which represents the last on-site study visit. [Table 2](#) summarises the procedures to be conducted at each visit.

Study assessments

Patient demographics

Patient demographics comprise the date of birth, sex and ethnic origin.

Medical history and concomitant medication

At screening, a detailed history will be taken to ensure that all participants are in good general and ocular health and meet the inclusion and exclusion criteria. All concomitant medications administered at any time during the period starting with the signature of the informed consent form (ICF) and ending with the patient's individual study end must be documented in the electronic case report form (eCRF). The patient and parents or legal guardians will be instructed to notify the investigational site of any new medication he/she starts taking after the start of the trial medication.

Parental refraction

Refraction of both eyes of both biological parents will be documented once at baseline. If only one parent is available, the other parent's refractive values will be handled as missing data.

Iris colour

Iris colour of the participants will be classified according to Franssen *et al*³⁷ as light (green, blue, grey and hazel;

numbers 1 to 17) or dark (brown, black-brown; numbers 18 to 24) once at baseline.

Pulse rate

Pulse rate will be measured at every visit.

Body height

Height (cm) will be measured at screening/baseline, visits 3, 6 and 8.

Visual acuity at distance

Subjective refraction will be performed to obtain the best-corrected visual acuity of each eye. It will be documented in a standardised form as a letter score using retro-illuminated ETDRS charts at 4m distance.

Visual acuity at near

Visual acuity at near will be assessed monocularly at 40 cm distance once per visit using Landolt-C near vision charts (non-crowded version) as decimal acuity. Measurements will be performed with the best optical correction for distance viewing.

Contrast sensitivity

Contrast sensitivity will be recorded as log CS monocularly using MARS charts in 50 cm distance at 60–120 cd/m². Illumination will be provided by overhead fluorescent tubes. No additional focal lighting will be used to ensure minimum casting of shadows. Patients will be asked to read all letters starting with the highest contrast letters. They will be encouraged to guess and sufficient time will be given to read each letter.

Table 2 Visit schedule

Periods/duration	Screening/baseline		Treatment phase 1			Treatment phase 2			Treatment phase 3			Follow-up	
	14 days	Randomisation	52 weeks	52 weeks	52 weeks	52 weeks	52 weeks	52 weeks	52 weeks	52 weeks	52 weeks	52 weeks	30 days
Visits	Screening/ baseline	Day 0	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 8	TC	EOS
Timepoint	Day -14 until day -1	Day 0	Week 2 (±3d)	Week 26 (±14d)	Week 52 (±14d)	Week 54* (±3d)	Week 78 (±14d)	Week 104 (±14d)	Week 130 (±14d)	Week 156 (±14d)	Week 156 (±14d)	EOT	EOT+30
Assessments													
Informed consent	X												
Inclusion/exclusion criteria	X												
Demographics	X												
Medical history	X												
Concomitant medication	X		X	X	X	X	X	X	X	X	X	X	X
Pregnancy test (only females aged ≥13 years in a relationship, starts with the day of the 13th birthday)	X		X	X	X	X	X	X	X	X	X	X	X
Randomisation		X											
IMP dispensing		X		X	X	X	X	X	X	X	X	X	X
Drug accountability				X	X	X	X	X	X	X	X	X	X
Parental refraction	X												
Iris colour	X												
Pulse rate	X		X	X	X	X	X	X	X	X	X	X	X
Body height	X			X	X	X	X	X	X	X	X	X	X
Visual acuity at distance	X			X	X	X	X	X	X	X	X	X	X
Visual acuity at near	X		X	X	X	X	X	X	X	X	X	X	X
Contrast sensitivity	X		X	X	X	X	X	X	X	X	X	X	X
Binocular alignment	X		X	X	X	X	X	X	X	X	X	X	X
Pupil size	X		X	X	X	X	X	X	X	X	X	X	X
Accommodation	X		X	X	X	X	X	X	X	X	X	X	X
Ocular biometry	X		X	X	X	X	X	X	X	X	X	X	X
Refraction	X		X	X	X	X	X	X	X	X	X	X	X
Slit lamp/fundus	X		X	X	X	X	X	X	X	X	X	X	X

Continued

Table 2 Continued

Periods/duration	Screening/baseline 14 days		Treatment phase 1 52 weeks				Treatment phase 2 52 weeks				Treatment phase 3 52 weeks		Follow-up 30 days	
	Screening/ baseline	Randomisation	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	TC	EOS		
Timepoint	Day -14 until day -1	Day 0	Week 2 (±3d)	Week 26 (±14d)	Week 52 (±14d)	Week 54* (±3d)	Week 78 (±14d)	Week 104 (±14d)	Week 130 (±14d)	Week 156 (±14d)	EOT+30	d†		
Tonometry	X		X		X		X		X					
Dispensing of patient diary		X		X		X		X		X				
Evaluation of patient diary			X	X	X	X	X	X	X	X				
Questionnaire				X			X		X					
Adverse events	X		X	X	X	X	X	X	X	X		X		

*14 days difference shall be assured between visits 3 and 4.
†EOS visit will be done by phone 30 days after regular or premature EOT. Ongoing and new (serious) adverse events have to be followed up and documented.
EOS, end of study; EOT, end of treatment; IMP, investigational medicinal product; TC, telephone call.

