18 September 2025
EMA/CHMP/239943/2025
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Atropine sulfate FGK

International non-proprietary name: atropine sulfate

Procedure No. EMEA/H/C/006385/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Table of contents

List of abbreviations

AAO	American Academy of Ophthalmology
AE	adverse event
AEDC	adverse event leading to discontinuation
AL	axial length
API	Active pharmaceutical ingredients=AS
APOS	American Association for Pediatric Ophthalmology and Strabismus
AS	Active substance =API
ATI	amblyopia treatment index
ATOM	Atropine for the Treatment of Myopia study
ATOM-J	ATOM-Japan study
BAK	Benzalkonium Chloride
BCVA	best corrected visual acuity
CEP	Certificate of Suitability of the EP
CfB	Change from baseline
CHAMP	Childhood Atropine for Myopia Progression
CHMP	Committee for Medicinal Products for Human use
CI	confidence interval
CPP	Critical process parameter
CQA	Critical Quality Attribute
CRL	complete response letter
CSR	clinical study report
D	diopter
DLP	data lock point
DOPAC	3,4-dihydroxyphenylacetic acid
EC	European Commission
EDTA	disodium edetate
EMA	European Medicines Agency
EP	European Pharmacopoeia= Ph. Eur.
EU	European Union
FDA	Food and Drug Administration
FP	finished product
FWP	Formulation Working Party

GABA	gaminobutyric acid
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
IC	informed consent
HED	human equivalent dose
HPLC	High performance liquid chromatography
ICD	International Classification of Disease
ICH	International Council for Harmonisation
IMP	investigational medicinal product
IOP	intraocular pressure
IPC	In process control
ISS	Investigator Sponsored Study/ies
ITT	Intent-to-Treat
LAMP	Low-Concentration Atropine for Myopia Progression study
LDPE	Low Density Polyethylene
LogMAR	logarithm of the Minimum Angle of Resolution
LSM	Least Square mean
MAA	Marketing Authorisation Application
mITT	modified Intent-to-Treat
MO	Major objection
MOSAIC	Myopia Outcome Study of Atropine in Children study
MTS1	Low-Dose Atropine for Treatment of Myopia study
NDA	New Drug Application
NOAEL	no observed adverse effect-level
OCT	organic cation transporter
Ph. Eur.	European Pharmacopoeia= EP
PK	Pharmacokinetics
PDCO	Paediatric Committee
PD	pharmacodynamics
PIP	Paediatric Investigation Plan
PT	preferred term
PEC	predicted environmental concentration
PUMA	Paediatric Use Marketing Authorisation

PND	Post natal day
RCT	randomized controlled trial
RH	Relative humidity
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SE	standard error
SER	spherical equivalent of refraction
SOC	system organ class
TEAE	treatment emergent adverse event
TOAST	Treatment Optimisation of Atropine Study
WA-ATOM	Western Australia-ATOM study
UK	United Kingdom
UPLC	Ultra high performance liquid chromatography
US	United States
USP	United States Pharmacopoeia
UV	Ultraviolet spectrometry
WHO	World Health Organisation

1. Background information on the procedure

1.1. Submission of the dossier

The applicant FGK Representative Service GmbH submitted on 29 April 2024 an application for a paediatric Use marketing authorisation in accordance with Article 30 of Regulation (EC) No 1901/2006, to the European Medicines Agency (EMA) for Atropine sulfate FGK, through the centralised procedure under Article 31 of Regulation (EC) No 1901/2006. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 22 June 2023.

The applicant applied for the following indication:

Atropine sulfate FGK is indicated to treat myopia progression in children aged 3 years and older.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 8(3) - full-mixed MAA (marketing-authorisation application dossiers where Module 4 and/or 5 consists of a combination of reports of limited non-clinical and/or clinical studies carried out by the applicant and of bibliographical references) of Directive 2001/83/EC, as amended.

1.3. Information on paediatric requirements

Pursuant to Article 30 of Regulation (EC) No 1901/2006 the applicant included an EMA Decision(s) P/0039/2024 on the agreement of a paediatric investigational plan (PIP).

The PDCO issued an opinion on compliance for the PIP P/0039/2024 (EMEA-C-002744-PIP01-19-M01).

However, with the opinion, the PDCO required the applicant to perform the statistical analysis of CHAMP twice: once following the initial SAP (see initial PIP procedure), and once following the modified SAP (see modification M01). This did not appear to have been performed. In Round 2 of the assessment of the initial MAA a revised analysis was provided.

1.4. Scientific advice

The applicant received the following scientific advice on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
27 June 2019	EMEA/H/SA/4135/1/2019/PED/II	Dieter Deforce, Nicolas Beix

The scientific advice pertained to the following clinical aspects:

- Design of the phase 3 Study CP-NVK002-0001 including primary and secondary efficacy endpoints, population, enrolment strategy, database lock, and adequacy of the safety database to support a marketing authorisation application in the intended indication.

1.5. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Peter Mol Co-Rapporteur: Maria Grazia Evandri

The application was received by the EMA on	29 April 2024
The procedure started on	23 May 2024
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	12 August 2024
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	26 August 2024
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	19 September 2024
The applicant submitted the responses to the CHMP consolidated List of Questions on	19 December 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	3 February 2025
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	13 February 2025
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	27 February 2025
The applicant submitted the responses to the CHMP List of Outstanding Issues on	25 March 2025
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	9 April 2025
The outstanding issues were addressed by the applicant during an oral explanation before the CHMP during the meeting on	23 April 2025
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a negative opinion for granting a marketing authorisation to Atropine sulfate FGK on	22 May 2025

1.6. Steps taken for the re-examination procedure

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Christian Gartner Co-Rapporteur: Nicolas Beix

On 19 June 2025 Jean-Michael Race (France) was appointed as Co-rapporteur for this re-examination procedure. His CHMP mandate terminated on 31 August 2025. Therefore, the Co-rapporteurship was transferred to Nicholas Beix, from the same national competent authority. In light of his expertise in ophthalmology, it was considered exceptionally justified that Nicolas Beix had previously been acting as coordinator for scientific advice on the development relevant for the indication subject to the present application.

The appointed rapporteur for this re-examination procedure had no such prominent role in scientific advice relevant for the indication subject to the present application.

The applicant submitted written notice to the EMA, to request a re-examination of Atropine sulfate FGK CHMP opinion of 22 May 2025, on	02 June 2025
The CHMP appointed Christian Gartner (AT) as Rapporteur and Jean Michael Race* (FR) as Co-Rapporteur on *(Due to completion of his CHMP mandate on 31 August 2025, Nicolas Beix subsequently appointed)	19 June 2025 01 September 2025
The applicant submitted the detailed grounds for the re-examination on	21 July 2025
The re-examination procedure started on	22 July 2025
The CHMP Rapporteur's re-examination assessment report was circulated to all CHMP members on	13 August 2025
The CHMP Co-Rapporteur's assessment report was circulated to all CHMP members on	27 August 2025
An Ad-Hoc-Expert Group (AHEG) meeting was convened to address questions raised by the CHMP on The CHMP considered the views of the AHEG as presented in the minutes of this meeting	3 September 2025
The CHMP Rapporteurs circulated the CHMP Rapporteurs Joint Updated Assessment Report on the detailed grounds for re-examination to all CHMP members on	9 September 2025
The detailed grounds for re-examination were presented by the applicant during an oral explanation before the CHMP on	16 September 2025
The CHMP, in the light of the scientific data available and the scientific discussion within the Committee, re-examined its initial opinion and in its final opinion concluded that the application did not satisfy the criteria for authorisation and did not recommend the granting of the paediatric use marketing authorisation on	18 September 2025

2. Scientific discussion

2.1. Problem statement

Atropine sulfate FGK (0.01%) has been evaluated for the treatment of myopia in children.

The indication claimed is to slow myopia progression in children aged 6 to 10 years with spherical equivalent refraction (SER) in the range of -0.50 to -6.00 diopter (D).

2.1.1. Disease or condition

Myopia, also called near-sightedness, is an eye disease that occurs when there is a refractive error in which light rays entering the eye are focused in front of the retina (Flitcroft, 2019). Myopia results from an increase of the axial length of the eye, or issues related to the cornea or lens.

Myopia onset usually occurs during childhood, most commonly in children aged 6 to 13 years but may occur in younger or older children as well (Zadnik et al., 2015; Nemeth et al., 2021; Wolffsohn, 2019). Myopia generally progresses most rapidly at 7-12 years, subsequently slowing through adolescence and adulthood. The rate of myopia progression is clearly influenced by age, sex and the present level of myopia (faster in younger children, female subjects, higher baseline myopia). On average, myopia stabilizes by ~15 years of age, with 95% of patients with myopia stabilizing by age 24 (Nemeth et al., 2021). Myopia progression varies widely between individuals, but generally occurs at a rate of 0.50 to 1.00 D per year during childhood (Gifford, 2019; Walline, 2011; Walline, 2020).

High myopia, defined as a refractive error of ≤−5 D (World Health Organization; 2015) and more recently as ≤−6 D (International Myopia Institute, 2020), places affected patients at increased risk for other ocular diseases. These include glaucoma, cataract, retinal tears which may lead to detachment, and myopic maculopathy or macular degeneration (Williams and Hammond, 2019). Ultimately this may result in permanent loss of vision

2.1.2. Epidemiology

As per the World Report on Vision published by the World Health Organization (WHO) in October 2019 an estimated 2.62 billion people worldwide were predicted to have myopia in 2020. Moreover, the number of individuals with severe myopia was expected to grow significantly from 399 million in 2020 to 516 million by 2030. These projections do not consider the potential impact of interventions designed to slow the progression of myopia.

It is anticipated that by 2050 approximately 50% of the world's population will be affected and 56% in Europe specifically (Holden, 2016; Morgan, 2021).

2.1.3. Aetiology and pathogenesis

The exact aetiology of myopia is not elucidated. It is believed to be the result of both hereditary and environmental factors. Different types of myopia may be classified, e.g. based on physical causes. Two of these are well-known: in axial myopia the axial eye length increases, while in refractive myopia is attributed to changing curvature of one or more refractive surfaces of the eye.

2.1.4. Clinical presentation, diagnosis and prognosis

Myopia is diagnosed and monitored through examination of patient history and eye examinations, which may include assessment of cycloplegic refraction and (axial) eye length.

According to recent classification systems, refractive error can be categorized into five groups: no myopia (SER > −0.5 D), any myopia (SER ≤ −0.5 D), low myopia (SER < −0.5 to > −3.00 D), moderate myopia (SER ≤ −3.00 to > −6.00 D), and high myopia (SER ≤ −6.00 D (Flitcroft et al., 2019).

There is a strong association between of myopia and myopic complications, such as myopic macular degeneration (MMD), retinal detachment (RD), cataract, and open angle glaucoma (OAG). More severe myopia resulted in an earlier onset of complications. (Haarman et al., 2020).

2.1.5. Management

There is currently no drug product approved in the EU to treat myopia in children (aged 3 years and older). Ryjunea (Atropine sulfate) (0.1 mg/ml eye drops, solution) received a positive CHMP opinion on 27 March 2025 for the treatment of progression of myopia in children aged 3 to 14 years.

Non-pharmacological approaches

Options in the EU include ordinary optical correction that do not treat myopia itself (spectacles, contact lenses), and interventional contact lenses: multifocal contact lenses and orthokeratology. Spectacles are generally the preferred option for young children with lenses reserved for older children as they are more challenging to use.

Orthokeratology are lenses that are used overnight to temporarily flatten the cornea and so temporarily reduction of myopia up to 6.00 D. Overnight wear of orthokeratology has an increased risk of microbial infections, and other ocular side effects including certain eye discomforts, blurred vision and photophobia.

Aside from spectacles and contact lenses used only for correction of refraction error, the main non-pharmacological interventions for controlling myopia include public health (lifestyle) interventions for optimization of environmental influences. Surgical interventions are not considered first line treatment modalities and combination treatments are under investigation.

Atropine

The European Society of Ophthalmology in cooperation with International Myopia Institute as well as the American Academy of Ophthalmology concluded on a benefit of atropine for the treatment of myopia progression and management of at-risk pre-myopic children. There were, however, uncertainties on the optimal concentration of atropine to be used (Németh J et al. EJO 2021).

In Australia, Eikance 0.01%, a preservative-free atropine sulfate ophthalmic solution, is approved for slowing progression of myopia in children aged from 4 to 14 years when myopia progresses ≥-1.0 D per year.

In the EU, magistral preparations with different concentrations of atropine sulfate (1%, 0.5%, 0.3%) are used for treating myopia and included in many (inter)national guidelines. E.g., atropine 0.01% has been proposed to have an appropriate benefit-risk ratio by the clinical field (World Society of Paediatric Ophthalmology and Strabismus myopia consensus statement, 2016).

In The Netherlands, magistral preparations of atropine eye drops are used for progressive high myopia in children >6 years (Nederlands Oogheelkundig Gezelschap, Myopie standpunt 2022).

2.2. About the product

Pharmacotherapeutic group: competitive, nonselective muscarinic acetylcholine receptor antagonist, ATC code: S01X.

Atropine is a tropane alkaloid that acts as a competitive, nonselective muscarinic acetylcholine receptor antagonist. Atropine has longstanding use in the ophthalmology. In higher concentrations (e.g., 1%) it is used for pupil dilation by antagonizing muscarinic receptors in order to facilitate eye examination.

For slowing progression of myopia, currently the role of atropine is believed to be multifactorial on the retina and/or sclera, affecting the thinning/stretching of the eye. However, how these mechanisms are exactly mediated by atropine remains unclear.

The applicant initially claimed indication was: "to treat myopia in children aged 3 years and older".

In the course of the procedure, Atropine sulfate FGK claimed indication was revised as "to slow myopia progression in children aged 6 to 10 years with spherical equivalent refraction (SER) in the range of -0.50 to -6.00 diopter (D). The proposed pharmaceutical form was 0.1 mg/ml eye drops, solution in single-dose container. The proposed dose recommendation was one eye drop in each to be treated eye, once daily at bedtime.

No novel excipients were used in the Atropine Sulfate FGK formulation. The single-dose containers (low-density polyethylene) containing 0.3 ml of eye drops solution would have been packed in a laminated foil pouch.

2.3. Type of application and aspects on development

The applicant did not make a request for an accelerated assessment.

2.4. Quality aspects

2.4.1. Introduction

The finished product is presented as eye drops, solution containing 0.1 mg/ml of atropine sulfate as active substance.

The product container closure system is single-dose containers (LDPE; low-density polyethylene) containing 0.3 ml of eye drops solution, packed in a laminated foil pouch

2.4.2. Active substance

2.4.2.1. General information

The chemical name of atropine sulfate is bis((1R,3R,5S)-8-methyl-8-azabicyclo[3.2.1]octan-3-yl 3-hydroxy-2-phenylpropanoate); sulfuric acid; hydrate, corresponding to the molecular formula $C_{34}H_{48}N_2O_{10}S$, H_2O. It has a relative molecular mass of 695 and the following structure:

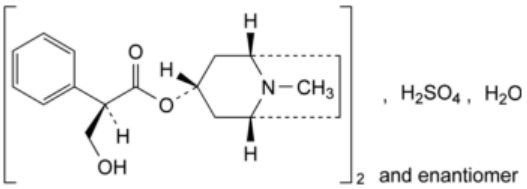


Figure 1. Active substance structure

Atropine sulfate is a white or almost white, hygroscopic crystalline powder or colourless crystals. It is very soluble in water and freely soluble in ethanol. Two pKa have been determined, 9.39 and 15.15, its logP is 1.57. It is manufactured as a racemic mixture.

As there is a monograph of atropine sulfate in the European Pharmacopoeia, the manufacturer of the active substance has been granted a Certificate of Suitability of the European Pharmacopoeia (CEP) for atropine sulfate which has been provided within the current Marketing Authorisation Application.

2.4.2.2. Manufacture, characterisation and process controls

The relevant information has been assessed by the EDQM before issuing the Certificate of Suitability.

The characterisation and manufacturing of the active substance as well as the discussion on impurities from the synthesis of the active substance are covered by the CEP.

2.4.2.3. Specification

The active substance specifications for atropine sulfate, as applied by the finished product manufacturer, includes tests for appearance (visual), identification of the active substance (Ph. Eur.), pH (Ph. Eur.), related substances (Ph. Eur.), water content (Ph. Eur.), sulfated ash (Ph. Eur.), assay (Ph. Eur.), paraformaldehyde (Ph. Eur.), residual solvent (Ph. Eur.), and microbiological quality (Ph. Eur.).

The specifications are compliant with the Ph. Eur. monograph for atropine sulfate. Additionally, tests for residual solvents (paraformaldehyde and isopropyl alcohol) are included, as specified in the Certificate of Suitability but with tighter acceptance criteria. A test for microbiological quality is also included.

Overall, the proposed specification limits in the active substance specification by the finished product manufacturer (FPM) are accepted.

Sufficient information on the description of analytical methods and validation/verfication of the same where needed has been provided. The presented information regarding the reference standards used in the analytical testing is satisfactory.

Batch analysis results have been provided for 3 industrial batches of the active substance demonstrating compliance with the proposed specification.

The active substance (AS) is packaged in double polyethylene film bags closed with Polyamide seals, further placed in a third low-density polyethylene bag. The AS packaged within bags is then placed in a high-density polyethylene drum with numbered tamper evident seals.

2.4.2.4. Stability

No information on re-test period is mentioned in the CEP.

Stability data from three commercial scale batches of active substance from the proposed manufacturer stored in the intended commercial package for up to 36 months under long term conditions (5 ºC ± 3 °C) and for up to six months under accelerated conditions (25°C/ 60% RH) according to the ICH guidelines were provided.

The following parameters were tested appearance, identification (optical rotation and IR), pH, water content, related substances, assay and microbial quality. The analytical methods used were the same as for release and were stability indicating. Stability results met the specifications at all timepoints and condition tested.

A study under stress conditions was performed on one batch of the AS subjected to acidic, alkaline, oxidative, elevated temperature and humidity and UV-light stress. Although no degradation has been observed for the AS subjected to thermal stress, it can be accepted that the long-term stability testing of the AS has been performed in refrigerated conditions, as this does not have any consequence for the patient. The proposed storage condition (refrigerated) is also acceptable. The analytical methods employed were found to be stability indicating by the forced degradation studies.

Overall, the proposed re-test period is acceptable based on the stability data provided.

2.4.3. Finished medicinal product

2.4.3.1. Description of the product and pharmaceutical development

The finished product (FP) is a clear colourless sterile eye drops solution containing 0.01% atropine sulfate in a single-dose LDPE container.

The proposed FP was developed to treat myopia in children aged 3 years and older. The finished product is preservative free and is intended to be supplied as five-pack low-density polyethylene (LDPE) single-dose containers in an aluminium pouch. The product is intended as locally applied locally acting.

All the excipients present in the formulation are commonly used in ophthalmic preparations; their specifications are compliant with the relevant Ph. Eur. monograph, except for sodium dihydrogen phosphate, which meets the compendial requirements of the USP; this is acceptable.

With regard to the microbial methods for all excipients, they are being developed and validated by the applicant. As these activities were still ongoing, and the applicant confirmed that they will be implementing them prior to commercialisation of product batches. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 2.4.1 of this report.

Compatibility studies between the AS and the excipients or between excipients were not performed since the excipients are well known and are used in other ophthalmic formulations. In addition, stability studies demonstrated the FP is sufficiently stable (refer to *Stability of the product* below). The indication for the paediatric population and the chronic use of the product was taken into account in the selection of the proposed excipients and their quantities. The acceptability of the proposed excipients has been adequately justified according to Guideline ICH Q8/Pharmaceutical Development and EMA/CHMP/QWP Guideline on 'Pharmaceutical development of medicines for paediatric use'.

The formulation development studies have been described in detail. The selection of the type and concentration of buffer, the concentration of EDTA as metal chelator, the concentration of sodium chloride as osmolality agent, the supplier of AS and the viscosity enhancer has been adequately discussed. The selection of the target pH is acceptable based on the data provided.

A systematic approach has been used in the manufacturing process development of the proposed FP. The applicant described the different phases of the manufacturing process development and the manufacturing process parameters with impact on the CQAs of the FP.

Initially, it has been demonstrated that (i) the manufacturing of the finished product either in one single phase or in two phases (AS-phase and polymer-phase), that (ii) the amount of water used for dissolving polymer, and (iii) that the order of addition of the excipients have no impact on the product's viscosity. The heat sterilisation of the polymer-phase did not impact product's CQAs. Considering the sensitivity of atropine sulfate to heat, "Process II" (AS-phase and polymer-phase separate sterilisation), was considered for further evaluation, where only the polymer phase was evaluated for heat sterilisation. In Process II, sterile filtration is employed for the AS Phase solution and heat sterilisation is employed for the polymer-phase. In addition, terminal sterilisation is not possible due to the packaging material that cannot withstand high temperatures, which is indeed accepted. The approach to select a two-phase manufacturing process is adequately justified.

A risk assessment approach was used throughout the product development to identify potential high risks due to formulation and process variables. In addition to the 0.01% strength proposed for registration, a 0.02% strength and placebo were also developed using the same approach as that of 0.01% and were used in the Phase 3 clinical study conducted in support of this application. The quality target product profile was used to determine the formulation composition, manufacturing process, and sterilisation process for the FP and the container closure system during the development activities. Product Critical Quality Attributes (CQA) were identified (pH, osmolality, viscosity, drop size, identification, assay of AS, related compounds, residual solvents, sterility, container closure integrity, elemental impurities, weight loss and nitrosamines), and justification is provided in the dossier.

The polymer-phase will be sterilised by heat sterilisation under compendial conditions (121 °C for 30 minutes). The AS-phase is sterilised by a double filtration step with 0.2 µm PES filter membranes. Prior to the sterile filtration, the applicant proposes the use of a clarifying polypropylene filter before filling to ensure that no particulate matter enters the sterile finished product solution, which is considered acceptable.

Both sterilising and clarifying filters have been adequately validated in line with table 3 of the Guideline on Sterilisation of the medicinal product, active substance, excipient, and primary container. Bacterial retention studies with the sterilising filter were carried out using formulations with a higher concentration of atropine sulfate (0.02% and 0.05%) than the concentration of 0.01%, which is the subject of this marketing authorization application. The impact of the different concentration has been discussed and is acceptable since the composition of all strengths is qualitatively and quantitatively the same. In addition, compatibility studies have been carried out with a filter which differed in terms of pore dimensions from the clarification filter used in the commercial manufacturing process. As the tested filter has a smaller pore size with respect to that intended to be used for commercial manufacturing, it is reasonable to consider it as a worst-case scenario in terms of surface area. Thus, an additional filter compatibility study is not needed.

Compatibility studies were conducted with materials and components (other than the filters) used in manufacturing process train. Optimisation of the manufacturing process during the manufacturing of the clinical batches has been described in detail and implemented changes are well justified. Based on studies conducted, the process was scaled up at the proposed manufacturing site for commercial production.

The proposed primary container closure system consists of a low-density polyethylene (LDPE) single-dose container, provided as 5 containers per card, with a glued label on the flag of each single-dose container. The fill volume is 0.3 mL.

Photos that show absence of sharp edges or burrs after opening of the containers are also provided. The proposed glued label on the flag of each single dose container is accepted. No risk of interaction between glue or ink with the product solution is expected.

The proposed container closure system is well-known for this type of finished product. As per EMA Q&A on Information on the functional qualities of plastic containers for eye drops, the usability of the product container in the target patient population has been discussed, and dose delivery performance has been qualified from the container in various orientations such as inverted or inclined. The applicant has demonstrated that no risk of extractable and leachable compounds from the container is expected when the product is stored under the proposed condition. Leachables in the FP were found above the AET only at accelerated conditions; in addition, adequate argumentation has been provided to ensure that the maximum systemic exposure level does not exceed the ICH M7 mutagenicity threshold of 1.5 µg/day for impurities. Therefore, no control in the specification is necessary.

The information on drop size show that drops are larger than the volume of the conjunctival sac and hence the drop size is acceptable.

2.4.3.2. Manufacture of the product and process controls

The FP is manufactured is a single manufacturing site. The site is also responsible for the primary and secondary packaging, quality control (chemical and microbiological), stability testing, storage, batch release and distribution. Satisfactory GMP compliance evidence has been presented.

The manufacturing process of the FP consists preparation of the bulk solution, pre-sterilisation filtration aseptic filling and labelling. The intended commercial batch size and batch formula are clearly stated in the dossier. No overages or factorisation are proposed.

The manufacturing process has been adequately described, including the information of the filters used. Compliance with the EMA NfG on start of shelf-life of the finished dosage form has been stated in P.3.3.

Critical steps of the process and the respective CPPs and IPCs have been clearly presented and are acceptable.

The proposed processing time of 168 hours between the start of the sterile filtration process and the end of the filling was initially not fully supported and thus the CHMP raised a Major objection requesting further justification. In their response the applicant provided additional data on four batches of the bulk sterile solution. Physico-chemical parameters have been investigated, and media fills have been provided. Moreover, justification for the proposed holding time based on the manufacturing capacity has been provided as per EMA Guideline on Sterilisation of the medicinal product, active substance, excipient and primary container and Annex I on Manufacture of sterile products to the Guideline on Good Manufacturing Practice. Since the processing time is justified and validated, no further control measures (e.g. additional sterile filtration step and/or additional bioburden than those already in place) are needed; the MO was resolved.

The manufacturing of the FP was initially considered to be a non-standard process as per Annex II to the EMA Guideline on process validation for finished products due to the use of aseptic processing during the manufacturing process, and since the content of the AS in the formulation is lower than 2.0%. Based on this, the CHMP raised an MO on the proposed process validation approach to not to fully validate the finished product manufacturing process prior to authorisation. In their response to the MO the applicant demonstrated that the process can be considered standard for the proposed manufacturer, since all requirements of point 8 of the Guideline on Process validation for finished

dosage forms are met (i.e. experience with the same or essentially similar product or process, amount of knowledge gained during the development of the product, history of GMP compliance of manufacturing sites for that type of process). In addition, the reproducibility and the robustness of the proposed commercial manufacturing process of the FP at 0.01% concentration has been adequately discussed. Therefore, validation of commercial scaled batches up to 100% filling can be performed post-authorisation as proposed by the applicant. The manufacturing process validation approach was accepted and the MO was resolved.

The proposed heat sterilisation process for the polymer-phase (i.e., 123 °C for 20 minutes) follows compendial criteria of Ph.Eur. 5.1.1 and, thus, does not require further validation.

A verification report has been provided for four commercial-scaled batches of the 0.01% strength (1000 L each) from the proposed manufacturing site. Three of the four batches were filled and packaged at 20% and one batch was filled and packaged at 100%. Additionally, four batches of the 0.02% strength as well as four batches of the placebo are also presented in the verification report. Also, for these two products (0.02% strength and placebo), three out of the four batches were filled at 20% and one out of four was filled and packaged at 100%. The verification data comprise the results of all the CPPs and IPCs as proposed in 3.2.P.3.3 and 3.2.P.3.4, with all results found within the proposed acceptance criteria. All batches have also met the proposed specification limits at release. The process can be considered adequately verified for the FP at commercial scale and up to 20% filling level.

The applicant committed to validate the first three commercial batches as per the provided validation protocol in 3.2.R, which complies with the requirements of Annex I of the Process Validation Guideline for finished products.

The sterilising PES filter has been adequately validated. The bacterial retention was validated for a contact time of 8 hours. This is acceptable based on the data provided. Regarding the sterilisation of the LDPE container, the ampule material is sterilised by the extrusion process. The sterility assurance of aseptically produced drugs in Blow-Fill-Seal containers has been provided and can be accepted.

Overall, it is considered that the manufacturing process has been satisfactorily validated, and it has been demonstrated that it is capable of producing the finished product of intended quality in a reproducible manner.

2.4.3.3. Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: appearance (visual), pH of solution (Ph. Eur.), osmolality (Ph. Eur.), viscosity (Ph. Eur.), identification (UPLC, UV), assay (UPLC), related substances (UPLC), and sterility (Ph. Eur.).

The proposed tests and limits are set according to common pharmaceutical practice, ICH guidelines, compendial requirements, batch and stability data and are considered acceptable. Regarding the proposed limits for impurities specifically, they are set as per ICH Q3B considering the MDD of 0.01 mg, except for the specification limit at shelf life for Tropic acid, which is set above qualification threshold. The applicant has adequately justified this limit from a quality perspective taking into account the limit set for this impurity in the USP monograph of Atropine sulfate 0.005% eye drops solution. The limit has been also adequately qualified based on toxicological data. For further discussion regarding the calculation of this qualification limit of tropic acid based on non-clinical data, see the non-clinical section.

Tests for fill weight, water loss, particulate contamination for sub-visible particles, residual solvents and EDTA were not included in the specification, and this has been adequately justified.

The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for elemental impurities. Based on the risk assessment and the presented data it can be concluded that it is not necessary to include any elemental impurity controls in the finished product specification. The information on the control of elemental impurities is satisfactory.

A risk assessment (RA) concerning the potential presence of nitrosamine impurities in the finished product has been presented in the initial submission. The CHMP raised a Major Objection because the submitted RA was not complete. In their response the applicant updated the RA as requested considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). The conclusions that no risk of nitrosamines in the finished product is expected is, overall, adequately supported. Although no risk of nitrosamine formation in the finished product is expected based on the nitrosamines RA and related documentation, confirmatory testing results on the finished product were submitted on three batches of finished product demonstrating that nitrosamines cannot be found above the LOD. The analytical method used during confirmatory testing has been adequately validated. Based on the information provided, it is accepted that there is no risk of nitrosamine impurities in the active substance or the related finished product. Therefore, no specific control measures are deemed necessary and the MO was resolved.

Sufficient descriptions were provided for all analytical methods included in the specification of the finished product. The information on reference standards is accepted. The in-house analytical method for assay and the compendial analytical method for sterility have been adequately validated. The in-house analytical method for related substances has been adequately validated and has been demonstrated to be stability indicating by forced degradation studies. The test used for the IPC bioburden and the analytical method for the determination of the content of EDTA (not included in the specification of the finished product) have been also adequately validated.

Batch analysis results were provided for three commercial scale batches. Additional batch data from five clinical development batches were also presented. Results confirm the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

2.4.3.4. Stability of the product

Stability data from three commercial scale batches of finished product stored for up to 24 months under long term conditions (25 ºC / 60% RH) for up to 12 months under intermediate conditions (30 ºC/65 % RH) and for up to six months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The batches of the FP are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Parameters tested were appearance, pH, osmolality, viscosity, assay, related substances, loss of weight, EDTA content and sterility.

Under long-term stability condition (i.e. 25 ºC / 40% RH), all results were found within the specification limits at shelf life upon 24 months testing. No upward or downward trends are observed. Under intermediate condition (i.e. 30 ºC / 65% RH) an upward trend for total impurities but remaining within the proposed specification limit has been detected in all three batches; all other results were also found within specification limits after 12 months. An out of specification (OOS) result has been

found at 6-months timepoint under accelerated stability condition for assay of the AS and for the content of tropic acid.

In view of this stability data, the proposed shelf life of 24 months can be accepted as per Decision tree of the Guideline on Stability testing of existing active substances and related finished products. The proposed storage claim "Store below 30 ºC" is acceptable as all results are found within the proposed specification limit at shelf life under intermediate condition. This is in line with the Guideline on Declaration of storage conditions and is reflected acceptable.

A photostability study has been conducted as per ICH Q1B for one commercial scale batch. The results showed that the FP is only sensitive to light when exposed to light outside the pouch. In view of this photostability data, the additional storage condition "Keep the unused single-dose containers in the foil pouch until ready to use, in order to protect from light", proposed by the applicant, is accepted as per Guideline on Declaration of storage conditions.

In-use stability studies have been performed on one commercial batch of the FP in the proposed single-dose LDPE container stored for 12 and 24 months at 15-25 ºC, then followed by the removal of the foil pouch and stored for 10 days at 20-25 ºC. All results were found within specification limits at shelf life and without significant trends. The proposed in-use shelf life after the opening of the foil pouch, and the in-use storage claim is accepted and in line with the NfG on In-use stability testing of human medicinal products.

Finally, the results of the freeze-thaw studies on one commercial batch of the FP packed in the proposed container demonstrate that the product is stable after three freeze-thaw cycles.

Based on available stability data, the proposed shelf-life and storage conditions, as well as the in-use shelf life after opening and in-use storage conditions, are acceptable.

2.4.3.5. Adventitious agents

No excipients derived from animal or human origin have been used.

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. During the procedure three MOs were raised by the CHMP related to the approach to finished product manufacturing process validation, the manufacturing processing time, and the risk assessment on the potential presence of nitrosamine impurities. All three MOs were fully resolved by provision of additional data and justifications from the applicant.

The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.4.6. Recommendations for future quality development

None.

2.5. Non-clinical aspects

2.5.1. Introduction

As this initial MAA concerned a full-mixed application, only the juvenile toxicity study was conducted in accordance with GLP regulations. Other non-clinical sections were based on bibliographical data, for which GLP aspects are not applicable.

2.5.2. Pharmacology

2.5.2.1. Primary pharmacodynamic studies

In vitro

The applicant provided a summary of the mechanism of action of atropine in myopia and described a few in vitro studies. Atropine's primary action in the eye is to block muscarinic acetylcholine receptors. A proteomic analysis of mouse retina showed that atropine may downregulate GABA transporter-1 in myopic retina. Furthermore, atropine was shown to decrease proliferation of scleral fibroblasts in vitro through downstream effects on growth factors.

The mechanism of action of atropine has been sufficiently described.

In vivo

The applicant provided literature information on the primary pharmacodynamics of atropine *in vivo*. In animal models the eye is deprived of clear visual input, usually through lenses or by fusion of eye lids, thereby causing myopia.

In mice, treatment with 1% atropine eye drops for 3 weeks slowed down the myopic shift (refraction as well as axial length).

In chicks, a species in which intraocular muscles of the eye contain predominantly nicotinic receptors rather than muscarinic receptors, intravitreal injection of 0.01% atropine improved experimental myopia. Reduction of relative axial elongation of the deprived eye via a nonaccommodative mechanism was suggested. In another study, atropine eye drops inhibited axial elongation in chicks at an EC_{50} of 0.06%. In healthy chick eyes, intravitreal injection of 0.01% atropine induced a transient increase in choroidal thickness, which was associated with dopamine release.

Three studies were described in primates, the most relevant species for studying myopia. In the first study, myopia was induced in prepubertal *Macaca nemestrina* monkeys by placing them under restricted visual space hoods. Treatment with 1% atropine eye drops slightly reversed the progression towards myopia. In the second study, 1% atropine eye drops prevented lid-sutured myopia and abnormal eye elongation in *Macaca actoides* but were ineffective in *Macaca mulatta*. In the third study, 0.25% atropine eye drops reduced both excessive axial eye elongation and myopic shift in black lens-occluded eyes of young Rhesus monkeys.

2.5.2.2. Secondary pharmacodynamic studies

The applicant provided limited information about the secondary pharmacology of atropine. Given its long history of clinical use, this is sufficient. Though atropine mostly acts on muscarinic receptors, it may to a lesser degree also block nicotinic, adrenergic and tyrosine kinases receptors. The effects are not well-established.

2.5.2.3. Safety pharmacology programme

According to ICH Topic S7A, safety pharmacology studies are not required since Atropine sulfate FGK is a locally applied drug (ocular) with negligible systemic exposure and well-characterized pharmacology. Nevertheless, the applicant has provided limited safety pharmacology bibliographic data based on systemic exposure of atropine. Due to its anticholinergic action, atropine can cause increased heart rate and relaxation of the smooth muscles in the airways. Studies with 1% atropine eye drops in animals showed increased ocular pressure which was short-lived (<24h) and reversible.

Systemic effects on the CNS, respiratory system, and cardiovascular system are not expected with ocular administration of 0.01% atropine.

2.5.2.4. Pharmacodynamic drug interactions

Pharmacodynamic interactions with atropine are not foreseen given the negligible systemic exposure.

2.5.3. Pharmacokinetics

The presented PK information is based on literature, which describes studies that used a variety of analytical methods.

A validated analytical method was used to measure plasma atropine concentration in the GLP-compliant juvenile rat toxicity/TK study (Study 3092-21728). The analyte measured was the racemic mixture of D-hyoscyamine and L-hyoscyamine similarly to human plasma quantification.

Absorption

Bioavailability of atropine administered to the eye is expected to be low (generally <5% for ocular therapeutics). Limited systemic absorption may occur via the conjunctiva and the nasal mucosa of the nasolacrimal duct. Atropine can bind to melanin.

Distribution

Ocular distribution was analysed in different animals after administration of atropine eye drops. Studies on ocular distribution of atropine in rabbits and ex vivo pig eyes demonstrate that after topical application, atropine penetrates all ocular tissues with the highest concentration found in the cornea, followed by the sclera, iris/ciliary body, and aqueous humor. It reaches the posterior segment and crosses over to the untreated eye, detectable up to 3 days post-application. Systemic distribution studies in rodents after IV or IP injection indicated rapid distribution to various organs with main localization in the kidney and liver. Systemic distribution after ocular administration was not described but is expected to be minimal.

After systemic administration, drug accumulation effect is not expected due to a short half-life: in humans, 2.5 hours after ocular instillation of atropine sulfate at concentrations of 0.02% and 0.05%.

Metabolism

Systemically available atropine is primarily metabolized in the liver through hydrolysis, mainly into tropine and tropic acid.

Excretion

Atropine and metabolites are mainly excreted by the kidneys.

Pharmacokinetic drug interactions

Atropine was shown to be a substrate and inhibitor of organic cation transporters 1-3 in the eye, which are functionally active in the uptake of their substrates from tear to aqueous humor. A study in rabbits showed that high dose atropine (48 µg per eye) can modulate the ocular bioavailability of OCT substrates (e.g., anti-infectives, anti-glaucoma, anti-inflammatory, and anti-histaminics) when administered concomitantly to the eye. Given that no lower doses were tested in this study, it is uncertain if these pharmacokinetic drug interactions could occur at the intended clinical dose.

2.5.4. Toxicology

2.5.4.1. Single dose toxicity

Single dose studies in animals by various routes other than ocular administration are reported, which are not deemed informative. Considering the limited relevance of single dose toxicity for the current product, this is acceptable.

2.5.4.2. Repeat dose toxicity

The applicant did not find non-clinical literature data of repeat-dose toxicity studies after ocular application of atropine. Limited animal data are presented by other routes of administration in different species. Due to atropine's pharmacological effect, mydriasis and/or incomplete pupillary responses to light were observed in animals. Systemic adverse effects of atropine in animal studies occurred at doses in excess of the proposed clinical ocular dose and were related to its anticholinergic effects, affecting especially the nervous system (respiratory failure, loss of consciousness, convulsions) and cardiovascular system (tachycardia, atrial arrhythmias, atrio-ventricular dissociation). Systemic reactions to atropine sulfate FGK eye drops are unlikely when administered ocularly given the low systemic exposure.

2.5.4.3. Genotoxicity

According to ICH Guideline S2, the standard test battery for the assessment of genotoxicity includes a bacterial reverse gene mutation test and in mammalian cells, usually in vitro and in vivo. For drugs like atropine eye drops which have negligible systemic absorption, in vitro tests are most appropriate. Atropine was shown to be negative in the Ames test, though S. typhimurium TA102, E. coli WP2 uvrA or E. coli WP2 uvrA (pKM101) were missing. These strains may detect certain oxidising mutagens, cross-linking agents and hydrazines, but according to the applicant none of these characteristics have been reported for atropine, although no literature references were provided.

No chromosomal aberrations or DNA damage were found in the in vitro chromosome aberration test in Chinese Hamster Lung cells or the in vitro comet assay in human hepatoma cells. Furthermore, in an in vivo study where atropine was administered orally, no clastogenic effects were seen in the bone marrow of the treated rats. Therefore, atropine is unlikely genotoxic.

2.5.4.4. Carcinogenicity

The applicant presented non-clinical studies found in literature which describe the carcinogenic potential of systemic atropine administration. IP administration of atropine did not show carcinogenic properties in one lifelong study in rats, at a human equivalent dose (HED) 286-fold the proposed clinical dose. The exposure margin based on plasma AUC is unknown, but is likely very large given the high systemic dose administered in this study and the expected negligible systemic exposure after ocular administration of atropine eye drops.

In three more studies in rats, where atropine was used (orally or SC) after or during treatment with gastric or hepatocellular tumour-initiating agents (nitrosamines), a tumour-promoting effect was identified. The clinical relevance of these studies is minimal given that human exposure to such high amounts of nitrosamines is unlikely.

Clinical experience from the use of atropine does not indicate a carcinogenic potential. In the EU, atropine is currently not registered for indications which require chronic treatment, however, magistral preparations have been used for treating myopia for several years.

Taken together, the carcinogenic potential of atropine eye drops is likely to be low.

2.5.4.5. Reproductive and developmental toxicity

Fertility and early embryonic development

No animal fertility and early embryonic development (EED) studies have been conducted with ocular atropine, hence the applicant described literature data on the effects of systemic atropine. In rats, atropine reduced mating behaviour, male fertility (inhibition of sperm and semen transport), female fertility (ovulation delay), and implantation (delay). Estimated human equivalent doses in these studies were at least 250-fold higher than the dose administered as eye drops. Exposure margins based on plasma AUC are unknown. Since the expected systemic exposure from the eye drops is negligible, the risk of effects on fertility is low.

Embryo-fetal development

No animal EFD studies have been conducted with ocular atropine, hence the applicant described literature data on the effects of systemic atropine. Atropine crosses the placenta. Subcutaneous (SC) atropine treatment of pregnant mice or rats on GD 8-9 did not lead to fetal malformations. Transient placental blood vessel constriction was noted in mice. Estimated human equivalent doses in these studies were at least 250-fold higher than the dose administered as eye drops. Exposure margins based on plasma AUC are unknown. Since the expected systemic exposure from atropine eye drops is negligible, embryofoetal toxicity is unlikely.

Pre- and postnatal development

No animal PPND studies have been conducted with ocular atropine, hence the applicant described literature data on the effects of systemic atropine. SC treatment of pregnant rats at GD19 showed placental transfer as well as blood-brain barrier transfer of atropine in fetuses (not in dams). No information on the potential transfer of atropine into milk was provided. In pups treated SC with atropine on day 2, 7 and 14 after birth, the brain to plasma concentration ratio was lower than in fetuses and decreased with development. Potential neurotoxicity was evaluated in rat pups from dams treated SC with atropine from GD7 to GD19. Reflex behavior and spontaneous motor activity were normal. Performance in the active avoidance learning test was impaired, though only in females. Estimated human equivalent doses in these studies were a least 250-fold higher than the dose

administered as eye drops. Exposure margins based on plasma AUC are unknown. Since the expected systemic exposure from atropine eye drops is negligible, pre- or post-natal developmental toxicity is unlikely.

Juvenile toxicity

The applicant performed a GLP-compliant juvenile animal study. Sprague Dawley rats were dosed from PND 22 to 63 (6 weeks), covering a developmental period from weaning to puberty, with 0.02%, 0.2% or 2.0% atropine eye drops (20 µL/eye) once daily to both eyes. Terminal samples were collected at PND 22 and 63. In addition, between PND 50 and 61, behavioural tests were performed. A toxicokinetics group as well as a 4-week recovery group were included.

TK data are presented in Table 1. Evidence of contamination was observed in the control plasma samples, though this only had an impact on TK results on Day 22 at the 0.02% dose level and on Day 63 at the 0.02% dose level. Generally, quantifiable atropine concentrations in plasma were observed from 0.5 h post-dose (Tmax) to 8 h post-dose across the dose range on PNDD 22 and 63. Cmax increased in a dose-proportional manner on PND 63 (818 pg/ml, 7420 pg/ml, 78500 pg/ml for 0.02%, 0.2% or 2.0% atropine, respectively). At PND22, however, Cmax was greater than dose-proportional at doses 0.2% and 2%, indicating a higher absorption, and AUClast was increased at all dose levels in comparison to AUClast at PND63. According to the applicant, this is probably attributed to the growth of the animals during the 6-week study period.

Table 1. Toxicokinetic data

PND	Group	Dose Level (%)	Sex	C_{max} (pg/mL)	SE C_{max} (pg/mL)	T_{max} (hr)	$AUCl_{ast}$ (hrxpg/mL)	SE AUC_{last} (hrxpg/mL)	T_{last} (hr)	RA C_{max}	RA AUC_{last}
22	2	0.02	F	840	211	0.50	2210	656	8.0	-	-
			M	771	188	0.50	2010	888	8.0	-	-
	3	0.2	F	16200	2010	0.50	11400	1190	8.0	-	-
			M	14200	1880	0.50	10600	1210	8.0	-	-
	4	2	F	203000	23000	0.50	130000	12400	8.0	-	-
			M	214000	57100	0.50	144000	30100	8.0	-	-
63	2	0.02	F	818	158	0.50	782	100	4.0	0.973	0.354
			M	696	240	0.50	978	183	24	0.902	0.485
	3	0.2	F	3930	855	0.50	5770	719	24	0.243	0.505
			M	7420	2230	0.50	8670	2100	8.0	0.522	0.817
	4	2	F	78500	13300	0.50	90600	13400	24	0.386	0.697
			M	55800	3960	0.50	79900	9710	24	0.261	0.556

AUC = area under the curve; AUC_{last} = AUC from time of dosing to time of last measurable concentration; C_{max} = maximum concentration; F = female; M = male; PND = postnatal date; RA = accumulation ratio; SE = sedimentation equilibrium method; T_{max} = time at which C_{max} occurred.
Source: Study No. 3092-21728

Treatment at doses up to 2.0% atropine had no effect on clinical observations, body weights, body weight changes, food consumption, behavioural observations, ophthalmic examination findings, clinical pathology, macroscopic pathology observations, absolute and relative organ weights, and microscopic pathology observations.

Behavioural observations did not show any effect of treatment at doses up to 2.0% atropine on locomotor activity, auditory startle response, or learning and memory.

The NOAEL of atropine when administered ocularly to juvenile rats in this study was 2.0%/40 µL (0.8 mg/day). This corresponds to a safety margin of at least 6163-fold based on AUC.

2.5.4.6. Toxicokinetic data and interspecies comparison

Toxicokinetic investigations were evaluated as part of the toxicity study conducted in juvenile rats.

Human PK information from the clinical trial was used to calculate the safety margin of the NOAEL (2%/day) established in the juvenile rat study. Plasma samples collected from Chinese adult myopic subjects treated with 0.01% atropine eye drops (intended clinical concentration) did not provide measurable atropine sulfate plasma levels, therefore AUC data from subjects treated with 0.02% atropine sulfate eye drops was used, resulting in a more conservative calculation. The lowest calculated margin based on AUC was 6163-fold at PND 63. The extrapolation of exposure-based safety margins to paediatric age, however is uncertain, also considering the higher absorption observed in younger rats. As such, comparison to human equivalent dose (HED) appears more adequate. The NOAEL corresponds to a HED of 0.117 mg/day assuming a mean body weight of 20 kg for a child, which is approximately 12-fold the human recommended daily dose.

2.5.4.7. Local tolerance

In the performed juvenile rat study, atropine eye drops were well-tolerated by the eye and no local toxicity was found up to a dose of 2.0%.

In a study in rats which was described in literature, no corneal epithelium damage was found in rabbits after repeated ocular atropine sulfate (1.0%) treatment, applied three times daily.

Local toxicity of Atropine sulfate FGK 0.01% eye drops is unlikely.

2.5.4.8. Other toxicity studies

Atropine sulfate 0.01% Eye Drops has no potential for antigenicity, immunotoxicity, or dependence.

There are no major human metabolites that are insufficiently present in animals, so no metabolite toxicity studies are warranted.

Given that the MDD < 10 mg, the qualification limit of impurities is 1.0%, following ICH Q3B guideline. The applicant proposes a specification limit of 4.0% for tropic acid and argues that this is qualified because tropic acid is a major metabolite (3%). This argument is not accepted given that 4% impurity on top of 3% metabolite is more than a doubling. However, there is another argument for qualifying the specification limit of 4.0%, namely on the basis of the TTC, following ICH M7 guideline. With a specification limit of NMT 4.0%, the total maximum daily intake of tropic acid is well below the 1.5 µg TTC. The specification limit of 4.0% for tropic acid is therefore toxicologically qualified.

All the potential sources such as drug substance, excipients, solvent/ water, container closure system, manufacturing process of Atropine sulfate FGK eye drops as well as formation during storage were evaluated for nitrosamine impurities. No risk of presence of nitrosamine-related impurities were identified.

All excipients are well-known and therefore no specific studies on excipients are necessary.

No literature data on phototoxicity testing was found and no studies were performed by the applicant. Even though photosafety generally has to be evaluated for ocular products, clinical experience does not

indicate any photoreactive potential of atropine. Furthermore, since Atropine sulfate FGK eye drops are intended for administration before bedtime, no phototoxicity is expected.

2.5.5. Ecotoxicity/environmental risk assessment

Following the Phase I requirements of the "Guideline on the environmental risk assessment of medicinal products for human use" (EMEA/CHMP/SWP/4447/00 corr 2, 2006), the applicant has provided an estimation of environmental exposure to the drug substance based on the default values for the determination of PEC_{sw}. Based on the formula, the estimated PEC_{sw} for atropine sulfate FGK eye drops is 0.00005 µg/L. Therefore, as this value is below the trigger value of 0.01 µg/L, it is agreed that the product is considered unlikely to represent a risk for the environment following its indicated use in patients.

In addition, the Phase I assessment also includes a screening for persistence, bioaccumulation and toxicity (PBT) and involves the determination of the log K_{ow} or log D_{ow}. Since atropine is an ionisable compound, it is more correct to refer to the log of the distribution coefficient, log D_{ow}. In a publication by Wang and Lieu (1980), the experimentally determined log D_{ow} was -0.05 at pH 7.4, which is below the trigger value of 4.5. Atropine is therefore not a PBT substance.

Table 2. Summary of main study results

Substance (INN/Invented Name): Atropin sulfate anhydrous			
CAS-number (if available): 55-48-1			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	Octanol-tris buffer (comparable to OECD107)	-0.05	Not PBT
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}		B/not B
	BCF		B/not B
Persistence	DT50 or ready biodegradability		P/not P
Toxicity	NOEC or CMR		T/not T
PBT-statement:	The compound is not considered as PBT nor vPvB The compound is considered as vPvB The compound is considered as PBT		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, default	0.00005	μg/L	> 0.01 threshold: N
Other concerns (e.g. chemical class)			N

2.5.6. Discussion on non-clinical aspects

Pharmacology

The pharmacology of atropine is well-known given its long clinical use, though the exact mechanism of atropine's beneficial effect on myopia progression is not clear. The primary pharmacology of atropine involves the action as a non-selective muscarinic receptor antagonist. When applied to the eye, atropine blocks the muscarinic receptors in the iris sphincter muscle, leading to pupil dilation (mydriasis), and in the ciliary body, resulting in paralysis of accommodation (cycloplegia). Atropine may also interact with muscarinic receptors in the retina, sclera, choroid and retinal pigment epithelium (RPE). Atropine has a binding affinity constant in the range of 0.4–0.7 nM for all five subtypes of muscarinic acetylcholine receptors. Indirect effects on dopaminergic and GABAergic systems in the retina and/or sclera were also described, which are involved in the control of eye growth and refractive state.

In animal models of myopia, atropine eye drops have been shown to slow the progression of the disease. In mice, 1% atropine eye drops reduced myopic shift. In chicks, 0.01% atropine intravitreal injections improved myopia through a nonaccommodative mechanism. In primates, the most relevant species model for myopia development in humans, atropine eye drops showed effectiveness already at a concentration of 0.25%.

Safety pharmacology studies are not required since Atropine sulfate FGK is a locally applied drug (ocular) with negligible systemic exposure and well-characterized pharmacology.

Literature data showed that 1% atropine eye drops in animals caused an increase in ocular pressure, which was short-lived (<24h) and reversible (see clinical safety section).

Pharmacodynamic interactions with atropine are not foreseen given the negligible systemic exposure. Nevertheless, functional interactions with other medicinal products administered ocularly e.g., para-sympathetic agonist like pilocarpine, cannot be excluded.

Pharmacokinetics

The pharmacokinetics of atropine are well-known given its long clinical use, not only via ocular application but also via intravenous and intramuscular injection. Bioavailability of atropine administered to the eye is expected to be low (generally <5% for ocular therapeutics) due to pre-corneal anatomical barriers. Limited systemic absorption may occur via the conjunctiva and the nasal mucosa of the nasolacrimal duct.

The applicant provided a review of animal data from literature on the PK profile of atropine. The rabbit is the preferred animal species to study eye drop formulations because of its ocular anatomical similarity to human eye. Ocular distribution studies in rabbits showed that atropine penetrates all ocular tissues when administered as eye drops, with the highest concentration in the cornea, followed by the sclera, iris/ciliary body, and aqueous humor. Atropine also reaches the posterior segment and can cross over to the untreated eye.

Atropine can bind to melanin resulting in slower elimination. Topically administered atropine in rabbits showed indeed that the drug effect was prolonged in pigmented animals as compared to albino animals.

After IV or IP injection in rodents, atropine was shown to distribute to various organs, particularly localizing in kidneys and liver. Systemic distribution after ocular administration was not described but is expected to be minimal.

Systemically available atropine is primarily metabolized in the liver through hydrolysis, mainly into tropine and tropic acid. Atropine and metabolites are mainly excreted by the kidneys.

Atropine was shown to be a substrate and inhibitor of organic cation transporters 1-3 in the eye, which are functionally active in the uptake of their substrates from tear to aqueous humor. A study in rabbits showed that high dose atropine (48 µg per eye) can modulate the ocular bioavailability of OCT substrates when administered concomitantly to the eye. Although the clinical dose of Atropine sulfate FGK is 9-6 fold lower than the dose used in the rabbit study, potential PK interactions with OCT substrates, including anti-infectives, anti-glaucoma, anti-inflammatory, and anti-histaminics, cannot be excluded.

Analytical methods

Analytical method LC/MS-MS to measure "atropine sulfate" in rat plasma in the juvenile study 3092-21728, was validated for a range of 10.0 – 10,000 pg/mL. The analyte measured was the racemic mixture of D-hyoscyamine and L-hyoscyamine, similar to the human plasma quantification in clinical PK study ZKO(HK)-ATP-202111.

Toxicology

Data included in the Atropine sulfate FGK non-clinical package submitted by the applicant are mainly derived from literature studies dating back to 1960's, thus the GLP compliance is uncertain. This is acceptable considering the clinical safety profile of atropine is well-known for both systemic and

ophthalmic formulations. Nevertheless, the effects of its chronic use in paediatric population, although at very low concentration, are not characterised.

Repeat-dose toxicity

The applicant did not find non-clinical literature data of toxicity studies after ocular application of atropine. Limited animal data are presented by other routes of administration in different species. Due to atropine's pharmacological effect, mydriasis and/or incomplete pupillary responses to light were observed in animals. Systemic adverse effects of atropine in animal studies occurred at doses in excess of the proposed clinical ocular dose and were related to its anticholinergic effects, affecting especially the nervous system (respiratory failure, loss of consciousness, convulsions) and cardiovascular system (tachycardia, atrial arrhythmias, atrio-ventricular dissociation). Systemic reactions to Atropine sulfate FGK 0.01% eye drops are unlikely when administered ocularly given the low systemic exposure.

Genotoxicity

Genotoxicity information was collected from literature. Atropine was shown to be negative in the Ames test, though *S. typhimurium* TA102, *E. coli* WP2 uvrA or *E. coli* WP2 uvrA (pKM101) were missing. These strains may detect certain oxidising mutagens, cross-linking agents and hydrazines, but none of these characteristics have been reported for atropine. Furthermore, in silico analysis did not identify any reactive groups in atropine that would indicate oxidising or cross-linking properties. The absence of S. typhimurium TA102, E. coli WP2 uvrA or E. coli WP2 uvrA (pKM101) strains in the Ames test data can therefore be accepted.

No chromosomal aberrations or DNA damage were found in the *in vitro* chromosome aberration test in Chinese Hamster Lung cells or the *in vitro* comet assay in human hepatoma cells. Furthermore, in an *in vivo* study where atropine was administered orally, no clastogenic effects were seen in the bone marrow of the treated rats. The relevance of this *in vivo* study is uncertain since, exposure following oral administration of atropine, which is an ionisable compound, is expected to be variable and low. The acidity of the stomach may explain the lack of absorption from the gastric mucosa (Murrin, 1973).

Taken together all the information, atropine is unlikely genotoxic.

Carcinogenicity

The applicant presented non-clinical studies found in literature which describe the carcinogenic potential of systemic atropine administration. IP administration of atropine did not show carcinogenic properties in one lifelong study in rats, at a human equivalent dose (HED) 286-fold the proposed clinical dose. The exposure's margin based on plasma AUC is unknown, but is likely very large given the high systemic dose administered in this study and the expected negligible systemic exposure after ocular administration of atropine eye drops. A drawback to this study, however, is that only one dose level was used so that no dose-response is available, affecting the relevance of the study results.

In three more studies in rats, where atropine was used (orally or SC) after or during treatment with gastric or hepatocellular tumour-initiating agents (nitrosamines), a tumor-promoting effect was identified. The clinical relevance of these studies is minimal given that human exposure to such high amounts of nitrosamines is unlikely. Clinical experience from the use of atropine does not indicate a carcinogenic potential. In the EU, atropine is currently not registered for indications which require chronic treatment, however, magistral preparations have been used for treating myopia for several years. Taken together, the carcinogenic potential of atropine eye drops is likely to be low.

Developmental and reproductive toxicity

No animal FEED, EFD or PPPND studies have been conducted with ocular atropine, hence the applicant described literature data on the effects of systemic atropine. In rats, atropine reduced mating behaviour, male fertility (inhibition of sperm and semen transport), female fertility (ovulation delay), and implantation (delay). Atropine was shown to cross the placenta. SC atropine treatment of pregnant mice or rats, at a much higher dose compared to ocular dosing of eye drops, on GD 8-9 did not lead to fetal malformations. Transient placental blood vessel constriction was noted in mice. SC treatment of pregnant rats at GD19 showed placental transfer as well as blood-brain barrier transfer of atropine in fetuses (not in dams). No information on the potential transfer of atropine into milk was provided. In pups treated SC with atropine on day 2, 7 and 14 after birth, the brain to plasma concentration ratio was lower than in fetuses and decreased with development. Potential neurotoxicity was evaluated in rat pups from dams treated SC with atropine from GD7 to GD19. Reflex behavior and spontaneous motor activity were normal. Performance in the active avoidance learning test was impaired, though only in females. Though exposure margins based on plasma AUC in the reported DART studies are unknown, estimated human equivalent doses were at least 250-fold higher than the dose administered as eye drops.

Clinical data from atropine exposure during the first trimester of pregnancy in 400 mother and child pairs are available, indicating no risk of malformations (Briggs GG and Freeman RK. Drugs in pregnancy and lactation. A reference guide to fetal and neonatal risk. Wolters Kluwer, 10th Ed. 2015: 333-335) (see clinical sub- section Use in pregnancy and lactation).

Since the expected systemic exposure from Atropine sulfate FGK 0.01% eye drops is negligible, reproductive or developmental toxicity is unlikely. Nevertheless, as there are no clinical data on the (long-term) use of atropine eye drops during pregnancy, a warning was proposed in the drafted SmPC (section 4.6), in accordance with applicable guidance (EMEA/CHMP/203927/2005).

Juvenile toxicity

The applicant performed a GLP-compliant juvenile animal study, which was conducted for registration in China, but was not requested by the PIP for the current full-mixed MAA. For the intended hybrid MAA, the Pediatric Committee (PDCO) also did not require a dedicated juvenile toxicity study or additional studies, as the safety profile for the pediatric age group was expected to be consistent with clinical experience with 1% atropine eye drops already approved in the EU. Therefore, the submitted juvenile rat toxicity study could be considered as supportive information.

Sprague Dawley rats were dosed from PND 22 to 63 (6 weeks), covering a developmental period from weaning to puberty, with 0.02%, 0.2% or 2.0% atropine eye drops (20 µL/eye) once daily to both eyes. Terminal samples were collected at PND 22 and 63. In addition, between PND 50 and 61, behavioral test were performed. A toxicokinetics group as well as a 4-week recovery group were included.

Quantifiable atropine sulfate concentrations in plasma were observed from 0.5 h post-dose (Tmax) to 8 h post-dose across the dose range on PNDD 22 and 63. No accumulation of atropine sulfate in rat plasma was observed. Cmax increased in a dose-proportional manner on PND 63 (818 pg/ml, 7420 pg/ml, 78500 pg/ml for 0.02%, 0.2% or 2.0% atropine, respectively). At PND22, however, Cmax was greater than dose-proportional at doses 0.2% and 2%, indicating a higher absorption, and AUClast was increased at all dose levels in comparison to AUClast at PND63. The reason for the difference in exposure between PND22 and PND63 is uncertain. Nevertheless, since there were no corresponding toxicological findings, the exposure difference is considered of negligible clinical relevance.

Atropine eye drops were well-tolerated by the eye, however, no fluorescein examination for cornea blood vessel stain was carried out nor intraocular pressure was measured. The lack of these endpoints

represents a drawback of this study. Treatment at doses up to 2.0% atropine had no effect on clinical, behavioural, macroscopic or microscopic observations. The NOAEL of atropine in the juvenile rat study was 2.0%/40 µL (0.8 mg/day), corresponding to a safety margin of at least 6163-fold based on AUC. The extrapolation of exposure-based safety margins to paediatric age, however is uncertain, also considering the higher absorption observed in younger rats. As such, comparison to human equivalent dose (HED) appears more adequate. The NOAEL corresponds to a HED of 0.117 mg/day assuming a mean body weight of 20 Kg for a child, which is approximately 12-fold the human recommended daily dose.

The relevance of the performed juvenile rat study for the intended clinical use is minimal due to important limitations: the choice of the rat species, without a full PK profile, and the short duration. The applicant justified the rat being a standard species for use in juvenile toxicology studies. While this is in principle true, the rabbit is widely preferred in ophthalmic research and historical data from the long use of rabbits in ophthalmic research are available. Furthermore, the lack of a full PK characterisation of atropine administered via the eye in the rat prevents appropriate extrapolation of the results to human. It is also noted that, although, according to the applicant, the rat eye has the same basic structure and function of all mammalian eyes, including the human eye, and muscarinic receptor subtypes M2, M3, and M4 have all been found in the rat iris, no animal model of myopia has ever been developed in the rat. The rabbit remains the preferred species for PK and toxicity assessment of eye drop formulations.

Regarding the duration of this study, 6 weeks of treatment do not cover the clinical study duration (3 years) nor the chronic clinical use of Atropine sulfate FGK (see ICH M3 guideline for duration of the toxicity studies in support of MAA). Moreover, the study was not designed to assess any rebound effect in terms of safety during the 4-week recovery period. Thus, although the large amount of non-clinical and clinical data available in the literature and the experience with systemic and ophthalmic use of atropine, the long-term safety in paediatric population of atropine in this indication is not entirely known. However, based on the 4-year safety data and the clinical experience with atropine for myopia, there were no specific safety concerns requiring e.g. additional risk minimisation measures.

Excipients

Atropine sulfate FGK tested in the juvenile rat study was representative of clinical material and the intended marketed product in terms of excipient composition. EDTA is a common excipient used in eye drop formulations, including EU-approved ophthalmic products indicated for the paediatric population.

Phototoxicity

No literature data on phototoxicity testing was found and no studies were performed by the applicant. Even though photosafety generally has to be evaluated for ocular products, clinical experience does not indicate any photoreactive potential of atropine. Furthermore, since Atropine sulfate FGK 0.01% eye drops are intended for administration before bedtime, no phototoxicity is expected.

Environmental Risk Assessment

$PEC_{surfacewater}$ for atropine sulfate is below the action limit of 0.01 µg/L. Atropine is not a PBT substance as log Dow (more appropriate than log K_{ow} given that atropine is an ionisable compound) does not exceed 4.5. Therefore, Atropine sulfate FGK 0.01% eye drops are not expected to pose a risk to the environment.

2.5.7. Conclusion on the non-clinical aspects

For the application of Atropine sulfate FGK 0.01% eye drops, to slow myopia progression in children aged 6 to 10 years with spherical equivalent refraction (SER) in the range of -0.50 to -6.00 diopter (D), the applicant summarised non-clinical pharmacodynamic and pharmacokinetic properties of atropine based on literature. Given the long history of clinical use of atropine, often at higher strengths than proposed for the current application and administered to the eye as well as parenterally, the provided information is sufficient.

However, some uncertainties remained from non-clinical perspective, since Atropine sulfate FGK 0.01% eye drops was proposed for a new condition in children expected to be treated for a long period. These uncertainties were mostly mitigated by the low systemic exposure of Atropine sulfate FGK 0.01% eye drops measured in animals and in adult myopic humans, without accumulation in plasma.

Information on long-term safety of atropine given ocularly does not seem available, however, literature data on repeat-dose toxicity studies with systemic atropine formulations in animals indicate that adverse effects occurred at doses in excess of the proposed clinical ocular dose.

Based on the 4-year safety data and the clinical experience with atropine for myopia, there are no specific safety concerns. Routine risk minimisation measures were therefore considered adequate.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

The clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

2.6.2. Clinical pharmacology

Atropine has a long and well-established use in Europe and is a competitive, nonselective muscarinic acetylcholine receptor antagonist. Atropine is also used topically (ocular administration) for induction of cycloplegia and mydriasis amongst other uses. Various Atropine 1% eye drop formulations for ocular use have been authorized in member states of the European Union (EU) since at least 1964.

For the proposed Atropine Sulfate 0.01% Eye Drops, two clinical pharmacology studies, of which one PK and one PD study, with the proposed strength (and other strengths of that product) were conducted by third parties. In these studies also Atropine Sulfate Eye Drops in 0.02% and/or 0.05% strengths were investigated. Also no *in vitro* studies using human biomaterial studies were conducted. Additional relevant PK information is provided from literature.

Table 3. Summary of Phase 1 studies supporting the clinical pharmacology

Study identifier	Study design	Population (incl number of subjects, healthy vs patient and gender ratio)	Dosing regimen	Main PK parameters/PD endpoint
ZKO(HK)-ATP-202111	randomised, open-label, phase I clinical study evaluating the systemic PK and safety of atropine sulfate eye drops in healthy Chinese volunteers	30 healthy volunteers were enrolled in the study: 10 subjects in each 0.01 %, 0.02%, and 0.05% group.	each subject received the study drug at the designated concentration for their respective group in 7 consecutive mornings	AUC_{0-t}, AUC_{0-inf}, C_{max}, C_{min}, $T_{1/2}$, t_{max}, Vz/F, λz, and CL/F
PJ21084 TOAST	randomised, partially masked, PD and safety study investigating the short-term effects of low-concentration atropine of varying concentration and frequency on ocular outcomes in adults with myopia	104 myopic patients (48 in pilot phase and 56 in definitive phase) with blue, green, or brown eyes were randomly assigned to use either one drop of 0.01%, 0.02% or 0.05% atropine once or twice per night for 2 weeks	Participant assigned to the twice daily regimen continued to use the eye drops from day 14 to day 21 (once per day) followed by a 1-week washout period. Participants assigned to the once daily regimen used the eye drops up to day 14 followed by a 1-week washout period from day 14 to day 21.	ocular outcomes such as pupil size and responsiveness, accommodative function, and ocular biometry

2.6.2.1. Pharmacokinetics

Bioanalytical methods

Validated LC-MS/MS methods were developed for the analysis of atropine sulfate concentrations in serum. The calibration ranges were 10 to 10000 pg/mL. The bioanalytical method is acceptable for accuracy and precision, sensitivity and range, selectivity, dilution integrity, analyte stability, and specificity.

A bioanalytical report was provided for study **ZKO(HK)-ATP-202111**, which indicated that the bioanalysis was appropriately validated during study sample analysis. Limited incurred sample reanalysis was performed. Nevertheless, as this was due to the low initial concentrations measured for the study samples and the samples that were reanalysed met the acceptance criteria, this is considered acceptable.

Absorption

To support the current application, one PK study (study **ZKO(HK)-ATP-20211**) was performed, which is a randomised, open-label, Phase I clinical study evaluating the systemic PK of atropine in healthy adult volunteers following atropine sulfate eye drops (0.01%, 0.02%, and 0.05% formulation) as described in the study report. The average size of a topical eye drop of the proposed atropine sulfate 0.01% drug product is ~50 µL. However, this volume is dropped into a "reservoir" (i.e., the ocular

surface), which is 30 µL. Hence, there is inevitably some spillage and nasolacrimal drainage. Therefore, it is assumed approximately 30 µL of the administered 50 µL will eventually reach the ocular surface.

In the performed study **ZKO(HK)-ATP-202111,** no subjects (N=10) in the 0.01% group had measurable plasma drug concentrations. For the higher doses, plasma drug levels above the LLOQ (10 pg/mL) were observed for 2 of 10 subjects receiving 0.02% formulation and 7 of 10 subjects receiving 0.05% formulation. For the 0.02% group, the C_{max} was 12.3 pg/mL (N=2),AUC_{0-t} was 14.7 h•pg/mL (N=2), $AUC_{0-\infty}$ was 47.3 h•pg/mL (N=1), and $t_{½}$ 2.56 h (N=1). For the 0.05% group, the C_{max} was 19.5 pg/mL (N=7),AUC_{0-t} was 34.7 pg•h/mL (N=7), $AUC_{0-\infty}$ was 82.3 pg•h/mL (N=1), and$t_{½}$ 2.22 h (N=1). Even though these results should be approached carefully due to the small number of subjects, these results were compared to a previously performed European study (Kaila 1999), where after dose correction based on the assumption of linear PK of atropine sulfate, the $AUC_{0-\infty}$ was 0.51 ng•h/mL (N=6) and the C_{max} was 144 pg/mL (N=6) based on a 0.15 mg dose. The estimated $t_{1/2}$ (2.45 h) and T_{max} (27.8 min) of l-hyoscyamine from this European study are considered generally comparable with those for d- and l-hyoscyamine estimated in Chinese Study **ZKO(HK)-ATP-202111**. However, the C_{max} and AUC cannot be considered comparable, but as these results are all based on limited data and the exposure measured is low, it is not expected that this will have a clinical relevant impact.

The low atropine sulfate exposures were further supported by a study in older subjects (56 to 66 years of age) performed by Lahdess (1988), where an AUC_{0-90} of 43,245 pg•min/mL and a C_{max} of 860 pg/mL were observed following a single ocular administration of 0.4 mg atropine sulfate.

All studies that were discussed from literature only measured l-hyoscyamine, while in study **ZKO(HK)-ATP-202111** no distinction between the two isomers, d- and l-hyoscyamine, was made. Therefore, the comparison between the performed study and the literature studies should be approached carefully. Nevertheless, as the systemic exposure is expected to be neglectable.

Systemic exposure at the proposed dose of 0.01% atropine sulfate is expected to be neglectable. Furthermore, even if there would be a small amount of systemic absorption as seen in higher doses of atropine sulfate, no safety issues are expected (see also section 4. Clinical safety).

Distribution

Literature indicates that protein binding of systemically available atropine ranges from 14% to 44%, while other literature showed serum protein binding to the 22.5 ± 20.6% in the paediatric population <10 years of age, with no effect of age on the serum protein binding of atropine.

Systemically bioavailable atropine is widely distributed throughout the tissue. Previous studies in literature indicated that the total apparent volume of distribution of atropine ranged between 1.0 and 1.7 L/kg.

Nevertheless, since the systemic exposure is very limited to none at the proposed dose of Atropine Sulfate 0.01% eye drop solution, distribution is not expected to be relevant and is thus not further discussed.

Metabolism

Systemic atropine is metabolised for ~50% of the absorbed dose with d-hyoscyamine not metabolised and l-hyoscyamine metabolised to a very significant extent (~90%). Noratropine (24%) and atropine-N-oxide (15%) are the major metabolites, whereas tropine (2%) and tropic acid (3%) are two hydrolysis products that are considered minor metabolites.

Elimination

No mass balance study was conducted which is also not needed due to the low systemic bioavailability of atropine administered as 0.01% formulation drops to the eye.

In study **ZKO(HK)-ATP-202111**, the elimination half-life of atropine was determined to be approximately 2.4 hours based on data of two subjects. Even though this value should be approached carefully due to the small number of subjects, the determined half-life was in line with literature data where the half-life following ophthalmic administration of 0.3 mg atropine was found to be approximately 2.5 hours.

Paediatric population

No clinical studies in paediatric patients were performed using Atropine Sulfate 0.01% eye drop solution, which is in accordance with the approved PIP, **EMEA-002744-PIP01-19-M0** (PIP decision number: P/0039/2024). Published literature in relation to PK of atropine in paediatric patients was provided to support this application. The amount absorbed is not expected to be affected by age. Since the exposure is negligible, the effect of intrinsic factors is of no importance.

Literature data indicated general comparability in PK between paediatric patients 3 years of age and older after, for whom C_{max} could be approximated 9.6 pg/mL after administration of Atropine sulfate 0.02% in only 1 eye (10 µg), and adult patients, for whom a C_{max} of 12.3 pg/mL was observed in study **ZKO(HK)-ATP-202111** after dose correction to 10 µg.

Pharmacokinetic interaction studies

Based on the negligible systemic availability, no relevant drug-drug interactions (DDIs) are expected and therefore, no DDI study were performed.

2.6.2.2. Pharmacodynamics

Mechanism of action

Atropine has longstanding use in the ophthalmology. In higher concentrations (e.g., 1%) it is used for pupil dilation by antagonizing muscarinic receptors in order to facilitate eye examination. This action mechanism, however, appears not primarily responsible for atropine's effect on myopia progression.

The applicant provided a summary of the mechanism of action of atropine in myopia and described a few in vitro studies. Atropine's primary action in the eye is to block muscarinic acetylcholine receptors. A proteomic analysis of mouse retina showed that atropine may downregulate GABA transporter-1 in myopic retina. Furthermore, atropine was shown to decrease proliferation of scleral fibroblasts *in vitro* through downstream effects on growth factors.

The applicant briefly touched upon the muscarinic and non-muscarinic pathways potentially involved in myopia control. Possible roles of atropine include action on muscarinic and non-muscarinic receptors responsible for increasing dopamine and its metabolite 3,4-dihydroxyphenylacetic acid (DOPAC) in the retina; regulation of gamma-aminobutyric acid (GABA) transporters involved in eye growth; and modulation of growth factors and proliferation of scleral fibroblasts during the scleral remodeling process (Upadhyay 2020; García Del Valle 2021). In animal models of myopia, atropine eye drops have been shown to slow the progression of the disease.

How these mechanisms are exactly mediated by atropine remains unclear.

Primary and Secondary pharmacology

For primary pharmacology, the applicant discussed the safety profile of atropine 0.01% in relation to mydriasis and cycloplegia. On the one hand, the antimuscarinic effect appears not primarily responsible for atropine's effect on myopia as discussed in the previous section 'mechanism of action'. On the other hand if the antimuscarinic effect plays a role, the absence of a dose response in CHAMP is not well understood. A link between primary pharmacology and (abnormal) clinical findings are considered of importance but are currently missing.

The systemic PD effects of atropine are well known and include:

- Heart: increased heart rate possibly preceded by a temporally bradycardia
- Gastrointestinal (GI) tract: slowing in GI motility
- Central nervous system: larger doses can cause excitation, delirium, and hallucinations
- Respiratory system: inhibition of secretions of the nose, mouth, pharynx, and bronchi, and thus dries the mucous membranes of the respiratory tract. Potentially mucus plugs
- Secretions: Abolishment or marked reduction of salivary and gastric secretions (cephalic and fasting phases)
- Urinary tract: decrease of normal tone and amplitude of contractions of the ureter and bladder, leading to urinary retention
- Sweat glands and temperature control: inhibition of activity of sweat glands innervated by sympathetic cholinergic fibers, causing the skin to become hot and dry. Sweating may be depressed enough to raise body temperature but only notably at high doses or high environmental temperatures.

2.6.3. Discussion on clinical pharmacology

Pharmacokinetics

The one performed PK study **ZKO(HK)-ATP-20211** is a randomised, open-label, Phase I clinical study evaluating the systemic PK of atropine in healthy adult volunteers following Atropine sulfate eye drops (0.01%, 0.02%, and 0.05% formulation) as described in the study report. In the performed study**,** no subjects (N=10) in the 0.01% group had measurable plasma drug concentrations. For the higher doses, some exposure was observed for 2 of 10 subjects receiving 0.02% and for 7 of 10 subjects receiving 0.05%.

Additional relevant PK information is provided from literature and was compared to the results of study **ZKO(HK)-ATP-20211**, meaning the PK of atropine sulfate eye drops was mainly bridged from literature. The estimated $t_{1/2}$ (2.45 h) and T_{max} (27.8 min) of l-hyoscyamine from a study described in literature (Kaila 1999) are considered generally comparable with those for d- and l-hyoscyamine estimated in study **ZKO(HK)-ATP-202111**. However, the C_{max} (19.5 pg/mL in study **ZKO(HK)-ATP-20211** based on a 0.15 mg dose versus 144 pg/mL based on a 0.15 mg dose (Kaila 1999)) and $AUC_{0-\infty}$ (82.3 pg•h/mL in study **ZKO(HK)-ATP-20211** based on a 0.15 mg dose versus 510 pg•h/mL based on a 0.15 mg dose (Kaila 1999)) cannot be considered comparable, but as these results were all based on limited data and the exposure is measured to be low, it is not expected that this will have a clinical relevant impact. The low atropine sulfate exposures were further supported by a study in older subjects (56 to 66 years of age) where an AUC_{0-90} of 43,245 pg•min/mL and a C_{max} of 860 pg/mL were observed following a single ocular administration of 0.4 mg atropine sulfate (Lahdess 1988).

Systemic exposure at the proposed dose of 0.01% atropine sulfate is expected to be very limited to none. Furthermore, even if there would be a small amount of systemic absorption as seen in higher doses of atropine sulfate, no safety issues are expected (see also section 4. Clinical safety). Due to the neglectable systemic exposure at the proposed dose, the distribution, metabolic, and elimination characteristics of Atropine Sulfate 0.01% eye drop solution is not expected to be relevant and is thus not further discussed.

Pharmacodynamics

Atropine has longstanding use in the ophthalmology. In higher concentrations (e.g. 1%) it is used for pupil dilation by antagonizing muscarinic receptors in order to facilitate eye examination. The mechanism of action for slowing progression of myopia was not investigated as part of this submission. Currently the role of atropine is believed to be on the retina and/or sclera, affecting the thinning/stretching of the eye. However, how these mechanisms are exactly mediated by atropine remains unclear.

Short-term pharmacodynamic ocular effects of atropine were investigated in young adults (18-25 years) in the Treatment Optimisation of Atropine Study (TOAST; refer to section 3.3.4.1. for details on that study). Among the different ocular parameters tested, accommodative lag, anterior chamber depth and lens thickness showed a certain degree of dose-response relationship; change in pupil size showed a clear dose-response relationship. For pupil latency, peak pupil velocity, accommodative convergence, changes in axial length or choroidal thickness the dose-response relationship was not evident. Eye colour had little to no modifying impact on the ocular effects of atropine. Non-ocular effects of atropine are well-established and are adequately discussed by the applicant.

Initially, no pharmacodynamic interactions were considered relevant based on negligible systemic availability of atropine 0.01%. In Round 2, SmPC section 4.5 was revised by adding potential pharmacodynamic DDI on antimuscarinic agents (potentiating of atropine effects), muscarinic agents (reducing of atropine effects) and sympathomimetics (potentiating of atropine effects).

2.6.4. Conclusions on clinical pharmacology

Pharmacokinetics

The PK of Atropine Sulfate 0.01% eye drop solution is sufficiently addressed. Systemic exposure at the proposed dose of 0.01% atropine sulfate is expected to be neglectable based on the performed PK study and additional literature.

Pharmacodynamics

The action mechanism of atropine in myopia was not investigated as part of this submission. Short-term pharmacodynamic ocular effects of atropine were adequately investigated in the TOAST study.

2.6.5. Clinical efficacy

Table 4. Clinical efficacy studies performed with Atropine sulfate FGK (0.01%)

Study ID	Enrolment status Start date Total enrolment/ enrolment goal	Design Control type	Study & control drugs Dose, route of administration and duration Regimen	Population Main inclusion/ exclusion criteria

CHAMP (NVK002 – 0001) Sponsored by Applicant	Completed First subject enrolled: 20nov2017 Last subject completed: 10feb2022 (stage 1) 29jul2023 (stage 2) Enrolled: n=576/ planned: n=436 Enrollment was to proceed until n=436 6-10 years, and at least n=483 overall had been randomized. Enrollment subjects ⩾11 years could stop when n=50 in this group was achieved.	**Stage 1**: 36-month, 3-Arm, Randomized (2:2:3), Double-Masked, Placebo-Controlled **Stage 2**: 12-month, 3-Arm, Randomized, Double-Masked, Placebo-Controlled. Stage 1 atropine groups completers re-randomized 1:1:1 to 0.01%, 0.02% or vehicle. Stage 1 placebo group re randomized 1:1 to atropine 0.01%, 0.02%	Atropine Sulfate 0.01% and 0.02%, and corresponding vehicle (placebo) One eye drop in each eye at bedtime, for 36 months (Stage 1); or an additional 12 months (Stage 2)	3-17 years -0.50 to -6.0 D Ireland, The Netherlands, United Kingdom, Spain, Hungary, United States
Mini-CHAMP (ZKO-ATP-202105-Mini-CHAMP) Partner-sponsored	Ongoing / 12 month data available First subject enrolled: 13may2022 Last subject completed: 20aug2023 (stage 1) Enrolled: n=526/ planned: n=526	**Part 1**: 12-month, 3-Arm, Randomized (2:2:3), Double-Masked, Placebo-Controlled **Part 2**: 12-month, 3-Arm, Randomized, Double-Masked, Placebo-Controlled. Part 1 atropine groups completers re-randomized 1:1:1 to 0.01%, 0.02% or vehicle. Part 1 placebo group re-randomized 1:1 to atropine 0.01%, 0.02%	Atropine Sulfate 0.01% and 0.02%, and corresponding vehicle (placebo) One eye drop in each eye at bedtime, for 12 months (part 1); or an additional 12 months (part 2)	6-10 years -0.50 to -6.0 D China
China-CHAMP (ZKO-ATP-202105-China-CHAMP) Partner-sponsored	Ongoing / final efficacy data not available First subject enrolled: 15mar2022 Enrolled: n=777 / Planned: 777	**Part 1**: 24-month, 3-Arm, Randomized (2:2:3), Double-Masked, Placebo-Controlled **Part 2**: 12-month, 3-Arm, Randomized, Double-Masked, Placebo-Controlled. Part 1 atropine groups completers re-randomized 1:1:1 to 0.01%, 0.02% or vehicle. Part 1 placebo group re-randomized 1:1 to atropine 0.01%, 0.02%	Atropine Sulfate 0.01% and 0.02%, and corresponding vehicle (placebo) One eye drop in each eye at bedtime, for 24 months (part 1); or an additional 12 months (part 2)	6-12 years -0.50 to -6.0 D China

MOSAIC (Loughman 2023, 2024) ISS	Completed Start date: jul2019 End date: sept2023 Enrolled: n=250/ planned: n=250	**Phase 1**: 24-month, 2-Arm, Randomized (2:1), Double-Masked, Placebo-Controlled. **Phase 2**: 12-month, 4-arm, Randomized (2:2:1; 1), Double-Masked, Placebo-Controlled. 0.01% group re-randomized to placebo for 12 months, to tapered dosing of 0.01% or to tapered dosing of placebo. Phase 1 placebo group switched to 0.05%	Atropine Sulfate 0.01%, 0.05% and corresponding vehicle (placebo) Phase 1: One eye drop in each eye at bedtime for 24 months Phase 2: one eye drop in each eye at bedtime for 12 months. When tapered: alternate day dosing in Q1, twice weekly dosing in Q2, once weekly dosing in Q3, no treatment in Q4.	6-16 years At least -1.00 D Ireland
MTS1 Repka, 2023) ISS	Completed Start date: jun2018 End date: sep2022 Enrolled: n=187/ planned: 186 to be randomized	24 + 6-month, 2-arm, randomized (2:1), Double-Masked, Placebo-Controlled.	Atropine Sulfate 0.01% and corresponding vehicle (placebo) 0.01% for 24 months → no treatment for 6 months Placebo for 24 months → no treatment for 6 months	5-12 years -1.0 D to -6.0 D United States

Source: module 2.7.3. table 1; ISS: investigator sponsored study

2.6.5.1. Dose response studies

TOAST study

The TOAST study was a randomised (1:1:1) double-blind (2 weeks) dose-response phase 2 study, assessing the mydriatic effect of 0.01%, 0.02%, or 0.05% atropine in adults aged 18-25 years with a refractive error of -0.5 - -6.00 D in both eyes. Pupil size was the PD endpoint of interest. See details and sample size in Figure 2.

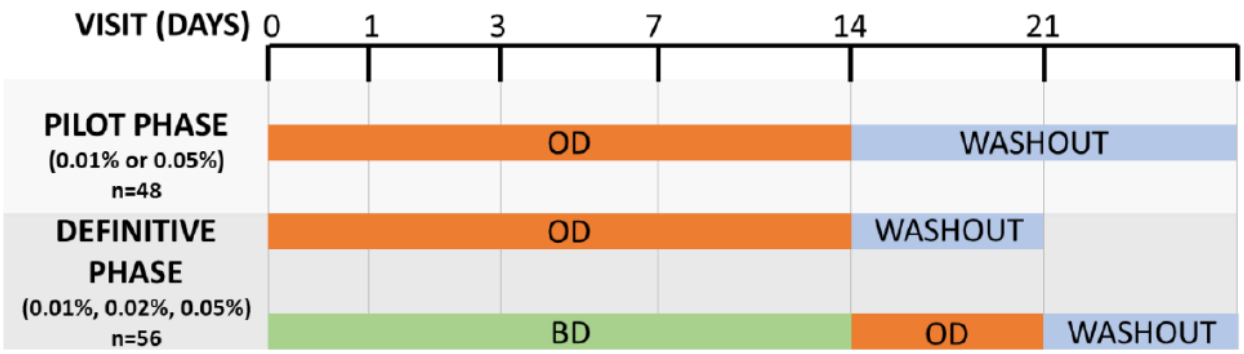


Figure 2. Design of the TOAST study

Visit schedule (Day 0 [baseline], Day 1, Day 3, etc.), atropine treatment concentration (0.01%, 0.02% or 0.05%), dosing regimen (OD: one drop once daily; BD: one drop twice daily; washout: ceased using eye drops) in the pilot and definitive phases of the study.

Dose response in terms of pupil diameter were observed both across the single daily dose regimens (Atropine Sulfate 0.01%, 0.02%, and 0.05%) and the twice daily dosing regimens (of the same 3 concentrations) evaluated. Furthermore, the investigators observed that dose response to a twice daily dose was comparable to a once daily dose of half such strength. For example, the pupil size response to two drops of 0.01% atropine was comparable to one daily drop of 0.02% atropine.
On average, all ocular effects of low-concentration atropine returned to baseline within one week of ceasing eye drops.

2.6.5.2. Main studies

CHAMP (Childhood Atropine For Myopia Progression; NVK002-0001)

Methods

This was a 3-arm, randomized, multi-center, double-masked, placebo-controlled study which was had two stages. Referred is to the study scheme in the figure below.

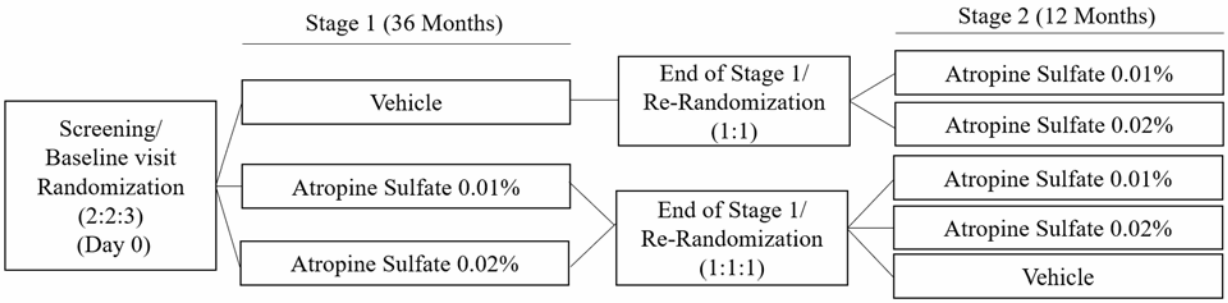


Figure 3. Schematic overview CHAMP study

Stage 1 was a 3-year (36-month) double-blind parallel-design primary treatment phase in which subjects were randomized to Vehicle, Atropine Sulfate Ophthalmic Solution, 0.01%, or Atropine Sulfate Ophthalmic Solution 0.02%.

Stage 2 was a subsequent 1-year (12-month) phase during which subjects were either re-randomized to one of the three treatment groups (subjects originally randomized to one of the two Atropine Sulfate

Ophthalmic Solution doses) or to one of the two active treatment arms (subjects who were initially randomized to Vehicle).

Enrollment was to proceed until 436 subjects aged 6 to 10 years were randomized and at least 483 subjects overall had been randomized.

CHAMP was performed at 20 sites in the US and 6 sites in Europe (2 sites in the United Kingdom [UK] and 1 site each in Ireland, Hungary, the Netherlands, and Spain).

For SER error measurement, children $\geqslant$ 6 years old at study entry received 1.0% tropicamide and children < 6 years old at study entry received cyclopentolate.

For SER and axial length measurements the devices for an individual was standardized but various devices were allowed to be used between individuals.

Study Participants
Key inclusion criteria were male or female aged 3 to ≤17 years; myopia -0.50 D to -6.00 D in each eye; astigmatism ≤ -1.50 D in each eye; anisometropia SER of < 1.50 D; intraocular pressure (IOP) of <21 mmHg in each eye and a visual acuity of Snellen 20/25 or better.

Exclusion criteria were designed to exclude patients with potentially confounding diseases and/or who were using/might need to use confounding therapies.

Medications with the potential to confound interpretation of the efficacy data were also prohibited per-protocol during the study.

Treatments
Atropine sulfate 0.02% or 0.01% or placebo, administered in both eyes, 1 drop 1 time daily at bedtime. Treatment duration was 36 months (Stage 1) and an additional 12 months (part 2) for subjects also participating in Stage 2.

Objectives

Primary Objective (only Stage 1): To evaluate the safety and efficacy of two concentrations of Atropine Sulfate Ophthalmic Solution (0.01% and 0.02%) compared to Vehicle (placebo) for slowing the progression of myopia in children over a 3-year treatment period.

Exploratory Objective (Stage 2): To observe the safety and efficacy in subjects re-randomized to 1 year of treatment with Atropine Sulfate Ophthalmic Solution, 0.01% or 0.02% or Vehicle following 3 years of treatment in children with myopia.

Outcomes/endpoints

Primary efficacy endpoint:

Between-treatment group (Atropine 0.02% versus Vehicle) difference in the proportion of subjects' eyes that showed < -0.50 D myopia progression (SER) at the Month 36 visit.

Secondary endpoints:

Between-treatment group (Atropine 0.02% versus Vehicle) difference in the mean change from baseline in SER at the Month 36 visit.
Between-treatment group (Atropine 0.01% versus Vehicle) difference in the proportion of subjects' eyes that showed < -0.50 D myopia progression (SER) at the Month 36 visit.

Between-treatment group (Atropine 0.01% versus Vehicle) difference in the mean change from baseline in SER at the Month 36 visit.

Between-treatment group (Atropine 0.02% versus Vehicle) difference in the mean change from baseline in axial length at the Month 36 visit.

Between-treatment group (Atropine 0.01% versus Vehicle) difference in the mean change from baseline in axial length at the Month 36 visit.

Sample size

The sample size calculation specified in the protocol was based on the proportions of subjects who met response criteria, i.e., a subject with less than 0.50 D myopia progression (SER) from baseline.