Binocular alignment

It will be assessed by alternate prism cover testing in degrees at each visit.

Pupil size

The photopic pupil size will be documented in mm using the IOL Master 500 or 700 (Zeiss) or a Plusoptix device (Plusoptix GmbH; preferred) at 200–300 lux room illumination.

Accommodation

The accommodative response will be measured in D as the near point by the Royal air force near point rule or by the Accommodation Convergence Rule (VISUS GmbH) as the mean of three measurements of both eyes.

Ocular biometry

Ocular dimensions of both eyes will be measured once per visit using the IOL Master 500 or 700 (preferred; Zeiss, Oberkochen, Germany). Axial length, corneal curvature radii at the two perpendicular axes, anterior chamber depth and lens thickness will be documented.

Refraction

Cycloplegic refraction will be performed using the Retinomax K-Plus autorefractor (Right Manufacturing Company, Tokyo, Japan). Five measurements diverging by less than 0.25 D will be recorded 30 min after the first of two topical instillations of cyclopentolate (preferably 1%, otherwise 0.5%), 10 min apart. The amount of spherical and cylindrical refraction and cylinder axis will be recorded for each eye to allow for subsequent calculation of the mean spherical equivalent (SE) of both eyes.

In case a Retinomax measurement is not feasible, a certified orthoptist will perform streak retinoscopy as a substitute under cycloplegia as mentioned above.

Slit lamp/fundus

A routine slit lamp examination focusing on the anterior eye segments and fundus will be performed at all visits.

Tonometry

Intraocular pressure will be documented at each study visit using the iCare device (iCare tonometer, iCare Finland Oy). If unavailable, other tonometer or palpation may be used as a substitute.

Patient diary

A patient diary covering a 6-month period will be provided to the patient and his/her parents/legal guardians (online supplemental material 2). It covers the following topics:

- ▶ frequency of eye drop application
- ▶ log of outdoor time
- ▶ log of near work time
- ▶ documentation of near vision deficits
- ▶ documentation of light sensitivity
- ▶ documentation of eye drop associated complaints such as redness, burning sensation or others

- ▶ documentation of other complaints (adverse events)
- ▶ documentation of new concomitant medication

Questionnaire

The patient and his/her parents/legal guardians will be asked to complete a questionnaire on the patient's lifestyle three times during the study course (online supplemental material 3). The data will be documented in the eCRF by the site staff.

Pregnancy test

A urine pregnancy test shall be performed if female patients aged ≥ 13 years (starts with the day of the 13th birthday) are in a relationship. In case of confirmed pregnancy, trial medication and study participation shall be terminated and the pregnancy must be reported to the sponsor. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of birth, and the presence or absence of any birth defects, congenital abnormalities or maternal and new-born complications.

Sample size

The sample size calculation is based on the primary endpoint—the rate of myopic progression, measured as the change in dioptres per year (D/year).

Assumptions are mainly based on the results of a meta-analysis presented by Gong *et al*³⁸ in 2017 and our own pilot trial published in 2019.³⁹ The meta-analysis summarises 9 RCT conducted in Asian children and 10 cohort studies, 3 of which analyse Caucasian children. Most of the studies employed higher doses of atropine.

Mean differences between atropine and control treatment among children treated with lower doses of atropine ($<0.5\%$) range between 0.44 and 0.78 D/year. SD of the mean change in all low-dose trials ranged between 0.24 and 0.60 D/year in the atropine group and 0.30 and 0.61 D/year in the control group.³⁸

Our own pilot trial was performed with atropine 0.01% in 54 children. Prior to treatment, a progression rate of -1.05 D/year was observed. After 12 months of treatment, the observed progression rate was -0.40 D (SD 0.49 D).³⁹ In accordance with the results cited above, we performed a sample size calculation:

The required sample size for a treatment group comparison of the primary endpoint was calculated based on a two-sample t-test at a two-sided significance level of $\alpha=0.05$, an SD of 0.7 and a conservatively anticipated effect size of 0.25 D/year. To achieve a power of 80%, 250 patients in total (125 per treatment arm) are required. The primary analysis will be performed according to the intention-to-treat principle including all randomised patients. However, this may lead to a treatment effect slightly smaller than assumed. Therefore, allowing for a dropout rate of 20%, 300 patients will be randomised.