Using this definition and assuming response rates of 25% and 7% in the Atropine 0.02% and Vehicle (placebo) arms, respectively, sample sizes of 136 and 91 subjects would have 95% power to detect a difference when tested using a Fisher's exact test with a 0.05 two-sided significance level. For the comparison in subjects 6 to 10 years of age, the target enrolments were 186 and 125 in the Atropine 0.02% and Vehicle (placebo) arms, respectively. This sample was considered to suffice up to a drop-out rate 27% over the first 3 years of the study.

Target enrolment in the Atropine 0.01% was smaller than Atropine 0.02%, at 125 subjects. With an assumed response rate in this dose group of 25%, a sample size of 91 subjects would have 90% power to detect a difference from the Vehicle (placebo) group.

Randomisation and blinding (masking)

Refer to Figure 4 for the randomization scheme.

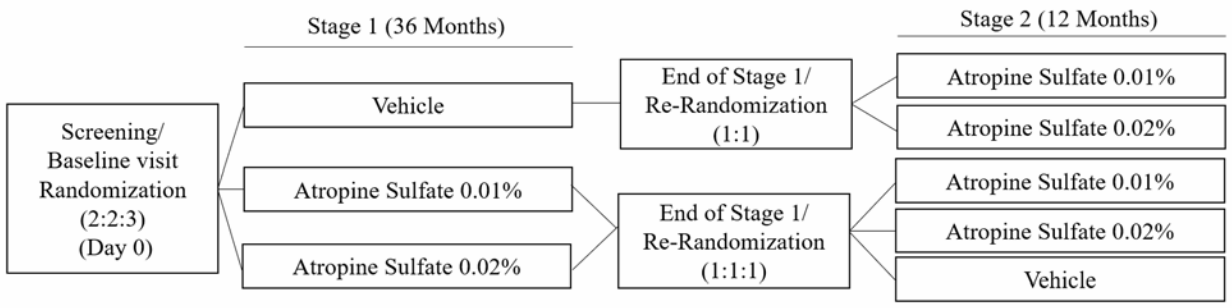


Figure 4. Study scheme

The randomization was stratified (1) by age (subjects < 9 years; subjects ≥ 9 years) and (2) refractive error (less myopic: SER -0.50 to -3.00 D; more myopic: one or more eyes with SER -3.01 to -6.00 D).

Enrolment was to proceed until 436 subjects aged 6 to 10 years were randomized and at least 483 subjects overall had been randomized. Enrolment could be closed to subjects ≥ 11 years following enrolment of 50 subjects in this age group to avoid over-enrolment into the study.

Statistical methods

Post-hoc an estimand was defined. For the primary objective, this was: What is the difference of atropine 0.02% versus placebo in the proportion of subjects' eyes that showed less than 0.5 D myopia progression at month 36 in pediatric subjects aged 6 to 10 years with myopia at baseline, regardless of treatment discontinuation, use of prohibited treatments and missed visits.

Three analyses sets were defined:

- The modified Intent-to-Treat (mITT) set: all randomized subjects who were aged 6 to 10 years at the time of randomization.
- The Intent-to-Treat (ITT) set: all randomized subjects.
- The Safety set: all subjects who were administered at least one dose of study medication.

The primary analysis was performed in the mITT population.

The primary efficacy endpoint was tested using the odds ratio at a two-sided level of significance of 0.05. All data collected through Month 36 were used, regardless of when treatment was stopped. The primary analysis was performed using a mixed effects model based on the binomial distribution. The model included progression as the dependent variable; subject, treatment, visit, eye (left or right), baseline age group (as stratified), and baseline SER (as stratified) as independent variables; and treatment-by-visit as an interaction term. Random intercepts for subject and eye-within-subject were included using variance components and compound symmetry covariance structures, respectively.

Sensitivity analyses were performed for the primary efficacy endpoint using different analysis sets (ITT, modified Per Protocol and Per Protocol populations) and on-treatment set (excluding data collected more than 4 weeks after the last day of treatment).

A supportive analysis was planned using subject, rather than eyes within subject. The supportive analysis used the same model as described above for the primary analysis, but eyes within subjects were not included as an explanatory variable.

The proportion of subjects' eyes responding in the Atropine Sulfate 0.01% versus Vehicle comparison was tested using the same model as for the primary comparison of the higher dose and Vehicle. The remaining secondary endpoints are continuous variables. The treatment group differences were tested using a similar mixed effects model as for the primary analysis but with change from baseline included as the dependent variable.

Responder analyses (proportion of eyes that showed less than 0.5 D progression of myopia from baseline) and analyses of mean change from baseline in SER were performed for six prespecified subgroups:

- Region (United States or Europe)
- Age at baseline (6 to 8 years or 9 to 10 years)
- Degree of myopia at baseline (-0.50 to -3.00 D SER or -3.01 to -6.00 D SER)
- Race (Asian [Japanese, East Asian, South Asian] or non-Asian [all other self-described races])
- Iris color (dark irides [Grade 4 and Grade 5] or light irides [Grade 1 to Grade 3])
- Sex (female or male).

All statistical testing was to be performed using a hierarchal testing procedure as described for the primary and secondary endpoints above. Each test was planned to be performed using a two-sided 5% significance level until the first non-significant test.

Results

Participant flow

First subject enrolled: 20nov2017; Last subject completed: 10feb2022 (stage 1); 29jul2023 (stage 2)

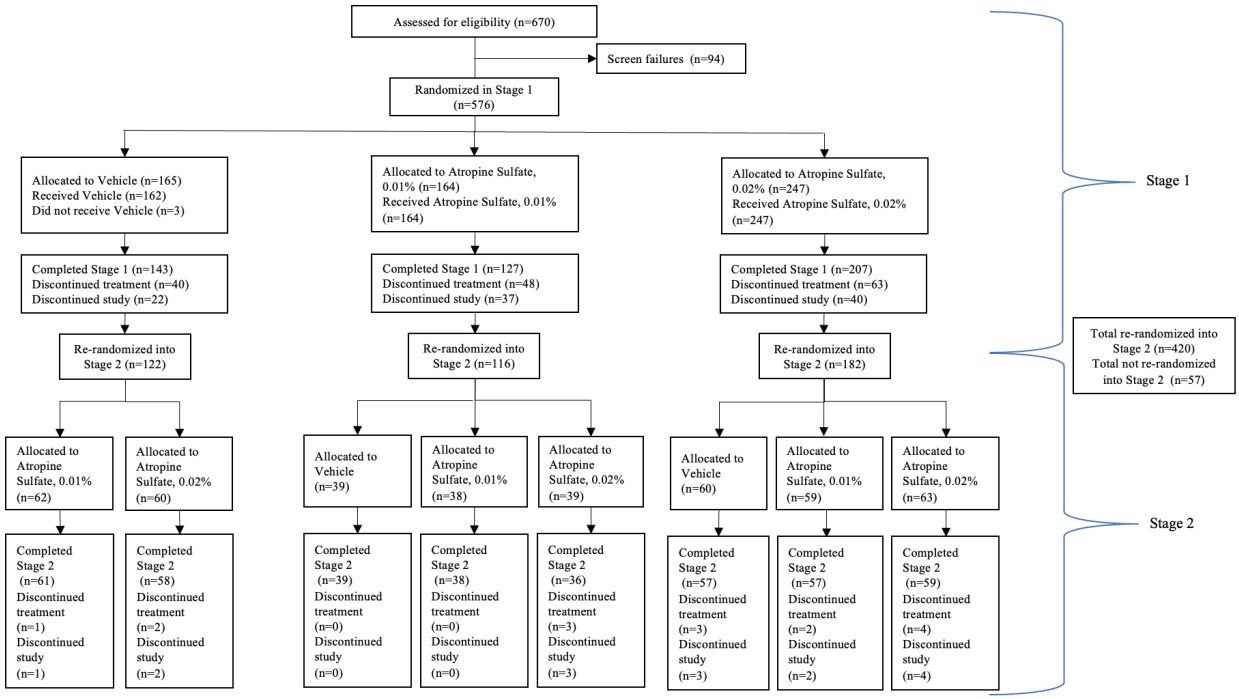


Figure 5. Overview of stage 1 and stage 2 subject disposition

Conduct of the study

Four protocol amendments were implemented during the conduct of the study.

Changes to Inclusion and Exclusion Criteria

- Exclusion rule in Protocol Amendment 2 (10 April 2018): female subjects who are pregnant, nursing, or plan to become pregnant at any time during the study;
- Exclusion rule in Protocol Amendment 2 (10 April 2018): Employees of the study site and their family members are not permitted to participate as subjects in the study. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted;
- Inclusion rule in Protocol Amendment 3 (2 August 2019): inclusion, correctable distance vision was updated to include 20/25 Snellen equivalent in each eye. The following inclusion and exclusion criteria were added in Protocol Amendment 3 (dated 2 August 2019);
- Exclusion rule Protocol Amendment 3 (dated 2 August 2019): Current or history of significant or severe damage to the cornea.

Changes to Study Assessments

Protocol Amendment 2 (10 April 2018):

- Crystalline lens thickness was to be measured, if feasible, for an exploratory endpoint.

- The requirement for urine pregnancy testing every 6 months in female subjects of childbearing potential or subjects who reach the age of childbearing potential during the study was removed.

Protocol Amendment 4 (dated 09 October 2020):
use of an electronic diary for reporting study drug dosing during Stage 2.

Protocol Amendment 5 (dated 14 June 2021):

- the Modified ATI, quality of life questionnaire was as an assessment during Stage 2, to be completed at the Month 42 and Month 48 visits.

In addition, during study conduct, the unit of responders in the primary endpoint was changed from number of subjects to the number of eyes. I.e., both eyes were used separately in the analysis.

Changes Implemented Due to COVID-19
17 March 2020: clarification that alternate accommodations for dispensing study medication (i.e., alternate pick-up sites or shipment of study medication) would not be restricted to subjects residing greater than 150 miles from a study site. In addition, assessments of treatment adherence, concomitant medication use, and adverse events for both 3-month and 6-month study visits could be completed over the phone for subjects who were not able to visit the sites.

Protocol deviations

Stage 1

Overall, 16.5% of subjects in the ITT population had at least one major protocol deviation; there were no critical deviations. The proportions of subjects with major protocol deviations were generally similar across treatment groups. The following protocol deviations were considered comment-worthy by the applicant:

• At one site, drug kits were dispensed to the sub-investigator and driven to another clinic where assessment for AEs and new concomitant medications as well as study drug dispensing was conducted. This secondary clinic site was not registered with the FDA. Further, no temperature monitoring of study drug supply was conducted but it is noted that drug was stored in either a car or office with air conditioning. This deviation affected 4 of the 41 subjects at this site and is not listed per subject in the protocol deviation listing or summarized in the table.

• Another site did not document informed consent/assent process for v5.0 for all subjects, at the next subject visit after the approval of v5.0, as the primary site coordinator was on maternity leave during implementation. This deviation is not listed for individual subjects in the protocol deviation listing or summarized in the table.

• Twenty-five of the 49 major informed consent protocol deviations presented in the table above were related to the requirement for parents to sign and date the California Experimental Subject's Bill of Rights at Site 016.

• SAE information on 3 subjects was not reported within 24 hours of awareness. For one subject, the initial SAE report "was not submitted to Syneos Health within 24 hrs of awareness," and for another, the "SAE, appendicitis, was reported > 24 hours after awareness".

• Mis-stratifications relating to baseline SER were reported as major protocol deviations for 12 subjects: 2 subjects for Atropine 0.02%, 7 subjects for Atropine 0.01%, and 3 subject for Vehicle. Although not included in the listing or table, one subject was mis-stratified based on age (mis-stratified

as < 9 years when actual age was 10 years). The subjects were kept as mis-stratified, and no subjects were excluded from the pre-specified ITT/mITT subgroup analyses in accordance with the SAP.

• 25 of the 52 subjects in the ITT population who discontinued study treatment but stayed in the study for at least one subsequent study assessment, reportedly initiated confounding treatments (orthokeratology, multifocal contact lenses, or compounded atropine). This included 23 subjects in the mITT population and 14 subjects in the mPP population. For some subjects who had discontinued study treatment, their use of the confounding treatment after study treatment discontinuation was not reported in the eCRF, and these subjects were identified via site query after database lock.

Stage 2
The Stage 2 protocol deviations that were classified as major are listed below. There were no major protocol deviations related to COVID-19 in Stage 2.

• An SAE was not reported within 24 hours after awareness for 1 subject (SAE of attempted suicide).

• Prohibited medications were taken by the 6 subjects (three subjects in Atropine 0.02% to Atropine 0.01% group; one subject in Atropine 0.01% to Atropine 0.01% group, one subject in the Atropine 0.02% to Atropine 0.02% group; and one subject in the Vehicle to Atropine 0.01% group).

• One subject (Vehicle to Atropine 0.02%) was dosed with the study medication kit from Stage 1 instead of the newly assigned Stage 2 study medication. This deviation continued for approximately 2.5 months after Stage 2 re-randomization. The subject's Stage 2 data are summarized in accordance with ITT principles based on the randomized treatment (Atropine Sulfate Ophthalmic Solution, 0.02%).

• Consent or re-assent for the latest protocol amendment was not signed at the earliest possible visit or visits for 8 subjects

• Signature was not obtained for the California Experimental subject's bill of rights for 1 subject

• The parent of 1 subject inadvertently signed the adult ICF.

• An assessment (cycloplegic autorefraction) was not done at Month 36 for one subject (Atropine 0.01% to Atropine 0.02%).

• Study drug kits were returned to the site but could not be located on site for 4 subjects. The deviation listing indicated that reconciliation was performed at the site for at least 2 of these subjects.

• Study drug kit was not returned for one subject.

• Subject confidentiality was breached by names and/or addresses not being redacted or not being fully redacted for 11 subjects.

Baseline data

Key characteristics for subjects in CHAMP stage 1 are summarized in Table 5 and Table 6 below.

In total, 465 of 576 (81%) randomized subjects were from the US, and 111 (19%) randomized subjects from Europe (29 subjects were from the UK, and 82 (14.2%) were from member states of the European Union (EU) [Ireland 52; the Netherlands 24; Hungary 3; Spain 3]).

Table 5. Demographic and baseline characteristics (CHAMP stage 1, ITT and mITT populations)

Characteristic		ITT Population				mITT Population			
		Vehicle N=165	Atropine Sulfate 0.01% N=164	Atropine Sulfate 0.02% N=247	Total N=576	Vehicle N=144	Atropine Sulfate 0.01% N=133	Atropine Sulfate 0.02% N=212	Total N=489
Age (years)a	Mean (SD)	8.8 (1.83)	9.0 (2.14)	9.0 (2.06)	8.9 (2.02)	8.6 (1.30)	8.7 (1.15)	8.6 (1.29)	8.6 (1.25)
	Median (min, max)	9.0 (4, 15)	9.0 (3, 16)	9.0 (3, 16)	9.0 (3, 16)	9.0 (6, 10)	9.0 (6, 10)	9.0 (6, 10)	9.0 (6, 10)
Age Group, n (%)a, b	< 9 years	63 (38.2)	64 (39.0)	94 (38.1)	221 (38.4)	58 (40.3)	55 (41.4)	87 (41.0)	200 (40.9)
	≥ 9 years	102 (61.8)	100 (61.0)	153 (61.9)	355 (61.6)	86 (59.7)	78 (58.6)	125 (59.0)	289 (59.1)
Sex, n (%)	Female	94 (57.0)	85 (51.8)	136 (55.1)	315 (54.7)	82 (56.9)	69 (51.9)	115 (54.2)	266 (54.4)
	Male	71 (43.0)	79 (48.2)	111 (44.9)	261 (45.3)	62 (43.1)	64 (48.1)	97 (45.8)	223 (45.6)
Ethnicity, n (%)	Hispanic or Latino	47 (28.5)	44 (26.8)	64 (25.9)	155 (26.9)	37 (25.7)	35 (26.3)	53 (25.0)	125 (25.6)
	Not Hispanic or Latino	112 (67.9)	114 (69.5)	171 (69.2)	397 (68.9)	101 (70.1)	92 (69.2)	148 (69.8)	341 (69.7)
	Missing	6 (3.6)	6 (3.7)	12 (4.9)	24 (4.1)	6 (4.2)	6 (4.5)	11 (5.2)	23 (4.7)
Race, n (%)	American Indian or Alaska Native	1 (0.6)	3 (1.8)	3 (1.2)	7 (1.2)	1 (0.7)	2 (1.5)	3 (1.4)	6 (1.2)
	Asianc	26 (15.7)	29 (17.7)	54 (21.9)	109 (18.9)	23 (16.0)	27 (20.3)	48 (22.6)	98 (20.0)
	Black or African American	27 (16.4)	23 (14.0)	31 (12.6)	81 (14.1)	21 (14.6)	16 (12.0)	28 (13.2)	65 (13.3)
	Native Hawaiian or Other Pacific Islander	3 (1.8)	1 (0.6)	0	4 (0.7)	3 (2.1)	1 (0.8)	0	4 (0.8)
	White or Caucasian	93 (56.4)	84 (51.2)	132 (53.4)	309 (53.6)	81 (56.3)	68 (51.1)	111 (52.4)	260 (53.2)
	Other	8 (4.8)	15 (9.1)	7 (2.8)	30 (5.2)	8 (5.6)	11 (8.3)	4 (1.9)	23 (4.7)
	Missing	7 (4.2)	9 (5.5)	20 (8.1)	36 (6.3)	7 (4.9)	8 (6.0)	18 (8.5)	33 (6.7)
Refractive Error Group n (%)e	Less myopic: SER -0.50 to -3.00 D	111 (67.3)	110 (67.1)	164 (66.4)	385 (66.8)	97 (67.4)	91 (68.4)	144 (67.9)	332 (67.9)
	More myopic: SER -3.01 to -6.00 D	54 (32.7)	54 (32.9)	83 (33.6)	191 (33.2)	47 (32.6)	42 (31.6)	68 (32.1)	157 (32.1)

Source: CHAMP Stage 1 CSR, Table 14.1.3.1.2.1, Table 10; Note: source tables also include height, body weight, and body mass index data.a: Age at informed consent (IC). Age = (date of IC – date of birth + 1) / 365.25 and truncated to complete years. b: In the source table, subject summary for each age category was incorrectly footnoted as being calculated based on age strata entered at time of randomization, however, because Subject [redacted] was mis-stratified, actual age at IC was used. c: Asian includes subjects presented in the source table as Japanese, East Asian, and South Asian (Pakistan, India, and Bangladesh).d: Body mass index is calculated from height at baseline and body weight at baseline (BMI=weight (kg)/height (m)^2).e: For Refractive Error, less myopic: SER -0.50 to -3.00 D; more myopic: one or more eyes with SER -3.01 to -6.00 D.

Table 6. Baseline disease characteristics (CHAMP stage 1, ITT and mITT populations)

Characteristic		ITT Population				mITT Population			
		Vehicle N=165	Atropine Sulfate 0.01% N=164	Atropine Sulfate 0.02% N=247	Total N=573	Vehicle N=144	Atropine Sulfate 0.01% N=133	Atropine Sulfate 0.02% N=212	Total N=489
SER (D)	n (eyes)	328	328	494	1150	286	266	424	976
	Mean	-2.541	-2.505	-2.484	-2.506	-2.535	-2.477	-2.469	-2.491
	SD	1.1874	1.2582	1.2068	1.2154	1.1934	1.2301	1.2119	1.2106
	Median	-2.410	-2.250	-2.325	-2.330	-2.460	-2.250	-2.300	-2.310
	IQR	1.710	1.635	1.630	1.660	1.720	1.620	1.635	1.660
	Min, Max	-5.90, -0.50	-5.87, -0.50	-5.86, -0.50	-5.90, -0.50	-5.90, -0.50	-5.81, -0.50	-5.86, -0.50	-5.90, -0.50
Axial Length (mm)	n (eyes)	327	328	489	1144	287	266	419	972
	Mean	24.340	24.358	24.317	24.335	24.329	24.371	24.304	24.330
	SD	0.8509	0.8663	0.8920	0.8725	0.8330	0.8085	0.8684	0.8415
	Median	24.400	24.345	24.300	24.340	24.400	24.385	24.290	24.340
	IQR	1.180	1.130	1.140	1.160	1.180	1.090	1.140	1.125
	Min, Max	22.01, 26.51	21.75, 27.39	22.17, 27.02	21.75, 27.39	22.01, 26.49	21.75, 26.82	22.19, 26.86	21.75, 26.86

Source: CHAMP Stage 1 CSR, Table 14.1.3.2.2.1, Table 12; Note: see source tables for astigmatism, anisometropia, crystalline lens thickness, sphere, cylinder, and axis which were balanced across treatment groups. CRF=case report form; D=diopter; IQR=interquartile range, the difference between the upper (75th percentile) and lower (25th percentile) quartile; N=number of subjects in population; n=number of non-missing observations (n=eyes for all parameters except anisometropia for which n=subjects); SD=standard deviation; SER=spherical equivalent refraction. Note: Normalized SER = 100/((100/SER)-(Vertex Distance/10)) The SER on the right side of the equation is the original SER from CRF.

Stage 2

Compared with Stage 1, the proportions of subjects in the less vs more myopic subgroups were different in Stage 2. Specifically, in Stage 1, the majority of subjects were less myopic (< 3 D;), whereas in Stage 2 the majority of subjects all treatment groups were more myopic by Stage 2 baseline:

- In the Safety population (n=420), 31.9% of subjects overall were categorized as less myopic at the start of Stage 2 (SER: 0 to -3.00 D) and 67.6% were categorized as more myopic (SER: 3.01 D or worse in either eye). Median Stage 2 baseline values for SER and axial length were -3.500 D and 24.990 mm, respectively.

- In the mITT population, the corresponding proportions were 30.5% and 69.3%, respectively. Median Stage 2 baseline values for SER and axial length were -3.530 D and 25.015 mm, respectively.

Treatment compliance

Stage 1

Treatment compliance (defined as ⩾80%) was comparable in both the Safety (mean 87.4% overall) and mITT (88.0%) populations and across treatment groups in those populations during Stage 1. Approximately a fifth of subjects switched to self-dosing during Stage 1.

Stage 2

Overall mean compliance was in the safety population 88.9% and mITT population 88.8%. Mean compliance was generally similar across treatment groups ranging between 84.9% and 93.4% in the mITT population.

Numbers analysed

The numbers of randomized subjects included in each analysis population is summarized in the table below. Four hundred seventy-seven (82.8%) subjects completed Stage 1.

Table 7. Numbers (%) of subjects in each of the analysis sets (CHAMP stage 1)

Analysis population/set	**Vehicle n (%)**	**Atropine Sulfate 0.01% n (%)**	**Atropine Sulfate 0.02% n (%)**	**Total n (%)**
Intent-to-Treat (all randomized)	165 (100)	164 (100)	247 (100)	576 (100)
Safety (all dosed)	162 (98.2)	164 (100)	247 (100)	573 (99.5)
Modified Intent-to-Treat (ITT age 6-10 years) **Primary efficacy analysis set**	144 (87.3)	133 (81.1)	212 (85.8)	489 (84.9)
Per-protocol	127 (77.0)	112 (68.3)	190 (76.9)	429 (74.5)
Modified Per-protocol	111 (67.3)	87 (53.0)	167 (67.6)	365 (63.4)

Outcomes and estimation

Primary efficacy analysis: responder (<0.50 D myopia progression) where eyes are experimental unit

The data described below include side-by-side comparisons of the CHAMP Stage 1 study results of both Atropine strengths, and irrespective of whether an endpoint was defined as primary, secondary or tertiary.

Since the primary endpoint result was not significant, in line with the hierarchical testing strategy used, all p-values presented below are nominal, except for the primary efficacy analysis (i.e., less than 0.5 D myopia progression (SER) at Month 36 compared to baseline, for Atropine 0.02% vs Vehicle).

A numerically greater proportion of eyes showed less than 0.5 D myopia with each dose level of Atropine than with Vehicle. A statistically significant treatment effect was not observed for Atropine 0.02% at Month 36, the primary endpoint (see Table 8 below). Nominally significant treatment effects were observed for Atropine 0.01% compared with Vehicle across all 12-monthly visits to 36 months, and for Atropine 0.02% at Month 12 in the mITT population (see Table 8).

Table 8. Proportion of subjects' eyes that showed less than 0.50 D myopia progression (normalized SER) from baseline at the month 12, 24, and 36 visits (CHAMP stage 1, mITT population)

Visit	**Statistic**	**Vehicle N=144**	**Atropine Sulfate 0.01% N=133**	**Atropine Sulfate 0.02% N=212**
Month 12	Less than 0.50 D myopia progression, n (%)			
	Yes	116 (47.5)	131 (60.6)	218 (60.6)
	No	128 (52.5)	85 (39.4)	142 (39.4)
	Odds ratio (Atropine Sulfate/Vehicle)	--	3.898	4.780
	95% confidence interval of odds ratio	--	1.349, 11.259	1.752, 13.039
	p-value	--	0.012	0.002

Visit	Statistic	Vehicle N=144	Atropine Sulfate 0.01% N=133	Atropine Sulfate 0.02% N=212
Month 24	Less than 0.50 D myopia progression, n (%)			
	Yes	63 (26.5)	71 (36.6)	106 (30.6)
	No	175 (73.5)	123 (63.4)	240 (69.4)
	Odds ratio (Atropine Sulfate/Vehicle)	--	3.389	1.524
	95% confidence interval of odds ratio	--	1.004, 11.442	0.493, 4.708
	p-value	--	0.049	0.464
Month 36 Primary timepoint	Less than 0.50 D myopia progression, n (%)			
	Yes	44 (17.5)	57 (28.5)	81 (22.1)
	No	208 (82.5)	143 (71.5)	285 (77.9)
	Odds ratio (Atropine Sulfate/Vehicle)	--	4.540	1.774
	95% confidence interval of odds ratio	--	1.147, 17.965	0.503, 6.260
	p-value	--	0.031	0.373

Source: CHAMP Stage 1 CSR, Table 25; D=diopter; mITT=Modified Intent-to-Treat; N=number of subjects in population; n=number of eyes assessed; SER=spherical equivalent refraction; --=not applicable. Notes: Normalized SER = 100/((100/SER)-(Vertex Distance/10)). The SER on the right side of the equation is the original SER from the case report form. Each subject contributes up to two results per visit, one for each eye. Analysis was performed using a mixed model based on the binomial distribution using a logit link function with progression as the dependent variable and subject, treatment, and visit, eye (left of right), baseline age strata, and baseline myopia strata as independent variables and treatment-by-visit interaction term included. Random intercepts for subject and eye within subject were included using variance components and compound symmetry covariance structures, respectively.

Risk ratios were calculated from odds ratio (95% CI) of the Atropine 0.01% group and the risk of the Vehicle group (17.5%, 95% CI: 12.8, 22.6) according to a published method (Grant, 2014). Based on this analysis the risk ratio was 2.8 (likely range 2.5 to 3.1) from a central estimate of the odds ratio of 4.54 and absolute risk of the Vehicle group of 17.5%.The absolute risk difference between Atropine 0.01% and Vehicle in the proportions of subjects' eyes with less than 0.5 D myopia progression at Month 36, calculated without using the mixed effects model or adjustments for covariates, was 0.110 (95% Wald CI: 0.032, 0.189; p=0.006). The absolute risk difference between Atropine 0.02% and Vehicle was 0.047 (95% Wald CI: -0.017, 0.11; p=0.148).

Similar treatment differences were observed for ITT (table below).

Table 9. Proportion of subjects' eyes that showed less than 0.50 D myopia progression (normalized SER) from baseline at the month 12, 24, and 36 visits (CHAMP stage 1, ITT population)

Analysis of the Proportion of Subjects' Eyes who Show less than 0.5 D Myopia Progression (Normalized SER) from Baseline in Stage 1 by Treatment Group and Visit
Sensitivity Analysis
Stage 1 Intent-to-Treat Set

Visit	Statistic	Vehicle N=165	Atropine Sulfate 0.01% N=164	Atropine Sulfate 0.02% N=247
Month 12	less than 0.50 D Myopia Progression, n (%)			
	Yes	142 (50.4)	169 (63.1)	262 (62.7)
	No	140 (49.6)	99 (36.9)	156 (37.3)
	Odds Ratio (Atropine Sulfate / Vehicle)		4.245	4.650
	95% Confidence Limits of Odds Ratio		1.504, 11.979	1.745, 12.392
	p-value		0.006	0.002
Month 24	less than 0.50 D Myopia Progression, n (%)			
	Yes	78 (29.3)	95 (40.6)	130 (34.0)
	No	188 (70.7)	139 (59.4)	252 (66.0)
	Odds Ratio (Atropine Sulfate / Vehicle)		3.963	1.782
	95% Confidence Limits of Odds Ratio		1.257, 12.491	0.605, 5.246
	p-value		0.019	0.294

Month 36	less than 0.50 D Myopia Progression, n (%)			
	Yes	61 (21.3)	79 (31.3)	106 (25.6)
	No	225 (78.7)	173 (68.7)	308 (74.4)
	Odds Ratio (Atropine Sulfate / Vehicle)		3.900	1.564
	95% Confidence Limits of Odds Ratio		1.097, 13.858	0.480, 5.101
	p-value		0.035	0.458
	Absolute Risk Difference (Atropine Sulfate - Vehicle)		0.100	0.043
	95% Wald Confidence Interval		0.026, 0.175	-0.021, 0.106
	p-value		0.008	0.186

Note: Normalized SER = 100/((100/SER)-(Vertex Distance/10)) The SER on the right side of the equation is the original SER from CRF.
Note: Stage 1 Intent-to-Treat (ITT) Set is defined by randomization of a subject into a Stage 1 treatment.
Note: Each subject (N) contributes up to 2 results (n) per visit, one for each eye.
Note: Analysis was performed using a Mixed Effects Model based on the binomial distribution using a logit link function with progression as the dependent variable and treatment, and visit, eye (left or right), baseline age strata, and baseline myopia strata as independent variables and treatment by visit interaction term included. Random intercepts for subject and eye within subject will be included using variance components and compound symmetry covariance structures respectively.
Note: Absolute Risk Difference was not calculated using a Mixed Effects Model and is therefore not adjusted for any covariates.

Cross Reference: Listing 16.2.4.4, 16.2.6.1

Source: CHAMP Stage 1 CSR, Table 14.2.1.2.2

Secondary/tertiary endpoint: Change from baseline in normalized SER

Nominally significant differences were observed between Atropine 0.01% and Vehicle in change from baseline in normalized SER at Months 24 and 36 mITT (Table 10) and ITT (Table 11). Results in the mITT population were generally similar to those in the ITT population albeit nominally smaller.

Nominally significant treatment effects were observed in the Atropine Sulfate 0.01% vs Vehicle comparisons at each timepoint. In the ITT set, the Atropine Sulfate 0.02% strength also demonstrated nominally significant differences from Vehicle at each time point.

Table 10. Change from baseline in normalized SER (D) at month 12, month 24, and month 36 visits (CHAMP stage 1, mITT population)

Visit	Statistic	Vehicle N=144	Atropine Sulfate 0.01% N=133	Atropine Sulfate 0.02% N=212
Actual values for normalized SER (D) at baseline				
Baseline	N	282	266	424
	Mean (SD)	-2.448 (1.1309)	-2.414 (1.1700)	-2.416 (1.1719)
	Median (IQR)	-2.384 (1.656)	-2.200 (1.533)	-2.257 (1.568)
Changes from baseline in normalized SER (D)				
Month 12	N	244	216	360
	Mean (SD)	-0.535 (0.5428)	-0.394 (0.5026)	-0.408 (0.4436)
	Median (IQR)	-0.542 (0.620)	-0.405 (0.591)	-0.397 (0.567)
	LS mean	-0.568	-0.448	-0.448
	95% confidence interval for LS mean	-0.662, -0.474	-0.547, -0.349	-0.525, -0.370
	LS mean difference (Atropine Sulfate – Vehicle)	--	0.120	0.120
	95% confidence interval for difference	--	-0.014, 0.253	0.001, 0.239
	p-value	--	0.079	0.047
Month 24	N	238	194	346
	Mean (SD)	-0.981 (0.6783)	-0.742 (0.6071)	-0.854 (0.6941)
	Median (IQR)	-0.955 (0.890)	-0.730 (0.874)	-0.841 (0.901)

Visit	Statistic	Vehicle N=144	Atropine Sulfate 0.01% N=133	Atropine Sulfate 0.02% N=212
	LS Mean	-1.004	-0.787	-0.897
	95% confidence interval for LS mean	-1.098, -0.910	-0.887, -0.686	-0.975, -0.819
	LS mean difference (Atropine Sulfate – Vehicle)	--	0.217	0.107
	95% confidence interval for difference	--	0.082, 0.352	-0.012, 0.227
	p-value	--	0.002	0.079
Month 36	N	252	200	366
	Mean (SD)	-1.244 (0.8590)	-0.963 (0.7358)	-1.139 (0.8238)
Primary timepoint	Median (IQR)	-1.194 (0.985)	-0.963 (0.960)	-1.100 (1.049)
	LS mean	-1.279	-1.039	-1.180
	95% confidence interval for LS mean	-1.373, -1.185	-1.139, -0.939	-1.257, -1.102
	LS mean difference (Atropine Sulfate – Vehicle)	--	0.240	0.099
	95% confidence interval for difference	--	0.106, 0.374	-0.020, 0.218
	p-value	--	<0.001	0.101

Source: CHAMP Stage 1 CSR, Table 26; D=diopter; IQR=interquartile range, the difference between the upper (75th percentile) and lower (25th percentile) quartile; LS=least square; mITT=Modified Intent-to-Treat; N=number of subjects in population; n=number of eyes assessed; SD=standard deviation; SER=spherical equivalent refraction; --=not applicable. Notes: the normalized SER= 100/((100/SER)-(Vertex Distance/10)). The SER on the right side of the equation is the original SER from the case report form. Each subject contributes up to two results per visit, one for each eye. A strong correlation between eyes within a subject may affect the standard deviation. The analysis was performed using a mixed effects model with a random intercept with change from baseline as the dependent variable and treatment, visit, eye (left or right), baseline age, and baseline SER as independent variables and treatment by visit interaction term included. Degrees of freedom were determined using the Kenward-Roger approximation. Random intercepts for subject and eye within subject were included using unstructured covariance structures.

Table 11. Change from baseline in normalized SER (D) at month 12, month 24, and month 36 visits (CHAMP stage 1, ITT population)

Analysis of the Change from Baseline in Normalized SER (D) in Stage 1 by Treatment Group and Visit
Mixed Effect Model
Stage 1 Intent-to-Treat Set

		Vehicle N=165		Atropine Sulfate 0.01% N=164		Atropine Sulfate 0.02% N=247	
Visit	Statistic	Actual Value	Change from Baseline	Actual Value	Change from Baseline	Actual Value	Change from Baseline
Baseline	n	324		328		494	
	Mean	-2.457		-2.444		-2.429	
	SD	1.1253		1.2023		1.1653	
	Median	-2.346		-2.200		-2.270	
	IQR	1.646		1.537		1.600	
	Min, Max	-5.68, -0.50		-5.87, -0.50		-5.63, -0.50	
Month 12	n	282	282	268	268	418	418
	Mean	-3.043	-0.523	-2.890	-0.376	-2.852	-0.387
	SD	1.2811	0.5518	1.4473	0.5024	1.3342	0.4359
	Median	-3.001	-0.491	-2.718	-0.370	-2.707	-0.371
	IQR	1.743	0.659	1.997	0.577	1.823	0.566
	Min, Max	-6.59, 0.79	-2.14, 2.51	-6.96, 0.48	-2.43, 1.62	-6.48, -0.10	-1.75, 1.01
	Least Squares Mean		-0.574		-0.433		-0.446
	95% Confidence Limits for Least Squares Mean		(-0.663, -0.485)		(-0.523, -0.343)		(-0.519, -0.373)
	Least Squares Mean Difference (Atropine Sulfate - Vehicle)				0.140		0.128
	95% Confidence Limits for Difference				(0.017, 0.264)		(0.016, 0.240)
	p-value				0.026		0.025

Month 24	n	266	266	234	234	382	382
	Mean	-3.358	-0.932	-3.113	-0.691	-3.201	-0.810
	SD	1.3248	0.6792	1.4210	0.6419	1.4529	0.6978
	Median	-3.225	-0.900	-2.939	-0.705	-3.017	-0.771
	IQR	1.977	0.880	1.943	0.900	1.980	0.881
	Min, Max	-7.51, -0.37	-3.30, 0.42	-7.56, -0.33	-3.33, 0.99	-6.83, -0.10	-3.58, 0.89
	Least Squares Mean		-0.991		-0.744		-0.861
	95% Confidence Limits for Least Squares Mean		(-1.081, -0.902)		(-0.836, -0.652)		(-0.935, -0.787)
	Least Squares Mean Difference (Atropine Sulfate - Vehicle)				0.247		0.130
	95% Confidence Limits for Difference				(0.122, 0.373)		(0.017, 0.243)
	p-value				<.001		0.024
Month 36	n	286	286	250	250	414	414
	Mean	-3.690	-1.206	-3.421	-0.925	-3.520	-1.066
	SD	1.4761	0.9087	1.5343	0.7476	1.5360	0.8256
	Median	-3.591	-1.096	-3.277	-0.854	-3.430	-1.020
	IQR	2.217	1.080	2.120	1.031	2.067	1.093
	Min, Max	-8.17, -0.37	-4.44, 3.60	-7.69, -0.39	-3.28, 1.22	-7.78, 0.05	-3.94, 0.89
	Least Squares Mean		-1.256		-1.003		-1.124
	95% Confidence Limits for Least Squares Mean		(-1.345, -1.167)		(-1.094, -0.912)		(-1.197, -1.051)
	Least Squares Mean Difference (Atropine Sulfate - Vehicle)				0.253		0.132
	95% Confidence Limits for Difference				(0.129, 0.377)		(0.020, 0.244)
	p-value				<.001		0.021

Note: SER = Spherical Equivalent Refraction. Normalized SER = 100/((100/SER)-(Vertex Distance/10)) The SER on the right side of the equation is the original SER from CRF.
Note: Stage 1 Intent-to-Treat (ITT) Set is defined by randomization of a subject into a Stage 1 treatment.
Note: Each subject (N) contributes up to 2 results (n) per visit, one for each eye. A strong correlation between eyes within a subject may affect the standard deviation.
Note: The analysis was performed using a Mixed Effect model with a random intercept. Change from baseline as the dependent variable treatment, visit, eye (left or right), baseline age, and SER as independent variables and treatment by visit interaction term included. Degrees of freedom was determined using the Kenward-Roger approximation. Random intercepts for subject and eye within subject were included using unstructured covariance structures.

Source: CHAMP Stage 1 CSR, Table 14.2.2.1.4

Secondary/tertiary endpoint: Change from baseline in axial length

Nominally significant differences (slowing) in axial length elongation were observed between Atropine 0.01% and Vehicle at Month 36 and earlier in the mITT (Table 12) and in ITT (Table 13). Similar results but of numerically smaller magnitudes were observed for Atropine 0.02%.

Table 12. Change from baseline in axial length at month 36 visit (CHAMP stage 1, mITT population)

Visit	Statistic	Vehicle N=144	Atropine Sulfate 0.01% N=133	Atropine Sulfate 0.02% N=212
Actual values for axial length (mm) at baseline				
Baseline	n	281	266	419
	Mean (SD)	24.328 (0.8401)	24.371 (0.8085)	24.304 (0.8684)
	Median (IQR)	24.400 (1.200)	24.385 (1.090)	24.290 (1.140)
Changes from baseline in axial length (mm)				
Month 36	n	252	200	361
	Mean (SD)	0.781 (0.4042)	0.636 (0.3652)	0.707 (0.3900)
	Median (IQR)	0.740 (0.490)	0.625 (0.450)	0.670 (0.540)
	LS mean	0.805	0.676	0.728
	95% confidence interval for LS Mean	0.763, 0.848	0.630, 0.721	0.693, 0.763

	LS mean difference (Atropine Sulfate – Vehicle)	--	-0.130	-0.077
	95% confidence interval for difference	--	-0.191, -0.069	-0.131, -0.024
	p-value	--	<0.001	0.005

Source: CHAMP Stage 1 CSR, Table 24; IQR=difference between the upper (75th percentile) and lower (25th percentile) quartile; LS=least square; mITT=Modified Intent-to-Treat; N=number of subjects in population; n=number of eyes assessed; SD=standard deviation; --=not applicable. Note: Each subject contributes up to two results per visit, one for each eye. A strong correlation between eyes within a subject may affect the standard deviation. The analysis was performed using a mixed effects model with a random intercept and with change from baseline as the dependent variable and treatment, visit, eye (left or right), baseline age, and baseline SER as independent variables, and treatment-by-visit interaction term included. Degrees of freedom were determined using the Kenward-Roger approximation. Random intercepts for subject and eye within subject were included using unstructured covariance structures.

Table 13. Change from baseline in axial length at month 36 visit (CHAMP stage 1, ITT population)

Analysis of the Change from Baseline in Axial Length (mm) in Stage 1 by Treatment Group and Visit
Mixed Effect Model
Stage 1 Intent-to-Treat Set

		Vehicle N=165		Atropine Sulfate 0.01% N=164		Atropine Sulfate 0.02% N=247	
Visit	Statistic	Actual Value	Change from Baseline	Actual Value	Change from Baseline	Actual Value	Change from Baseline
Baseline	n	321		328		489	
	Mean	24.340		24.358		24.317	
	SD	0.8573		0.8663		0.8920	
	Median	24.400		24.345		24.300	
	IQR	1.180		1.130		1.140	
	Min, Max	22.01, 26.51		21.75, 27.39		22.17, 27.02	
Month 12	n	278	276	265	265	418	413
	Mean	24.664	0.333	24.719	0.230	24.567	0.257
	SD	0.8730	0.2132	0.8554	0.3591	0.9408	0.1857
	Median	24.730	0.300	24.720	0.250	24.550	0.250
	IQR	1.270	0.255	1.220	0.260	1.170	0.240
	Min, Max	21.96, 27.04	-0.24, 1.01	22.70, 27.05	-4.05, 1.00	22.43, 27.26	-0.34, 0.82
	Least Squares Mean		0.368		0.267		0.298
	95% Confidence Limits for Least Squares Mean		(0.323, 0.413)		(0.221, 0.312)		(0.261, 0.335)
	Least Squares Mean Difference (Atropine Sulfate - Vehicle)				-0.101		-0.070
	95% Confidence Limits for Difference				(-0.164, -0.039)		(-0.127, -0.014)
	p-value				0.002		0.015
Month 24	n	270	270	236	236	382	377
	Mean	24.883	0.581	24.870	0.487	24.770	0.508
	SD	0.8876	0.3417	0.8663	0.4289	0.9700	0.3248
	Median	24.990	0.565	24.825	0.445	24.750	0.490
	IQR	1.180	0.450	1.295	0.435	1.230	0.440
	Min, Max	22.16, 27.14	-0.10, 1.87	22.88, 27.27	-3.57, 1.61	22.56, 27.70	-0.31, 1.53
	Least Squares Mean		0.610		0.475		0.535
	95% Confidence Limits for Least Squares Mean		(0.565, 0.655)		(0.429, 0.521)		(0.498, 0.572)
	Least Squares Mean Difference (Atropine Sulfate - Vehicle)				-0.135		-0.075
	95% Confidence Limits for Difference				(-0.198, -0.072)		(-0.132, -0.018)
	p-value				<.001		0.010

Month 36	n	286	284	250	250	414	409
	Mean	25.074	0.744	25.067	0.605	24.946	0.664
	SD	0.9071	0.4202	0.9259	0.4852	0.9884	0.4065
	Median	25.120	0.710	25.050	0.605	24.945	0.620
	IQR	1.330	0.510	1.420	0.520	1.320	0.550
	Min, Max	22.88, 27.42	-0.15, 2.35	23.14, 27.61	-3.05, 1.74	22.58, 28.40	-0.76, 1.96
	Least Squares Mean		0.780		0.652		0.697
	95% Confidence Limits for Least Squares Mean		(0.735, 0.825)		(0.607, 0.698)		(0.660, 0.734)
	Least Squares Mean Difference (Atropine Sulfate - Vehicle)				-0.128		-0.083
	95% Confidence Limits for Difference				(-0.190, -0.065)		(-0.140, -0.027)
	p-value				<.001		0.004

Note: Stage 1 Intent-to-Treat (ITT) Set is defined by randomization of a subject into a Stage 1 treatment.
Note: Each subject (N) contributes up to 2 results (n) per visit, one for each eye. A strong correlation between eyes within a subject may affect the standard deviation.
Note: The analysis was performed using a Mixed Effect model with a random intercept. Change from baseline as the dependent variable treatment, visit, eye (left or right), baseline age, and SER as independent variables and treatment by visit interaction term included. Degrees of freedom was determined using the Kenward-Roger approximation. Random intercepts for subject and eye within subject were included using unstructured covariance structures.

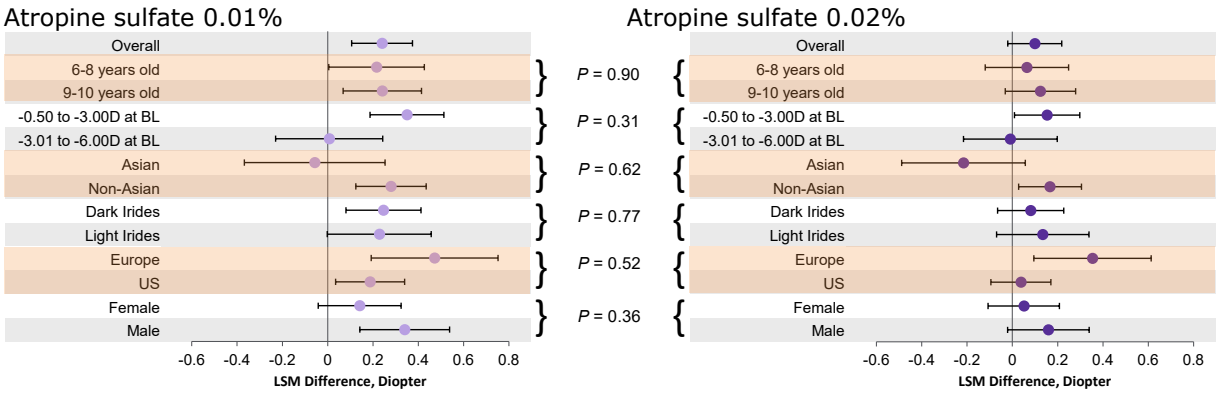
Source: CHAMP CSR Stage 1, Table 14.2.2.2.4

Ancillary analyses

- Predefined subgroup analyses in mITT, for change from baseline in normalized SER

Subgroups analysis in mITT majorly favour atropine over Vehicle (see Figure 6). Exceptions are the Asian (favouring Vehicle) and SER of -3.01—6 D at baseline (favouring neither treatment). Using a post-hoc analysis, the applicant showed that confounding therapies may have led to increased numeric disagreement between the Asian and non-Asian subgroups.

Figure 6. Least square mean difference in change from baseline in normalized SER by subgroup and subgroup-by-treatment interaction (CHAMP stage 1, mITT population)



Source: CHAMP Stage 1 CSR, Figure 5; BL=baseline; D=diopter; LSM=least square mean; mITT=Modified Intent-to-Treat; US=United States
Note: P-values represent statistics of overall subgroup-by-treatment interaction. Error bars represent 95% confidence intervals for LSM difference (Atropine Sulfate - Vehicle).

Predefined rebound assessment: change from Stage 2 baseline in normalized SER

In the mITT population, the median changes from the Stage 2 baseline were from -0.159 D to -0.208 D across the specified treatment groups at Month 48. In the ITT population, median changes from the

Stage 2 baseline were similar (from -0.149 D to -0.229 D across the specified treatment groups) at Month 48.

Table 14. Rebound assessment based on the change from stage 2 baseline (month 36) in normaliszed SER (D) at months 42 and 48 (ITT)

		Atropine Sulfate 0.02% to 0.02% N=63		Atropine Sulfate 0.02% to 0.01% N=59		Atropine Sulfate 0.02% to Vehicle N=60		Atropine Sulfate 0.01% to 0.01% N=38		Atropine Sulfate 0.01% to Vehicle N=39	
Visit	Statistic	Actual Value	Change from Baseline	Actual Value	Change from Baseline	Actual Value	Change from Baseline	Actual Value	Change from Baseline	Actual Value	Change from Baseline
Stage 2 Baseline	n	126		116		120		76		78	
	Mean	-3.494		-3.644		-3.340		-3.274		-3.351	
	SD	1.4998		1.5641		1.5820		1.5505		1.5190	
	Median	-3.588		-3.430		-3.286		-3.149		-3.277	
	Min, Max	-7.05, -0.25		-7.78, -0.61		-7.13, 0.05		-7.69, -0.80		-6.76, -0.66	
Month 42	n	114	114	104	102	108	108	68	68	68	68
	Mean	-3.570	-0.111	-3.864	-0.123	-3.385	-0.111	-3.352	-0.042	-3.428	-0.107
	SD	1.5582	0.3621	1.5801	0.2978	1.6285	0.2695	1.5570	0.2620	1.5726	0.2525
	Median	-3.704	-0.065	-3.579	-0.109	-3.326	-0.097	-3.307	-0.040	-3.339	-0.084
	Min, Max	-7.36, -0.33	-2.49, 0.56	-8.07, -1.17	-1.29, 0.57	-7.45, -0.25	-0.73, 1.06	-7.01, -0.62	-0.76, 0.68	-7.25, -0.42	-0.84, 0.44
Month 48	n	116	116	102	100	108	108	70	70	68	68
	Mean	-3.615	-0.198	-4.061	-0.291	-3.468	-0.188	-3.390	-0.124	-3.586	-0.266
	SD	1.5673	0.3651	1.7049	0.7852	1.6375	0.3004	1.5974	0.3531	1.5735	0.3333
	Median	-3.905	-0.152	-3.909	-0.190	-3.200	-0.179	-3.290	-0.149	-3.586	-0.229
	Min, Max	-7.16, -0.13	-1.31, 0.66	-10.48, -1.22	-6.80, 0.79	-7.73, -0.05	-0.94, 0.94	-7.17, -0.77	-0.76, 1.39	-7.35, -0.98	-1.43, 0.78

Note: D = Diopter, SER = Spherical Equivalent Refraction. Normalized SER = 100/((100/SER)-(Vertex Distance/10)) The SER on the right side of the equation is the original SER from CRF.
Note: Stage 2 Intent-to-Treat (ITT) Set is defined by randomization of a subject into a Stage 2 treatment.
Note: Each subject (N) contributes up to 2 results (n) per visit, one for each eye. A strong correlation between eyes within a subject may affect the standard deviation.
Note: Stage 2 Baseline is defined as Month 36.
Note: This summary table is for rebound assessment based on the change from Stage 2 Baseline (Month 36) at Months 42 and 48. Treatment group is based on treatment Stage 1 subjects who received the same or lower dose, including vehicle.

Cross Reference: Listing 16.2.4.1, 16.2.4.4, 16.2.6.1

Table 15. Rebound assessment of Atropine Sulfate 0.01% stage 1 responder eyes in stage 2 (CHAMP stage 2, ITT)

Visit	Statistic	Atropine Sulfate 0.02% to 0.02% N=63	Atropine Sulfate 0.02% to 0.01% N=59	Atropine Sulfate 0.02% to Vehicle N=60	Atropine Sulfate 0.01% to 0.01% N=38	Atropine Sulfate 0.01% to Vehicle N=39
Month 42	Responders, n (%)					
	Yes	27 (90.0)	22 (84.6)	32 (94.1)	27 (100.0)	24 (92.3)
	No	3 (10.0)	4 (15.4)	2 (5.9)	0 (0.0)	2 (7.7)
Month 48	Responders, n (%)					
	Yes	28 (87.5)	17 (77.3)	31 (91.2)	25 (92.6)	18 (72.0)
	No	4 (12.5)	5 (22.7)	3 (8.8)	2 (7.4)	7 (28.0)

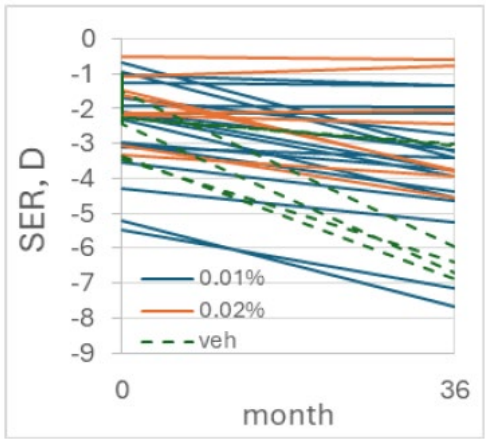
Note: Stage 2 Intent-to-Treat Set is defined by randomization of a subject into a Stage 2 treatment.
Note: Stage 2 Baseline is defined as Month 36. Stage 2 responders are defined as subjects' eyes that showed less than 0.50 D myopia progression (Normalized SER) from Stage 2 baseline.
Note: Stage 1 Responders are defined as subjects' eyes that showed less than 0.50 D myopia progression (Normalized SER) from baseline at the Month 36 visit.
Note: Percentages are based on number of subjects in the Safety Analysis Set within Stage 1 and Stage 2 treatment combinations and visit.

Cross Reference: Listing 16.2.4.4, 16.2.6.1

Post-hoc analysis: Children aged 3-5 years in CHAMP

To evaluate whether the youngest subgroup (3-5 years) of children may exhibit myopia regression or emmetropization during the study, the SER progression of the 21 children aged 3-5 years were analysed. The mean SER change from baseline at Month 36 for vehicle, 0.01% and 0.02% were -2.78 D (n=5), -1.21 D (n=9), and -0.89 D (n=7), respectively.

Figure 7. SER progression for 21 subjects with baseline age of 3-5 years. Both eyes are plotted individually for each subject



Source: CSR Listing 16.2.6.1

- Post-hoc analysis: subgroups based on SER at baseline (-1 to -3 D, and -3.01 to -6 D)

There is an overall dependence on baseline SER strata with lower effect in the subgroup that had higher SER at baseline (e.g., risk ratio for proportion responders, atropine 0.01% vs Vehicle for subgroup SER (-1 - -3 D): 3.29 vs risk ratio for subgroup (-3.01 - -6 D): 1.14; Table 16). Similar results were observed for change-in SER (Table 16) and similar in the SAP-prespecified baseline SER subgroup analysis**.**

Table 16. Subgroup analyses; SER at baseline of -1.00 to -3.00 D, or -3.01 to -6.00 D; stage 1 mITT)

	Statistic	Vehicle N=125	Atropine Sulfate 0.01% N=117	Atropine Sulfate 0.02% N=184
SER -1.00 D to -3.00 D	Less than 0.5 D Myopia Progression, n (%)			
	Yes	22 (16.4)	38 (32.8)	43 (22.2)
	No	112 (83.6)	78 (67.2)	151 (77.8)
	Odds Ratio (Atropine Sulfate/Vehicle)	--	5.963	1.982
	95% Confidence Limits of Odds Ratio	--	0.905, 39.297	0.326, 12.039
	p-value	--	0.0634	0.4573
	Risk Ratio calculated from Odds Ratio and Risk of the Vehicle group	--	3.29	1.71
SER -3.01 D to -6.00 D	Less than 0.5 D Myopia Progression, n (%)			
	Yes	13 (15.1)	8 (12.5)	19 (15.3)
	No	73 (84.9)	54 (87.1)	105 (84.7)
	Odds Ratio (Atropine Sulfate/Vehicle)	--	1.175	1.070
	95% Confidence Limits of Odds Ratio	--	0.104, 13.258	0.121, 9.444
	p-value	--	0.8961	0.9513
	Risk Ratio calculated from Odds Ratio and Risk of the Vehicle group		1.14	1.06
Overall	p-value (Baseline SER -1.00 to -3.00 D vs. -3.01 to -6.00 D)			0.0042
	p-value (Interaction Baseline SER Group-by-Treatment)			0.654

Source: Table 14.2.1.6.1.1

		Vehicle N=125	Atropine Sulfate 0.01% N=117	Atropine Sulfate 0.02% N=184
SER -1.00 D to -3.00 D				
Month 36	N	134	116	194
	Mean (SD) at Month 36	-1.292 (0.8710)	-0.944 (0.7243)	-1.137 (0.8180)
	Median (min, max)	-1.205 (-4.34, 0.42)	-0.834 (-3.28, 0.55)	-1.102 (-3.94, 0.89)
	LS Mean	-1.281	-1.013	-1.140
	95% Confidence Limits for LS Mean	-1.404, -1.159	-1.142, -0.884	-1.241, -1.040
	LS Mean Difference (Atropine Sulfate – Vehicle)	--	0.269	0.141
	95% Confidence Limits for Difference	--	0.091, 0.446	-0.017, 0.299
	p-value	--	0.003	0.0802
SER -3.01 D to -6.00 D				
Month 36	N	86	62	124
	Mean (SD) at Month 36	-1.225 (0.8750)	-1.184 (0.6681)	-1.235 (0.7591)
	Median (min, max)	-1.226 (-3.26, 3.60)	-1.105 (-2.77, 0.25)	-1.257 (-3.11, 0.58)
	LS Mean	-1.263	-1.257	-1.273
	95% Confidence Limits for LS Mean	-1.420, -1.106	-1.430, -1.085	-1.402, -1.144
	LS Mean Difference (Atropine Sulfate – Vehicle)	--	0.006	-0.010
	95% Confidence Limits for Difference	--	-0.227, 0.238	-0.213, 0.193
	p-value	--	0.9619	0.9248
Overall				
	p-value (Baseline SER -1.00 to -3.00 D vs -3.01 to -6.00 D)		0.0645	
	p-value (Interaction Baseline SER Group-by-Treatment)		0.4844	

Source: Table 14.2.3.5.2.1.1

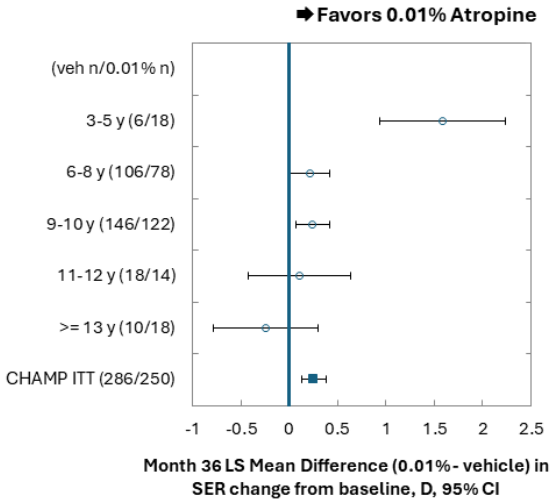
Left: Proportion of Subjects' Eyes That Showed <0.5 D Myopia Progression (Normalized SER) from Baseline at the Month 36 Visit. Right: Change from Baseline in Normalized SER (D) at the Month 36 Visit

Post-hoc analysis: ITT age subgroup analysis

- **Post-hoc analysis: ITT age subgroup analysis**

Five subgroups in the ITT set were evaluated at the request of the CHMP. A trend that the treatment effect decreases by increasing age was observed (see figure below). The number of eyes in the subgroups of 3-5 years, 11-12 and >= 13 years are small (ranging from 6 to 18 eyes per group).

Figure 8. Comparison of least square mean difference (0.01% - vehicle) in month 36 SER change from baseline in 5 age subgroups



- Post-hoc analysis: retrieved dropout analysis (requested by CHMP)

In Round 2 of this MAA, the applicant provided an estimate of the treatment effect in mITT and ITT of atropine 0.01% compared to placebo based on the primary estimand, i.e., the difference in responder subjects with both eyes < 0.5 D, based on a model that uses SER values from all visits, assuming missing at random for intermediate missing values and using retrieved drop-out imputation for terminate missing values. The same analysis was performed for SER-change-from baseline, and change-in-axial length, but using the average result of both eyes.

For full details of this analysis refer to Appendix/section 9.2. Briefly:
For the responder analysis (<0.5D/3 year), in the retrieved-dropout analysis in mITT at subject level the between-treatment group difference for Atropine Sulfate 0.01% versus Vehicle was 7.6% (95% WALD CI: -1.4%, 16.5%, p=0.1).

For the change-in-SER endpoint, the LSM difference for atropine 0.01% vs Vehicle was 0.146 D (95% CI -0.04; 0.34; p<0.13).

For the change-from-baseline for axial the LSM difference for atropine 0.01% vs Vehicle was -0.098 mm (95% CI -0.175, -0.02; p=0.01).

Post-hoc analysis: progression over-time (requested by CHMP)
In Round 2, the applicant provided the table below which lists the number and proportion of subjects in CHAMP for each study arm (atropine 0.01%, atropine 0.02%, vehicle) by degree of disease severity and study timepoints.

As the applicant restricted the indication to mITT in Round 2, only that population is shown.

Table 17. Summary of SER progression (average eyes) by severity and by treatment group (CHAMP)

	mITT			
Visit	Statistics	Vehicle, N=144 SER -0.5 to -3.00 D	SER -3.01 to -6.00 D	SER < -6.0 D
Baseline	n	98	43	0
	% relative to N	68.1	29.9	0

Month 12	n	61	59	1
	% relative to N	42.4	41.0	0.7
Month 24	n	51	66	2
	% relative to N	35.4	45.8	1.4
Month 36	n	39	81	6
	% relative to N	27.1	56.3	4.2
		0.01%, N=133		
		SER -0.5 to -3.00 D	SER -3.01 to -6.00 D	SER < -6.0 D
Baseline	n	100	33	0
	% relative to N	75.2	24.8	0
Month 12	n	61	44	1
	% relative to N	45.9	33.1	0.8
Month 24	n	50	46	1
	% relative to N	37.6	34.6	0.8
Month 36	n	39	55	5
	% relative to N	29.3	41.1	3.8
		0.02%, N=212		
Visit	Statistics	SER -0.5 to -3.00 D	SER -3.01 to -6.00 D	SER < -6.0 D
Baseline	n	155	57	0
	% relative to N	73.1	26.9	0
Month 12	n	98	78	2
	% relative to N	46.2	36.8	0.9
Month 24	n	81	84	7
	% relative to N	38.2	39.6	3.3
Month 36	n	64	106	13
	% relative to N	30.2	50.0	6.1

Supportive study: Mini-CHAMP (ZKO-ATP-202105-Mini-CHAMP)

Methods

Mini-CHAMP is an on-going randomized, double-blind, placebo parallel-controlled, multi-center, Phase 3 study of the efficacy and safety of Atropine Sulfate (0.01%, 0.02%) for delaying myopia progression in children. The study is being conducted in China by the Sponsor's commercial partner.

The study comprises of two parts (Stages) in a similar manner to the CHAMP study:

- Stage 1: Approximately 526 subjects were planned to be randomized 2:2:3 to receive placebo, Atropine Sulfate 0.01%, or 0.02% for 12 months. This is the primary safety and efficacy evaluation phase of the study, which is complete, with the results summarized herein.

- Stage 2: Subjects completing Stage 1 will be re-randomized in the same manner as in CHAMP to one of the three treatments. This part is on-going.

Efficacy assessments were performed at baseline and at 6-monthly visits thereafter. Like CHAMP, responder proportion, cycloplegic SER and axial length are efficacy endpoints.

Per subject, the same autorefractor was to be used throughout the study (except if equipment failure prevented this). Similarly, axial length was to be measured using the same instrument throughout the study. SER for each eye was normalized to a vertex distance of 0 mm (the corneal plane).

Study participants

Key inclusion criteria were similar to those of CHAMP (mITT population) and included: Male or female aged 6 to ≤10 years; myopia -0.50 D to -6.00 D in each eye; astigmatism ≤ 1.50 D in each eye; anisometropia SER of < 1.50 D; IOP of < 21 mmHg in each eye.

Exclusion criteria are similar to those used in CHAMP.

Treatments

During both stages, Vehicle, Atropine Sulfate 0.01%, or 0.02% medication was/is administered as one drop in each eye, once daily at bedtime.

Medications with the potential to confound interpretation of the efficacy data were prohibited during Mini-CHAMP in an analogous manner to the prohibitions in CHAMP.

Objectives

Primary: To assess the effectiveness and safety of Atropine Sulfate compared with placebo for 12 months in delaying myopia progression in children.

Secondary: To observe the safety and efficacy of children with myopia who received 12 months of treatment and were then randomized to 0.01% or 0.02% Atropine Sulfate or placebo for 12 months (Part 2 objective).

Outcomes/endpoints

Primary: Between-group difference in the proportion of participants with myopia progression (SER) less than 0.50 D at the Month 12 visit with Atropine Sulfate 0.02% versus placebo.

Key secondary: Between-group difference in the proportion of eyes of participants with myopia progression (SER) less than 0.50 D at the Month 12 visit with Atropine Sulfate 0.01% versus placebo

Other secondary endpoints relating to the Month 12 analyses, that were not part of the fixed sequence, included:

- Between-group difference in the proportion of subjects with myopia progression (SER) less than 0.75 D at the Month 12 visit.
- Between-group differences in median time to myopia progression (SER) -0.25 D, -0.50 D, and -0.75 D.
- Between-group difference in mean of change from baseline in SER at the Month 12 visit.
- Difference in the proportion of subjects with myopia progression (SER) less than 0.50 D at the Month 12 visit.
- Between-group difference in the proportion of participants who progressed to high myopia (≤ -6.00 D) at the Month 12 visit.

Sample size

The sample size calculation of mini-CHAMP assumed different responder proportions than CHAMP. The proportion of subjects with SER less than -0.50 D at the M12 visit for placebo was expected to be 30%, and for atropine 0.01% and atropine 0.02% both, 52%. For the comparison placebo versus atropine

0.02%, assuming a Type I 2-sided error of 0.05 with 95% power, a 2:2:3 randomization and a 30% dropout rate, using the Fischer's exact test, the samples were estimated at n=150 (placebo); n=150 (atropine 0.01%) and n=226 (atropine 0.02%).

Randomisation and blinding (masking)

Randomization was stratified by age at the time of randomization (< 9 years vs ≥ 9 years); and refractive error (lower myopia: SER -0.50 to -3.00 D; higher myopia: uniocular or multi-ocular SER -3.01 to -6.00 D).

Statistical methods

The primary analysis was performed in the ITT i.e., subjects between the ages of 6 to 10 years, inclusive. Note: this corresponds to CHAMP **m**ITT due to the differences in age restrictions between studies.

All statistical testing was to be performed using a hierarchal testing procedure as described for the primary and secondary endpoints above. Each test was planned to be performed using a two-sided 5% significance level until the first non-significant test.

Post-hoc an estimand was defined which was the same as for the CHAMP study.

Results

Participant flow
First subject enrolled: 13may2022; last subject completed: 20aug2023 (Stage 1).

A total of 526 subjects were randomized: 151 to Atropine Sulfate 0.01%, 227 to Atropine Sulfate 0.02%, and 148 to placebo, comprising the ITT population. Four subjects did not receive any study medication: 2 (1.3%) in the Atropine Sulfate 0.01% group, 1 (0.4%) in the atropine Drug Product 0.02%, group, and 1 (0.7%) in the placebo group, but remained in the ITT population.

A total of 486 subjects (92.4%) completed Stage 1 of the study: 139 (92.1%) in the Atropine Sulfate 0.01% group, 210 (92.5%) in the Atropine Sulfate 0.02%, and 137 (92.6%) in the placebo group.

Withdrawals from the study occurred with similar frequency across treatment groups: 12 (7.9%) in the Atropine Sulfate 0.01% group, 17 (7.5%) in the Atropine Sulfate 0.02% group, and 11 (7.4% in the placebo group (Mini-CHAMP Stage 1 CSR, Table 4). In most cases, the reason for withdrawal was subject decision: 9 (6.0%), 14 (6.2%) and 6 (4.1%), respectively.

Conduct of the study

In the analysis of the primary endpoint, Proportion of subjects" was changed to "Proportion of subjects' eyes", and use of a logit connection function was included.

Standardization of SER was applied alike CHAMP.

Other changes were related to ancillary and/or post-hoc analysis.

Baseline data

All subjects were Asian, the majority being Han Chinese (97.5%) (Table 18). Mean (SD) and median age were 8.4 ± 1.20 years and 8.0 years, respectively. Approximately half of all subjects were <9-year-old (50.4%) or ≥ 9-year-old (49.6%) at baseline.

Table 18. Demographic and baseline characteristics (Mini-CHAMP stage 1, ITT population)

Characteristic	Placebo N=148	Atropine Sulfate 0.01% N=151	Atropine Sulfate 0.02% N=227	Total N=526
Age (years)				
Mean (SD)	8.4 (1.23)	8.3 (1.27)	8.4 (1.12)	8.4 (1.20
Median (min, max)	8.0 (6, 10)	8.0 (6, 10)	8.0 (6, 10)	8.0 (6, 10)
Age group, n (%)				
< 9 years	75 (50.7)	77 (51.0)	113 (49.8)	265 (50.4)
≥ 9 years	73 (49.3)	74 (49.0)	114 (50.2)	261 (49.6)
Gender, n (%)				
Female	63 (42.6)	71 (47.0)	124 (54.6)	258 (49.0)
Male	85 (57.4)	80 (53.0)	103 (45.4)	268 (51.0)
Race, n (%)				
Asian	148 (100)	151 (100)	227 (100)	526 (100)
Ethnic group, n (%)				
Chinese	144 (97.3)	148 (98.0)	221 (97.4)	513 (97.5)
Other	4 (2.7)	3 (2.0)	6 (2.6)	13 (2.5)
Genetic history of high myopia, n (%)				
Yes	21 (14.2)	23 (15.2)	43 (18.9)	87 (16.5)
No	127 (85.8)	128 (84.8)	184 (81.1)	439 (83.5)

Source: Mini-CHAMP Stage 1 CSR, Table 7; See source for height, body weight and body mass index. All but one subject (in the Atropine Sulfate 0.02% group) had brown irides.

Across all treatment groups, mean (SD) standardized SER for both eyes was -2.0086 ± 1.0297 D, with minimal differences between individual treatment groups (see table below).

Most subjects (81%) were in the less myopic (-0.50 to -3.0 D) subgroup. The mean (SD) axial length (both eyes) was 24.156 ± 0.8228 mm and balanced across treatment groups.

Table 19. Baseline disease characteristics (Mini-CHAMP stage 1, ITT populations)

Characteristic	Placebo N=148	Atropine Sulfate 0.01% N=151	Atropine Sulfate 0.02% N=227	Total N=526
Standardized SER (binocular) (D)				
n (eyes)	294	298	452	1044
Mean (SD)	-1.9539 (1.0656)	-1.9822 (1.0275)	-2.0615 (1.0069)	-2.0086 (1.0297)
Median	-1.7500	-1.7500	-1.7500	-1.7500
IQR	-2.6250, -1.0000	-2.6250, -1.2500	-2.6250, -1.2500	-2.6250, -1.2500
Min, max	-5.125, -0.500	-5.000, -0.500	-5.750, -0.500	-5.750, -0.500
Refractive error stratum, n (%)				
Less myopic: -0.50 to -3.00 D	121 (81.8)	122 (80.8)	183 (80.6)	426 (81.0)
More myopic: -3.01 to -6.00 D	27 (18.2)	29 (19.2)	44 (19.4)	27 (18.2)
Axial length (binocular) (mm)				
n (eyes)	294	298	452	1044
Mean (SD)	24.155 (0.8649)	24.179 (0.8716)	24.140 (0.7609)	24.156 (0.8228)
Median	24.135	24.130	24.130	24.130
IQR	23.560, 24.720	23.560, 24.700	23.625, 24.640	23.580, 24.675
Min, max	21.00, 27.04	22.25, 26.95	22.25, 26.42	21.00, 27.04

Source: Mini-CHAMP Stage 1 CSR, Table 8

Numbers analysed

Table 20. Numbers (%) of subjects in each of the analysis sets (mini-CHAMP stage 1)

Analysis population/set	Vehicle n (%)	Atropine Sulfate 0.01% n (%)	Atropine Sulfate 0.02% n (%)	Total n (%)
Intent-to-Treat (all randomized)	151 (100)	227 (100)	148 (100)	526 (100)
Per-protocol	134 (88.7)	199 (87.7)	131 (88.5)	464 (88.2)
Safety (all dosed)	147 (97.4)	225 (99.1)	146 (98.6)	518 (98.5)

Outcomes and estimation

Primary and key secondary endpoint analysis

A statistically significant effect was observed for both atropine groups versus placebo. The proportion responders (<0.50 D myopia progression) was numerical higher for the Atropine Sulfate 0.02% as compared to Atropine Sulfate 0.01%.

Table 21. Proportion of subjects' eyes that showed less than 0.50 D myopia progression (normalized SER) from baseline at the month 12 visit (mini-CHAMP stage 1, ITT population)

Statistic	Placebo N=148	Atropine Sulfate 0.01% N=151	Atropine Sulfate 0.02% N=227
Less than 0.50 D myopia progression, n (%)			
n (eyes)	274	278	420
Yes			
No			
Odds ratio (Atropine Sulfate/Placebo)a			
95% confidence interval of odds ratioa			
p-valuea			
Absolute difference in proportions (Atropine Sulfate – placebo)			
Wald 95% confidence interval			
p-valueb			
Odds ratio (Atropine sulfate 0.02%/0.01%)a			
95% confidence interval of odds ratioa			
p-valuea			
Absolute difference in proportions (Atropine Sulfate 0.02% - 0.01%)			
Wald 95% confidence interval			
p-valueb			

Other secondary efficacy endpoint analyses

Responder analysis: (<0.75 D myopia progression)

A higher proportion of subjects in the Atropine Sulfate 0.02% group were responders (%) at Month 12 based on a responder criterion of <0.75 D myopia progression when compared with the placebo group (%; 95% CI:; p=). Numerical differences in responder proportion between the Atropine Sulfate 0.01% group (%) and placebo were not statistically significant (95% CI: -p~).

Change from baseline in normalized SER at Month 12

After 12 Months of treatment, both Atropine Sulfate groups demonstrated smaller changes from baseline in least square mean normalized SER relative to placebo (Table 22). The treatment difference was significant for the 0.02% strength.

Table 22. Change from baseline in normalized SER by treatment at month 12 (mini-CHAMP part 1, ITT)

Statistic	Placebo N=148	Atropine Sulfate 0.01% N=151	Atropine Sulfate 0.02% N=227
Normalized SER (D) at Baseline			
n (eyes)	294	298	452
Mean (SD)			
Median (IQR)			
Changes from Baseline to Month 12 in Normalized SER (D)			
n (eyes)	274	278	420
Mean (SD)			
Median (IQR)			
LS mean (95% CI)a			
LS mean difference(95% CI) (Atropine Sulfate – Placebo)			
p-value			
LS mean difference (95% CI) (Atropine Sulfate 0.02%– 0.01%)			
p-value			

Source: Mini-CHAMP Stage 1 CSR, Table 24; Baseline was defined as the last non-missing assessment prior to the administration of the first investigational drug product in Phase 1. a: Analyses were performed using Repeated Measurements Mixed-Effects Model (MMRM), which included only actual observed data, and did not plan to fill in missing data before or after early withdrawal from the study, which were processed as putative random missing data (MARs) by MMRM analysis. The model used the treatment group as a fixed effect, and the visit, eye (left or right), baseline age group (by randomization), and baseline SER group (by randomization) were used as covariates, while the treatment group-visit interaction term was included. The degrees of freedom are determined using the Kenward-Roger approximation. Randomized intercepts for subjects and subjects' eyes were included using an unstructured covariance structure.

Ancillary analyses

Exploratory endpoints: Change from baseline in axial length

Change from baseline in axial length was an exploratory endpoint at Month 12. Both Atropine Sulfate groups demonstrated smaller changes from baseline in least square mean axial length at Month 12 relative to placebo. The treatment difference was significant for the 0.02% strength.

Table 23. Change from baseline in axial length (mm) at month 12 (mini-CHAMP part 1, ITT)

Statistic	Vehicle N=148	Atropine Sulfate 0.01% N=151	Atropine Sulfate 0.02% N=227
Axial Length (mm) at Baseline			
n (eyes)	294	298	452
Mean	24.155	24.179	24.140
Changes from Baseline to Month 12 in Axial Length (mm)			
n (eyes)	274	278	418
Mean			
LS mean (95% CI)a			
LS mean difference (95% CI) (Atropine Sulfate – Vehicle)			
p-value			

Source: Mini-CHAMP Stage 1 CSR, Table 31; MMRM = Repeated Measurements Mixed-Effects Model
Baseline was defined as the last non-missing assessment prior to the administration of the first investigational drug product in Phase 1. A: Analyses were performed using MMRM, which included only actual observed data, and did not plan to fill in missing data before or after early withdrawal from the study, which were processed as putative random missing data (MARs) by MMRM analysis. The model used the treatment group as a fixed effect, and the visit, eye (left or right), baseline age group (by randomization), and baseline SER group (by randomization) were used as covariates, while the treatment group-visit interaction term was included. The degrees of freedom are determined using the Kenward-Roger approximation. Randomized intercepts for subjects and subjects' eyes were included using an unstructured covariance structure.

Sensitivity analyses

Additional covariates

Inclusion of additional covariates (genetic history of high myopia, time spent in near work, and time spent outdoors) to the mixed-effects model did not alter the conclusions of the primary analysis. Odds ratios for Atropine sulfate 0.01% vs placebo: and Atropine sulfate 0.02% vs placebo. Atropine Sulfate 0.02% was numerically favoured compared to Atropine Sulfate 0.01%.

Tipping point analysis

Adjusting the imputed missing data by up to -0.50 D in both Atropine Sulfate groups did not alter the main conclusions (for the respective comparison with placebo at Month 12 for 0.01%: p=; 0.02%: p=).

Subgroup analyses

Effect consistently favoured atropine in all subgroups in ITT. It is recalled that mini-CHAMP had a different age enrolment criterium (6-10 years) than CHAMP (3 to ≤17 years).

MOSAIC study (Myopia Outcome Study of Atropine in Children; Loughman 2023, 2024)

Methods

A double-masked, placebo-controlled, randomized study conducted at a single center in Ireland.

The study was Investigator Sponsored; the applicant's role was limited to providing the atropine, but reserved the right to require studies to be conducted according to GCP, and to review study protocols. The applicant indicated to be not involved in the conduct, management, and oversight of these studies. Examinations were scheduled at 6 monthly intervals. However, the 6-month visit was interrupted by the COVID-19 pandemic and subsequently abandoned.

Cycloplegic autorefraction (for SER calculation) was performed using the Grand Seiko Open Field autorefractor. Axial length was measured with a low-coherence interferometry biometer (TOPCON Aladdin HW3.0).

Treatment compliance was not reported for the primary treatment period (24 months). In Phase 2, study treatment compliance, based on returned used ampules.

Study participants

Key inclusion criteria were: Male or female aged 3 to 16 years; myopia of -0.50 D or worse in both eyes; astigmatism $\leqslant$ 2.50 D; least myopic meridian $\geqslant$ -0.50 D; anisometropia SER of > 1.00 D; IOP of < 21 mmHg in each eye.

Recruitment limitations were implemented to ensure the study population was approximately representative of the predominantly White (90%) Irish population.

Treatments

The atropine tested in this study was provided by the applicant.

Stage 1: Atropine Sulfate 0.01% or Vehicle: one drop in each eye, once daily at bedtime.

Stage 2 Atropine 0.01%, Atropine Sulfate 0.05% or Vehicle: one drop in each eye, once daily at bedtime or by means of a tapering regimen.

The tapering regimen involved using one eye drop in both eyes every 2nd night for 3 months, then twice weekly for 3 months, followed by once weekly for 3 months. Subjects ceased eye drop use entirely for the 3 months prior to the 36 month visit. Subjects in the placebo group all crossed over to Atropine Sulfate 0.05% once nightly in both eyes for 12 months.

Objectives

- To evaluate the efficacy of 0.01% atropine eye drops for the treatment of myopia.
- To Evaluate the safety and tolerability of 0.01% atropine eye drops

Outcomes/endpoints

Efficacy endpoints were:

- Primary: Change in SER from baseline to the 24-month visit.
- Secondary: Change in axial length from baseline to the 24-month visit.

Sample size

192 children (128 in the intervention group; 64 in the placebo group) would be sufficient for a power of 90% with a 2-sided test, adopting a significance value of 5%. Allowing for a potential 30% attrition rate, a total of 250 children were planned to be recruited (167 in atropine group; 83 in placebo group).

Randomisation and blinding (masking)

In Stage 1 of the study, eligible subjects were randomized in double-blinded manner 2:1 to Atropine Sulfate 0.01% or placebo (Vehicle) for a 24 month treatment period.

In Stage 2, subjects originally randomized to Atropine Sulfate 0.01% were re-randomized (double-blind) in a 1:1:2 ratio to received either placebo once nightly in both eyes, placebo in a tapering regimen, or Atropine Sulfate 0.01% in a tapering regimen respectively.

Statistical methods

The primary population for efficacy analyses was the ITT population in both parts of the study. Alpha (α) was set to 5%. Power (β) was 95% for the primary endpoint. No direct adjustment for multiplicity was made.

Efficacy over Stage 1 was analysed using linear mixed models with visit and treatment group as fixed effects, random intercepts for eye nested within subject, a fixed effect visit by treatment interaction, and adjustment for the baseline value of the outcome.

Outcome changes in Stage 2 were calculated relative to the Month 24 visit. The placebo tapered, and placebo nightly arms were considered as a single treatment arm.

Linear mixed models were used to model change in the parameter of interest from Part 2 baseline (Month 24) against visit, treatment arm, treatment by-visit as and interaction term, sex, age and the value of the outcome at the study baseline visit (i.e. enrollment visit). Adjustment for change in the parameter of interest from baseline to the Month 24 visit, and a random intercept term for eye nested within subject, were included.

Subgroups analyses were performed using linear mixed models that also included a three-way interaction term between visit, treatment group and the modifier. Adjustment for the baseline value of the variable, age and sex were included, unless already included as an exposure variable (e.g. baseline age and myopia category).

Results

Participant flow

Of the 250 participants enrolled into MOSAIC, 204 (81.6%) completed the 24-month visit. Of these, 199 (97.0%) reconsented to continue onto the third year. Of these, 182 (91.5%) completed Month 36 visit (67 [36.8%] 0.01% atropine group, 61 [33.5%] 0.05% atropine, 54 [29.7%] placebo) (Loughman 2024, Figure 1).

Study discontinuation rates in the Atropine Sulfate 0.01% (18.6%) and placebo (18.1%) groups were comparable over 24 months (Loughman 2023, Table S1). Relatively few subjects discontinued treatment in Year 3, primarily being lost to follow-up (Loughman 2024, Table 2).

Table 24. Overview of subject disposition and reasons for discontinuation (MOSAIC study*)*

	Year 1&2a		**Year 3b**		
Withdrawal/ Lost to follow up	**Placebo N=83 n (%)**	**Atropine Sulfate 0.01% N=167 n(%)**	**Atropine Sulfate 0.01%-to-Placebo† n=60 n (%)**	**Atropine Sulfate 0.01% -to-Atropine Sulfate 0.01% tapering**	**Placebo-to-Atropine Sulfate 0.05% N=66 n (%)**

				N=73 n (%)	
Randomized	83	167	60	73	66
Completed	68 (81.9)	136 (81.4))	54 (90.0)	67(91.8)	61 (92.4)
Discontinued	15 (18.1)	31 (18.6)	6 (10.0)	6 (8.2)	5 (7.6)
Unable to make visits	1 (1.2)	4 (2.4)	--	--	--
Discomfort with eye drops	3 (3.6)	7 (4.2)	--	--	--
Tired of using eye drops	2 (2.4)	5 (3.0)	1 (1.7)	0	0
Advised to stop by external party	0	2 (1.2)	0	1 (1.4)	0
Lost contact	4 (4.8)	9 (5.4)	4 (6.7)	3 (4.1)	5 (7.6)
Perceived lack of efficacy	4 (4.8)	2 (1.2)	--	--	--
Seeking alternate myopia treatment	1 (1.2)	1 (0.6)	0	1 (1.4)	0
Personal reason	0	1 (0.6)	1 (1.7)	1 (1.4)	0

Source: Loughman 2023; Loughman 2024; † Year 3 placebo is the combined group of subjects re-randomized to placebo tapered dosing or placebo nightly. a: Reasons for study discontinuation in Years 1&2. For discontinuations of treatment, which mirror the reported numbers discontinuing the study, see Loughman 2023, Table S1. b: In Year 3, reasons for treatment discontinuation. Treatment discontinuation rates mirror study completion rates.

Conduct of the study

The protocol was amended three times, of which one after start of enrolment. This amendment primarily reflects the addition of the atropine 0.05% and tapering dosing regimen in part 2. No information was provided on protocol deviations.

Baseline data

- Phase 1

Demographic and other baseline characteristics are summarized by treatment group in the table below.

There were no notable differences between the treatment groups. Approximately one third of subjects were male, lower than that in CHAMP. Mean age was ~2.5 years older than that in CHAMP. The study population was biased towards females (62%) and toward non-White race group (17%) when compared with 5 to 19- year-olds in the overall Irish population (49% female, 10% non-White).

Table 25. Demographic and baseline (disease) characteristics (MOSAIC study, ITT population, phase 1 baseline)

Baseline characteristic (Part 1)	**Placebo (N=83)**	**Atropine Sulfate 0.01% (N=167)**
Age (years), mean (SD)	11.78 (2.17)	11.84 (2.47)
Sex		
Male , n (%)	30 (36.1)	65 (38.9)
Female, n (%)	53 (63.9)	102 (61.1)
Parents with myopia, n (%)		
Zero	18 (21.7)	32 (19.2)
One	43 (51.8)	97 (58.1)
Two	22 (26.5)	38 (22.8)
Race, n (%)		
White	72 (86.7)	135 (80.8)
Asian	7 (8.4)	15 (9.0)
Black	2 (2.4)	3 (1.8)

Mixed	2 (2.4)	12 (7.2)
Other	1 (1.2)	2 (1.2)
Iris color, n (%)		
Blue	42 (50.6)	78 (46.7)
Green	24 (28.9)	45 (26.9)
Brown	17 (20.5)	44 (26.3)
Disease characteristics (part 1)		
SER (D), median (IQR)	-3.38 (-4.34, -1.95)	-3.21 (-4.51, -2.12)
Axial length (mm), mean (SD)	24.93 (1.09)	24.85 (1.02)

Source: Loughman 2023, Table 1; For age at first prescribed glasses, daily outdoor time and body mass index see source. See source for distance visual acuity, near visual acuity, amplitude of accommodation, accommodative facility, accommodative lag, and photopic /mesopic pupil size which were balanced across treatment groups. D: diopters; IQR: interquartile range; SD: standard deviation; SER: spherical equivalent refraction. Ocular data are average of both eyes. Approximately normally distributed variables are described with mean (standard deviation [SD]) and skewed data are described with median (interquartile range [IQR]).

Baseline disease characteristics were balanced across treatment groups at baseline. The population in MOSAIC was less male, more myopic at baseline than in CHAMP (approximately -3.3 D vs -2.5 D, respectively), and had an older age on average.

- Phase 2

Demographic and other baseline characteristics at entry to Phase 2 are summarized by treatment group in Table 26 and baseline disease characteristics in the pupil diameter was larger in participants using atropine 0.01% eye drops up until the Month 24 visit, but characteristics were otherwise relatively well-balanced across the treatment arms.

There were no significant differences in baseline characteristics between subjects who did and did not continue to Phase 2, except for accommodative facility, which was slightly higher in the group who reconsented to Phase 2 (median 5 vs 4 cycles/minute).

Table 26. Demographic and baseline characteristics (MOSAIC study, ITT population, phase 2 baseline)

Baseline characteristic (Phase 2)	**Placebo (tapering and nightly combined) N=60**	**Atropine Sulfate 0.01% tapering N=73**	**Atropine Sulfate 0.05% N=66**
Age (years), mean (SD)	13.66 (2.60)	14.21 (2.32)	13.71 (2.19)
Sex			
Male , n (%)	36 (60.0)	43 (58.9)	42 (43.6)
Female, n (%)	24 (40.0)	30 (41.1)	24 (36.4)
Parents with myopia, n (%)			
Zero	8 (13.3)	17 (23.3)	12 (18.2)
One	33 (55.0)	44 (60.3)	37 (56.1)
Two	19 (31.7)	12 (16.4)	17 (25.8)
Race, n (%)			
White	46 (76.7)	62 (84.9)	58 (87.9)
Asian	6 (10.0)	5 (6.8)	4 (6.1)
Black	2 (3.3)	1 (1.4)	1 (1.5)
Mixed	6 (10.0)	3 (4.1)	2 (3.0)
Other	0	1 (1.4)	1 (1.5)
Iris color, n (%)			
Blue	29 (48.3)	35 (47.9)	36 (54.5)
Green	13 (21.7)	23 (30.1)	18 (27.3)
Brown	18 (30.0)	16 (21.9)	12 (18.2)

Source: Loughman 2024, Table 1

Table 27. Baseline disease characteristics (MOSAIC study, ITT population, phase 2 baseline)

Disease characteristic (Phase 2)	Placebo (tapering and nightly combined) N=60	Atropine Sulfate 0.01% tapering N=73	Atropine Sulfate 0.05% N=66
SER (D), median (IQR)	-4.04 (-4.84, -3.11)	-3.62 (-5.06, -2.50)	-3.98 (-4.69, -2.60)
Change in SER from baseline to Month 24 (mm), mean (SD)	-0.60 (0.50)	-0.48 (0.55)	-0.63 (0.62)
Axial length (mm), mean (SD)	25.12 (0.99)	25.27 (1.08)	25.29 (1.17)
Change in axial length from baseline to Month 24 (mm), mean (SD)	0.36 (0.28)	0.30 (0.24)	0.40 (0.30)

Source: Loughman 2024, Table 1; See source for amplitude of accommodation, accommodative facility, accommodative lag, and photopic /mesopic pupil size. D: diopters; IQR: interquartile range; SD: standard deviation; SER: spherical equivalent refraction.

Treatment compliance

No data were reported over the first 24 months of Phase 1. In Phase 2, study treatment compliance, based on returned used ampules and defined as using ≥75% of expected doses, was equally across the placebo taper (90%), placebo nightly (81%), atropine 0.01% taper (83%), and atropine 0.05% nightly (81%) groups, respectively.

Outcomes and estimation

Primary efficacy endpoint (SER) at Month 24

Changes in the primary (SER) efficacy outcome are shown in Table 28. Myopia progression was not significantly different between the Atropine Sulfate 0.01% and placebo groups at the Month 24 visit (difference = 0.12 D, p=0.07) but lower in the treatment group at the Month 18 visit (nominal p=0.049). A post-hoc analysis including age strata (< 9 years and ≥ 9 years) as covariate showed a treatment difference at 24 months in SER of 0.13 D (nominal p = 0.035).

Table 28. Change in spherical equivalent refraction by study visit (MOSAIC study, ITT population)

Visit	Statistic	Placebo (N=83)	Atropine Sulfate 0.01% (N=167)
Changes from Baseline in SER (D)			
Month 12	n (eyes)	154	298
	Mean (SD)	-0.27 (0.47)	-0.24 (0.41)
	Group difference (Atropine sulfate – Vehicle)		0.02 (0.07)
	p-value		0.76
Month 18	n (eyes)	138	280
	Mean (SD)	-0.53 (0.56)	-0.41 (0.49)
	Group difference (Atropine sulfate – Vehicle)		0.13 (0.07)
	p-value		0.049
Month 24	n (eyes)	134	272
	Mean (SD)	-0.63 (0.65)	-0.53 (0.56)
Primary timepoint	Group difference (Atropine sulfate – Vehicle)		0.12 (0.07)
	p-value		0.07
Overall	p-value (treatment by visit interaction)		<0.001

Source: Loughman, 2023, Table 3; D=diopter; ITT=Intent-to-Treat; N=number of subjects in population; n=number of eyes assessed; SD=standard deviation; SER=spherical equivalent

refraction. a: Group differences are the difference [standard error] in the estimated marginal means derived from the linear mixed model and are adjusted for the baseline value of the outcome. Note that p-values are nominal as the primary endpoint was not met and there was no correction for multiple testing.