Recruitment

Recruitment into this study is being facilitated through several avenues:

1. Information leaflets (containing clinical trial information) were sent to local ophthalmology practices, optometrists and schools to inform them of the study and to relate information to potential participants and their parents/legal guardians.
2. Professional associations such as the Bielschowsky Gesellschaft and Deutsche Ophthalmologische Gesellschaft were approached to promote involvement of German ophthalmologists.
3. A dedicated web site (www.aim-studie.de) was created to inform potential participants and collaborators.
4. A newspaper advertisement (30 April 2022, newspaper: Badische Zeitung) and a press release by the Medical Center–University of Freiburg (11 October 2021) were disseminated.

Data management

The data management will be performed with secuTrial, a professional browser-based GCP-compliant EDC system which was developed and validated by interActive Systems, Berlin. Details on data management (software, procedures, responsibilities, etc) were described in the Data Management Manual at the beginning of the trial. The Data Management Manual is a working document which will be continuously updated and maintained during the trial, that is, performance of data management and any deviations from the first version of the Data Management Manual will be documented therein. At the end of the study, a second version of the Data Management Manual will be finalised.

Information about trial patients will be kept confidential. The trial's data collection system uses built-in security features to encrypt all data for transmission in both directions, preventing unauthorised access to confidential participant information. Access to the system will be controlled by individually assigned user identification codes and passwords, made available only to authorised personnel who have completed prerequisite training.

The investigator, or a deputy who is designated by the investigator, will document the trial data in a trial-specific eCRF as promptly as possible.

Randomisation and blinding

Blinding

The investigators and participants will remain blinded to the patient's assigned treatment group. The study medication will be assembled to medication kits and distributed to the trial sites in a blinded manner by the pharmacy of the Medical Center –University of Freiburg.

Unblinding

General unblinding is only performed after closure of the database for the final analysis.

However, the following reasons can prompt premature unblinding:

- ▶ emergency situations when necessary for the trial patient's safety, for example, event of administration of an incorrect dose, in particular overdose of the

investigational medicinal product (IMP) which might put the patient at risk

- ▶ event of accidental administration of the IMP to a person who is not a trial patient

For analysis of the primary endpoint after the first year of treatment, the study statistician will be unblinded. The database for the first year of the study will then be locked.

Randomisation of patients will be conducted in the eCRF using the integrated randomisation feature of secuTrial. Authorised site staff will randomise eligible patients via a randomisation form according to the predefined randomisation algorithm (see next section below). The result of the randomisation is displayed in the eCRF as a unique therapy number for the patient, which will be valid for the whole duration of the trial. The pharmacy of the Medical Center–University of Freiburg will be informed about the randomisation and the therapy number at the same time via email. The pharmacy is unblinded and links the therapy number to a distinct kit number related to the trial medication which the patient was randomised to. The pharmacy then enters the kit number in the eCRF to communicate it to the trial site and assign it to the patient. At the trial site, the respective medication kit is dispensed to the patient/parents or legal guardians.

Randomisation methodology

The randomisation code will be generated by the Clinical Trials Unit, Medical Center–University of Freiburg using the following procedure to ensure that treatment assignment is unbiased and concealed from patients and investigator staff. Randomisation will be performed in a ratio of 1:1, stratified by trial site and patient's age (8–9 vs 10–12 years at inclusion). Block randomisation will be used, with blocks of variable length. The block lengths will be documented separately and will not be disclosed to the trial sites. The randomisation code will be produced by validated programmes based on the Statistical Analysis System.

Statistical analysis

A blind review of the data will be performed after the end of the planned follow-up period. Before data analysis, a detailed statistical analysis plan will be prepared.

Definition of populations included in the analyses

The primary efficacy analysis will be performed according to the intention-to-treat principle and will therefore be based on the full analysis set (FAS) of all randomised patients with post baseline measurements. They will be analysed as belonging to their randomised arm, regardless of whether they refused therapy or protocol deviations have occurred. Patients will be randomised as late as possible (ie, as close as possible to the day of the first IMP administration) to achieve high compliance.

The per-protocol (PP) population is a subset of the FAS defined as the group of patients who had no major protocol violations, received a predefined minimum dose of the treatment and underwent the examinations

required for the assessment of the endpoints at relevant, predefined times. The analysis of the PP population will be performed for the purpose of a sensitivity analysis.