MOSAIC did not analyse the responder using the less than 0.5 D progression criterion. The proportion of participants with less than 0.75 D progression was higher in the 0.01% group (70.8%) than the placebo group (63.6%) (Loughman 2023, Figure S1).

Secondary endpoint (axial length) at Month 24

Axial elongation was lower in the atropine group at the 18- month and 24-month visits, compared to the placebo group (see Table 29).

Table 29. Change in axial length by study visit (MOSAIC study, ITT population)

Visit	Statistic	Placebo (N=83)	Atropine Sulfate 0.01% (N=167)
Changes from Baseline in axial length (mm)			
Month 12	n (eyes)	154	298
	Mean (SD)	0.24 (0.20)	0.20 (0.19)
	Group difference (Atropine Sulfate – Vehicle)	--	-0.04 (0.03)
	p-value	--	0.25
Month 18	n (eyes)	138	280
	Mean (SD)	0.35 (0.26)	0.29 (0.23)
	Group difference (Atropine Sulfate – Vehicle)	--	-0.06 (0.03)
	p-value	--	0.04
Month 24	n (eyes)	136	272
	Mean (SD)	0.40 (0.31)	0.33 (0.27)
Primary timepoint	Group difference (Atropine Sulfate – Vehicle)	--	-0.07 (0.03)
	p-value	--	0.009
Overall	p-value (treatment-by-visit interaction)	--	<0.0001

Source: Loughman, 2023, Table 3. A: Group differences are the difference [standard error] in the estimated marginal means derived from the linear mixed model and are adjusted for the baseline value of the outcome. Note that p-values are nominal as the primary endpoint was not met and there was no correction for multiple testing.

Ancillary analyses

Subgroup analyses of primary and secondary efficacy endpoints at Month 24

The proportions of non-White participants in MOSAIC were relatively small in both treatment groups. Treatment effects for SER at 18 months and axial length at 18 and 24 months were found among White, but not non-White, subjects, likely a chance finding due to the smaller size of the latter group (MAA Module 2.7.3., Table 99).

Treatment effects were observed among blue-eyed participants at 18 months (SER difference = 0.17 D; axial length difference = −0.10 mm) and 24 months (SER difference = 0.18 D; axial length difference = −0.12 mm), but not among subjects with green or brown eyes (MAA Module 2.7.3., Table 99). Note that the sample size of non-blue-eyed individuals was small.

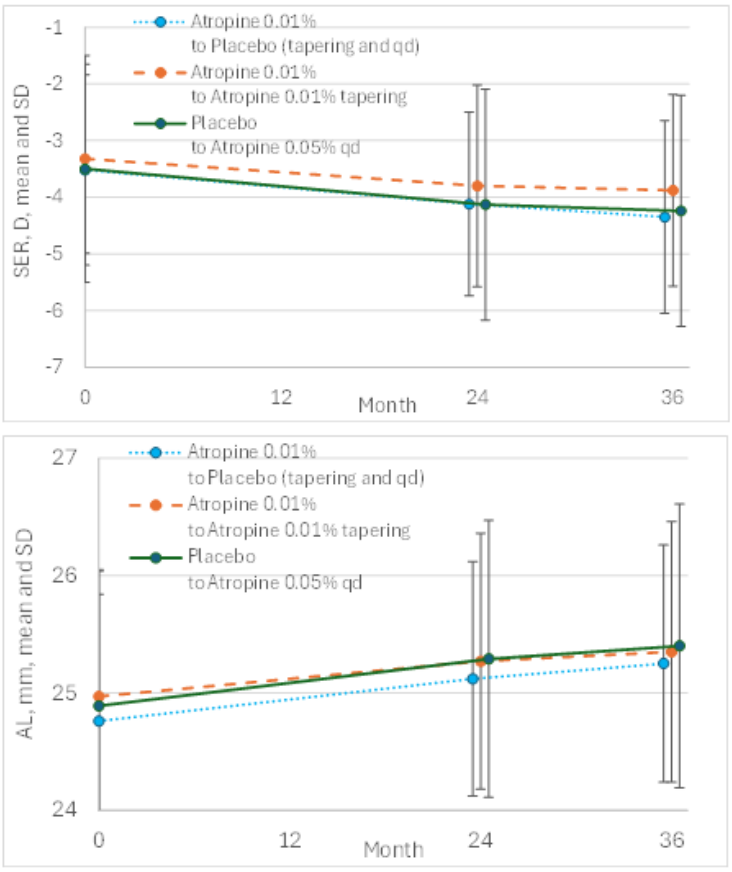
Treatment effects were similar for participants with low (≥−3.00 D) vs high (<−3.00 D) myopia at baseline (MAA Module 2.7.3., Table 99).

Additional analysis adjusting for baseline age

Axial elongation was lower in older (≥11 years) subjects assigned to Atropine Sulfate 0.01%, compared with placebo, at Month 18 (difference = −0.08 mm) and Month 24 (difference = −0.09 mm), no differences were observed among subjects <11 years. Observed differences in axial length across other subgroups were considered minimal and/or confounded by small sample sizes by the applicant (MAA Module 2.7.3., Table 99).

Phase 2, Month 36 outcomes (rebound analysis)

Figure 9. Change in spherical equivalent refractive error (top) and axial length (bottom) (MOSAIC phase 2 population)



The Atropine 0.01%-Placebo group combined both placebo tapered and placebo nightly in Year 3. The Atropine 0.01%-Atropine 0.01% group represents atropine 0.01% tapered dosing in Year 3.

Based on SER progression, a rebound effect (increased myopia progression) was not obvious in either Phase 2 group after switching from Atropine Sulfate 0.01% to:

- Placebo: -0.38 D/year in Phase 1 and -0.23 D/year in Phase 2
- Atropine sulfate 0.01% tapering: -0.29 D/year in Phase 1 to -0.18 D/year in Phase 2.

MTS1 study (Myopia Treatment Study 1; Repka, 2023)

Methods

A randomized, placebo-controlled, double-masked study conducted in the United States.

The study was Investigator Sponsored; the applicant's role was limited to providing the atropine, but reserved the right to require studies to be conducted according to GCP, and to review study protocols. The applicant indicated to be not involved in the conduct, management, and oversight of these studies.

Study visits occurred at Month 6, 12, 18 and 24 (primary outcome). At Month 30 there was a follow-up evaluation effects after 6 months treatment cessation. SER was assessed by cycloplegic autorefraction. Axial length was assessed using optical biometry with cycloplegia.

For treatment compliance, calendars were provided to record eye drop use and eyeglass wear. Unused ampules were collected and counted.

Study Participants

Key inclusion criteria included: age 5 to <13 years, myopia -1.00 D to -6.00 D in both eyes; astigmatism ≤ -1.50 D; anisometropia < 1.00 D.

Treatments

Atropine 0.01% or placebo was administered one drop in each eye nightly for 24 months.

Non-randomized treatments for myopia other than changes in refractive error (spectacles) were not permitted, including during the final 6 months (no study treatment period) of the study.

Objectives

Primary objective: to determine the efficacy of atropine for slowing progression of myopia after 24 months of treatment.

Secondary objective: to determine the efficacy of atropine treatment for slowing progression of myopia after a period of 6 months off treatment.

Outcomes/endpoints

Primary endpoint:

- Treatment group comparison of changes from baseline to 24-months in SER.

Secondary endpoints:

- Proportion of subjects with progression ≥ 2 D at 24 months.
- Change in axial length at 12 and 24 months.
- Refractive error at 12 months.

Proportion of subjects with progression ≥ 1 D at 12 months.
Each of the primary and secondary endpoints was also assessed at the Month 30 (6-months off treatment) visit.

Sample size

A sample size of 186 participants provided 97% power to reject the null hypothesis of no difference in mean change in SER from baseline to 24 months under the following assumptions: (1) 2:1 randomization, (2) treatment group difference of 0.50 D, (3) SD of 0.80 D, (4) type I error of 5% (2-sided), and (5) up to 10% loss to follow-up.

Randomisation and blinding (masking)

Eligible subjects were randomized (double-blind) 2:1 to Atropine Sulfate 0.01% or placebo stratified by iris color (brown or not brown) and clinical site. Per-protocol, the proportion of the total randomized population who self-reported East Asian ethnicity was to be restricted to 25% (47 subjects).

Statistical methods

The primary population for efficacy analyses was the ITT population.

The primary endpoint was assessed using a longitudinal discrete-time mixed model adjusting for baseline SER, age, iris color (brown vs not brown), and race (East Asian vs non–East Asian participants). The mean change in SER from baseline to 24 months and from baseline to 30 months in each treatment group and the treatment group difference (atropine − placebo) with corresponding 95% CI were estimated using the maximum likelihood method.

Continuous secondary outcomes were analysed using the same method as the primary analysis, and the proportions of the binary secondary outcomes were calculated within each treatment group and compared between the groups using the Barnard unconditional exact test.

A sensitivity analysis was conducted to compare the mean change in SER from baseline to 24 months between treatment groups using analysis of covariance (ANCOVA), adjusting for baseline SER, age, iris color (brown vs. not brown), and race (East Asian vs. non-East Asian participants) and not considering SER at the intermediate 6-, 12-, or 18-month visit.

The overall false discovery rate for secondary and subgroup analyses was controlled at the 5% level and the 95% CIs were adjusted using the 2-stage step-up procedure.

Results

Participant flow

First subject enrolled: jun2018; last subject completed: sep2022.

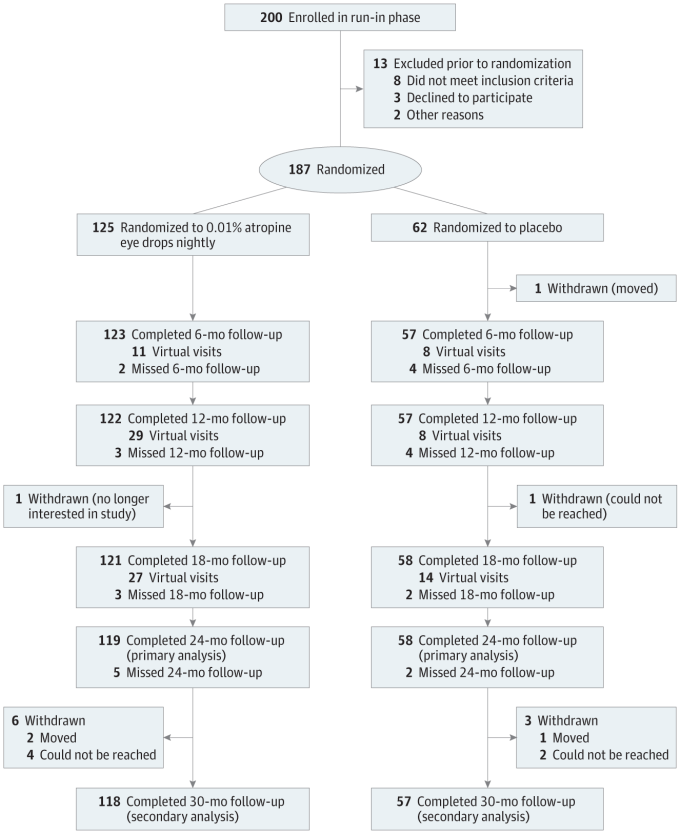


Figure 10. MTS1 subject flow diagram (source: Repka et al., 2023 figure 1)

Conduct of the study

The protocol was amended four times, of which three after start of enrolment. The adjustments considered of most impact were:

- Enrolment criteria were added to exclude patients with conditions affect accommodation, vergence, or ocular motility; to exclude those with conditions which may influence refractive development; to exclude those with a any condition that could potentially influence refractive development, or affect the long-term health of the eye, or require regular pharmacologic treatment that may adversely interact with study medication, and those unable to complete tests.

- Conduct of visits adjusted due to COVID-19 pandemic.

No information was provided on protocol deviations.

Baseline data

Subjects in MTS1 were older (aged ~10 years; Table 30) than in CHAMP (~8.5 years), but younger than in MOSAIC (~12 years). In MTS1, overall age of enrolment was comparable between groups although a disbalance was noted in the subgroups of 9-11 years (in favour of atropine 0.01%) and 11-<13 years (in favour of Vehicle). There was also a disbalance across groups in the number of East Asian subjects enrolled (6% in vehicle; 13% in atropine 0.01%).

Table 30. Demographic and baseline characteristics (MTS1 study, ITT population)

Characteristic	Placebo (N=62)	Atropine Sulfate 0.01% (N=125)
Sex, n (%)		
Female	36 (58)	65 (52)
Male	26 (42)	60 (48)
Age, n (%)		
5-<7	3 (5)	6 (5)
7-<9	13 (21)	28 (22)
9-<11	20 (32)	50 (40)
11-<13	26 (42)	41 (33)
Mean (SD) [range]	10.1 (1.8) [5.1, 12.9]	10.1 (1.8) [5.1, 12.9]
Race/ethnicity, n (%)		
Black	14 (23)	20 (16)
East Asian	4 (6)	16 (13)
Hispanic or Latino	9 (15)	21 (17)
Multiracial	5 (8)	6 (5)
West Asian/South Asian	2 (3)	4 (3)
White	28 (45)	58 (46)
Eye color, n (%)		
Brown	41 (66)	82 (66)
Not brown	21 (34)	43 (34)
Biological parents with myopia, n (%)		
0	11 (18)	16 (13)
1	24 (39)	51 (41)
2	20 (32)	52 (42)
Unknown	7 (11)	6 (5)

Source: Repka 2023 Table 1; See source for distance visual acuity, flat corneal radius, anterior chamber depth, and lens thickness which were comparable across treatment groups.

Mean (SD) SER at baseline was −2.83 (1.10) D and mean (SD) axial length was 24.4 (0.8) mm across the two treatment groups (see below Table 31).

Table 31. Baseline disease characteristics (MTS1 study, ITT population)

Characteristic	Placebo (N=62)	Atropine Sulfate 0.01% (N=125)
SER (D), n (%)		
-6.00 to < -5.00	1 (2)	5 (4)
-5.00 to < -4.00	5 (8)	17 (14)
-4.00 to < -3.00	19 (31)	27 (22)
-3.00 to < -2.00	22 (35)	37 (30)
-2.00 to < -100	15 (24)	39 (31)
Mean (SD)	-2.83 (0.97)	-2.83 (1.17)
Median	-2.81	-2.60
Axial length (mm), n (%)		
22.0 to <23.0	3 (5)	5 (4)
23.0 to <24.0	12 (19)	33 (26)
24.0 to <25.0	30 (48)	51 (41)
25.0 to <26.0	15 (24)	33 (26)
26.0 to <27.0	2 (3)	3 (2)
Mean (SD)	24.4 (0.8)	24.4 (0.8)
Median	24.3	24.4

Source: Repka 2023, Table 2; Data are mean of the right and left eye

Treatment compliance

Compliance was estimated by subjective calendar logs. At least 93% of the Atropine Sulfate 0.01% group and at least 96% of the placebo group were adherent (≥76% of planned doses) across all visits.

Two subjects in the Atropine Sulfate 0.01% group received additional myopia interventions (multifocal soft contact lens wear and correction lens from Month 18 in one case and atropine 1% in the other case).

Outcomes and estimation

Change from baseline in SER at Month 24 and Month 30

The adjusted mean (95% CI) change in SER from baseline to Month 24 was comparable in the Atropine Sulfate 0.01% and placebo groups, respectively, resulting in an adjusted difference (atropine – placebo) of −0.02 D (95% CI, −0.19 to 0.15 D; p = 0.83) (see table below).

Table 32. Spherical equivalent refraction error by treatment and visit (MTS1 study, ITT population)

Visit	Statistic		Placebo N=144	Atropine Sulfate 0.01% N=133
SER (D) at Baseline				
Baseline	Mean (SD)		-2.83 (0.97)	-2.83 (1.17)
	Median		-2.81	-2.60
Changes from Baseline in Normalized SER (D)				
Month 24 Primary timepoint	Mean (SD)		-0.74 (0.60)	-0.78 (0.64)
	Median		-0.63	-0.58
	Adjusted mean		-0.80	-0.82
	Adjusted treatment group difference (Atropine sulfate – Placebo)b		-0.02	
	95% confidence interval for difference		-0.19 to 0.15	
	p-value		0.83	
	Myopia progression	≥ 0.5 D	37 (64)	78 (66)
		≥ 1.0 D	18 (31)	34 (29)
		≥ 2.0 D	2 (3)	7 (6)
Month 30a	Mean (SD)		-0.88 (0.71)	-0.94 (0.77)
	Median		-0.77	-0.72
	Adjusted mean		-0.92	-0.97
	Adjusted treatment group difference (Atropine sulfate – Placebo)b		-0.04	
	95% confidence interval for difference		-0.25 to 0.17	
	Myopia progression	≥ 0.5 D	41 (72)	83 (70)
		≥ 1.0 D	21 (37)	44 (37)
		≥ 2.0 D	4 (7)	14 (12)

Source: Repka 2023, Table 2; a: After 6 months without treatment. b: The adjusted treatment group difference of mean change in SER from baseline adjusted for baseline SER, age, iris color (brown vs non-brown), and race (East Asian vs non–East Asian).

Neither a treatment nor rebound effect was observed at Month 30, 6 months after completing study treatment (difference atropine − placebo = −0.04D, (95% CI :-0.25, 0.17).

The proportions of subjects with ≥ 0.5 D, ≥ 1.0 D, or ≥ 2.0 D myopia progression were comparable across treatment groups at both time points.

Change from baseline in axial length at Month 24 and Month 30

Change from baseline in axial length was comparable in the Atropine Sulfate 0.01% and placebo groups, respectively, resulting in an adjusted difference (atropine – placebo) of adjusted difference of -0.002 mm (95% CI, -0.106 to 0.102 mm) (Table 33).

Neither a treatment nor rebound effect was observed at Month 30, 6 months after completing study treatment (difference atropine − placebo = 0.009 mm).

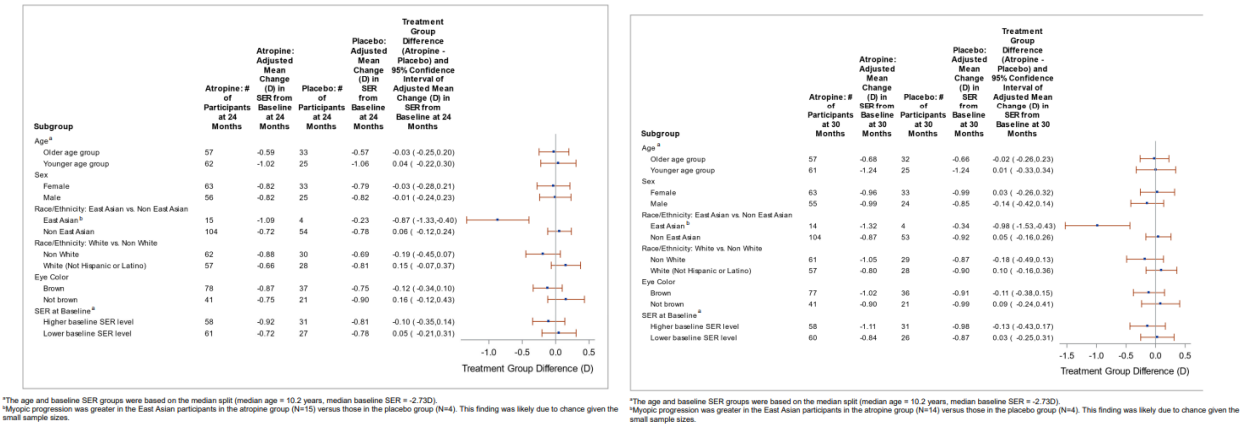
Table 33. Axial length by treatment group and visit (MTS1 study, ITT population)

Visit	Statistic	Placebo N=144	Atropine Sulfate 0.01% N=133
Axial length (mm) at Baseline			
Baseline	Mean (SD)	24.4 (0.8)	24.4 (0.8)
	Median	24.3	24.4
Changes from Baseline in axial length (mm)			
Month 24 Primary timepoint	Mean (SD)	0.41 (0.27)	0.42 (0.29)
	Median	0.36	0.38
	Adjusted mean	0.45	0.44
	Adjusted treatment group difference (Atropine sulfate – Placebo)	-0.002	
	95% confidence interval for difference	-0.106 to 0.102	
Month 30	Mean (SD)	0.49 (0.32)	0.51 (0.35)
	Median	0.45	0.44
	Adjusted mean	0.52	0.53
	Adjusted treatment group difference (Atropine sulfate – Placebo)	0.009	
	95% confidence interval for difference	-0.115 to 0.134	

Source: Repka 2023, Table 2

Ancillary analyses

Subgroup analyses did not reveal any trend inconsistent with the primary outcome data at Month 24 and Month 30 (Figure 11). The exception is the East Asian subgroup showing unfavourable effect of 0.01%. The applicant indicated that this was due to the small number of Asian subjects.



Source: Repka 2023, eFigure 6 and 7

Figure 11. MTS1 subgroup analysis at month 24 (left) and month 30 (right)

Summary of main efficacy results

Following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Note that all p-values except those reported for the primary endpoints are nominal.

Table 34. Summary of efficacy for trial CHAMP – stage 1 and stage 2

Title: Childhood Atropine for Myopia Progression (CHAMP): A 3-arm randomised, double-masked, placebo-controlled, Phase 3 study of atropine sulfate ophthalmic solution 0.01% and 0.02%		
Study identifier	**EudraCT: 2018-001077-24** **Sponsor Protocol Number: CP-NVK002-0001**	
Design	This study was a randomized, double-masked, parallel group, placebo-controlled, multi-center, superiority design comparing the efficacy and safety of 0.01% or 0.02% atropine sulfate eye drops versus placebo in slowing the progression of myopia in children aged 3 to 16 years. The study was performed in 26 sites across the US (20 sites) and Europe (6 sites). In stage 1 of the study, subjects were randomized 2:2:3 to placebo, 0.01% and 0.02% atropine. The study was double masked and dosing was by parallel group for a total of 3 years nightly dosing with investigational product. In stage 2, subjects were re-randomised 1:1:1 at Month 36 such that any subject on active treatment in stage 1 could be randomised to any of the 3 treatments, but placebo subjects from Stage 1 could be randomised to one of the two active arms.	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	36 months Not Applicable 12 months
Hypothesis	Superiority hypothesis. Primary and secondary endpoints were between-group (atropine vs placebo) difference in responder proportion, mean change from baseline in SER or mean change from baseline in AL at the Month 36 visit.	
Treatments groups in main phase (Stage 1)	Placebo	Placebo was the vehicle. One hundred and sixty five (165) subjects were randomised to nightly dosing for 36 months
	0.01%	0.01% atropine sulfate. One hundred and sixty four (164) subjects were randomised to nightly dosing for 36 months
	0.02%	0.02% atropine sulfate. Two hundred and forty seven (247) subjects were randomised to nightly dosing for 36 months
Treatments groups in extension phase (Stage 2)	Placebo-to-0.01%	0.01%, 12 months, 62 subjects randomized from Stage 1
	Placebo-to-0.02%	0.02%, 12 months, 60 subjects randomized from Stage 1
	0.01%-to-placebo	Placebo, 12 months, 39 subjects randomized from Stage 1
	0.01%-to-0.01%	0.01%, 12 months, 38 subjects randomized from Stage 1
	0.01%-to-0.02%	0.02%, 12 months, 39 subjects randomized from Stage 1

Title: Childhood Atropine for Myopia Progression (CHAMP): A 3-arm randomised, double-masked, placebo-controlled, Phase 3 study of atropine sulfate ophthalmic solution 0.01% and 0.02%			
Study identifier	**EudraCT: 2018-001077-24** **Sponsor Protocol Number: CP-NVK002-0001**		
	0.02%-to-placebo		Placebo, 12 months, 60 subjects randomized from Stage 1
	0.02%-to-0.01%		0.01%, 12 months, 59 subjects randomized from Stage 1
	0.02%-to-0.02%		0.02%, 12 months, 63 subjects randomized from Stage 1
Endpoints and definitions	Primary endpoint	Responder proportion of 0.02%	Between-treatment group (Atropine Sulfate Ophthalmic Solution, 0.02% versus Vehicle) difference in the proportion of subjects' eyes who show less than 0.5 D myopia progression (SER) from baseline at the Month 36 visit.
	Secondary endpoint	CFB SER 0.02%	Between-treatment group (Atropine Sulfate Ophthalmic Solution, 0.02% versus Vehicle) difference in the mean change from baseline (CFB) in SER at the Month 36 visit.
	Secondary endpoint	Responder proportion of 0.01%	Between-treatment group (Atropine Sulfate Ophthalmic Solution, 0.01% versus Vehicle) difference in the proportion of subjects' eyes who show less than 0.5 D myopia progression (SER) from baseline at the Month 36 visit
	Secondary endpoint	CFB SER 0.01%	Between-treatment group (Atropine Sulfate Ophthalmic Solution, 0.01% versus Vehicle) difference in the mean change from baseline in SER at the Month 36 visit
	Secondary endpoint	CFB AL 0.02%	Between-treatment group (Atropine Sulfate Ophthalmic Solution, 0.02% versus Vehicle) difference in the mean change from baseline in axial length at the Month 36 visit
	Secondary endpoint	CFB AL 0.01%	Between-treatment group (Atropine Sulfate Ophthalmic Solution, 0.01% versus Vehicle) difference in the mean change from baseline in axial length at the Month 36 visit
	Tertiary endpoint	Time-to-change in progression of -0.75D	Between-group (atropine vs placebo) difference in time-to-change from baseline in progression of -0.75D
	Tertiary endpoint	Change from stage 2 baseline in SER	Change from stage 2 baseline in SER for subjects who received active treatment in stage 1 and received the same or placebo in stage 2
	Tertiary endpoint	Stage 2 Responder proportion for stage 1 responders	Responder (<0.5D progression from stage 2 baseline) proportion at Month 48 for eyes that were responders in the Atropine Sulfate Ophthalmic Solution treatment groups at Month 36.
Database lock	Stage 1: 7th September 2022; Stage 2: 19th October 2023		

Title: Childhood Atropine for Myopia Progression (CHAMP): A 3-arm randomised, double-masked, placebo-controlled, Phase 3 study of atropine sulfate ophthalmic solution 0.01% and 0.02%					
Study identifier	**EudraCT: 2018-001077-24** **Sponsor Protocol Number: CP-NVK002-0001**				
Results and Analysis					
Analysis description	Primary Analysis (Prespecified)				
Analysis population and time point description	mITT (Modified Intent-to-Treat). Analysis included all randomized subjects who were aged 6 to 10 years at stage 1 baseline. 36 months.				
Descriptive statistics and estimate variability (Stage 1)	Treatment group	Placebo	0.01%	0.02%	
	Number of subjects	144	133	212	
	Responder proportion (<0.5D progression) at 36 months, n (%); Number of evaluable eyes	44 (17.5) 252	57 (28.5) 200	81 (22.1) 366	
	CFB SER at 36 months, Least Square Mean (D); 95% CI	-1.279 -1.373, -1.185	-1.039 -1.139, -0.939	-1.180 -01.257, -1.102	
	CFB AL at 36 months, Least Square Mean (mm); 95% CI	0.805 0.763, 0.848	0.676 0.630, 0.721	0.728 0.693, 0.763	
	Time-to-change in progression of -0.75D, median (days); 95% CI from Kaplan-Meier estimates	542 497, 551	715 546, 757	589 553, 726	
Descriptive statistics and estimate variability (Stage 2)	Treatment group	0.02%-to-0.02%	0.02%-to-placebo	0.01%-to-0.01%	0.02%-to-placebo
	Number of subjects	56	52	29	31
	Change from stage 2 baseline in SER at Month 48, Mean (D); SD; Number of evaluable eyes at Month 48	-0.207 0.3773 102	-0.207 0.3015 96	-0.185 0.2655 54	-0.205 0.2888 52
	Stage 2 Responder proportion for stage 1 responders, n (%); Number of evaluable eyes at Month 48	22 (84.6) 26	22 (88.0%) 25	17 (89.5) 19	15 (83.3) 18
Effect estimate per comparison	Primary endpoint, Responder proportion	Comparison groups		0.02% vs placebo	

Title: Childhood Atropine for Myopia Progression (CHAMP): A 3-arm randomised, double-masked, placebo-controlled, Phase 3 study of atropine sulfate ophthalmic solution 0.01% and 0.02%			
Study identifier	**EudraCT: 2018-001077-24 Sponsor Protocol Number: CP-NVK002-0001**		
		OR	1.774
		95% CI	0.503, 6.260
		P value (mixed effects model)	0.373
	Secondary endpoint, CFB SER at 36 months, 0.02% vs placebo	Comparison groups	0.02% vs placebo
		LS Mean Difference, D	0.099
		95% CI	-0.020, 0.218
		P value (mixed effects model)	0.101
	Secondary endpoint, Responder proportion (<0.5D progression) at 36 months, 0.01% vs placebo	Comparison groups	0.01% vs placebo
		OR	4.540
		95% CI	1.147, 17.965
		P value (mixed effects model)	0.031
	Secondary Endpoint, CFB SER at 36 months, 0.01% vs placebo	Comparison groups	0.01% vs placebo
		LS Mean Difference, D	0.240
		95% CI	0.106, 0.374
		P value (mixed effects model)	<0.001
	Secondary Endpoint, CFB AL at 36 months, 0.02% vs placebo	Comparison groups	0.02% vs placebo
		LS Mean Difference, mm	-0.077
		95% CI	-0.131, -0.024
		P value (mixed effects model)	0.005
	Secondary Endpoint, CFB AL at 36 months, 0.01% vs placebo	Comparison groups	0.01% vs placebo
		LS Mean Difference, mm	-0.130
		95% CI	-0.191, -0.069
		P value (mixed effects model)	<0.001
	Tertiary endpoint, Time-to-change in progression of -0.75D, 0.02% vs placebo	Comparison groups	0.02% vs placebo
		HR	0.757
		95% CI	0.593, 0.967
		P value (Cox regression model)	0.026
	Tertiary endpoint, Time-to-change in progression of -0.75D, 0.01% vs placebo	Comparison groups	0.01% vs placebo
		HR	0.679
		95% CI	0.511, 0.903
		P value (Cox regression model)	0.008

Title: Childhood Atropine for Myopia Progression (CHAMP): A 3-arm randomised, double-masked, placebo-controlled, Phase 3 study of atropine sulfate ophthalmic solution 0.01% and 0.02%			
Study identifier	**EudraCT: 2018-001077-24** **Sponsor Protocol Number: CP-NVK002-0001**		
	Tertiary endpoint, Change from stage 2 baseline in SER at Month 48, 0.02%-to-0.02% vs 0.02%-to-placebo	Comparison groups	0.02%-to-0.02% vs 0.02%-to-placebo
		LS Mean Difference, D	0.008
		95% CI	-0.109, 0.125
		P value (mixed effects model)	0.891
	Tertiary endpoint, Change from stage 2 baseline in SER at Month 48, 0.01%-to-0.01% vs 0.01%-to-placebo	Comparison groups	0.01%-to-0.01% vs 0.01%-to-placebo
		LS Mean Difference, D	0.019
		95% CI	-0.144, 0.182
		P value (mixed effects model)	0.82
Notes	Dropouts (discontinuing study) among ITT subjects were 13.3%, 22.6%, 16.2%, 17.2% in placebo, 0.01%, 0.02%, and total, respectively. Reasons for dropouts were lost to follow up (7.3% of total randomized subjects), withdrawal of consent (total 5.4%), medical reasons (AE) (total 0.7%), lack of efficacy (total 0.3%), physician decision (total 0.5%), and others including blank (total 3.0%). Most of the dropouts were due to lost to follow up or withdrawal of consent. Treatment-related (AE or lack of efficacy) dropouts represents only a small fraction of the dropouts.		
Analysis description	Post hoc analysis		
Analysis population and time point description	mITT (Modified Intent-to-Treat) sub-dataset. Analysis included all randomized subjects who were aged 6 to 10 years at stage 1 baseline, with the exclusion of post-last dose data from 23 subjects who discontinued treatment, switched to confounding therapies and stayed in the study. 36 months.		
Descriptive statistics and estimate variability (Stage 1)	Treatment group	Placebo	0.01%	0.02%
	Number of subjects	144	133	212
	Responder proportion (<0.5D progression) at 36 months, n (%); Number of evaluable eyes	41 (17.2) 238	57 (29.4) 194	79 (22.6) 350
	CFB SER at 36 months, Least Square Mean (D); 95% CI	-1.307 -1.398, -1.215	-1.047 -1.145, -0.950	-1.160 -1.236, -1.084
	CFB AL at 36 months, Least Square Mean (mm); 95% CI	0.805 0.763, 0.848	0.676 0.630, 0.721	0.728 0.693, 0.763
Effect estimate per comparison	Responder proportion (<0.5D progression) at 36 months, 0.02% vs placebo	Comparison groups	0.02% vs placebo	

Title: Childhood Atropine for Myopia Progression (CHAMP): A 3-arm randomised, double-masked, placebo-controlled, Phase 3 study of atropine sulfate ophthalmic solution 0.01% and 0.02%			
Study identifier	**EudraCT: 2018-001077-24 Sponsor Protocol Number: CP-NVK002-0001**		
		OR	2.479
		95% CI	0.710, 8.661
		P value (mixed effects model)	0.155
	Responder proportion (<0.5D progression) at 36	Comparison groups	0.01% vs placebo
		OR	7.316
		95% CI	1.880, 28.470
		P value (mixed effects model)	0.004
	CFB SER at 36 months, 0.02% vs placebo	Comparison groups	0.02% vs placebo
		LS Mean Difference, D	0.147
		95% CI	0.031, 0.263
		P value (mixed effects model)	0.013
	CFB SER at 36 months, 0.01% vs placebo	Comparison groups	0.01% vs placebo
		LS Mean Difference, D	0.259
		95% CI	0.128, 0.390
		P value (mixed effects model)	<0.001
	CFB AL at 36 months, 0.02% vs placebo	Comparison groups	0.02% vs placebo
		LS Mean Difference, D	-0.077
		95% CI	-0.131, -0.024
		P value (mixed effects model)	0.005
	CFB AL at 36 months, 0.01% vs placebo	Comparison groups	0.01% vs placebo
		LS Mean Difference, D	-0.130
		95% CI	-0.191, -0.069
		P value (mixed effects model)	<0.001

Table 35. Summary of efficacy for trial mini-CHAMP - stage 1

Title: A randomized, double-blind, placebo-parallel-controlled, multi-center, Stage III clinical study on the efficacy and safety of two low-concentration atropine sulfate eye drops for slowing the progression of myopia in children.			
Study identifier	**Sponsor protocol number: ZKO-ATP-202105-Mini-CHAMP Clinical Trial Approval Notification Number: 2021LP01545&2021LP01546**		
Design	This study is a randomized, double-blind, parallel group, placebo-controlled, multi-center, superiority design comparing the efficacy and safety of 0.01% or 0.02% atropine sulfate eye drops versus placebo in slowing the progression of myopia in children		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		12 months (completed) Not Applicable 12 months (on-going)
Hypothesis	Superiority hypothesis. Primary endpoint and key secondary endpoint were between-group (atropine vs placebo) difference in the proportion of subjects with myopia progression (spherical equivalent, SER) less than 0.50 D at the Month 12 visit for 0.02% or 0.01% atropine versus placebo.		
Treatments groups in main phase (Stage 1)	0.02% atropine		0.02% atropine, 12 months, 227 subjects randomized
	0.01% atropine		0.01% atropine, 12 months, 151 subjects randomized
	Placebo		Placebo, 12 months, 148 subjects randomized
Endpoints and definitions	Primary endpoint	Responder (<0.5D progression) proportion of 0.02% at 12 months	Between-group (0.02% vs placebo) difference in the proportion of subjects' eyes with myopia progression (spherical equivalent, SER) less than 0.50 D at the Month 12 visit
	Key secondary endpoint	Responder (<0.5D progression) proportion of 0.01% at 12 months	Between-group (0.01% vs placebo) difference in the proportion of subjects' eyes with myopia progression (spherical equivalent, SER) less than 0.50 D at the Month 12 visit
	Secondary endpoints	Mean change from baseline in SER at 12 months	Between-group (atropine vs placebo) difference in mean change from baseline in SER at the Month 12 visit for 0.02% or 0.01% vs placebo
	Exploratory endpoints	Mean change from baseline in AL at 12 months	Between-group (atropine vs placebo) difference in mean change from baseline in AL at the Month 12 visit for 0.02% or 0.01% vs placebo
	Post hoc endpoints	Proportion of eyes with a 50% reduction in SER progression compared to placebo at 12 months	Proportion of eyes with a 50% reduction in SER progression compared to least square mean change of placebo at 12 months for 0.02% or 0.01% vs placebo
Database lock	October 12, 2023		
Results and Analysis			
Analysis description	Primary Analysis (Prespecified)		

Title: A randomized, double-blind, placebo-parallel-controlled, multi-center, Stage III clinical study on the efficacy and safety of two low-concentration atropine sulfate eye drops for slowing the progression of myopia in children.				
Study identifier	**Sponsor protocol number: ZKO-ATP-202105-Mini-CHAMP Clinical Trial Approval Notification Number: 2021LP01545&2021LP01546**			
Analysis population and time point description	ITT. Analysis included all randomized subjects. 12 months			
Descriptive statistics and estimate variability	Treatment group	0.02% atropine	0.01% atropine	Placebo
	Number of subjects	227	151	148
	Responder (<0.5D progression) proportion at 12 months, n (%); Number of evaluable eyes; 95% Clopper-Pearson CI, %			
	Mean change from baseline in SER at 12 months, least square mean D; 95% CI			
	Mean change from baseline in AL at 12 months, least square mean, mm; 95% CI			

Effect estimate per comparison	Primary endpoint, Between-group	Comparison groups	0.02% vs placebo
		OR	
		95% CI	
		P-value (mixed effects model)	
	Key secondary endpoint,	Comparison groups	
		OR	
		95% CI	
		P-value (mixed effects model)	
	Secondary endpoint, Mean change from baseline in SER at 12 months for 0.02% vs placebo	Comparison groups	
		Least square mean difference, D	
		95% CI	
		P-value (mixed effects model)	
		Comparison groups	

Title: A randomized, double-blind, placebo-parallel-controlled, multi-center, Stage III clinical study on the efficacy and safety of two low-concentration atropine sulfate eye drops for slowing the progression of myopia in children.			
Study identifier	**Sponsor protocol number: ZKO-ATP-202105-Mini-CHAMP Clinical Trial Approval Notification Number: 2021LP01545&2021LP01546**		
	Secondary endpoint, Mean change from baseline in SER at 12 months for 0.01% vs placebo	Least square mean difference, D	
		95% CI	
		P-value (mixed effects model)	
	Exploratory endpoint, Mean change from baseline in AL at 12 months for 0.02% vs placebo	Comparison groups	
		Least square mean difference, mm	
		95% CI	
		P-value (mixed effects model)	
	Exploratory endpoint, Mean change from baseline in AL at 12 months for 0.01% vs placebo	Comparison groups	
		Least square mean difference, mm	
		95% CI	
		P-value (mixed effects model)	
Notes	Drop-out (discontinuing study) rate was similarly low in all 3 groups (7.5%, 7.9%, 7.4% and 7.6% in 0.02%, 0.01%, placebo and total, respectively). Reasons for dropout were self-withdrawal by subject (5.5 % of total randomized subjects), due to AE (1.1%), withdrawal at the discretion of the investigator (0.4%), lost to follow up (0.2%), and others (0.4%).		
Analysis description	Post hoc analysis		
Analysis population and time point description	ITT. Analysis included all randomized subjects. 12 months		

Descriptive statistics and estimate variability	Treatment group	0.02% atropine	0.01% atropine	Placebo
	Number of subjects	227	151	148
	Proportion of eyes with at least 50% reduction in SER progression compared to placebo at 12 months, n (%); Number of evaluable eyes; 95% Clopper-Pearson CI, %			

Effect estimate per comparison	Post hoc endpoint, Proportion of eyes with at least 50% reduction in SER progression compared to placebo at 12 months for 0.02% vs placebo	Comparison groups	0.02% vs placebo
		OR	
		95% CI	

Title: A randomized, double-blind, placebo-parallel-controlled, multi-center, Stage III clinical study on the efficacy and safety of two low-concentration atropine sulfate eye drops for slowing the progression of myopia in children.			
Study identifier	**Sponsor protocol number: ZKO-ATP-202105-Mini-CHAMP Clinical Trial Approval Notification Number: 2021LP01545&2021LP01546**		
		P-value (mixed effects model)	
	Post hoc endpoint, Proportion of eyes with at least 50% reduction in SER progression compared to placebo at 12 months for 0.01% vs placebo	Comparison groups	
		OR	
		95% CI	
		P-value (mixed effects model)	

Table 36. Summary of efficacy for trial MOSAIC

Title: Myopia outcome study of atropine in children			
Study identifier	**Sponsor study name: MOSAIC ISRCTN registry: ISRCTN36732601**		
Design	Randomized placebo-controlled, double-masked, single-center clinical trial, with an extension phase different treatment assignments.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		12 months. Not applicable. 12 months.
Hypothesis	Superiority hypothesis. The primary analysis was a comparison of mean change in SER from baseline to 24 months between groups.		
Treatments groups in main phase (stage 1)	0.01% Atropine		0.01% atropine. 2 years. number of subjects randomized was 167.
	Placebo		Placebo. 2 years. number of subjects randomized was 83.
Treatments groups in extension phase (stage 2)	placebo-to-0.05%		1 year. Number of subjects randomized was 66.
	0.01%-to-0.01% tapered		1 year. Number of subjects randomized was 73.
	0.01%-to-placebo tapered		1 year. Number of subjects randomized was 29.
	0.01%-to-placebo nightly		1 year. Number of subjects randomized was 31.
Endpoints and definitions	Primary endpoint	Between group difference in SER change from baseline to 24 months	Comparison of mean change in SER from baseline to 24 months between treatment groups.

Title: Myopia outcome study of atropine in children				
Study identifier	**Sponsor study name: MOSAIC** **ISRCTN registry: ISRCTN36732601**			
	Secondary endpoint	Between group difference in AL change from baseline to 24 months	Comparison of mean change in AL from baseline to 24 months between treatment groups.	
Database lock	Not reported			
Results and Analysis				
Analysis description	Primary Endpoint (Prespecified)			
Analysis population and time point description	ITT. Analysis included all randomized subjects. 24 months			
Descriptive statistics and estimate variability (Stage 1)	Treatment group		0.01% atropine	Placebo
	Number of subjects		167	83
	SER change from baseline to 24 months. Mean: SD:		-0.53 D 0.56	-0.63 D 0.65
	AL change from baseline to 24 months. Mean: SD:		0.33 mm 0.27	0.40 mm 0.31
Descriptive statistics and estimate variability (Stage 2)	Treatment group		0.01%-to-0.01% tapered dosing	0.01%-to-Placebo (tapered and nightly)
	Number of subjects		73	60
	SER change from month 24 to month 36. Mean: SD:		-0.18 D 0.26	-0.23 0.34
	AL change from month 24 to month 36. Mean: SD:		0.10 0.11	0.14 0.17
Effect estimate per comparison	Primary endpoint	Comparison groups	0.01% vs Placebo	
		Adjusted treatment group difference of mean change in SER from baseline at 24 months	0.12 D	
		SE	0.07	
		P-value, linear mixed model adjusted for baseline SER value	0.07	
	Secondary	Comparison groups	0.01% vs Placebo	
		Adjusted treatment group difference of mean change in AL from baseline at 24 months	-0.07 mm	
		SE	0.03	
		P-value, linear mixed model adjusted for baseline SER value	0.009	

Title: Myopia outcome study of atropine in children					
Study identifier	**Sponsor study name: MOSAIC** **ISRCTN registry: ISRCTN36732601**				
	Stage 2 SER endpoint	Comparison groups	0.01%-to-Placebo (tapered and nightly) vs 0.01%-to-0.01% tapered dosing		
		Adjusted treatment group difference of mean change in SER from Month 24 to Month 36	-0.04 D		
		95% CI	-0.12, 0.04		
		P-value, linear mixed model	0.63		
	Stage 2 AL endpoint	Comparison groups	0.01%-to-Placebo (tapered and nightly) vs 0.01%-to-0.01% tapered dosing		
		Adjusted treatment group difference of mean change in AL from Month 24 to Month 36	0.01		
		95% CI	-0.02, 0.05		
		P-value, linear mixed model	0.76		
Notes	Dropouts during Stage 1 were 31 subjects (18.6%) in the 0.01% group and 15 subjects (18.1%) in the placebo group. Reasons for dropout were unable to make visit (2.0% of total randomized subjects), discomfort with eye drops (4.0%), tired of using eye drop (2.8%), advised to stop by external party (0.8%), lost contact (5.2%), perceived lack of efficacy (2.4%), seeking alternative myopia treatment (0.8%), and personal reason (0.4%). The primary analysis in Stage 1 was conducted without using the baseline age as covariate. The post hoc analysis below included baseline age strata (< 9 years, or >= 9 years) as a fixed effect in the mixed model.				
Analysis description	Post hoc analysis				
Analysis population and time point description	Statistical analyses followed the intent-to-treat principle and included all randomized participants. Baseline age strata (< 9 years, or >= 9 years) were included as a fixed effect in the mixed model. 24 months				
Descriptive statistics and estimate variability	Treatment group			0.01% atropine	Placebo
	Number of subjects			167	83
	SER change from baseline to 24 months. Mean: SD:			-0.53 D 0.56	-0.63 D 0.65
	AL change from baseline to 24 months. Mean: SD:			0.33 mm 0.27	0.40 mm 0.31
Effect estimate per comparison	Post hoc primary endpoint, SER	Comparison groups		0.01% vs Placebo	
		Adjusted treatment group difference of mean change in SER from baseline at 24 months		0.13 D	

Title: Myopia outcome study of atropine in children			
Study identifier	**Sponsor study name: MOSAIC ISRCTN registry: ISRCTN36732601**		
		P-value, linear mixed model with age strata as covariate	0.035
	Post hoc secondary	Comparison groups	0.01% vs Placebo
		Adjusted treatment group difference of mean change in AL from baseline at 24 months	-0.09 mm
		P-value, linear mixed model with age strata as covariate	<0.001
Notes	Almost 2/3 of MOSAIC subjects were recruited prior to the 2020 COVID lockdown (March 2020, termed high COVID impact group). The high COVID impact group was older (mean age 12.04 years, SD=2.32) compared to the low COVID impact group (recruited after the first COVID lockdown of Sept 2020, mean age 11.37 years, SD=2.42. p=0.04 vs high impact). Post hoc analysis of SER change indicated significant treatment effect in the low COVID impact group (mean difference of SER change from baseline at 24 months = 0.28D, p=0.006), but not in the high COVID impact group (mean difference of SER change from baseline at 24 months = 0.01D, p=0.80). Post hoc analysis of AL change indicated significant treatment effect in the low COVID impact group (mean difference of AL change from baseline at 24 months = -0.13 mm, p=0.004), but not in the high COVID impact group (mean difference of AL change from baseline at 24 months = -0.04 mm, p=0.24).		

Table 37. Summary of efficacy for trial MTS1

Title: Low-Dose Atropine for Treatment of Myopia (MTS1)			
Study identifier	**Sponsor Protocol Number: MTS1 ClinicalTrials.gov ID: NCT03334253**		
Design	Randomized placebo-controlled, double-masked, multi-center clinical trial, and an observation stage of off-treatment.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		12 months. 2- to 4-week of nightly artificial tears. 6 months of observation off-treatment
Hypothesis	Superiority hypothesis. The primary analysis was a comparison of mean change in SER from baseline to 24 months (while receiving treatment) between treatment groups.		
Treatments groups in main phase	0.01% Atropine		0.01% atropine. 2 years. number of subjects randomized was 125.
	Placebo		Placebo. 2 years. number of subjects randomized was 62.
Treatments groups in extension phase	No treatment		no treatment for all subjects.
Endpoints and definitions	Primary outcome (main phase)	Between group difference in SER change from baseline to 24 months	Comparison of mean change in SER from baseline to 24 months (while receiving treatment) between treatment groups.

Title: Low-Dose Atropine for Treatment of Myopia (MTS1)			
Study identifier	**Sponsor Protocol Number: MTS1** **ClinicalTrials.gov ID: NCT03334253**		
	Key secondary outcome (main + extension phase)	Between group difference in SER change from baseline to 30 months	Comparison of mean change in SER from baseline to 30 months (24 months on treatment plus 6 months off treatment) between treatment groups.
	Secondary outcome at 12 (main phase)	Between group difference in SER change from baseline to 12 months	Comparison of mean change in SER from baseline to 12 months (while receiving treatment) between treatment groups.
	Secondary outcome at 24 (main phase)	Proportion of subjects with <0.5D progression at 24 months	Proportion of subjects with mean right and left eye SER progression < 0.5D at 24 months
Database lock	Not reported		
Results and Analysis			
Analysis description	Primary outcome (prespecified)		
Analysis population and time point description	Statistical analyses followed the intent-to-treat principle and included all randomized participants. 24 months		
Descriptive statistics and estimate variability	Treatment group	0.01% atropine	Placebo
	Number of subjects	125	62
	SER change from baseline to 24 months. Mean:	-0.78 D	-0.74 D
	SD:	0.64	0.60
Effect estimate per	Primary	Comparison groups	0.01% vs Placebo
		Adjusted treatment group difference of mean change in SER from baseline at 24 months	-0.02 D
		95% CI	-0.19, 0.15
		P-value, longitudinal discrete time mixed model	0.82
Notes	In the main phase: Drop out in 0.01% group: 1 (lack of interest). Drop out in Placebo group: 1 (relocation), 1 (lost to follow up) Missing SER visits in 0.01% group: 20% of the visits were missed. Missing SER visits in Placebo group: 22% of the visits were missed. Limitation of the study include lack of objective measure of eye drop use, even though the protocol planned to collect unused study medication ampules at all visits and were to be counted as an objective measure of treatment compliance. Patients without ampule count were assumed to be 100% compliant. Patients who missed visits were asked to recall their compliance.		
Analysis description	Secondary Outcomes (prespecified)		
Analysis population and time point description	Statistical analyses followed the intent-to-treat principle and included all randomized participants. 12, 24, 30 months		

Title: Low-Dose Atropine for Treatment of Myopia (MTS1)			
Study identifier	**Sponsor Protocol Number: MTS1 ClinicalTrials.gov ID: NCT03334253**		
Descriptive statistics and estimate variability	Treatment group	0.01% atropine	Placebo
	Number of subjects	125	62
	SER change from baseline to 30 months. Mean: SD:	 -0.94 0.77	 -0.88 0.71
	SER change from baseline to 12 months. Mean: SD:	 -0.39 0.36	 -0.45 0.35
	Proportion of subjects with <0.5D progression at 24 months, n (%)	48 (41%)	22 (38%)
Effect estimate per comparison	SER change from baseline to 30 months	Comparison groups	0.01% vs Placebo
		Adjusted treatment group difference of mean change in SER from baseline at 30 months	-0.04 D
		95% CI	-0.25, 0.17
		P-value, longitudinal discrete time mixed model	Not reported
	SER change from baseline	Comparison groups	0.01% vs Placebo
		Adjusted treatment group difference of mean change in SER from baseline at 12 months	Not reported
	Proportion of subjects	Comparison groups	0.01% vs Placebo
		Absolute risk difference	Not reported
Notes	Drop out in 0.01% group during the 6-month observation period: 2 (relocation), 4 (lost to follow up). Drop out in Placebo group during the 6-month observation period: 1 (relocation), 2 (lost to follow up)		

2.6.5.3. Clinical studies in special populations

Not applicable.

For subgroup analysis please refer to the section 'main studies'.

2.6.5.4. In vitro biomarker test for patient selection for efficacy

Not applicable.

2.6.5.5. Analysis performed across trials (pooled analyses and meta-analysis)

The applicant performed pooled analyses across studies with Atropine Sulfate FGK 0.01% (CHAMP, mini-CHAMP, MOSAIC, MTS1) and other published studies that tested atropine 0.01% eye drops from other sources.

The pooled analyses for placebo-subtracted changes-from-baseline in SER and axial length are presented here.

A pooled analysis based on responders was also provided but not additionally presented as results there were less eligible studies for that analysis yet results were in line with the SER and axial length pooled analyses.

Study populations

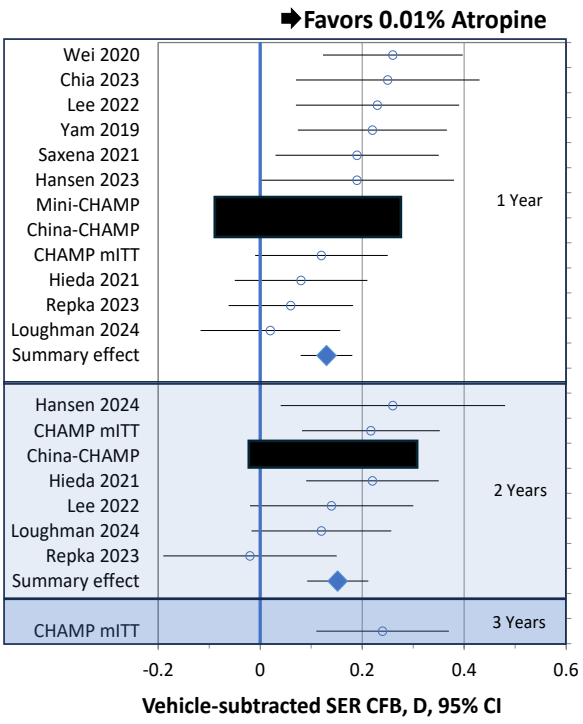
The primary differences in study populations are those related to requiring prior documented myopia progression, the distribution of baseline myopia, baseline age and racial composition. SER data at baseline demonstrate that subjects in CHAMP had, on average, a lesser degree of myopia as compared with that of the study populations of each of other published studies. Mean AL at baseline was comparable among the studies.

Efficacy results based on change from baseline SER, and axial length

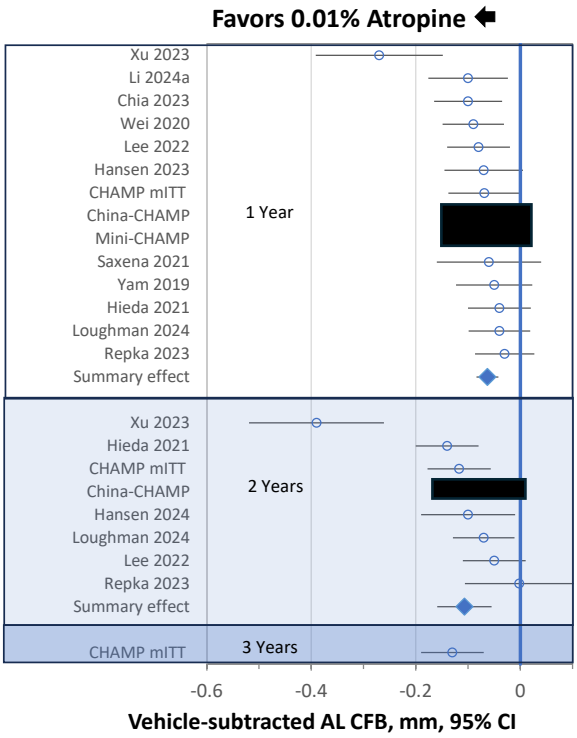
For the majority of studies, observed benefit in terms of change in refraction, is generally mirrored in change in axial elongation (see Figure 12).

Apart from Mini-CHAMP, baseline SER for CHAMP (~ -2.4 D across treatment groups) was smaller than that each of the published studies, suggestive of a less myopic population at study entry. The applicant indicated that this may be as CHAMP eligibility criteria included subjects with from -0.5 D SER, while the majority of other studies restricted entry to at least SER -1.00 D.

Placebo-subtracted SER change from baseline



Placebo-subtracted axial length change from baseline



Chia 2023=APPLE study; Lee=WA-ATOM; Hansen=APP study; CHAMP=mITT data; Sexena=I-ATOM; Yam=LAMP study, Hieda=ATOM-J study; Loughman=MOSAIC study; Repka=MTS1 study

Figure 12. SER and AL change from baseline for CHAMP, mini-CHAMP and published RCT's of Atropine Sulfate 0.01%

Retrieved drop-out analysis results (requested by CHMP at D120)

Table 38. Responder analyses comparing pre-specified analysis at eye level, supportive analysis at subject level and revised analysis with retrieved dropout imputation at subject level (CHAMP). All analyses listed here are month 36 endpoints

Analysis dataset	Experimental unit in analysis	Missing data imputation and analysis model	Statistics	Vehicle	Atropine Sulfate FGK 0.01%	0.01% vs vehicle	Atropine Sulfate 0.02%	0.02% vs vehicle
Proportion of responder (<0.5 D progression)								
mITT	Eye (Pre-specified)	no imputation, no modelling	Absolute risk	17.5%	28.5%	--	22.1%	--
			Absolute risk difference, (95% WALD CI), p value	--	--	11% (3.3%, 18.9%) 0.006	--	4.7% (-1.7%, 11%) 0.148
		no imputation, mixed effect model,	Odds ratio, (95% CI), p value	--	--	4.54 (1.147, 17.965) 0.031	--	1.774 (0.503, 6.26) 0.373
		Calculated from odds ratio and vehicle risk	Relative risk (95% CI)	--	--	2.8 (1.12, 4.53)	--	1.56 (0.55, 3.26)
	Subject (supportive analysis, both eyes < 0.5 D progression)	no imputation, no modelling	Absolute risk	10.3%	20.8%	--	15.8%	--
			Absolute risk difference, (95% WALD CI), p value	--	--	10.5% (0.9%, 20%), 0.031	--	5.5% (-2%, 13%), 0.148
		no imputation, mixed effect model,	Odds ratio, (95% CI), p value	--	--	6.445 (1.04, 39.933), 0.045	--	2.335 (0.447, 12.187), 0.314
		Calculated from odds ratio and vehicle risk	Relative risk (95% CI)	--	--	4.13 (1.04, 7.97)	--	2.05 (0.47, 5.66)
	Subject (Revised analysis, both eyes < 0.5 D progression)	retrieved dropout imputation, no modelling,	Absolute risk	11.1%	18.6%	--	14.8%	--
			Absolute risk difference, (95% WALD CI), p value	--	--	7.6% (-1.4%, 16.5%), 0.096	--	3.7% (-3.8%, 11.2%), 0.336
		retrieved dropout imputation, mixed effect model,	Odds ratio, (95% CI), p value	--	--	3.925 (0.739, 20.839), 0.108	--	1.433 (0.298, 6.884), 0.653
		Calculated from odds ratio and vehicle risk	Relative risk (95% CI)	--	--	2.96 (0.76, 6.51)	--	1.37 (0.32, 4.16)

Analysis dataset	Experimental unit in analysis	Missing data imputation and analysis model	Statistics	Vehicle	Atropine Sulfate FGK 0.01%	0.01% vs vehicle	Atropine Sulfate 0.02%	0.02% vs vehicle
Proportion of responder (<0.5 D progression)								
ITT	Eye (Pre-specified)	no imputation, no modelling	Absolute risk	21.3%	31.6%		25.6%	
			Absolute risk difference, (95% WALD CI), p value			10.3% (2.8%, 17.7%) 0.007		4.4% (-2.1%, 10.6%) 0.186
		no imputation, mixed effect model,	Odds ratio, (95% CI), p value			3.902 (1.098, 13.866) 0.035		1.564 (0.48, 5.101) 0.458
		Calculated from odds ratio and vehicle risk	Relative risk (95% CI)			2.41 (1.08, 3.71)		1.40 (0.54, 2.72)
	Subject (supportive analysis, both eyes < 0.5 D progression)	no imputation, no modelling	Absolute risk	14.7%	23.2%		18.8%	
			Absolute risk difference, (95% WALD CI), p value			8.5% (-0.9%, 17.9%) 0.76		4.2% (-3.7%, 12%) 0.301
		no imputation, mixed effect model,	Odds ratio, (95% CI), p value			3.639 (0.801, 16.524) 0.094		1.458 (0.362, 5.867) 0.595
		Calculated from odds ratio and vehicle risk	Relative risk (95% CI)			2.62 (0.83, 5.03)		1.37 (0.40, 3.42)
	Subject (Revised analysis, both eyes < 0.5 D progression)	retrieved dropout imputation, no modelling,	Absolute risk	15.4%	21.5%		17.6%	
			Absolute risk difference, (95% WALD CI), p value			6.1% (-2.8%, 15%) 0.176		2.2% (-5.5%, 9.9%) 0.576
		retrieved dropout imputation, mixed effect model,	Odds ratio, (95% CI), p value			2.892 (0.681, 12.273) 0.15		1.191 (0.303, 4.687) 0.802)
		Calculated from odds ratio and vehicle risk	Relative risk (95% CI)			2.24 (0.72, 4.49)		1.16 (0.34, 2.99)

Table 39. Analyses of SER change from baseline (D) comparing pre-specified analysis at eye level, supportive analysis at subject level and revised analysis with retrieved dropout imputation at subject level (CHAMP). All analyses listed here are month 36 endpoints

Analysis dataset	Experimental unit in analysis	Missing data imputation and analysis model	Statistics	Vehicle	Atropine Sulfate FGK 0.01%	0.01% vs vehicle	Atropine Sulfate 0.02%	0.02% vs vehicle
SER change from baseline (average eyes), mm								
mITT	Eye (Pre-specified)	no imputation, mixed effect model	LS mean, (95% CI)	-1.279 (-1.373, -1.185)	-1.039 (-1.139, -0.939)	--	-1.18 (-1.257, -1.102)	--
			LS mean difference, (95% CI), p value	--	--	0.24 (0.106, 0.374) < 0.001	--	0.099 (-0.020, 0.218) 0.101
	Subject (supportive analysis, average eyes)	no imputation, mixed effect model	LS mean, (95% CI)	-1.279 (-1.378, -1.180)	-1.038 (-1.145, -0.931)	--	-1.18 (-1.262, -1.098)	--
			LS mean difference, (95% CI), p value	--	--	0.241 (0.098, 0.384) 0.001	--	0.099 (-0.026, 0.225) 0.121
	Subject (Revised analysis, average eyes)	retrieved dropout imputation, mixed effect model	LS mean, (95% CI)	-1.256 (-1.370, -1.143)	-1.11 (-1.257, -0.963)	--	-1.208 (-1.302, -1.115)	--
			LS mean difference, (95% CI), p value	--	--	0.146 (-0.043, 0.336) 0.13	--	0.048 (-0.101, 0.197) 0.526
ITT	Eye (Pre-specified)	no imputation, mixed effect model	LS mean, (95% CI)	-1.256 (-1.345, -1.167)	-1.003 (-1.094, -0.912)	--	-1.124 (-1.197, -1.051)	--
			LS mean difference, (95% CI), p value	--	--	0.253 (0.129, 0.377) <0.001	--	0.132 (0.02, 0.244) 0.021
	Subject (supportive analysis, average eyes)	no imputation, mixed effect model	LS mean, (95% CI)	-1.257 (-1.35, -1.163)	-1.003 (-1.1, -0.906)	--	-1.124 (-1.202, -1.046)	--
			LS mean difference, (95% CI), p value	--	--	0.254 (0.122, 0.386) <0.001	--	0.133 (0.014, 0.251) 0.029
	Subject (Revised analysis, average eyes)	retrieved dropout imputation, mixed effect model	LS mean, (95% CI)	-1.235 (-1.341, -1.129)	-1.045 (-1.181, -0.909)	--	-1.154 (-1.245, -1.063)	--
			LS mean difference, (95% CI), p value	--	--	0.19 (0.016, 0.364) 0.032	--	0.081 (-0.059, 0.221) 0.255

Table 40. Analyses of AL change from baseline (mm) comparing pre-specified analysis at eye level, supportive analysis at subject level and revised analysis with retrieved dropout imputation at subject level (CHAMP). All analyses listed here are month 36 endpoints

Analysis dataset	Experimental unit in analysis	Missing data imputation and analysis model	Statistics	Vehicle	Atropine Sulfate FGK 0.01%	0.01% vs vehicle	Atropine Sulfate 0.02%	0.02% vs vehicle
AL change from baseline (average eyes), mm								
mITT	Eye (Pre-specified)	no imputation, mixed effect model	LS mean, (95% CI)	0.805 (0.763, 0.848)	0.676 (0.63, 0.721)	--	0.728 (0.693, 0.763)	--
			LS mean difference, (95% CI), p value	--	--	-0.13 (-0.191, -0.069) <0.001	--	-0.077 (-0.131, -0.024) 0.005
	Subject (supportive analysis, average eyes)	no imputation, mixed effect model	LS mean, (95% CI)	0.805 (0.760, 0.850)	0.675 (0.627, 0.723)	--	0.728 (0.691, 0.765)	--
			LS mean difference, (95% CI), p value	--	--	-0.13 (-0.195, -0.066) <0.001	--	-0.077 (-0.134, -0.02) 0.008
	Subject (Revised analysis, average eyes)	retrieved dropout imputation, mixed effect model	LS mean, (95% CI)	0.800 (0.751, 0.849)	0.702 (0.641, 0.763)	--	0.739 (0.698, 0.78)	--
			LS mean difference, (95% CI), p value	--	--	-0.098 (-0.175, -0.02) 0.014	--	-0.061 (-0.125, 0.002) 0.058
ITT	Eye (Pre-specified)	no imputation, mixed effect model	LS mean, (95% CI)	0.780 (0.735, 0.825)	0.652 (0.607, 0.698)	--	0.697 (0.66, 0.734)	--
			LS mean difference, (95% CI), p value	--	--	-0.128 (-0.190, -0.065) <0.001	--	-0.083 (-0.140, -0.027) 0.004
	Subject (supportive analysis, average eyes)	no imputation, mixed effect model	LS mean, (95% CI)	0.780 (0.733, 0.827)	0.652 (0.603, 0.700)	--	0.697 (0.658, 0.736)	--
			LS mean difference, (95% CI), p value	--	--	-0.128 (-0.194, -0.062) <0.001	--	-0.083 (-0.143, -0.024) 0.006
	Subject (Revised analysis, average eyes)	retrieved dropout imputation, mixed effect model	LS mean, (95% CI)	0.779 (0.726, 0.833)	0.675 (0.615, 0.736)	--	0.705 (0.662, 0.749)	--
			LS mean difference, (95% CI), p value	--	--	-0.104 (-0.186, -0.022) 0.013	--	-0.074 (-0.141, -0.006) 0.032

2.6.5.6. Supportive studies

Efficacy studies considered supportive by the applicant were mini-CHAMP, MOSAIC and MTS1. As they tested the same atropine product for which MA is requested in a similar population and had a considerable study duration, they are discussed in the section 'main studies'.

The data from published studies with atropine 0.01% eye drops from other sources are collectively discussed in the pooled analysis performed by the applicant.

2.6.6. Discussion on clinical efficacy

Design and conduct of clinical studies

Four randomized, placebo-controlled trials were submitted that tested efficacy of Atropine Sulfate FGK 0.01% eye drops in myopia: CHAMP, mini-CHAMP, MOSAIC and MTS1. The applicant coined the CHAMP study as the pivotal study and the others as supportive. In Round 2, the applicant acknowledged that CHAMP, MOSAIC and MTS1 are all relevant for efficacy and safety assessment, although they represent different levels of Applicant involvement, rigour and control. It was also reiterated that MTS1 had significant deficiencies in its conduct (discussed below).

Additional data submitted concerned a dose-finding study (TOAST) and several published clinical studies that tested atropine sulfate eye drops of other sources.

Considerations on dose selection for CHAMP

The applicant requested approval for Atropine Sulfate 0.01% eyedrops only, however, clinical development also evaluated Atropine Sulfate 0.02%. These two doses were selected based on literature data; no proper dose-finding study was performed. It is agreed that the TOAST study was not used as primary source for dose selection as TOAST evaluated dose-dependency based on mydriasis, which is unlikely the primary mechanism of atropine in the treatment of myopia. Based on the literature review the applicant concluded that doses as low as 0.01% could be effective without any significant side effects. Two doses were tested in CHAMP (0.01% and 0.02%) to provide the applicant the ability to demonstrate a dose effect whilst selecting a dose with optimal risk/benefit. Given that the mechanism of action of atropine in myopia progression is not fully understood, and that a dose-effect relationship for this specific atropine product in myopia was not established prior to CHAMP, the choice to include two strengths in CHAMP is considered rational.

Considerations on design and conduct of CHAMP study

The CHAMP study had two stages. Stage 1 was the primary treatment phase: a 36-month randomized (2:2:3), double-masked, placebo-controlled, parallel-group study that tested Vehicle, atropine 0.01% and atropine 0.02%. The aim of stage 2 was to evaluate maintenance of effect and possible occurrence of rebound after stopping atropine. Subjects were re-randomised and followed-up for 12-month while the blind was maintained. Subjects that received Vehicle in Stage 1 were re-randomised to either atropine 0.01%, or atropine 0.02%. Subjects in the active treatment arms were re-randomised to either Vehicle, or to atropine 0.01%, or to atropine 0.02%. The overall study design is accepted. The randomized double-blind placebo-control study design allows the generation of unbiased results. The randomisation and blinding procedures are adequate. The total duration was 36 + 12 months which is substantial. As indicated during CHMP scientific advice, for stage 2 a randomized withdrawal design would have been preferred, but stage 2 as proposed does allow an evaluation of the maintenance of efficacy and occurrence of possible rebound. Nevertheless the duration is short relatively to the

duration of treatment needed. As a consequence it is difficult to draw firm conclusions if the effect will be maintained for the whole myopia 'risk period'.

The stratification factors (age, SER) are supported, although the age cut-off (< 9 and ≥ 9 years, based on expected median age) appears somewhat arbitrary and is not aligned with the primary interested group from the applicant (6-10 years).

Enrolled participants were 3 to 16 years of age with −0.50 diopter (D) to −6.00 D spherical equivalent refractive error (SER) and no worse than −1.50 D astigmatism. Subjects aged 16 are 20 years at time of study completion of Stage 2 which in principle is in line with the indication. No data were obtained for subjects initiating treatment at the upper age of the initially requested range (17-18 years).

No enrolment criterium or collection of data on history of myopia progression was part of CHAMP. Recently, the CLEERE study showed that prior progression may be of limited value in predicting future myopia in children 7-14 years old. (Mutti et al., 2022). The absence of an enrolment criteria for history of myopia progression is therefore acceptable, although this information could have been collected. Indeed, it also renders the request made during Scientific Advice to provide data on patients with at least -1.00 D and progressive myopia, unfeasible to perform.

Further, considering that myopia is caused by a complex interplay between genetic and environmental factors, data on past/current outdoor time, near work activities, and parental myopia status should have been collected in the CHAMP study, as they may impact study outcomes. As such data were not collected it is unlikely that the applicant can assess this impact for this MAA, therefore this will not be pursued.

Subjects were allowed to continue use of single-vision corrective lenses (spectacles or soft toric contact lenses). The prohibited treatment strategy, as defined in the study protocol, is acceptable; no rescue treatment was foreseen.

The main efficacy endpoints were the proportion responder defined as a subject with myopia progression less than 0.50 D at 36 months (**primary**), change in spherical equivalent refraction (SER) and axial length.

A progression of less <0.5 D is justified by the argument that it as is a surrogate for being 'essentially progression-free'. This is reasonable considering that the degree of myopia exceeds multiples of 0.5 D.

For the SER and axial length measurements between subjects various devices were allowed to be used.

In Round 2, the applicant clarified that for SER measurements four different devices were used in CHAMP. Most subjects (58.1%) used the same (Grand Seiko) device throughout the study and only 7 of 573 subjects were tested with different autorefractors. The applicant clarified that each SER at each visit was derived from the average of 5 measurements. The within-subject-SD from the 5 readings at baseline was calculated, and the average within-subject-SD from all subjects using the same brand of autorefractor was used to calculate the repeatability limit, which was lower for all devices than reported in Venkataraman et al., 2022 (although this study included subjects with considerably higher mean age).

For axial length measurement, the applicant clarified that all but two sites used either Carl Zeiss Meditec IOLMaster or Haag Streit LENSTAR over the entire duration of the study. One site used Nidek Optical Biometer for two subjects due to malfunction of a Carl Zeiss Meditec IOLMaster and another site used Alladin Biometer for all visits. Moreover, a third site started with Carl Zeiss Meditec IOLMaster but, due to the malfunction, switched to Haag Streit LENSTAR. Since the precision of AL measurements

is overall higher than that of SER measurements, it is not expected that use of the different devices have notably influenced outcomes.

Change-from-baseline SER was included as secondary endpoint. However, during CHMP scientific advice, preference was expressed for a continuous variable, i.e., change-from-baseline SER, over a dichotomous responder variable, i.e., responder analysis. Change-from-baseline SER was considered more sensitive to show an effect as there is no loss of information. Nonetheless, in this MAA for this indication proportion of responders may be easier interpretable for the prescriber and user than change-from-baseline results. As a consequence, both endpoints – responder rate and change in SER – are considered of equal importance for the efficacy assessment by the Rapporteurs.

Axial length is a primary component for determining the eye's refractive state and provides a more mechanistic insight in potential effects of atropine compared to SER. It is therefore considered a relevant and important endpoint in support the primary assessment (SER). Nonetheless, cycloplegic SER has been shown to be highly correlated with axial length (Zhao et al., 202).

Given the assumptions on the treatment effect, the sample size calculations can be followed. The experimental unit of the analysis was the subject's eyes, which increased the statistical power. By hindsight, the anticipated response rates (25% vs 7%) did not meet the expectations especially the vehicle repose rate was 2.5 larger than anticipated.

The primary analysis population is the mITT, which in practice is a subpopulation of ITT based on age (6-10 years). However, approval for ages 3-18 years of age was initially requested. The ITT is therefore considered of primary importance for evaluation of benefit-risk in the intended population.

The definitions of the analysis sets are considered standard and acceptable. However, the primary analysis (in mITT) does not correspond with the age stratification (<9 and ≥ 9 years). This means that the balance afforded by randomisation may not have been fully preserved in the mITT. Nevertheless, as no clear imbalances are observed in the baseline characteristics, this is not of concern.

Post-hoc, an estimand was defined for the primary and secondary objectives. It is acknowledged that the attributes of the estimands were predefined as elements in the SAP. The proposed estimand definition now is a combination of several estimands, covering different populations (mITT and ITT) and endpoints (responder and continuous). It also lacks important details, e.g. the primary comparison (0.02% versus placebo), the unit of analysis of the endpoint (subjects' eyes). Furthermore, "missing data" should not be listed as intercurrent event, rather reasons for missing data, such as study discontinuation and missed visits due to COVID-measures, should have been included as intercurrent event. Nevertheless, refining the estimand definition will largely be a post-hoc discussion and therefore not be further pursued.

The treatment policy strategy proposed for handling the intercurrent events would have been acceptable. However, this does not correspond completely with the statistical analysis methods used, as these rely on missing at random which corresponds more to a hypothetical strategy.

The primary analysis uses a mixed effects model on the mITT population, focussing on eyes instead of subjects and relying on a missing at random assumption for missing values. During the PIP compliance check of the PDCO, the applicant committed to also provide the primary analysis based on the initial SAP at MAA, but this was not performed (EMA/PDCO/40253/2024 p.36 of 39). A retrieved drop-out analysis on subject level was therefore requested by CHMP and provided by the applicant in Round 2 (discussed below). The applicant also provided a breakdown on reasons for discontinuation to discuss the missing-at-randomness assumption.

To assess the sensitivity of missing data handling, full tipping-point analyses were provided in round 2 for mITT for two endpoints: responder analysis at eye level, and change-in-SER. The responder analysis was performed by imputing 12% or 25% of random subjects that did not have Month 36 data as non-responder. In contrast to the applicant's conclusion, results appeared to suggest that the tipping point was closer to 12% than 25%. 12% translates to 8 eyes and not considered a large penalty. The change-in-SER analysis used multiple imputation, for which the exact method was not clear. The tipping point was at the incremental penalty of -0.16 D. The applicant recalculated this to an overall penalty of -0.66 D. It is not entirely clear how the applicant came to this number, but it appears to be because the penalties added up at subsequent missing visits. It is agreed that a penalty of -0.66 would be large.

Analysis of change from baseline secondary endpoints were performed using a similar model but using continues values, which is acceptable.

As raised during CHMP scientific advice, the statistical hierarchy of testing the 0.01% dose only after the 0.02% dose could prove problematic if the 0.02% dose does not show significant effect. This worst-case scenario unfortunately turned out to be the case in the CHAMP study.

Odds ratios (ODs) were used for reporting, which is not recommended. In Round 2, absolute risk differences were provided.

The quality assurance measures were conventional. There was no evidence that the four substantial protocol amendments, COVID-19 pandemic or protocol deviations that occurred in/during CHAMP conduct resulted in an unbalanced effect in one of the three treatment groups (atropine 0.01%, atropine 0.02% or Vehicle).

Efficacy data and additional analyses

CHAMP

In the Stage 1 there were 247 subjects randomised to receive 0.02% atropine, 164 subjects to 0.01% atropine and 165 subjects to placebo.

The overall drop-out rate (17.2% on a total of n=576) was acceptable considering the target population and study duration. A higher discontinuation rate was observed for atropine 0.01% (Vehicle: 13.3%; atropine 0.01%: 22.6%, atropine 0.02%: 16.2%) but there was no clear connection to lack of efficacy or discontinuations due to AEs. Twelve subjects were mis-stratified relating to baseline SER in Stage 1, which were not corrected in the analysis in accordance with the SAP.

A considerable proportion of ITT subjects,16.5% in total, had a major protocol deviation, but these were balanced across the treatment groups (Vehicle: 18.2%, atropine 0.01%: 17.7%; atropine 0.02%: 14.6%).

Considering a study duration of 48 months, overall treatment compliance in CHAMP was reasonably high (mean compliance >80% in both Stage 1 and 2) and similar across treatment groups. Compliance was primarily based on number of (un)used ampules. The applicant investigated but could not find that compliance may have influenced results, with focus on the atropine 0.02% group. The adequate compliance and necessary collaboration of younger children is questioned for Stage 1 (in the Stage 2 there are also records and children were older).

In Round 2, semi-annual compliance was provided by three age groups (3-5, 6-10, 11-16 years) and by treatment group (Atropine Sulfate FGK 0.01%, vehicle). Generally, compliance by semester was ~80%–100%, although variability was larger in the 3-5y group than in the other groups, potentially

due to the small sample (Vehicle: n=5; atropine 0.01%: n=9). There was high variability with low compliance in the Vehicle group between M15 - M30. This may have influenced the three key efficacy endpoints (responder; change-in-SER and change-in-AL), as the effect size was largest in the 3-5y group. Nonetheless, as the applicant restricted the age limits to 6-10 y.o., this concern is resolved.

The proportion of eyes with less than 0.5 D myopia progression at Month 36 was 17.5% (Vehicle), 28.5% (atropine 0.01%) and 22.1% (atropine 0.02%). The mean change-from-baseline in SER at Month 36 was -1.24 D (Vehicle), -0.96 D (atropine 0.01%) and -1.14 D (atropine 0.02%). The change-in-SER between atropine 0.02% and placebo was not statistically significant (LSM 0.099; p=0.10). The difference between atropine 0.01% and placebo (LSM 0.24) had a nominal p-value <0.001.

The primary endpoint, which was limited to testing the 0.02% dose versus placebo, was not met, not even a trend (p=0.373) was observed. Formally the CHAMP study failed. The applicant subsequently applies for the lower strength, 0.01%, apparently based on nominal significant effects of that dose vs Vehicle at Month 36.

From a methodological perspective this is not allowed. The hierarchical test procedure accounting for multiplicity stopped after the primary endpoint analysis did not reach statistical significance. Hence, the statistical results that followed the primary analyses cannot be readily interpreted and are considered exploratory.

Further both eyes were used separately in the analysis. While acknowledged that eyes from a single individual may progress differently, a responder was defined as a subject with myopia progression less than 0.50 D at Month 36 visit for atropine 0.02% vs Vehicle, irrespective if this occurs in one or both eyes. The unit of analysis should be the subjects. Thus, instead, an ITT analysis for responder rate <0.5 D, change-from-baseline SER and change-in-axial length all at Month 36 was requested on a subject basis, alike study MTS1. For responders the results of both the 0.01% and 0.02% should be expressed as RR and risk differences. For the continuous variables the results of both eyes could be averaged. This analysis was provided in round 2 of this initial MAA.

The revised analysis supported the concern that the initial analysis was overestimated the treatment effect and consequently support the issues on the credibility and relevance of the results. For the responder analysis, in the retrieved-dropout analysis the effect was no longer nominally significant and the treatment difference reduced to 7.6% (95% WALD CI: -1.4%, 16.5%, p=0.1). Similar trends were observed for the other endpoints (change-from-baseline SER, and change-in-AL), and both in mITT and ITT, although for AL differences remained nominally significant.

The applicant argued that the lower precision in the revised analysis may be due to 1) lower power due to averaging eyes, and 2) possible bias introduced by dropout who used confounding therapies. While agreed that power is indeed (artificially) increased, it is not considered an argument for not using the revised analyses on subject level, as that more readily allows to investigate clinical relevance of findings. Further, while acknowledged that confounding therapies may influence a retrieved drop-out analysis, the effect here likely is limited as it concerns a small sample which is roughly comparable between groups. I.e., in mITT n=23 of 44 dropouts that remained in the study used confounding therapies, of which n=9 in the Vehicle group and n=6 in the atropine 0.01% group. Thus, only for a small sample the imputation may not have been accurate, which does not refute that the initial analysis was too optimistic. Consequently, the actual effect likely is closer to the non-nominal significant result observed in the retrieved dropout analysis than the initial analysis result.

In the sample size calculations, an effect of 25% versus 7% responders was anticipated (difference of 18%), but this result was not achieved.

The clinical relevance of the observed effect size for atropine 0.01% was a key point of discussion in the course of the procedure. In the <0.5 D responder analysis (primary), the treatment difference at Month 36 (atropine 0.01% vs vehicle) was 11% (n=13) in the mITT and 10.3% in the ITT (n=18). In change-from-baseline SER results, the LS means difference for atropine 0.01% vs Vehicle at Month 36 is 0.24 D (mITT). Similar effects were observed for change-in-axial length (LSM difference ~0.13mm; ITT). The relevance of these results was of questionable relevance and weighed against the burden of long-term treatment (beyond the 4 years of the study) in a young population.

In Round 2 of this initial MAA, the applicant agreed that the key goal for myopia treatment was to prevent high myopia and related complications. The responder analysis (progression <0.5D/3y) was argued to be most appropriate for assessing relevance as that is the cut-off used by e.g., WHO to define stable myopia. One head-to-head study performed in China was found; a different formulation of atropine 0.01% vs Ortho-K showed similar efficacy (PMID: 36229177). There is no consensus on a relevant magnitude for a treatment effect of atropine. These arguments are accepted. Still, the choice for 18% as expected treatment effect in CHAMP remains unclear and not agreed that all analyses consistently show that 18% was included in the 95% CI (i.e., not in any ITT analysis nor in the retrieved drop-out analysis in mITT). Further, in Round 2 and 3 of this MAA the applicant argued that the point estimates were clinically significant because they apply to a large group (0.5-1.2% of the EU population). This was not considered an argument for clinical relevance. Benefit should be clear irrespective of the target population size. Yet CHAMP, MOSAIC and MTS1 results, if they were credible, would suggest that the vast majority will be burdened with a treatment with an effect of questionable relevance (i.e., difference of 0.24 D).

Also in round 2 of this MAA, the applicant claimed benefit on a) more subjects on atropine 0.01% had stable myopia (i.e., primary endpoint) and b) atropine 0.01% slowed myopia progression in those that did not achieve stable myopia, which was supported by a projection of treatment effect over 6 years. This was not agreed. The primary endpoint results were not convincing, and the 6-year projections were too optimistic as they did not take Stage 2 results into account. I.e., it assumed that 'responders' remain 'responders' over 6 years, yet 7.4% of eyes were no longer 'responders' from Month 36 to Month 48 in the group receiving atropine 0.01% over 48 months. The treatment difference in the projection was already considered small, but likely would have been even less if CHAMP Stage 2 results would have been used.

The absence of dose-dependent or at least similar effects was of concern as this finding is in contrast with results from other clinical studies with low-concentration atropine (e.g., LAMP study: Yam et al., 2019). Potential reasons for absence of dose-dependency in CHAMP were discussed in Round 1 of this MAA: issues related to study conduct, abnormal results in subgroups, absence of pharmacodynamic effects (in terms of pupil response), and COVID-19 impact. No explanatory factor could be identified except that the COVID-19 pandemic may have lowered the treatment effect. While plausible considering outdoor activities were limited during lockdown regulations, it did not explain full absence of dose-dependency. Baseline characteristics between treatment groups were comparable, therefore it was assumed that COVID-19 influence across treatment groups would have been equal. The lack of dose effect is counterintuitive. At least it would have been expected that the 0.02% strength performed similarly as the 0.01% strength. In Round 2, the applicant argued that CHAMP was not meant to formally test 0.01% vs 0.02% formulation, and that acute pupillometry effects may not fully synchronize with efficacy. This is accepted, and considered unlikely that there are further data to resolve the mechanistic uncertainty.

In Round 2 and 3, relevance was emphasized of a meta-analysis of available randomized controlled trials (CHAMP, Mini-CHAMP, MTS1, MOSAIC plus 9 published RCTs evaluating atropine 0.01%), and deficiencies of MTS1 were recited (discussed below).

Together they were used to argue that rather MTS1 is the outlier and results for atropine 0.01% are otherwise consistent with literature. This is not agreed. Use of the point estimates in the meta-analysis is with caution as: i) CHAMP, MOSAIC and MTS1 did not meet their primary endpoint; ii) most other RCTs tested different atropine formulations which may influence efficacy, and for those products no efficacy is established in the EEA; iii) most studies included only Asian patients enrolled in Asia for which is it debatable if myopia progression and atropine effects are fully comparable to the EU situation (e.g., Brennan et al., 2024, Lawrenson et al., 2025; Li et al., 2014), and iv) because CHAMP is the only study with data up to 3-years. Hence, the meta-analysis cannot readily support that CHAMP results of Atropine Sulfate FGK 0.01% at 3-year are credible. Further, while the deficiencies of MTS1 are acknowledged they do not fully explain the treatment difference of ~0 (also see below). Altogether, CHAMP, MOSAIC and MTS1 remain of most support for EU MAA but their 0.01% result is not compelling.

Moreover, 0.01% and 0.02% were argued to be in the minimum effective dose range and that a much larger sample is needed to show superiority of 0.02%. In Round 2 it was also argued that effects for 0.01% and 0.02% are similar, although at start of MAA the treatment differences for 0.02% were presented as less compared to 0.01%.

In round 3, the applicant acknowledged that 0.02% are not persuasive at this time. 0.01% results are argued to be persuasive as 1) results on all endpoints considered important were nominally significant, 2) align with mini-CHAMP results, and 3) align with published RCTs (i.e., the meta-analysis). This was not agreed. The endpoints are based on the same variable or otherwise partly correlated, thus consistency across endpoints was expected and do not resolve the concern that the result may be spurious. The meta-analysis was discussed above; and mini-CHAMP below. Thus, with CHAMP formally being a failed study and with non-persuasive results for 0.02%, the 0.01% result still is not credible and unsuitable to support a benefit claim.

Subgroups analyses were performed in mITT. In Round 2, revised analysis subgroup analysis in ITT based on the revised retrieved drop-out analysis were provided, which were generally consistent across the three endpoints (responder analysis, change-in-SER, and change-in-AL). No new outliers were observed.

The treatment difference for the subgroup with -3.01- -6.00 D at baseline approximate 'no effect' (i.e., RR for atropine 0.01% vs vehicle: 1.14). This raised concerns on a) the clinical relevance as primarily patients with high myopia (≥ -6D) benefit from myopia control as they are most at increased risk for ocular complications due to myopia; b) if atropine 0.01% is truly efficacious in subjects with higher myopia at baseline, and c) if treatment should be continued in cases when myopia progresses towards -3.01 to -6.00 D at a later time point.

In round 2 of this MAA, a breakdown was provided showing, per treatment and disease subgroup (-0.5D;-3D // -3D;-6D // <-6D), the number of subjects progressing over-time. While agreed with the applicant that numbers in the <-6D group are small and that CHAMP was not designed to assess prevention of high myopia, the effects in both groups for <-6 D were comparable and so, no indication of a benefit of atropine 0.01% in preventing progression to high myopia.

Further in Round 2 and 3 of this MAA, the applicant argued that less patients progress from [-0.5D;-3.0D] to SER [-3.01;-6.0D] at Month 36 for atropine 0.01% vs Vehicle using a breakdown of patients with SER data. This, however, likely is due to disbalances between groups. The baseline sample differed (atropine 0.01%=133; vehicle n=144) with more patients with less severe myopia in the atropine 0.01% group (in mITT: SER -0.5;-3D, vehicle: n=98/68.1% vs atropine 0.01%: n=100/75.2%. SER -3.01;-6.0D, vehicle: n=43/29.9% vs atropine 0.01%: n=33/24.8%). At month 36, a similar number of patients remained in the [-0.5;-3D group] (0.01%: 39 of 100; vehicle: 38 of

98). There were fewer patients in the [-3D;-6D] group for 0.01% vs vehicle (n=35 vs n=48). However, that difference is similar to the imbalance of dropouts between groups (dropouts 0.01%: 32; vehicle: 18 = difference of n=14). When taking the imbalances into account these data do not convince that there is a benefit for 0.01%. Further discussion of subgroups (i.e., [-0.5;-3.0D] and [-3.0D;-6.0D]) is not warranted as major issues persist on overall credibility and relevance of results in mITT.

In an effect-by-age analysis, a decreasing effect by age is observed. It is agreed that the subgroups are small, which is unfortunate as CHMP raised concerns during Scientific Advice that a too small sample outside the primary group of 6-10 years may not support approval of a wide age-range. As it stands, an effect of questionable relevance is observed in all groups >6 years. Vehicle is favoured in the highest age group (≥13 years). Further, myopia in children <5 years is often associated with other aetiologies and may be corrected naturally. In Round 2, the applicant restricted the age limits to that of the primary analysis population (i.e., mITT: children 6-10 years).

Subjects < 6 years at study entry were administered cyclopentolate, all others tropicamide, while spherical equivalent change measurements may significantly differ when using these different pharmaceutical agents. (Al-Thawabieh et al., 2024) In round 2 the applicant clarified that apart from 5 children all used cyclopentolate in all visits. Moreover, the applicant restricted the age limits to 6-10 years old.

Subgroups analysis in mITT suggests divergent effects for the Asian (favouring neither option) and EU subpopulations (favouring Vehicle). This divergent effect is not observed for 0.02% and a wide confidence interval in the European subgroup is observed that includes the point estimate of the overall effect in mITT. The explanation of the applicant that confounding therapies may have led to increased numeric disagreement between the Asian and non-Asian subgroups is plausible. It is therefore agreed with the applicant that the small sample of subjects in these groups (EU and Asian subgroups) may have contributed to these abnormal findings.

The applicant performed a post-hoc analysis in CHAMP on use of confounding therapies in mITT. Based on this analysis it is plausible that this reduced the treatment effect, albeit the influence is limited (difference in change-in-SER at Month 36 for atropine 0.01% vs Vehicle: 0.26 D (95% CI: 0.13-0.39), atropine 0.02% vs Vehicle: 0.14 D (95% CI: 0.03-0.26). The applicant did not perform this analysis in ITT but it can be assumed that the influence is less pronounced as the proportion of subjects with confounding therapy in ITT is smaller (mITT: 23/489=4.7% and ITT n=25/576=4.3%). Altogether this analysis does not address concerns on absence of dose-dependency or the clinical relevance of observed effect.