Safety analyses will be performed in the safety population. Patients in the safety population are analysed as belonging to the treatment arm defined by treatment received. Patients are included in the respective treatment arm, if they received at least one dose of the respective study medication.

Methods of analysis

Primary endpoint

The primary analysis of the change in cycloplegic refraction after 1 year will be performed using an analysis of covariance model with the annual change in refraction as the dependent variable. The model will include treatment and baseline cycloplegic refraction as covariates, and the stratification variables trial site and age (8–9 vs 10–12 years). The primary hypothesis will be tested at a two-sided level of $\alpha=5\%$. The estimated treatment effect will be presented with a two-sided 95% CI.

Missing values for the primary endpoint will be replaced by estimated annual progression rates based on the actual observation period.

Multiple imputation methods to replace missing values will be used for sensitivity analyses. The frequency and type of protocol violations and missing values will be described, and the drop out pattern and the reasons for missing values will be investigated. The imputation model will include as many variables as possible to make the 'missing at random' assumption more plausible.

The primary analysis will be conducted in the FAS, imputing for missing values irrespective of the occurrence of intercurrent events. This is consistent with the treatment policy strategy of the estimands framework described in the ICH E9 (R1) addendum.

As a further sensitivity analysis, the analysis will be repeated in the PP set, excluding patients with major protocol violations.

Secondary endpoints for efficacy

Analyses of the change in axial length after 1 year, a key secondary endpoint, will be performed in a regression model as described for the primary endpoint.

The change in cycloplegic refraction after 1 year will be categorised (patients progressing <0.25 D, 0.25 – 0.75 D and >0.75 D after 1 year of treatment) and analysed descriptively, giving absolute and relative frequencies of these categories as a supportive analysis.

Subgroup analyses

Subgroup analyses of the treatment effect will be conducted in both aforementioned age groups (8–9 vs 10–12 years at inclusion) and separately for sex and iris colour (dark /light).

Interim analysis

No formal interim analysis will be performed. The data monitoring committee (DMC) will be provided with

interim results concerning patient recruitment, adherence to protocol, serious adverse events.

Data monitoring committee (DMC)

An independent DMC has been established. Its function is to monitor the course of the study and if necessary to give a recommendation to the coordinating investigator and sponsor of the trial for discontinuation, modification or continuation of the study. The underlying principles for the DMC are ethical and safety aspects for the patients. It is the task of the DMC to examine whether the conduct of the trial is still ethically justifiable, whether security of the patients is ensured and whether the process of the trial is acceptable. To be able to perform these tasks, the DMC will need to be informed of the adherence to the protocol, patient recruitment and observed serious adverse events. This is justified since the study population under investigation is paediatric. The DMC and all authors of the main publications of the trial result have access to the full trial dataset in order to ensure that the validity of the results can be verified. The DMC consists of two ophthalmologists with surgical expertise and a statistician with expertise in biomedical research. The members of the DMC are independent of the trial and have no competing interests.

Drug manufacture and supply

The drug is manufactured by the pharmaceutical company Pharma Stulln (Pharma Stulln GmbH, Stulln) for the duration of the trial.

Primary and secondary packaging, as well as primary labelling will also be performed by Pharma Stulln. At primary packaging, atropine sulfate solution or placebo solution, respectively, will be filled in low-density polyethylene single-dose containers. The placebo solution will be identical in appearance to the solution containing the active pharmaceutical ingredient. Each single-dose container will be labelled in a blinding manner according to the study requirements (primary labelling). As a secondary packaging step, strips of five of the labelled single-dose containers will be sealed in an aluminium laminated foil pouch. The pouches will remain unlabelled and each dosage strengths will be separately packed as bulk in shipping boxes. All information specifying the product will be given on the labels of the respective shipping boxes which will be sealed and shipped to the pharmacy of the Medical Center–University of Freiburg. The pouches will then be study specifically labelled in a blinded manner (secondary labelling). Sufficient pouches to cover a 6-month supply will be packed into a folding carton (tertiary packaging). Each carton will be labelled in a blinded manner and will receive a specific kit number according to the blinded medication kit number list provided by Biostatistician of Medical Center–University of Freiburg, Clinical Trials Unit (tertiary labelling). The pharmacy of the Medical Center–University of Freiburg will dispense the study specifically labelled cartons to the respective sites according to the respective site-specific

randomisation list. All medication labels will be designed in German language and will comply with GMP Annex 13 and GCP-V.