In previous studies involving children, the differential effect of sex on myopia progression and axial elongation may be influenced by pubertal growth spurts (Yip et al., 2012). However, as it was confirmed that CHAMP did not record puberty status, further investigation is not possible.

In CHAMP Stage 2, treatment cessation (atropine 0.01%-> Vehicle) suggested loss of efficacy. Compared to Month 36 there were 28% less responder eyes at Month 48 in that group. However, also in the subjects who continued atropine 0.01% in stage 2 (atropine 0.01% -> atropine 0.01%) there were 8% less responder eyes. Also a considerable proportion of subjects discontinued of which 8.9% plausibly due to an AE or lack of efficacy in mITT. However, as major issues persist on data credibility and relevance up to M36, further dissection of Stage 2 results is not warranted.

In Round 2 of this MAA, maintenance of effect was discussed using the 6-year projection, but that analysis was not considered appropriate (see discussion above). Moreover, 6 years is considered too short in relation to the envisaged treatment duration. Six years was based on mean baseline age in CHAMP and median myopia stabilization at 15 years. However, (at least) 9 years seems more

appropriate, also when recalling that stabilization may only occur at ~25 years (9 years is based on lower age limit (6y) till median myopia stabilization (15y)). Further dissection on these data is not applicable as major issues persist on data credibility and relevance of findings up to Month 36.

As long-term treatment is envisaged, long-term treatment policies should have been provided but were missing in the proposed SmPC. In round 2, based on CHAMP, an initial treatment period of 3 years with annual eye examination was proposed, which was accepted. In round 3, the applicant indicated that they did not collect or otherwise had data to recommend alternative therapies after 3 years if patients progressed >0.5D/3y, and therefore that the posology proposes that the physician decides after 3 years whether to continue or stop treatment. This concept was accepted, but textual updates were needed to explicate what (limited) effects can be expected for this group. During the oral explanation in Round 3, the applicant proposed updates in the SmPC on this matter.

In Round 2 it was clarified that rebound effect was defined as excess of myopia progression from Stage 1 to Stage 2 for subjects who switched from atropine treatment to vehicle, versus subjects who continued with the same atropine strength. Based on data provided, this did not appear to be a rebound effect.

Considerations on results of other studies

Next to CHAMP, results from MOSAIC, MTS1 and mini-CHAMP were provided. These studies also tested Atropine Sulfate FGK 0.01% eye drops.

MOSAIC (n=250) and MTS1 (n=187) are in principle well-designed 24-month randomized (2:1), double-blind, placebo-controlled, parallel-group studies, performed by independent investigators, that tested Atropine Sulfate FGK 0.01% vs Vehicle. Whereas the applicant coined the CHAMP study as the pivotal study and MOSAIC and MTS1 studies as supportive, they fully contribute to the primary efficacy assessment in the intended indication.

The MOSAIC ran exclusively in Ireland and had a tapering period of 12 months; MTS1 exclusively in the USA and had a follow-up of 6 months.

Enrolment criteria were similar to CHAMP, except that in MTS1 a stricter age-range was employed (5-12 years) and in the MOSAIC myopia progression (-0.5 D/year at enrolment) was an inclusion criterion. As most other design elements are similar to that of CHAMP, the reader is referred to the discussion on the CHAMP design for details. Both studies were performed during the COVID-19 pandemic.

MOSAIC and MTS1 also failed to meet their primary efficacy endpoint, i.e., change-from-baseline in SER at Month 24. The effect sizes of atropine 0.01% versus Vehicle were of smaller size compared to CHAMP. Ultimately, three ≥24-month studies with Atropine Sulfate FGK 0.01% were provided that formally had failed. The observed effect sizes remained of questionable relevance. Altogether, the foregoing allowed to conclude that said studies do not sufficiently demonstrate efficacy of Atropine sulfate FGK in the proposed indication.

In Round 2, the applicant discussed that MTS1 results as outlying because this study had significant deficiencies in its conduct (i.e., underpowered study according to the applicant, more younger children in the atropine 0.01% group (9-11 years old), potential for partial aliasing in the mixed analysis model as a small number of participants of East Asian race are expected to have non-brown iris; and uncertainties on treatment adherence, which also could not be confirmed by pupillometry data as that was not measured). While agreed that some were significant deficiencies, it is not agreed that they fully explained the negative result of MTS1. E.g., CHAMP results suggested that the treatment difference is larger in younger and less myopic patients, thus the disbalance may actually be favouring

atropine 0.01%. Rather, MTS1 results agreed with CHAMP and MOSAIC in that: they all do not demonstrate efficacy.

Mini-CHAMP is an ongoing study also performed with 0.01% by a partner of the applicant. In principle the study is methodologically sound, but the primary treatment period of 12 months is too short to allow for proper efficacy assessment. In addition, it enrolled only Chinese children exclusively from China. In round 3 and the oral explanation that followed, the applicant argued that mini-CHAMP results corroborated with 2-year China-CHAMP results, and that there is no evidence that atropine has different effects on myopia in Asian vs non-Asian patients. The latter was supported by an explorative analysis showing a regression for SER vs AL change in Asian vs non-Asian patients in CHAMP. This analysis was not of use as CHAMP enrolled Asian patients *in Europe and USA*, i.e., it did not address uncertainty of extrapolating data from *Chinese children enrolled in* China to the EU situation. Specifically, mini-CHAMP had a treatment duration up to 1 year which is without clear relevance to later timepoints. E.g., in CHAMP at 1-year the results for 0.01% and 0.02% were still similar yet divergence was seen at Month 24 and 36. The results of China-CHAMP were from preliminary analyses. Further, both studies showed treatment differences smaller than in CHAMP, which was already of questionable relevance. Moreover, the representativeness of data of Chinese children from studies *exclusively performed in China* for this EU MAA remains unclear as differences for Asian vs non-Asian patients have been suggested in terms of myopia progression (e.g., Brennan et al., 2024) and atropine effects (e.g., Lawrenson et al., 2025; Li et al., 2014). Altogether, for this MAA the mini-CHAMP and China-CHAMP results are of limited importance in the context of CHAMP, MOSAIC and MTS1.

The applicant provided a combined analysis from three individual secondary endpoints in CHAMP which showed that effects consistently favoured atropine 0.01% over Vehicle. A z-score was used to standardize the observed treatment differences across the different endpoints. However, the analysis was performed with post-hoc knowledge in mITT, at eye-level, reports ODs and combines data from a formally failed study. Moreover, apart form the fact that z-scores are difficult to interpret, the z-score combines different endpoints (responder, SER, axial length) without taking into account that these are highly correlated. Most important, a combined analysis cannot compensate for the fact that the individual studies failed to meet their primary endpoint. Thus, the combined analysis is considered of limited additional value in support of the MA.

Additional expert consultation

Not applicable.

2.6.7. Conclusions on the clinical efficacy

Three ≥24-month studies with Atropine Sulfate FGK 0.01% eye drops were performed but all failed to meet their primary efficacy endpoint and the observed effect was of questionable relevance. Results from the requested retrieved dropout analysis supported the concern that the initial analysis overestimated the treatment effect.

In CHAMP, at least a similar effect of atropine 0.01% and 0.02% was expected yet the atropine 0.02% did not statistically differ from placebo, which called into question the credibility of the results for atropine 0.01%.

For results, primarily prevention of progression to <-6.0D was key, but no treatment difference was seen. The number of 'responders' (<0.5D in 3 years) in CHAMP was small and related treatment difference did not reach the expected level of the sample size calculation (18%). I.e., the myopia of most patients did progress, comparably to Vehicle. Given these major issues on credibility and

relevance of results up to Month 36, dissection of Stage 2 results (i.e., Month 36-48) was not warranted.

Altogether, efficacy is not considered demonstrated as major issues persisted on data credibility and on if effects up to M36 are relevant at all.

2.6.8. Clinical safety

2.6.8.1. Patient exposure

Information on patient exposure was provided separately for each study part in which Atropine sulfate FGK (0.01%) was tested.

Table 41. Patient exposure (as of Feb. 9, 2024)

	Patients enrolled*	Patients exposed**	Patients exposed to the proposed dose (0.01%)	Patients with long term*** safety data (0.01%)
Blinded studies (placebo-controlled)****	1719	1078	605	550
Blinded studies (active -controlled)	0	0	0	0
Open studies	0	0	0	0
Post marketing	0	0	0	0
Compassionate use	0	0	0	0

* Screened; ** Received at least 1 dose of active treatment; *** This refers to 6 months and 12 months continuous exposure data, or intermittent exposure.; **** Combined from CHAMP, Mini-CHAMP, MOSAIC and MTS1.

CHAMP, China-CHAMP, mini-CHAMP, MOSAIC and MTS1

In CHAMP Stage 1, a total of 411 subjects were exposed to Atropine Sulfate eye drops (0.01% or 0.02%). Of these, 164 subjects were exposed to Atropine Sulfate 0.01% eye drops and 247 subjects to Atropine Sulfate 0.02% eye drops for up to 3 years. In Stage 2, a total of 321 subjects were exposed to Atropine Sulfate eye drops (0.01% or 0.02%) for another year. Of these, 159 subjects were exposed to Atropine Sulfate 0.01% eye drops and 162 subjects to Atropine Sulfate 0.02% eye drops.

In mini-CHAMP Stage 1, a total of 372 subjects were exposed to Atropine Sulfate eye drops (0.01% or 0.02%). Of these 147 subjects were exposed to atropine 0.01% and 225 subjects to atropine 0.02% for up to 1 year.

In China-CHAMP, 777 subjects ranging from 6-12 years of age are randomized for Atropine Sulfate Eye Drops treatment (as of data lock point of 15 November 2023). As this study is ongoing and treatment

assignments are masked, the total number of subjects treated with Atropine Sulfate 0.01% Eye Drops is not known (at the time of authoring this assessment report).

In MOSAIC, 250 children were exposed; in MTS1 the sample was 187.

The applicant also included 107 subjects from the TOAST study in their exposure count but did not further discuss related data. TOAST enrolled adult subjects with myopia. Children and adults are not readily comparable for safety evaluation for this indication. Hence, TOAST safety data are considered of limited value for safety evaluation in context of this MAA and it is acceptable that the applicant did not discuss related data in the majority of the safety assessment.

Published Literature

Across all published literature, studies ranged in total duration from 0.5 to 5 years, involving once daily dosing in most. They were conducted in children ranging from 4 to 16 years of age. Within the 16 studies that reported safety data, 3683 children are represented. Of these, 932 received atropine, 0.01% (Chia, 2012; Chia 2023; Hansen 2023; Yam, 2019; Wei, 2020; Wei, 2022; Hieda, 2021; Saxena, 2021; Lee, 2022; Yu, 2022; Fu 2020); 1527 children received atropine in higher doses (0.02% to 1%) (Chia 2012; Fu 2020; Shih 1999; Yen, 1989; Chua, 2006; Yi, 2015; Wang, 2017; Yam, 2019; Yam, 2020; Zhu, 2020; Hansen 2023).

2.6.8.2. Adverse events

CHAMP

Overall TEAEs in Stage 1 were reported in 377 subjects (65.8%). The Vehicle group had a higher proportion of subjects with TEAEs (71.6%) compared with the atropine 0.01% group (59.8%) or atropine 0.02% group (66%).

Ocular TEAEs in Stage 1 were reported most in the Vehicle group (40.7%) followed by atropine 0.02% (33.2%) and atropine 0.01% (25.6%). This switched in Stage 2: most TEAEs were reported in the 0.01% group (10.1%), followed by the 0.02% group (8.0%), and Vehicle group (5.1).

Table 42. Overall summary of treatment-emergent adverse events – CHAMP stage 1 safety population

AE Type	Vehicle (N=162) n (%)	Atropine Sulfate, 0.01% (N=164) n (%)	Atropine Sulfate, 0.02% (N=247) n (%)
Subjects with any TEAE[a]	116 (71.6)	98 (59.8)	163 (66.0)
Subjects with any Ocular TEAE	66 (40.7)	42 (25.6)	82 (33.2)
Subjects with any Non-Ocular TEAE	95 (58.6)	87 (53.0)	137 (55.5)
Subjects with any Treatment-Related TEAE[b]	27 (16.7)	18 (11.0)	29 (11.7)
Subjects with any Ocular Treatment-Related TEAE	24 (14.8)	16 (9.8)	25 (10.1)
Subjects with any Non-Ocular Treatment-Related TEAE[b]	5 (3.1)	3 (1.8)	5 (2.0)
Subjects with any Serious TEAE	4 (2.5)	1 (0.6)	8 (3.2)
Subjects with any Ocular Serious TEAEs	0	0	0
Subjects with any Non-Ocular Serious TEAEs	4 (2.5)	1 (0.6)	8 (3.2)

AE Type	Vehicle (N=162) n (%)	Atropine Sulfate, 0.01% (N=164) n (%)	Atropine Sulfate, 0.02% (N=247) n (%)
Subjects with any Treatment-Related Serious TEAE	1 (0.6)	0	0
Subjects with any Ocular Treatment-Related Serious TEAE	0	0	0
Subjects with any Non-Ocular Treatment-Related Serious TEAE	1 (0.6)	0	0
Subjects with any TEAE leading to Permanent Discontinuation of Study Drug	10 (6.2)	0	5 (2.0)
Subjects with any Ocular TEAE leading to Permanent Discontinuation of Study Drug	8 (4.9)	0	3 (1.2)
Subjects with any Non-Ocular TEAE leading to Permanent Discontinuation of Study Drug	2 (1.2)	0	2 (0.8)
Subjects with any TEAE Leading to Death	0	0	0

Source: Study CP-NVK002-0001 Table 14.3.1.1.1; Table 14.3.1.2.1.1; Table 14.3.1.4.1.1; Table 14.3.1.6.1.1; Table 14.3.1.7.1.1; Table 14.3.1.9.1.1; Table 14.3.1.9.1.2; Table 14.3.1.9.1.3; Table 14.3.1.10.1.1 AE = adverse event; N=number of subjects in population; n=number of subjects assessed; TEAE = treatment-emergent adverse event. Note: Stage 1 Safety population is defined by administration of at least one dose of study medication in Stage 1. [a]: Adverse events are considered treatment emergent if they began or worsened in severity on or after the date of first dose of the study drug in Stage 1 and on or before the date of last dose of study drug in Stage 1. [b]: Adverse events are considered treatment-related if study drug causality is very likely/certain, probable, possible, or missing.

Table 43. Overall summary of treatment-emergent AEs – CHAMP stage 2 safety population

AE Type	Vehicle N=99 n (%)	Atropine Sulfate 0.01% N=159 n (%)	Atropine Sulfate 0.02% N=162 n (%)	Total N=420 n (%)
Subjects with any Ocular TEAE [a]	5 (5.1)	16 (10.1)	13 (8.0)	34 (8.1)
Subjects with any Non-Ocular TEAE [a]	32 (32.3)	66 (41.5)	54 (33.3)	152 (36.2)
Subjects with any Ocular Treatment-Related TEAEs [b]	0	2 (1.3)	2 (1.2)	4 (1.0)
Subjects with any Non-Ocular Treatment-Related TEAEs [b]	1 (1.0)	0	0	1 (0.2)
Subjects with any Serious Ocular TEAE	0	0	0	0
Subjects with any Serious Non-Ocular TEAE	2 (2.0)	3 (1.9)	2 (1.2)	7 (1.7)
Subjects with any Serious Ocular Treatment-Related TEAEs	0	0	0	0
Subjects with any Serious Non-Ocular Treatment-Related TEAEs	0	0	0	0
Subjects with any Ocular TEAE Leading to Study Discontinuation	0	0	1 (0.6)	1 (0.2)

Subjects with any Non-Ocular TEAE Leading to Study Discontinuation	1 (1.0)	0	0	1 (0.2)
Subjects with any Ocular TEAE Leading to Death	0	0	0	0
Subjects with any Non-Ocular TEAE Leading to Death	0	0	0	0

Source: Study CP-NVK002-0001 Stage 2 Table 14.3.1.1.2, Table 14.3.1.2.2.1, Table 14.3.1.4.2.1, Table 14.3.1.6.2.1, Table 14.3.1.7.2.1, Table 14.3.1.9.2.1 AE = adverse event; SAE = N=number of subjects in population; n=number of subjects assessed; TEAE = treatment-emergent adverse event. Note: Stage 2 Safety population is defined by administration of at least one dose of study medication in Stage 2. a: Adverse events are considered treatment emergent if they began or worsened in severity on or after the date of first dose of study drug in stage 2. b. Adverse events are considered treatment-related if study drug causality is very likely/certain, probable, possible, or missing.

In CHAMP, most of the ocular TEAE's occurred in the first year of the study, regardless of treatment assignment (see table below).

The applicant attributed the low TEAE incidence to installation before bedtime with TEAEs resolved upon waking. This argument was not supported by data.

Table 44. Time to onset of Ocular TEAE of interest by year of occurrence (safety set)

Ocular TEAE of interest	Vehicle N=162, n	Atropine 0.01% N=164, n	Atropine 0.02% N=247, n	Total N=573, n (%)
Photophobia	5 in year 1	4 in year 1	10 in year 1 1 in year 3	20 (3.5%)
Mydriasis	0	1 in year 1 1 in year3	3 in year 1 1 in year 3	6 (1.0%)
Allergic conjunctivitis	4 in year 1 1 in year 2	3 in year 1	7 in year1 3 in year 2 1 in year 3	19 (3.3%)
Blurred vision	0	2 in year 1	3 in year 1 1 in year 3	6 (1.0%)
Eyelid swelling	0	2 in year 1 1 in year 2	1 in year 1	4 (0.7%)
Eyelid irritation	1 in year 1	0	1 in year 1 1 in year 2	3 (0.5%)

Source: CSR Listing 16.2.7.1

a. Common adverse events

CHAMP - ocular AEs

In Stage 1, ocular TEAEs with a higher incidence than in the Vehicle group included photophobia, conjunctivitis allergic, mydriasis, vision blurred, swelling of eyelid, and conjunctivitis bacterial. Photophobia and instillation site pain did not appear to be dose-related, but mydriasis and vision blurred TEAEs did show a trend towards dose-dependency (mydriasis: 0% (Vehicle) vs 1.2% (atropine 0.01%) vs 1.6% (atropine 0.02%), vision blurred: 0 (Vehicle) vs 1.2% (atropine 0.01%) vs 1.6% (atropine 0.02%)) (Table 45).

In Stage 2 the most common TEAE was Dry eye (Vehicle: n=0; atropine 0.01%: n=2 (1.3%); atropine 0.02%: n=3 (1.9%); Retinal degeneration (Vehicle: n=0; atropine 0.01%: n=3 (1.9%); atropine 0.02%: n=1 (0.6%) and Conjunctivitis, which appeared dose-dependent (Vehicle: n=0; atropine

0.01%: n=1 (0.6%); atropine 0.02%: n=3(1.9%); (Table 46). The TEAEs of retinal degeneration were all considered unrelated to the study drug.

Table 45. Ocular treatment-emergent adverse events (incidence ≥ 1.0% in any treatment group) by system organ class and preferred term – CHAMP stage 1 safety population)

System Organ Class Preferred Term	Vehicle (N=162) n (%)	Atropine Sulfate, 0.01% (N=164) n (%)	Atropine Sulfate, 0.02% (N=247) n (%)
Any Ocular Treatment-Emergent AE[a]	66 (40.7)	42 (25.6)	82 (33.2)
Eye disorders	47 (29.0)	33 (20.1)	54 (21.9)
Ocular hyperaemia	10 (6.2)	4 (2.4)	8 (3.2)
Photophobia	5 (3.1)	4 (2.4)	11 (4.5)
Conjunctivitis allergic	5 (3.1)	3 (1.8)	11 (4.5)
Eye pruritus	5 (3.1)	4 (2.4)	5 (2.0)
Eye allergy	5 (3.1)	4 (2.4)	4 (1.6)
Eye irritation	6 (3.7)	1 (0.6)	2 (0.8)
Chalazion	5 (3.1)	3 (1.8)	0
Eye pain	4 (2.5)	3 (1.8)	1 (0.4)
Punctuate keratitis	4 (2.5)	2 (1.2)	2 (0.8)
Blepharitis	3 (1.9)	2 (1.2)	1 (0.4)
Mydriasis	0	2 (1.2)	4 (1.6)
Vision blurred	0	2 (1.2)	4 (1.6)
Noninfective conjunctivitis	3 (1.9)	2 (1.2)	0
Swelling of eyelid	0	3 (1.8)	1 (0.4)
Binocular eye movement disorder	2 (1.2)	1 (0.6)	0
Infections and infestations	19 (11.7)	7 (4.3)	17 (6.9)
Hordeolum	11 (6.8)	3 (1.8)	10 (4.0)
Conjunctivitis	5 (3.1)	2 (1.2)	4 (1.6)
Conjunctivitis bacterial	1 (0.6)	1 (0.6)	3 (1.2)
Conjunctivitis viral	3 (1.9)	0	1 (0.4)
Injury, poisoning and procedural complications	5 (3.1)	1 (0.6)	7 (2.8)
Foreign body in eye	2 (1.2)	0	2 (0.8)
Arthropod bite	2 (1.2)	0	0
Immune system disorders	5 (3.1)	3 (1.8)	4 (1.6)
Seasonal allergy	5 (3.1)	3 (1.8)	3 (1.2)
General disorders and administration site conditions	6 (3.7)	2 (1.2)	2 (0.8)
Instillation site pain	5 (3.1)	2 (1.2)	1 (0.4)

Source: Study CP-NVK002-0001 Table 14.3.1.2.1.2. AE = adverse event; N=number of subjects in population; n=number of subjects assessed. Note: Adverse events are classified by system organ class and preferred term using MedDRA version 25.0. Subjects who experience the same coded event more than once are counted only one time per preferred term and one time per system organ class. [a]*: Adverse events are considered treatment emergent if they began or worsened in severity on or after the date of first dose of study drug in Stage 1 and by administration of at least one dose of study medication in Stage 1.*

Table 46. Ocular treatment-emergent adverse events (incidence ≥ 1.0% in any treatment group) by system organ class and preferred term – CHAMP stage 2 safety population

System Organ Class Preferred Term	Vehicle N=99 n (%)	Atropine Sulfate 0.01% N=159 n (%)	Atropine Sulfate 0.02% N=162 n (%)	Total N=420 n (%)
Any Ocular Treatment-Emergent AE [a]	5 (5.1)	16 (10.1)	13 (8.0)	34 (8.1)
Eye disorders	2 (2.0)	12 (7.5)	8 (4.9)	22 (5.2)
Dry eye	0	2 (1.3)	3 (1.9)	5 (1.2)
Retinal degeneration	0	3 (1.9)	1 (0.6)	4 (1.0)
Conjunctivitis allergic	0	3 (1.9)	0	3 (0.7)
Blepharitis	0	2 (1.3)	0	2 (0.5)
Chalazion	1 (1.0)	0	0	1 (0.2)
Conjunctival hyperaemia	0	0	1 (0.6)	1 (0.2)
Eye irritation	0	0	1 (0.6)	1 (0.2)
Iridocyclitis	0	1 (0.6)	0	1 (0.2)
Noninfective conjunctivitis	0	1 (0.6)	0	1 (0.2)
Papilloedema	0	0	1 (0.6)	1 (0.2)
Punctate keratitis	0	0	1 (0.6)	1 (0.2)
Swelling of eyelid	1 (1.0)	0	0	1 (0.2)
Vision blurred	0	0	1 (0.6)	1 (0.2)
Infections and infestations	2 (2.0)	4 (2.5)	5 (3.1)	11 (2.6)
Hordeolum	1 (1.0)	2 (1.3)	2 (1.2)	5 (1.2)
Conjunctivitis	0	1 (0.6)	3 (1.9)	4 (1.0)
Conjunctivitis bacterial	1 (1.0)	0	0	1 (0.2)
Eye infection	0	1 (0.6)	0	1 (0.2)
Injury, poisoning and procedural complications	1 (1.0)	1 (0.6)	0	2 (0.5)
Corneal abrasion	0	1 (0.6)	0	1 (0.2)
Eye injury	1 (1.0)	0	0	1 (0.2)
Investigations	0	0	1 (0.6)	1 (0.2)
Intraocular pressure increased	0	0	1 (0.6)	1 (0.2)

Source: Study CP-NVK002-0001 Stage 2 Table 14.3.1.2.2.2. AE = Adverse Events; N=number of subjects in population; n=number of subjects assessed. Note: Stage 2 Safety Set is defined by administration of at least one dose of study medication in Stage 2. Note: Adverse events are classified by system organ class and preferred term using MedDRA version 20.1 or higher. Subjects who experience the same coded event more than once are counted only one time per preferred term and one time per system organ class. [a] Adverse events are considered treatment emergent if they began or worsened in severity between the first dose date of Stage 2 and last dose date of Stage 2. System organ classes and preferred terms within system organ class are sorted in descending frequency by the total column.

CHAMP - non-ocular AEs

In Stage 1, non-ocular TEAEs occurred most often in subjects in the Vehicle group (58.6%), followed by atropine 0.02% (55.5%), and the atropine 0.01% group (53.0%; Table 47).

In Stage 2, non-ocular TEAEs occurred most often in subjects in the atropine 0.01% group (41.5%), followed by atropine 0.02% (33.3%), and the Vehicle group (32.3%; Table 48).

Most common non-ocular AEs in Stage 1 were reported in the infections and infestations SOC (see table below). This is not surprising as CHAMP ran during the COVID-19 pandemic and young children, which are generally susceptible to infections, were included. In this SOC, a difference between vehicle (41.5%), and atropine 0.01% (27.4%) in observed, but are not of concern as the incidence was lower in the atropine 0.02% group (33.6%) and TEAEs in this SOC are not associated with atropine eye drop's mechanism of action.

Headache, a known systemic AE of atropine, was reported at comparable frequency between all three treatment arms. AEs related to heart-rate variability, which could also suggest systemic exposure, were reported in low frequency (three subjects: 1x Vehicle; 2x atropine 0.02%). Similar considerations apply to Stage 2. Altogether, atropine 0.01% or 0.02% did not appear to have reached systemic exposure levels that are of safety concern.

Table 47. Non-ocular treatment-emergent adverse events (incidence ≥ 5.0% in any treatment group) by system organ class and preferred term – CHAMP stage 1 safety population

System Organ Class Preferred Term	Vehicle (N=162) n (%)	Atropine Sulfate, 0.01% (N=164) n (%)	Atropine Sulfate, 0.02% (N=247) n (%)
Any Non-Ocular Treatment-Emergent AE[a]	95 (58.6)	87 (53.0)	137 (55.5)
Infections and infestations	67 (41.4)	45 (27.4)	83 (33.6)
Nasopharyngitis	22 (13.6)	17 (10.4)	30 (12.1)
COVID-19	18 (11.1)	9 (5.5)	27 (10.9)
Influenza	12 (7.4)	6 (3.7)	8 (3.2)
Nervous system disorders	17 (10.5)	20 (12.2)	29 (11.7)
Headache	14 (8.6)	14 (8.5)	23 (9.3)
Respiratory, thoracic and mediastinal disorders	22 (13.6)	14 (8.5)	26 (10.5)
Cough	9 (5.6)	3 (1.8)	7 (2.8)
Immune system disorders	10 (6.2)	18 (11.0)	21 (8.5)
Seasonal allergy	5 (3.1)	10 (6.1)	12 (4.9)
General disorders and administration site conditions	9 (5.6)	12 (7.3)	25 (10.1)
Pyrexia	6 (3.7)	8 (4.9)	21 (8.5)

Source: Study CP-NVK002-0001 Table 14.3.1.2.1.3 AE = adverse event; COVID-19= Coronavirus Disease 2019; N=number of subjects in population; n=number of subjects assessed. Note: Adverse events are classified by system organ class and preferred term using MedDRA version 25.0. Subjects who experience the same coded event more than once are counted only one time per preferred term and one time per system organ class.[a]: Adverse events are considered treatment emergent if they began or worsened in severity on or after the date of first dose of study drug in Stage 1 and by administration of at least one dose of study medication in Stage 1.

Table 48. Non-ocular treatment-emergent adverse events (incidence ≥ 5.0% in any treatment group) by system organ class and preferred term – CHAMP stage 2 safety population

System Organ Class Preferred Term	Vehicle N=99 n(%)	Atropine Sulfate 0.01% N=159 n(%)	Atropine Sulfate 0.02% N=162 n(%)	Total N=420 n(%)
Any Non-Ocular Treatment-Emergent AE [a]	32 (32.3)	66 (41.5)	54 (33.3)	152 (36.2)

Infections and infestations	18 (18.2)	37 (23.3)	25 (15.4)	80 (19.0)
COVID-19	8 (8.1)	14 (8.8)	13 (8.0)	35 (8.3)
Nasopharyngitis	6 (6.1)	14 (8.8)	5 (3.1)	25 (6.0)
Immune system disorders	**5 (5.1)**	**8 (5.0)**	**6 (3.7)**	19 (4.5)
Seasonal allergy	1 (1.0)	5 (3.1)	4 (2.5)	10 (2.4)
Immunisation reaction	3 (3.0)	2 (1.3)	1 (0.6)	6 (1.4)
General disorders and administration site conditions	**6 (6.1)**	**4 (2.5)**	**2 (1.2)**	12 (2.9)
Pyrexia	2 (2.0)	3 (1.9)	2 (1.2)	7 (1.7)
Nervous system disorders	**1 (1.0)**	**8 (5.0)**	**3 (1.9)**	12 (2.9)
Headache	1 (1.0)	5 (3.1)	2 (1.2)	8 (1.9)

Source: Study CP-NVK002-0001 Stage 2 Table 14.3.1.2.2.3. Note: AE = Adverse Events; COVID-19= Coronavirus Disease 2019; N=number of subjects in population; n=number of subjects assessed. Note: Stage 2 Safety Set is defined by administration of at least one dose of study medication in Stage 2.Note: Adverse events are classified by system organ class and preferred term using MedDRA version 20.1 or higher. Subjects who experience the same coded event more than once are counted only one time per preferred term and one time per system organ class.[a]: Adverse events are considered treatment emergent if they began or worsened in severity between the first dose date of Stage 2 and last dose date of Stage 2. System organ classes and preferred terms within system organ class are sorted in descending frequency by the total column.

Mini-CHAMP

A total of 393 (75.9%) subjects reported at least one TEAE. The most commonly reported TEAEs per SOC (≥10% incidence) were infections and infectious diseases (53.1%), eye diseases (22.2%), systemic diseases and reactions at the administration site (21.6%), respiratory/thoracic/mediastinal diseases (12.4%), and gastrointestinal system diseases (12.2%). The most commonly reported TEAEs (≥5% incidence) included COVID-19 (30.7%), upper respiratory tract infection (21.6%), fever (20.5%), respiratory tract infection (5.4%), allergic conjunctivitis (5.2%), and photophobia (5.0%).

MOSAIC

CHAMP TEAE frequencies were similar in MOSAIC. During the primary treatment period (24 months), 32 AEs were reported by the investigators, with 23 out of 136 (16.9%) occurring in the atropine group and 9 out of 68 (13.2%) in the placebo group ($p = 0.38$). There were no significant differences in AE severity, causality, or expectedness between the two groups.

As atropine 0.05% rather than 0.01% was evaluated during the second stage, related safety results will not be further discussed.

MTS1

Ocular AEs were prevalent: 87% of atropine group subjects and 90% of placebo group subjects experienced them at least once. These included eye irritation at time of instillation (atropine, 72% [90 of 125]; placebo, 82% [51 of 62]), photophobia (atropine, 26% [32 of 125]; placebo, 27% [17 of 62]), and blurred vision (atropine, 14% [17 of 125]; placebo, 16% [10 of 62]; Repka et al., 2023). While incidence within MTS1 was comparable between treatments, the overall higher number was notably higher in MTS1 than in CHAMP.

b. Treatment emergent adverse events by severity

CHAMP

In Stage 1, severity for Vehicle vs atropine 0.01% vs 0.02% was comparable (mild: 43.2% vs 37.2% vs 41.3%; moderate: 24.1% vs 20.7% vs 20.2%; severe: 4.3% vs 1.8% vs 4.5%). In total, 21

subjects (3.7%) had severe TEAEs, one was ocular. This subject received atropine 0.02% and had a severe ocular TEAE of administration site pain which was considered treatment-related and resulted in study drug discontinuation.

In Stage 2, severity for Vehicle vs atropine 0.01% vs 0.02% was also comparable (mild: 23.2% vs 35.2% vs 27.8%; moderate: 10.1% vs 10.7% vs 9.9%; severe: 2% vs 1.3% vs 1.9%). In total, 7 subjects (1.7%) had severe TEAEs, and alike Stage 1 one of these was ocular. This subject received atropine 0.02% in Stage 2 and had a severe ocular TEAE of eye irritation, which was considered treatment-related and resulted in study drug discontinuation.

Mini-CHAMP

The severity profile of the reported TEAEs was comparable to what was reported for CHAMP. Four subjects had a severe TEAE: one subject (atropine 0.01%) had respiratory infection, two subjects (1x atropine 0.01%; 1x Vehicle) had allergic conjunctivitis and one subject (atropine 0.01%) had pulmonary inflammation.

MOSAIC and MTS1

In MOSAIC there were no severe TEAEs at least possibly related to study treatment.

In MTS1 there were three subjects with severe TEAEs: two subjects received atropine 0.01% (1x burning in both eyes after drug instillation; 1x pain in both eyes); and one subject that received placebo (swelling due to injury non-study drug-related).

c. Treatment emergent adverse events by relationship to the study treatment

CHAMP

In Stage 1, 74 subjects (12.9%) reported at least 1 TEAE that was judged at least possibly treatment-related (or relationship was missing), with the highest incidence in the Vehicle group. The most common was photophobia (see table below).

In Stage 2, at least possibly related-TEAE was low with five TEAEs reported by one subject each. Dry eye was reported by two subjects (atropine 0.01% and 0.02%); the others were eye irritation (atropine 0.02%); noninfective conjunctivitis (atropine 0.01%); vision blurred (atropine 0.02%) and non-ocular TEAE dermatitis (Vehicle).

Table 49. Treatment related treatment-emergent adverse events by system organ class and preferred term – CHAMP stage 1 safety population)

System Organ Class **Preferred Term**	**Vehicle (N=162) n (%)**	**Atropine Sulfate, 0.01% (N=164) n (%)**	**Atropine Sulfate, 0.02% (N=247) n (%)**
Any Treatment-Related[a] Treatment-Emergent AE[b]	**27 (16.7)**	**18 (11.0)**	**29 (11.7)**
Any Treatment-Related[a] Ocular Treatment-Emergent AE[b]	**24 (14.8)**	**16 (9.8)**	**25 (10.1)**
Eye disorders	**18 (11.1)**	**14 (8.5)**	**22 (8.9)**
Photophobia	4 (2.5)	2 (1.2)	9 (3.6)
Mydriasis	0	2 (1.2)	4 (1.6)

System Organ Class **Preferred Term**	**Vehicle (N=162)** **n (%)**	**Atropine Sulfate, 0.01% (N=164)** **n (%)**	**Atropine Sulfate, 0.02% (N=247)** **n (%)**
Ocular hyperaemia	4 (2.5)	1 (0.6)	1 (0.4)
Eye irritation	3 (1.9)	0	2 (0.8)
Eye pruritus	3 (1.9)	1 (0.6)	1 (0.4)
Vision blurred	0	2 (1.2)	3 (1.2)
Eye pain	1 (0.6)	2 (1.2)	1 (0.4)
Punctuate keratitis	2 (1.2)	0	1 (0.4)
Dry eye	1 (0.6)	1 (0.6)	0
Eyelid irritation	0	0	2 (0.8)
Noninfective conjunctivitis	1 (0.6)	1 (0.6)	0
Anisocoria	0	0	1 (0.4)
Asthenopia	0	1 (0.6)	0
Conjunctivitis allergic	0	0	1 (0.4)
Episcleritis	0	1 (0.6)	0
Erythema of eyelid	1 (0.6)	0	0
Eye allergy	1 (0.6)	0	0
Eyelid rash	0	0	1 (0.4)
Lacrimation increased	0	1 (0.6)	0
Swelling of eyelid	0	1 (0.6)	0
General disorders and administration site conditions	**6 (3.7)**	**2 (1.2)**	**2 (0.8)**
Instillation site pain	5 (3.1)	2 (1.2)	1 (0.4)
Administration site pain	0	0	1 (0.4)
Instillation site pruritus	1 (0.6)	0	0
Infections and infestations	**0**	**0**	**2 (0.8)**
Conjunctivitis bacterial	0	0	2 (0.8)
Investigations	**1 (0.6)**	**0**	**1 (0.4)**
Intraocular pressure fluctuation	0	0	1 (0.4)
Intraocular pressure increased	1 (0.6)	0	0
Injury, poisoning and procedural complications	**1 (0.6)**	**0**	**0**
Foreign body in eye	1 (0.6)	0	0
Any Treatment-Related[a] Non-Ocular Treatment-Emergent AE[b]	**5 (3.1)**	**3 (1.8)**	**5 (2.0)**
Nervous system disorders	**2 (1.2)**	**3 (1.8)**	**1 (0.4)**
Headache	1 (0.6)	2 (1.2)	0
Dizziness	0	1 (0.6)	0
Epilepsy	1 (0.6)	0	0
Migraine	0	0	1 (0.4)
Seizure	1 (0.6)	0	0
Respiratory, thoracic and mediastinal disorders	**0**	**0**	**2 (0.8)**
Asthma	0	0	1 (0.4)
Epistaxis	0	0	1 (0.4)
Blood and lymphatic system disorders	**0**	**0**	**1 (0.4)**

System Organ Class Preferred Term	Vehicle (N=162) n (%)	Atropine Sulfate, 0.01% (N=164) n (%)	Atropine Sulfate, 0.02% (N=247) n (%)
Anaemia	0	0	1 (0.4)
Ear and labyrinth disorders	**1 (0.6)**	**0**	**0**
Ear pain	1 (0.6)	0	0
Investigations	**1 (0.6)**	**0**	**0**
Heart rate increased	1 (0.6)	0	0
Psychiatric disorders	**0**	**0**	**1 (0.4)**
Nightmare	0	0	1 (0.4)
Skin and subcutaneous tissue disorders	**1 (0.6)**	**0**	**0**
Rash erythematous	1 (0.6)	0	0
Vascular disorders	**1 (0.6)**	**0**	**0**
Flushing	1 (0.6)	0	0

Source: Study CP-NVK002-0001 Table 14.3.1.5.1.1; Table 14.3.1.5.1.2; Table 14.3.1.5.1.3 AE = adverse event; N=number of subjects in population; n=number of subjects assessed. Note: Stage 1 Safety population is defined by administration of at least one dose of study medication in Stage 1. Note: Adverse events are classified by system organ class and preferred term using MedDRA version 25.0. Subjects who experience the same coded event more than once are counted only one time per preferred term and one time per system organ class. [a]. Adverse events are considered treatment-related if study drug causality is very likely/certain, probable, possible, or missing. [b] :Adverse events are considered treatment emergent if they began or worsened in severity on or after the date of first dose of study drug in Stage 1 and on or before the date of last dose of study drug in Stage 1. System organ classes and preferred terms within system organ class are sorted in descending frequency by the total column.

Mini-CHAMP

In Stage 1 a total of 97 (18.7%) subjects reported at least one TEAE (Vehicle: n=32/21.9%; atropine 0.01%: n=18/12.2%; atropine 0.02%: n=47/20.9%). Ocular organ diseases were the most common TEAEs (17.0%), followed by infectious and invasive diseases (1.5%). As per PT classification, specific TEAEs included photophobia (5.0%), eye pain (4.4%), and allergic conjunctivitis (3.3%). Dose dependency was suggested for photophobia (vehicle: 3.4%; atropine 0.01%: 4.1%; atropine 0.02%: 6.7%). Other TEAE incidence was comparable across treatment groups.

China-CHAMP is still blinded hence no analysis of relatedness per treatment is available at the time of this CHMP AR authoring.

MOSAIC

During the primary treatment period (24 months), seven AEs were possibly/probably related to atropine 0.01%: eye discomfort (n = 3), temporary blurred vision at near (n = 1), temporary pupil dilation (n = 1), and rash on the eyelid (n = 2). Except for 'rash on eyelid', the AEs were also observed in CHAMP, albeit at a different frequency.

Relationship of non-serious AEs was not assessed in MTS1.

Serious adverse events, deaths, and other significant events

a. Deaths

There were no deaths reported in any of the studies that tested Atropine sulfate FGK.

b. Other serious adverse events

No ocular SAEs were reported in CHAMP, mini-CHAMP, MOSAIC or MTS1. There were no non-ocular SAEs that were dose-dependent and none were related to atropine 0.01% or 0.02%.

In China-CHAMP, there were two eye disorder SAEs reported (1x entropion, 1x strabismus). Causality assessment is not available at the time of this CHMP AR writing as that study is still blinded. These type of AEs have not been reported in CHAMP, mini-CHAMP, MOSAIC or MTS1, and are not a known ADR of atropine. They are therefore not a safety risk of concern. CHAMP results are discussed in more detail.

CHAMP

In the Stage 1 population, 13 subjects experienced a non-fatal SAE, including 8 subjects (3.2%) in the 0.02% Atropine Sulfate Eye Drops group, 4 subjects (2.5%) in the Vehicle group, and 1 subject (0.6%) in the 0.01% Atropine Sulfate Eye Drops group (SAEs of Parainfluenzae virus infection and Pneumonia). None of the SAEs were ocular. One event (seizure in a subject randomized to Vehicle) was judged to have a possible treatment relationship (classified as Suspected Unexpected Serious Adverse Reaction), and graded as severe.

In the Stage 2 population, 7 subjects experienced a non-fatal SAE including 2 subjects (1.2%) in the 0.02% Atropine Sulfate Eye Drops group, 2 subjects (2.0%) in the Vehicle group, and 3 subjects (1.9%) in the 0.01% Atropine Sulfate Eye Drops group (SAEs of Suicide attempt (1x); Appendicitis (1x); and Seizure (1x)). None of the SAEs were ocular nor were they judged to have a possible treatment relationship.

Laboratory findings

Clinical laboratory tests were only performed in case of safety concerns, which is acceptable for the type of product tested. In cases they were performed, no reasons for concern were observed.

Other observations related to safety

a. Heart rate, height and weight

Heart-rate variability is a known systemic side effect of atropine eye drops. Of the eight heart-rate related TEAEs in CHAMP, one was in the atropine 0.01% group. This TEAE was mild and considered unrelated (postural orthostatic tachycardia). No notable heart rate variability over-time was observed over 48 months in any of the treatment groups. This is in agreement with the minimal-to-absent systemic exposure of Atropine Sulfate FGK 0.01%.

In mini-CHAMP no heart rate-related AEs were identified as part of the assessment of antimuscarinic adverse events.

In MOSAIC no at least possibly related heart rate-related AEs were identified (it could not be confirmed if non-related heat rate-related AEs were reported). In MTS1 no heart rate-related AEs were reported.

There were no findings of concern in relation to height or weight measurements.

b. Ophthalmic safety evaluations

Visual acuity

In CHAMP, slight disbalances at baseline were noted with lowest LogMAR scores at baseline for atropine 0.01%. BVCA tests over 36 months showed minor changes over-time (decreasing LogMAR), at a comparable change-from-baseline rate for alle treatments. The changes-from-baseline that were observed were decreases, implying improving vision if anything. These changes were comparable between treatments.

Results of CHAMP are in line with MOSAIC and provided literature. No values were reported in the article of MTS1.

Pupil size

In CHAMP Stage 1 population, at baseline, mean pupil sizes were similar across all eyes and treatment groups, ranging from 4.59 to 4.63 mm. A dose-related increase in pupil size was observed with atropine treatment over 36 months, proving that Atropine Sulfate FGK was pharmacologically active.

In the vehicle group, the peak pupil size was between 4.72 and 4.75 mm at Month 6, and it varied from 4.50 to 4.67 mm throughout the study. The 0.01% Atropine Sulfate group saw an increase to 4.94 mm at Month 6, with sizes ranging from 4.76 to 4.95 mm up to Month 36. The 0.02% Atropine Sulfate group had larger mean pupil sizes, from 5.01 to 5.12 mm between Month 6 and 24, decreasing slightly at Month 30, then increasing again at Month 36 (See figure below).

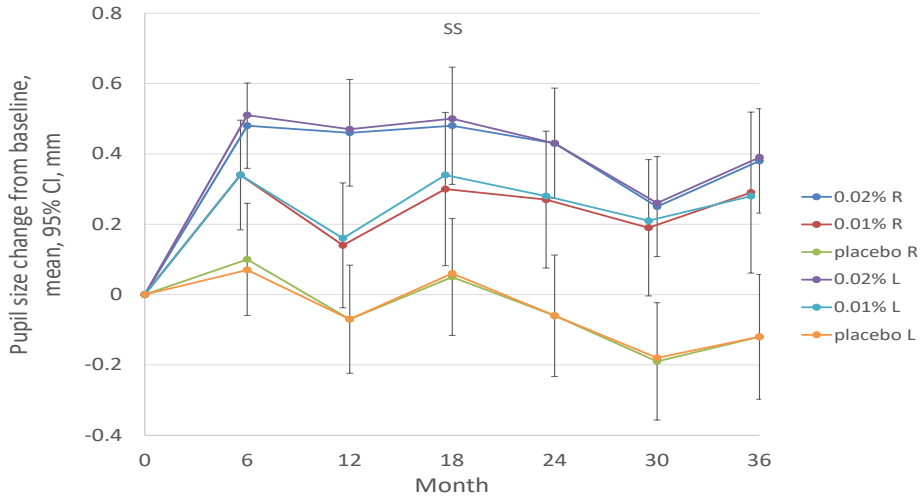


Figure 13. CHAMP stage 1, mean change from baseline in pupil size (safety set)

Slit lamp and dilated fundus examinations

Overall, in CHAMP, the number of clinically significant abnormalities were low, not dose-dependent, not eye-parameter-specific and no evident increase over-time was observed.

Tonometry/intraocular pressure (IOP) measurements

IOP was measured at screening/baseline and every 6 months during Stage 1, with mean baseline IOP ranging from 15.4-16.2 mmHg across treatment groups. Overall, no significant changes in IOP were observed at Month 36, and changes from baseline were less than 1 mmHg in each eye for all treatment groups after 36 months.