Drug storage, dispensing and compliance

Trial medication will be handled and stored safely and kept in a secured location to which only the investigator/pharmacists and/or designated study personnel have access. On receipt, all study drugs must be stored below 25°C.

Drug dispensing will start at the randomisation visit (day 0). The drug will then be dispensed at scheduled visits throughout the double-blind treatment period according to the visit schedule (see [table 1](#)). The patients/parents or legal guardians will receive instructions by an authorised person at the investigator site for transport, storage and application at home as well as for the need to return used and unused single-dose containers at each study visit for drug reconciliation purposes.

At the end of the trial, as appropriate during the course of the trial, and following drug accountability checks, the investigator and/or pharmacist or authorised designee will ensure GCP-conform destruction of all unused IMP at each study site as per local procedure. Destruction at the study site may only be performed after release by the sponsor and records of the destruction must be maintained.

The investigator will maintain an accurate record of the dispensing of the IMP in a drug accountability log. The patient and his/her parents/legal guardians are obligated to document the application of the eye drops in the patient diary and will be instructed to return all used and unused IMP to the site at each visit. Patients' trial treatment compliance will be assessed by the investigator or designee at each visit by checking the patient diary and resolving discrepancies between drug dispensing, return and patient diary. Treatment adherence reminder sessions will take place at the time of the initial drug dispensing and at each study visit thereafter.

Ethics and dissemination

This clinical trial was designed, shall be implemented and will be reported in accordance with the ICH-GCP, applicable local regulations (including European Directive 2001/20/EC), and the ethical principles laid down in the Declaration of Helsinki.

AIM has been approved by the Central Ethics Committee of the University Medical Center Freiburg (ID: 21-1106), local ethics committees of each participating centre (Ethics Committee of the Medical Faculty of the University of Bonn (ID: 056/21-AMG), Ethics Committee of the University of Erlangen-Nuremberg (ID: 77_21Ab), Ethics Committee of the University of Duisburg-Essen (ID: 21-9927-AB), Ethics committee of the University Medical Center Göttingen (ID: 15/11/21), Ethics Committee of the Hamburg Chamber of Physicians (ID: 2021-200226-AMG-bet), Ethics Committee of Hanover Medical School (ID: 9658_AMG_NM_2021),

Ethics Committee of the Medical Faculty of Heidelberg (ID: ABmu-097/2021), Ethics Committee of the Medical Faculty of the University of Cologne (ID: 21-1100-AMG), Ethics Committee of the Medical Faculty of the University of Leipzig (ID: 21-1106-AMG-ff multi), Ethics Committee of the Otto-von-Guericke-University Magdeburg (ID: 16/21), Ethics Commission of the State Chamber of Physicians of Rhineland-Palatinate (ID: 2021-15658-AMG), Ethics Committee of the Medical Faculty of the Ludwig Maximilian University Munich (ID: 21-0152mb), Ethics Committee of the Medical Association Westfalen-Lippe (ID: 21-1106-AMG-ff multi), Medical Ethics Committee of the Carl von Ossietzky University Oldenburg (ID: 2021-153), Ethics Committee of the University of Ulm (ID: 21-1106-AMG-ff multi), Ethics Committee of the Bavarian Chamber of Physicians (ID: 7/21018) and the German Federal Institute for Drugs and Medical Devices (61-3910-4044659). All participants and their parents/legal guardians must provide written informed assent/consent to the investigator before participating in the trial (online supplemental material 4 and 5).

In accordance with local regulations, subject insurance was obtained for all subjects participating in the clinical trial.

Results and underlying data from this trial will be disseminated through peer-reviewed publications and conference presentations.

Protocol adherence

Investigators ascertain they will apply due diligence to avoid protocol deviations. Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by sponsor, competent authorities where required and the independent ethics committee. Only changes of the protocol that are required for patient safety may be implemented prior to approval by the independent ethics committee. Information regarding important protocol modifications will be provided in due time to further relevant parties (eg, investigators, trial participants, trial registries, journals).

Ancillary substudy—Genetics of Atropine for Myopia control in childrEn (GAME)

The GAME study is a substudy to AIM. We plan to offer participants of the AIM study to determine their individual Genetic Myopia Risk Score (GRS) and to relate the GRS to the efficacy of low-dose atropine therapy. For this purpose, oral mucosa swabs will be collected and stored in the Hilda Biobank Freiburg. As of September 2022, the GAME study is under review by the Ethics Committee of the University Medical Center Freiburg.

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Study progress

The recruitment period has started in October 2021 with opening of the first study centre. As of November 2022, further 15 centres have been initialised and another two centres are going to be initialised until the end of 2022. As of November 2022, we have included a total of 80 patients.

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