Two subjects in the Vehicle group reported IOP increased as TEAE. One subject in the atropine 0.02% group reported IOP fluctuation, which was classified as mild, possibly treatment related and was resolved prior to database lock.

Modified amblyopia treatment index (mATI)

The ATI is commonly used in this field of study. It is a questionnaire for assessing impact of atropine treatment on the child and family in amblyopia treatment studies. That the applicant used a quality-of-life scale in Stage 2 is appreciated. However, the mATI data are not considered reliable due to the following methodological issues. A modified ATI is used, but the changes compared to ATI could not be found. Hence, validity of this mATI in the CHAMP study population could not be confirmed. In addition, many biases may be present questioning validity of the outcomes. Subjects were optionally invited to start completing mATI in Stage 2 when they were already using atropine for 36 months. This means that that the sample that responded is not random, and that subjects which stopped during or at completion of Stage 1 due to ill-toleration of atropine could not contribute to the results. Internal validity of the results is also questioned as no placebo arm was included during Stage 2. Finally, there are no change-from-baseline data collected, which precludes assessing if there is a change of view over-time of the parents/guardians and/or subjects on atropine use. Altogether, the mATI data are not considered reliable for use in the benefit-risk assessment and therefore not presented.

Accommodative amplitude

Changes-from-baseline were observed in MOSAIC and MTS1. In MOSAIC, mean accommodative amplitude for atropine 0.01% was -0.57 D and -1.88 D at 18 and 24 months respectively. For the placebo arm the mean accommodative amplitude was -0.76 D and -0.84 D at 18 and 24 months respectively. These changes were considered non-significant by the Investigators. The changes reported for atropine 0.01% in MTS1 are 6.03 cm. This approximates the reduction in the LAMP study (8.3-10 cm) which were indicated to be 'not a major issue clinically' (Yam et al., 2019).

3. In vitro biomarker test for patient selection for safety

Not applicable

Safety in special populations

a. General considerations on safety assessment in special populations

Safety in special populations was limited to subgroup assessment (by age, sex and race; see next sections) and discussion of use of atropine 0.01% in pregnancy and lactation. No discussion on patients that were excluded from study participation was provided.

A contraindication for patients with glaucoma was included in the PI, which is in line with other atropine products.

Note that no contraindications for patients with increased IOP or Rhinitis sicca were proposed while these are included for certain atropine eye drops for other indications in the EU (e.g. atropin-POS® 0.5).

b. Age

Data were analysed in two age categories (< 9 years old or ≥ 9 years old). For CHAMP Stage 1 they are summarized in the following 2 tables, Table 50 and Table 51, respectively.

In CHAMP Stage 1 and 2, a slight but consistent higher number of overall TEAEs was observed in older subjects (≥9 years), for all treatments, when compared to younger subjects (<9 years). However, the frequency of ocular TEAEs did not reveal such a trend (ocular TEAEs <9 years: 38.7% (vehicle), 31.3% (atropine 0.01%), 31.9% (atropine 0.02%) vs. ≥9 years: 42% (vehicle), 22% (atropine 0.01%), 34% (atropine 0.02%)). No individual TEAE was evidently more reported for either age group. Altogether it is not considered that the safety profile of this atropine product is different for subjects <9 years or ≥9 years. This applies to both atropine 0.01% and 0.02%.

Table 50. Treatment ocular TEAEs by system organ class, preferred term, and age (CHAMP stage 1 safety population, TEAEs with incidence ≥ 1.0% in any treatment group)

System Organ Class Preferred Term	< 9 years			≥ 9 years		
	Vehicle (N=62) n (%)	Atropine Sulfate, 0.01% (N=64) n (%)	Atropine Sulfate, 0.02% (N=94) n (%)	Vehicle (N=100) n (%)	Atropine Sulfate, 0.01% (N=100) n (%)	Atropine Sulfate, 0.02% (N=153) n (%)
Any Ocular Treatment-Emergent AE[a]	**24 (38.7)**	**20 (31.3)**	**30 (31.9)**	**42 (42.0)**	**22 (22.0)**	**52 (34.0)**
Eye disorders	**19 (30.6)**	**15 (23.4)**	**23 (24.5)**	**28 (28.0)**	**18 (18.0)**	**31 (20.3)**
Ocular hyperaemia	3 (4.8)	3 (4.7)	6 (6.4)	7 (7.0)	1 (1.0)	2 (1.3)
Photophobia	3 (4.8)	3 (4.7)	4 (4.3)	2 (2.0)	1 (1.0)	7 (4.6)
Conjunctivitis allergic	2 (3.2)	0	5 (5.3)	3 (3.0)	3 (3.0)	6 (3.9)
Eye pruritus	2 (3.2)	2 (3.1)	3 (3.2)	3 (3.0)	2 (2.0)	2 (1.3)
Eye allergy	3 (4.8)	3 (4.7)	0	2 (2.0)	1 (1.0)	4 (2.6)
Eye irritation	1 (1.6)	0	1 (1.1)	5 (5.0)	1 (1.0)	1 (0.7)
Chalazion	1 (1.6)	1 (1.6)	0	4 (4.0)	2 (2.0)	0
Eye pain	3 (4.8)	2 (3.1)	0	1 (1.0)	1 (1.0)	1 (0.7)
Punctuate keratitis	3 (4.8)	2 (3.1)	1 (1.1)	1 (1.0)	0	1 (0.7)
Blepharitis	1 (1.6)	2 (3.1)	0	2 (2.0)	0	1 (0.7)
Mydriasis	0	1 (1.6)	2 (2.1)	0	1 (1.0)	2 (1.3)
Vision blurred	0	2 (3.1)	2 (2.1)	0	0	2 (1.3)
Noninfective conjunctivitis	0	0	0	3 (3.0)	2 (2.0)	0
Swelling of eyelid	0	2 (3.1)	1 (1.1)	0	1 (1.0)	0
Binocular eye movement disorder	0	1 (1.6)	0	2 (2.0)	0	0
Infections and infestations	**3 (4.8)**	**5 (7.8)**	**4 (4.3)**	**16 (16.0)**	**2 (2.0)**	**13 (8.5)**
Hordeolum	1 (1.6)	1 (1.6)	2 (2.1)	10 (10.0)	2 (2.0)	8 (5.2)
Conjunctivitis	1 (1.6)	2 (3.1)	1 (1.1)	4 (4.0)	0	3 (2.0)
Conjunctivitis bacterial	0	1 (1.6)	0	1 (1.0)	0	3 (2.0)
Conjunctivitis viral	1 (1.6)	0	1 (1.1)	2 (2.0)	0	0
Injury, poisoning and procedural complications	**0**	**0**	**2 (2.1)**	**5 (5.0)**	**1 (1.0)**	**5 (3.3)**
Foreign body in eye	0	0	0	2 (2.0)	0	2 (1.3)
Arthropod bite	0	0	0	2 (2.0)	0	0
Immune system disorders	**2 (3.2)**	**0**	**0**	**3 (3.0)**	**3 (3.0)**	**4 (2.6)**
Seasonal allergy	2 (3.2)	0	0	3 (3.0)	3 (3.0)	3 (2.0)
General disorders and administration site conditions	**1 (1.6)**	**2 (3.1)**	**0**	**5 (5.0)**	**0**	**2 (1.3)**
Instillation site pain	1 (1.6)	2 (3.1)	0	4 (4.0)	0	1 (0.7)

Source: Study CP-NVK002-0001 Table 14.3.1.14.1.2. AE = adverse event; N=number of subjects in population; n=number of subjects assessed. Note: Adverse events are classified by system organ class and preferred term using MedDRA version 25.0. Subjects who experience the same coded event more than once are counted only one time per preferred term and one time per system organ class. [a] Adverse events are considered treatment emergent if they began or worsened in severity on or after the date of first dose of study drug in Stage 1 and by administration of at least one dose of study medication in Stage 1.

Table 51. Non-ocular TEAEs by system organ class, preferred term, and age (CHAMP [study CP-NVK002-0001] stage 1 safety population, TEAEs with incidence ≥ 5.0% in any treatment group)

System Organ Class Preferred Term	< 9 years			≥ 9 years		
	Vehicle (N=62) n (%)	Atropine Sulfate, 0.01% (N=64) n (%)	Atropine Sulfate, 0.02% (N=94) n (%)	Vehicle (N=100) n (%)	Atropine Sulfate, 0.01% (N=100) n (%)	Atropine Sulfate, 0.02% (N=153) n (%)
Any Non-Ocular Treatment-Emergent AE[a]	**30 (48.4)**	**32 (50.0)**	**44 (46.8)**	**65 (65.0)**	**55 (55.0)**	**93 (60.8)**
Infections and infestations	**22 (35.5)**	**18 (28.1)**	**25 (26.6)**	**45 (45.0)**	**27 (27.0)**	**58 (37.9)**
Nasopharyngitis	10 (16.1)	9 (14.1)	10 (10.6)	12 (12.0)	8 (8.0)	20 (13.1)
COVID-19	6 (9.7)	4 (6.3)	8 (8.5)	12 (12.0)	5 (5.0)	19 (12.4)
Influenza	2 (3.2)	1 (1.6)	3 (3.2)	10 (10.0)	5 (5.0)	5 (3.3)
Nervous system disorders	**6 (9.7)**	**7 (10.9)**	**9 (9.6)**	**11 (11.0)**	**13 (13.0)**	**20 (13.1)**
Headache	4 (6.5)	5 (7.8)	8 (8.5)	10 (10.0)	9 (9.0)	15 (9.8)
Respiratory, thoracic and mediastinal disorders	**6 (9.7)**	**8 (12.5)**	**9 (9.6)**	**16 (16.0)**	**6 (6.0)**	**17 (11.1)**
Cough	1 (1.6)	2 (3.1)	2 (2.1)	8 (8.0)	1 (1.0)	5 (3.3)
Immune system disorders	**2 (3.2)**	**5 (7.8)**	**7 (7.4)**	**8 (8.0)**	**13 (13.0)**	**14 (9.2)**
Seasonal allergy	2 (3.2)	1 (1.6)	4 (4.3)	3 (3.0)	9 (9.0)	8 (5.2)
General disorders and administration site conditions	**0**	**7 (10.9)**	**11 (11.7)**	**9 (9.0)**	**5 (5.0)**	**14 (9.2)**
Pyrexia	0	4 (6.3)	9 (9.6)	6 (6.0)	4 (4.0)	12 (7.8)

Source: Study CP-NVK002-0001 Table 14.3.1.14.1.3
AE = adverse event; COVID-19=Coronavirus Disease 2019; N=number of subjects in population; n=number of subjects assessed.
Note: Adverse events are classified by system organ class and preferred term using MedDRA version 25.0. Subjects who experience the same coded event more than once are counted only one time per preferred term and one time per system organ class.
[a] Adverse events are considered treatment emergent if they began or worsened in severity on or after the date of first dose of study drug in Stage 1 and by administration of at least one dose of study medication in Stage 1.

c. Sex

In the CHAMP Stage 1 population, a majority of subjects were female (54.5%). Analysis by sex showed a slightly higher number of overall TEAEs in females than males, which was consistent for all treatments. No individual TEAE was evidently more reported for either sex.

Number of ocular TEAEs in the atropine 0.01% group did not reveal an evident difference between females and males.

A difference was observed for Vehicle for TEAEs, in the infections and infestations SOC (females: 16.5%; males: 5.6%). It is unclear what the underlying reason is, but considering this difference was only observed in the Vehicle group it does not impact the risk assessment of atropine 0.01%.

Table 52. Ocular TEAEs by system organ class, preferred term, and sex (CHAMP stage 1 safety population, TEAEs with incidence ≥ 1.0% in any treatment group)

System Organ Class Preferred Term	Female			Male		
	Vehicle (N=91) n (%)	Atropine Sulfate, 0.01% (N=85) n (%)	Atropine Sulfate, 0.02% (N=136) n (%)	Vehicle (N=71) n (%)	Atropine Sulfate, 0.01% (N=79) n (%)	Atropine Sulfate, 0.02% (N=111) n (%)
Any Ocular Treatment-Emergent AE[a]	**40 (44.0)**	**21 (24.7)**	**48 (35.3)**	**26 (36.6)**	**21 (26.6)**	**34 (30.6)**
Eye disorders	**25 (27.5)**	**16 (18.8)**	**31 (22.8)**	**22 (31.0)**	**17 (21.5)**	**23 (20.7)**
Ocular hyperaemia	5 (5.5)	2 (2.4)	6 (4.4)	5 (7.0)	2 (2.5)	2 (1.8)
Photophobia	4 (4.4)	1 (1.2)	8 (5.9)	1 (1.4)	3 (3.8)	3 (2.7)
Conjunctivitis allergic	2 (2.2)	3 (3.5)	6 (4.4)	3 (4.2)	0	5 (4.5)
Eye pruritus	2 (2.2)	2 (2.4)	3 (2.2)	3 (4.2)	2 (2.5)	2 (1.8)
Eye allergy	1 (1.1)	1 (1.2)	1 (0.7)	4 (5.6)	3 (3.8)	3 (2.7)
Eye irritation	5 (5.5)	0	1 (0.7)	1 (1.4)	1 (1.3)	1 (0.9)
Chalazion	3 (3.3)	3 (3.5)	0	2 (2.8)	0	0
Eye pain	3 (3.3)	2 (2.4)	1 (0.7)	1 (1.4)	1 (1.3)	0
Punctuate keratitis	2 (2.2)	1 (1.2)	1 (0.7)	2 (2.8)	1 (1.3)	1 (0.9)
Blepharitis	1 (1.1)	1 (1.2)	1 (0.7)	2 (2.8)	1 (1.3)	0
Mydriasis	0	1 (1.2)	3 (2.2)	0	1 (1.3)	1 (0.9)
Vision blurred	0	1 (1.2)	2 (1.5)	0	1 (1.3)	2 (1.8)
Noninfective conjunctivitis	2 (2.2)	2 (2.4)	0	1 (1.4)	0	0
Swelling of eyelid	0	2 (2.4)	0	0	1 (1.3)	1 (0.9)
Binocular eye movement disorder	1 (1.1)	0	0	1 (1.4)	1 (1.3)	0
Infections and infestations	**15 (16.5)**	**4 (4.7)**	**10 (7.4)**	**4 (5.6)**	**3 (3.8)**	**7 (6.3)**
Hordeolum	9 (9.9)	2 (2.4)	7 (5.1)	2 (2.8)	1 (1.3)	3 (2.7)
Conjunctivitis	4 (4.4)	1 (1.2)	2 (1.5)	1 (1.4)	1 (1.3)	2 (1.8)
Conjunctivitis bacterial	1 (1.1)	0	1 (0.7)	0	1 (1.3)	2 (1.8)
Conjunctivitis viral	2 (2.2)	0	1 (0.7)	1 (1.4)	0	0
Injury, poisoning and procedural complications	**3 (3.3)**	**0**	**4 (2.9)**	**2 (2.8)**	**1 (1.3)**	**3 (2.7)**
Foreign body in eye	2 (2.2)	0	1 (0.7)	0	0	1 (0.9)
Arthropod bite	1 (1.1)	0	0	1 (1.4)	0	0
Immune system disorders	**3 (3.3)**	**2 (2.4)**	**2 (1.5)**	**2 (2.8)**	**1 (1.3)**	**2 (1.8)**
Seasonal allergy	3 (3.3)	2 (2.4)	1 (0.7)	2 (2.8)	1 (1.3)	2 (1.8)
General disorders and administration site conditions	**4 (4.4)**	**1 (1.2)**	**2 (1.5)**	**2 (2.8)**	**1 (1.3)**	**0**
Instillation site pain	3 (3.3)	1 (1.2)	1 (0.7)	2 (2.8)	1 (1.3)	0

Source: Study CP-NVK002-0001 Table 14.3.1.12.1.2
AE = adverse event; N=number of subjects in population; n=number of subjects assessed.
Note: Adverse events are classified by system organ class and preferred term using MedDRA version 25.0. Subjects who experience the same coded event more than once are counted only one time per preferred term and one time per system organ class.
[a] Adverse events are considered treatment emergent if they began or worsened in severity on or after the date of first dose of study drug in Stage 1 and by administration of at least one dose of study medication in Stage 1

Table 53. Non-ocular TEAEs by system organ class, preferred term, and sex (CHAMP stage 1 safety population, TEAEs with incidence ≥ 5.0% in any treatment group)

System Organ Class Preferred Term	Female			Male		
	Vehicle (N=91) n (%)	Atropine Sulfate, 0.01% (N=85) n (%)	Atropine Sulfate, 0.02% (N=136) n (%)	Vehicle (N=71) n (%)	Atropine Sulfate, 0.01% (N=79) n (%)	Atropine Sulfate, 0.02% (N=111) n (%)
Any Non-Ocular Treatment-Emergent AE[a]	**53 (58.2)**	**47 (55.3)**	**78 (57.4)**	**42 (59.2)**	**40 (50.6)**	**59 (53.2)**
Infections and infestations	**39 (42.9)**	**28 (32.9)**	**45 (33.1)**	**28 (39.4)**	**17 (21.5)**	**38 (34.2)**
Nasopharyngitis	13 (14.3)	8 (9.4)	19 (14.0)	9 (12.7)	9 (11.4)	11 (9.9)
COVID-19	8 (8.8)	6 (7.1)	14 (10.3)	10 (14.1)	3 (3.8)	13 (11.7)
Influenza	8 (8.8)	4 (4.7)	5 (3.7)	4 (5.6)	2 (2.5)	3 (2.7)
Nervous system disorders	**11 (12.1)**	**12 (14.1)**	**16 (11.8)**	**6 (8.5)**	**8 (10.1)**	**13 (11.7)**
Headache	9 (9.9)	6 (7.1)	12 (8.8)	5 (7.0)	8 (10.1)	11 (9.9)
Respiratory, thoracic and mediastinal disorders	**12 (13.2)**	**8 (9.4)**	**15 (11.0)**	**10 (14.1)**	**6 (7.6)**	**11 (9.9)**
Cough	5 (5.5)	1 (1.2)	4 (2.9)	4 (5.6)	2 (2.5)	3 (2.7)
Immune system disorders	**7 (7.7)**	**8 (9.4)**	**10 (7.4)**	**3 (4.2)**	**10 (12.7)**	**11 (9.9)**
Seasonal allergy	4 (4.4)	4 (4.7)	6 (4.4)	1 (1.4)	6 (7.6)	6 (5.4)
General disorders and administration site conditions	**6 (6.6)**	**5 (5.9)**	**13 (9.6)**	**3 (4.2)**	**7 (8.9)**	**12 (10.8)**
Pyrexia	4 (4.4)	3 (3.5)	11 (8.1)	2 (2.8)	5 (6.3)	10 (9.0)

Source: Study CP-NVK002-0001 Table 14.3.1.12.1.3
AE = adverse event; COVID-19=Coronavirus Disease 2019; N=number of subjects in population; n=number of subjects assessed.
Note: Adverse events are classified by system organ class and preferred term using MedDRA version 25.0. Subjects who experience the same coded event more than once are counted only one time per preferred term and one time per system organ class.
[a] Adverse events are considered treatment emergent if they began or worsened in severity on or after the date of first dose of study drug in Stage 1 and by administration of at least one dose of study medication in Stage 1.

d. Race

CHAMP results were compared for the Asian, White/Caucasian and Black/African American subgroups. Too few data were indicated to be available for the other races enrolled in the study.

In both the Vehicle and atropine 0.02% groups, a higher number of ocular TEAEs was observed in white/Caucasian subjects (47.8% resp. 36.4%) compared to Asian (26.9% resp. 25.9%) and black/African American subjects (25.9% resp. 25.8%). In the vehicle group, this difference was driven by TEAEs in the ocular infections and infestations SOC (primarily hordeolum and conjunctivitis); in atropine 0.02% no specific SOC was found primarily attributable.

In the atropine 0.01% group, ocular TEAEs were more reported in Asian (24.1%) and White/Caucasian (22.6%) subjects compared to Black/African American subjects (13%). This difference was driven in the eye disorders SOC. The difference does not appear driven by a single TEAE.

Table 54. Ocular TEAEs by system organ class, preferred term, and race (CHAMP stage 1 safety population, TEAEs with incidence ≥ 1.0% in any treatment group)

System Organ Class Preferred Term	Asian[a]			White or Caucasian			Black or African American		
	Vehicle (N=26)	Atropine Sulfate, 0.01% (N=29)	Atropine Sulfate, 0.02% (N=54)	Vehicle (N=92)	Atropine Sulfate, 0.01% (N=84)	Atropine Sulfate, 0.02% (N=132)	Vehicle (N=27)	Atropine Sulfate, 0.01% (N=23)	Atropine Sulfate, 0.02% (N=31)
Any Ocular Treatment-Emergent AE[b]	**7 (26.9)**	**7 (24.1)**	**14 (25.9)**	**44 (47.8)**	**19 (22.6)**	**48 (36.4)**	**7 (25.9)**	**3 (13.0)**	**8 (25.8)**
Eye disorders	**7 (26.9)**	**6 (20.7)**	**9 (16.7)**	**27 (29.3)**	**15 (17.9)**	**31 (23.5)**	**5 (18.5)**	**1 (4.3)**	**7 (22.6)**
Ocular hyperaemia	1 (3.8)	0	2 (3.7)	5 (5.4)	1 (1.2)	4 (3.0)	1 (3.7)	1 (4.3)	1 (3.2)
Photophobia	1 (3.8)	1 (3.4)	3 (5.6)	2 (2.2)	2 (2.4)	4 (3.0)	0	0	1 (3.2)
Conjunctivitis allergic	1 (3.8)	1 (3.4)	2 (3.7)	3 (3.3)	1 (1.2)	5 (3.8)	1 (3.7)	0	3 (9.7)
Eye pruritus	1 (3.8)	0	1 (1.9)	2 (2.2)	2 (2.4)	4 (3.0)	0	1 (4.3)	0
Eye allergy	2 (7.7)	1 (3.4)	0	3 (3.3)	2 (2.4)	2 (1.5)	0	0	1 (3.2)
Eye irritation	0	1 (3.4)	0	4 (4.3)	0	0	2 (7.4)	0	1 (3.2)
Chalazion	0	0	0	4 (4.3)	1 (1.2)	0	0	0	0
Eye pain	1 (3.8)	0	0	2 (2.2)	1 (1.2)	0	0	0	0
Punctuate keratitis	2 (7.7)	0	0	0	0	2 (1.5)	1 (3.7)	0	0
Blepharitis	1 (3.8)	1 (3.4)	0	2 (2.2)	1 (1.2)	0	0	0	0
Mydriasis	0	0	0	0	2 (2.4)	2 (1.5)	0	0	1 (3.2)
Vision blurred	0	0	0	0	2 (2.4)	4 (3.0)	0	0	0
Noninfective conjunctivitis	1 (3.8)	0	0	2 (2.2)	0	0	0	0	0
Swelling of eyelid	0	0	0	0	2 (2.4)	1 (0.8)	0	0	0
Binocular eye movement disorder	1 (3.8)	0	0	1 (1.1)	1 (1.2)	0	0	0	0
Infections and infestations	**1 (3.8)**	**1 (3.4)**	**2 (3.7)**	**17 (18.5)**	**3 (3.6)**	**11 (8.3)**	**1 (3.7)**	**1 (4.3)**	**2 (6.5)**
Hordeolum	1 (3.8)	1 (3.4)	1 (1.9)	9 (9.8)	1 (1.2)	7 (5.3)	1 (3.7)	1 (4.3)	1 (3.2)
Conjunctivitis	0	0	1 (1.9)	5 (5.4)	1 (1.2)	2 (1.5)	0	0	0
Conjunctivitis bacterial	0	0	0	1 (1.1)	1 (1.2)	3 (2.3)	0	0	0
Conjunctivitis viral	0	0	0	3 (3.3)	0	0	0	0	1 (3.2)
Injury, poisoning and procedural complications	**0**	**0**	**2 (3.7)**	**5 (5.4)**	**0**	**3 (2.3)**	**0**	**1 (4.3)**	**0**
Foreign body in eye	0	0	0	2 (2.2)	0	2 (1.5)	0	0	0
Arthropod bite	0	0	0	2 (2.2)	0	0	0	0	0
Immune system disorders	**0**	**0**	**0**	**5 (5.4)**	**1 (1.2)**	**4 (3.0)**	**0**	**0**	**0**
Seasonal allergy	0	0	0	5 (5.4)	1 (1.2)	3 (2.3)	0	0	0
General disorders and administration site conditions	**1 (3.8)**	**1 (3.4)**	**0**	**2 (2.2)**	**1 (1.2)**	**2 (1.5)**	**3 (11.1)**	**0**	**0**
Instillation site pain	0	1 (3.4)	0	2 (2.2)	1 (1.2)	1 (0.8)	3 (11.1)	0	0

Source: Study CP-NVK002-0001 Table 14.3.1.13.1.2

AE=adverse event; N=number of subjects in population.

Note: Adverse events are classified by system organ class and preferred term using MedDRA version 25.0. Subjects who experience the same coded event more than once are counted only one time per preferred term and one time per system organ class.

[a] Asian includes subjects presented in the source table as Japanese, East Asian, and South Asian (Pakistan, India, and Bangladesh).

[b] Adverse events are considered treatment emergent if they began or worsened in severity on or after the date of first dose of study drug in Stage 1 and by administration of at least one dose of study medication in Stage 1.

Table 55. Non-ocular TEAEs by system organ class, preferred term, and race (CHAMP stage 1 safety population, TEAEs with incidence ≥ 5.0% in any treatment group

System Organ Class Preferred Term	Asian[a]			White or Caucasian			Black or African American		
	Vehicle (N=26)	Atropine Sulfate, 0.01% (N=29)	Atropine Sulfate, 0.02% (N=54)	Vehicle (N=92)	Atropine Sulfate, 0.01% (N=84)	Atropine Sulfate, 0.02% (N=132)	Vehicle (N=27)	Atropine Sulfate, 0.01% (N=23)	Atropine Sulfate, 0.02% (N=31)
Any Non-Ocular Treatment-Emergent AE[b]	**14 (53.8)**	**10 (34.5)**	**20 (37.0)**	**61 (66.3)**	**50 (59.5)**	**87 (65.9)**	**8 (29.6)**	**7 (30.4)**	**11 (35.5)**
Infections and infestations	**6 (23.1)**	**7 (24.1)**	**10 (18.5)**	**47 (51.1)**	**25 (29.8)**	**57 (43.2)**	**4 (14.8)**	**3 (13.0)**	**5 (16.1)**
Nasopharyngitis	2 (7.7)	2 (6.9)	5 (9.3)	11 (12.0)	9 (10.7)	15 (11.4)	2 (7.4)	0	4 (12.9)
COVID-19	0	1 (3.4)	3 (5.6)	14 (15.2)	6 (7.1)	20 (15.2)	1 (3.7)	1 (4.3)	0
Influenza	2 (7.7)	2 (6.9)	1 (1.9)	9 (9.8)	3 (3.6)	5 (3.8)	0	1 (4.3)	1 (3.2)
Nervous system disorders	**0**	**1 (3.4)**	**4 (7.4)**	**8 (8.7)**	**8 (9.5)**	**14 (10.6)**	**4 (14.8)**	**1 (4.3)**	**2 (6.5)**
Headache	0	1 (3.4)	4 (7.4)	0	1 (1.2)	3 (2.3)	4 (14.8)	0	1 (3.2)
Respiratory, thoracic and mediastinal disorders	**4 (15.4)**	**0**	**7 (13.0)**	**14 (15.2)**	**12 (14.3)**	**16 (12.1)**	**3 (11.1)**	**1 (4.3)**	**1 (3.2)**
Cough	2 (7.7)	0	2 (3.7)	6 (6.5)	2 (2.4)	5 (3.8)	1 (3.7)	1 (4.3)	0
Immune system disorders	**1 (3.8)**	**0**	**2 (3.7)**	**6 (6.5)**	**12 (14.3)**	**19 (14.4)**	**2 (7.4)**	**0**	**0**
Seasonal allergy	0	0	1 (1.9)	4 (4.3)	9 (10.7)	11 (8.3)	1 (3.7)	0	0
General disorders and administration site conditions	**0**	**3 (10.3)**	**5 (9.3)**	**7 (7.6)**	**7 (8.3)**	**14 (10.6)**	**1 (3.7)**	**1 (4.3)**	**3 (9.7)**
Pyrexia	0	2 (6.9)	5 (9.3)	4 (4.3)	4 (4.8)	12 (9.1)	1 (3.7)	1 (4.3)	3 (9.7)

Source: Study CP-NVK002-0001 Table 14.3.1.13.1.3 AE = adverse event; COVID-19=Coronavirus Disease 2019; N=number of subjects in population. Note: Adverse events are classified by system organ class and preferred term using MedDRA version 25.0. Subjects who experience the same coded event more than once are counted only one time per preferred term and one time per system organ class.[a]: Asian includes subjects presented in the source table as Japanese, East Asian, and South Asian (Pakistan, India, and Bangladesh). Excludes Subject 003-025 (race: Japanese) who did not report any TEAEs.[b]: Adverse events are considered treatment emergent if they began or worsened in severity on or after the date of first dose of study drug in Stage 1 and by administration of at least one dose of study medication in Stage 1.

e. Use in pregnancy and lactation

There have been no studies conducted on the administration of Atropine Sulfate 0.01% Eye Drops in pregnant women to determine any associated risks and no pregnancies occurred during the CHAMP Stage 1 or 2 study.

In CHAMP, female subjects of childbearing potential were screened for pregnancy prior to enrolment (requirement every 6 months in this population was removed in Protocol Amendment 2). Urine pregnancy screening was performed but details of the test used is unknown. There were no pregnancies reported in CHAMP and it is considered that the targeted female population is only partly post-menarche.

Systemic exposure of atropine 0.01% is expected to be minor if not absent.

The reader could refer to the non-clinical assessment for further considerations that would have applied on SmPC section 4.6.

f. Overdose

The product is intended to be sold in single-dose containers, the risk for accidental overdose is therefore limited. Similarly, accidental ingestion is not likely. Even if so, a limited amount will be ingested.

The text included in the proposed SmPC in principle ~~is~~ was appropriate to address the expected risk of overdosing of this product with the intended container.

g. Drug abuse

The risk for abuse of this product is considered negligible.

Literature does not indicate a risk for abuse of this product. It is agreed with the applicant that there does not appear to be a need to discuss this risk in the proposed SmPC.

H. Effects on ability to drive or operate machinery or impairment of mental ability

Atropine may induce photophobia and blurred vision, impairing ability to drive and operate machines. A warning until effects have subsided was therefore supported.

For other atropine eye drops blurred vision is generally indicated to be up to 7 days after treatment and considered a moderate influence. Duration of impaired vision based on CHAMP data were not provided, but ~~a~~ were needed to determine the degree of influence and suitability of the proposed wording in SmPC section 4.7.

Safety related to drug-drug interactions and other interactions

The applicant indicated that no interaction was identified. This is not agreed; the reader is referred to the Discussion on clinical pharmacology section (3.3.2) for details.

Discontinuation due to adverse events

Overall, a low number of subjects discontinued or withdrew from study participation due to AEs. The number of TEAEs leading to discontinuation were comparable between studies CHAMP, mini-CHAMP, China-CHAMP, MOSAIC and MTS1.

CHAMP

In the Stage 1 population, an increased discontinuation rate was observed for the 0.01% group (77.4% completers in atropine 0.01% groups; 86.7% in the vehicle group). More subjects in the Vehicle group were coded as discontinued study drug due to an AE (10 subjects; 6.2%) compared to the atropine 0.01% group (0 subjects) or in the atropine 0.02% Drops group (5 subjects; 2.0%; - refer to the table below). Post-hoc investigations in ITT revealed that, of the 48 discontinued subjects, coded as Withdrawal of consent, Other or Blank, 19 dropouts can be associated with a reference to, or inference of, AE or lack of efficacy (6 in the vehicle group, 4 in the 0.01% group, and 9 in the 0.02% group).

In the Stage 2 population, a total of 2 subjects (0.4%) permanently discontinued the study drug due to a TEAE, of which 1 subject was randomized to 0.02% Atropine Sulfate Eye Drops (AEs of eye irritation and vision blurred) and 1 subject randomized to Vehicle (AE of Oppositional defiant disorder).

Table 56. Treatment-emergent adverse events leading to permanent discontinuation of study drug by system organ class and preferred term – CHAMP stage 1 safety population

System Organ Class Preferred Term	Vehicle (N=162) n (%)	Atropine Sulfate, 0.01% (N=164) n (%)	Atropine Sulfate, 0.02% (N=247) n (%)
Any Treatment-Emergent AE[a] Leading to Permanent Discontinuation	**10 (6.2)**	**0**	**5 (2.0)**
Any Ocular Treatment-Emergent AE[a] Leading to Permanent Discontinuation	**8 (4.9)**	**0**	**3 (1.2)**
General disorders and administration site conditions	**5 (3.1)**	**0**	**2 (0.8)**
Instillation site pain	5 (3.1)	0	1 (0.4)
Administration site pain	0	0	1 (0.4)
Eye disorders	**4 (2.5)**	**0**	**1 (0.4)**
Eye irritation	3 (1.9)	0	0
Eye inflammation	1 (0.6)	0	0
Eyelid irritation	0	0	1 (0.4)
Any Non-Ocular Treatment-Emergent AE[a] Leading to Permanent Discontinuation	**2 (1.2)**	**0**	**2 (0.8)**
Nervous system disorders	**1 (0.6)**	**0**	**2 (0.8)**
Headache	0	0	2 (0.8)
Epilepsy	1 (0.6)	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**0**	**0**	**1 (0.4)**
Brain neoplasm malignant	0	0	1 (0.4)
Vascular disorders	**1 (0.6)**	**0**	**0**
Flushing	1 (0.6)	0	0

Source: Study CP-NVK002-0001 Table 14.3.1.9.1.1; Table 14.3.1.9.1.2; Table 14.3.1.9.1.3
AE = adverse event; N=number of subjects in population; n=number of subjects assessed.
Note: Stage 1 Safety population is defined by administration of at least one dose of study medication in Stage 1.
Note: Adverse events are classified by system organ class and preferred term using MedDRA version 25.0. Subjects who experience the same coded event more than once are counted only one time per preferred term and one time per system organ class.
[a] Adverse events are considered treatment emergent if they began or worsened in severity on or after the date of first dose of study drug in Stage 1 and on or before the date of last dose of study drug in Stage 1. System organ classes and preferred terms within system organ class are sorted in descending frequency by the total column.

Partner and investigator sponsored studies

Mini-CHAMP

A total of 7 subjects (1.4%) in the Mini-CHAMP study, reported AEs leading to termination of the use of the Atropine Sulfate Eye Drops, of which eye pain (3 subjects, 0.6%) was the most common; referred is to the table below for a summary.

Table 57. Summary of TEAEs leading to permanent discontinuation by system organ class and preferred term - stage 1 of mini-CHAMP

System organ classification Preferred terminology	0.01% atropine (N = 147) n (%)	0.02% atropine (N = 225) n (%)	placebo (N = 146) n (%)	total (N = 518) n (%)
TEAE leading to termination of the study drug administration	**2 (1.4)**	**3 (1.3)**	**2 (1.4)**	**7 (1.4)**
Eye diseases	2 (1.4)	3 (1.3)	0	5 (1.0)
Eye pain	1 (0.7)	2 (0.9)	0	3 (0.6)
Eczematous blepharitis	0	1 (0.4)	0	1 (0.2)
Itchy eyes	0	1 (0.4)	0	1 (0.2)
Strabismus	1 (0.7)	0	0	1 (0.2)
Various inspections	0	0	1 (0.7)	1 (0.2)
Increased intraocular pressure	0	0	1 (0.7)	1 (0.2)
Systemic diseases and various reactions at the administration site	0	0	1 (0.7)	1 (0.2)
Fever	0	0	1 (0.7)	1 (0.2)

Source: Mini-CHAMP CSR Table 54
TEAE = Adverse events that occurred or worsened during treatment/administration.
Adverse events were coded using MedDRA 26.0.
Percentages were calculated based on the number of subjects in each treatment group in SS.
A total of 5 subjects (1.0%) in the Mini-CHAMP study, reported AEs related to the Atropine Sulfate Eye Drops that led to subject withdrawal from the study. Of which, eye pain (3 subjects, 0.6%) was the most common. The incidences of TEAEs that led to subject withdrawal from the study by SOC and PT are provided in Table 26.

China-CHAMP

Causality was not assessed as the study is still blinded. 18 subjects (2.3) experienced an TEAE leading to treatment discontinuation, the majority were eye disorders (16 subjects, 2.1 - Table 58 below).

Table 58. TEAEs leading to permanent treatment discontinuation by system organ class and preferred term in China-CHAMP, n (%)

System Organ Class Preferred Term	(N=777) n (%)
Any TEAE leading to discontinuation	**18 (2.3%)**
Eye disorders	16 (2.1%)
Eye pain	14 (1.8%)
Photophobia	1 (0.1%)
Strabismus	1 (0.1 %)
Respiratory, thoracic and mediastinal disorders	1 (0.1%)
Epistaxis	1 (0.1%)
Skin and subcutaneous tissue disorders	1 (0.1%)
Urticaria	1 (0.1%)

As of DLP, 15 November 2023
TEAE = treatment emergent adverse event; N=number of subjects in population; n=number of subjects assessed.

MOSAIC and MTS1

From the articles of MOSAIC (Loughman et al., 2023) and MTS1 (Repka et al., 2023) it could be confirmed that discontinuation rates in the atropine 0.01% groups were similarly low and roughly comparable to the Vehicle groups.

Post marketing experience

Not applicable.

2.6.9 Discussion on clinical safety

Considerations on the safety dataset

Overall, a reliable dataset comprising primarily four completed double-blind placebo-controlled studies (CHAMP, mini-CHAMP, MOSAIC, MTS1) was submitted.

Safety was mainly based on AE reporting and ophthalmologic assessments. AE reporting was performed every 2 weeks (CHAMP Stage 1 Year 1), otherwise every 3-6 months, or *ad hoc* by the subject at any time. This frequency of fixed reporting is considered limited and may have resulted in underreporting.

Evidence suggests that a lower concentration of atropine is associated with lower AE incidence. (Sun et al., 2023) I.e., data of different concentration such as 0.01% and 0.02% cannot be readily combined. Hence, data collected specifically for atropine 0.01% were of primary interest and considered of sufficient size.

Altogether, data were provided for 373 subjects exposed at least 24 months to Atropine Sulfate 0.01%, and an additional 932 subjects exposed to atropine 0.01% of other sources. Considering atropine is a well-known substance, the size of the safety database overall was sufficient.

Considerations on safety data in special populations

In Round 2 of this initial MAA, the applicant provided a summary of class effects based on the SmPCs of Eikance, Minims and Aspire, which led to a warning for corneal calcification based on that the product has phosphate. This risk has been acknowledged (EMA/CHMP/753373/2012); inclusion in section 4.4 of the proposed SmPC was agreed.

In the SmPC of Eikance (atropine 1%) there are warnings for 'keratoconus' and 'synechiae'. In round 3 they were added as class-related warning in section 4.4 of the proposed SmPC.

The applicant argued that a warning for CNS disorders is not appropriate for Atropine Sulfate FGK as there was no detectable exposure. This was agreed. It was also recalled that there were no CNS-related AEs reported.

The applicant did not include a warning on rebound effects, which was accepted as there was no clear sign of rebound in CHAMP Stage 2.

There have been no studies conducted on the administration of atropine 0.01% in pregnant women; no pregnancies occurred during the CHAMP study. Animal studies had not shown reproductive toxicity. The applicant had advised to avoid using atropine eye drops during pregnancy unless necessary in the proposed SmPC. In accordance with applicable guidance (EMEA/CHMP/203927/2005; appendix 3 label 5), the applicant updated the respective proposed Atropine FGK SmPC text to 'preferable to avoid'.

No data are available in humans with regard to overdose with atropine sulfate. The applicant added in the proposed SmPC a section about possible systemic reactions in the event of accidental ingestion or overdosage. The applicant did not find reports of possible atropine abuse in clinical literature.

Considerations on reported TEAEs

In CHAMP, based on the number of TEAEs overall good tolerance to atropine 0.01% was observed. The type of AEs reported for atropine 0.01% were in line with what is known for atropine eye drops, and the incidence was comparable to Vehicle.

Ocular AEs in Stage 1 more commonly reported for atropine than vehicle are in line with atropine's known safety profile. Ocular TEAEs overall were not dose-dependent. Most frequent TEAEs where

(vehicle vs atropine 0.01% vs atropine 0.02%, respectively): photophobia (3.1% vs 2.4% vs 4.5%), conjunctivitis allergic (3.1% vs 1.8% vs 4.5%), mydriasis (0% vs 1.2% vs 1.6%) and blurred vision (0% vs 1.2% vs 1.6%).

In Stage 2 the most common TEAE were (vehicle vs atropine 0.01% vs atropine 0.02%, respectively): dry eye (0% vs 1.3% vs 1.9%); retinal degeneration (0% vs 1.9% vs 0.6%) and conjunctivitis (0% vs 0.6% vs 1.9%).

The TEAEs of retinal degeneration were all deemed unrelated to the study drug, and clarified to be in all cases lattice degeneration of the retina. The applicant indicated that MTS1, another study with Atropine Sulfate FGK, also observed two cases but did not report these in the publication. The ATLAS study, evaluating other atropine formulations, reported 3 cases over 10-20 years. Further, it was indicated that lattice degeneration likely is not reported in publications of other RCTs as those included AEs of interest rather than full AE listings, and/or may not have used appropriate assessment methods to diagnose lattice degeneration. These arguments were accepted. It is also recalled that lattice degeneration is a relatively common condition with increased prevalence in myopic eyes, i.e., that these AEs were reported is not a concern on itself. There is, thus, no clear signal that Atropine Sulfate FGK 0.01% causes lattice degeneration.

In Round 2, it was shown that the AEs "Dry eye" and "Conjunctivitis allergic" were reported at comparable frequency for both atropine doses and placebo.

The applicant attributed the low number of TEAEs typically associated with atropine, e.g., blurred vision, to installation before bedtime with TEAEs resolved upon waking. This argument was not further supported by data (i.e. information whether these events occurred mainly around the time of administration is lacking). However, based on clinical practice with atropine eyedrops and eyedrops in general it was reasonable to assume that most of these events are related to installation.

The incidence of TEAEs in CHAMP is similar to MOSAIC, but not to MTS1. In MTS1 a much higher number of TEAEs around administration was reported (e.g., eye irritation at time of instillation (atropine: 72%; placebo: 82%), photophobia (atropine: 26%; placebo: 27%), and blurred vision (atropine: 14%; placebo: 16%). This difference was not explained by the applicant, but may be at least partly due to study design differences. Nonetheless, TEAE incidence for atropine 0.01% is comparable to placebo in both CHAMP and MTS1 and as such does not cause concern. This finding was therefore not further pursued.

Headache, a known systemic AE of atropine, was reported at comparable frequencies between all three treatment arms. AEs related to heart-rate variability, which would also suggest systemic exposure, were reported in low frequency (three subjects: 1x Vehicle; 2x atropine 0.02%). Similar considerations apply to Stage 2 and mini-CHAMP results. These data do not suggest that atropine 0.01% results in exposure levels that induce systemic side effects.

In CHAMP Stage 1, overall, the number of ADRs was low. There were less ADRs for atropine 0.01% and 0.02% compared to Vehicle and the type of reported ADRs are in line with the known safety profile of atropine eye drops. Similar findings apply to CHAMP Stage 2 and MOSAIC (MTS1 did not assess causality). The total number of ADRs in mini-CHAMP was slightly higher but of comparable nature to CHAMP.

The proposed ADR table was generally in line with findings from the four studies. However, justification or correction was requested for not including ADRs from mini-CHAMP and MOSAIC that were not observed in CHAMP (i.e., eye irritation, itchy eyes, blinking excessively, eczematous blepharitis and rash on eyelid). In Round 2, the AEs 'eye irritation' and 'excessive blinking' were added to the ADR table. It was accepted that 'itchy eyes discomfort', 'temporary blurred vision at near' and 'temporary

pupil dilation' overlap with these or other ADRs already included in the ADR table. As eczematous blepharitis was reported only in one subject receiving atropine 0.02%, not 0.01%, it was agreed to not include this as ADR. In round 3 ''rash on eyelid' was added based on MOSAIC safety results.

An overview of onset of TEAEs in CHAMP, categorized per year, was provided: most had an onset in Year 1. Further data on duration of AEs were provided in individual AE listings, which hampered assessing impact of AEs on daily life, e.g. if blurred vision was generally resolved the next day or not. Mydriasis may last up to 7 days. Potentially mydriasis and blurred vision if of long duration may affect daily performance. In Round 2, the applicant showed that the impact of mydriasis and blurred vision on daily life was low as the incidence of these AEs was low. Moreover, it was argued that impact likely was low as significant pupil diameter increase did not correspond to the low AE incidence. Lack of impact on vision was supported by negligible impact on BCVA, and section 4.4 of the proposed SmPC was updated to further discuss the risk for photophobia. Details provided showed that the reported duration of each AE, in general, was short (<60 min).

While the observation remained that the AE incidence may have been underestimated in CHAMP (section 3.3.9.), it was nonetheless agreed that, with the updates made to the proposed SmPC section 4.4., the AEs mydriasis and blurred vision were manageable.

There were no deaths in studies that tested Atropine Sulfate FGK 0.01%. Incidence of severe TEAEs was low. Frequency for atropine 0.01% was comparable (mini-CHAMP, MOSAIC, MTS1) or lower (CHAMP) than Vehicle. In these studies there were also no ocular SAEs. Number of subjects that permanently discontinued or withdrew from the study was acceptable. No dose-dependency was observed.

No trends of a different safety profile between the subgroups age, sex or race were observed for atropine 0.01%.

Considerations on other noteworthy ophthalmologic evaluations

In CHAMP Stage 1, a dose-related increase in pupil size was observed (. The increase was most evident at Month 6, which was also the timepoint at which the pupils were of largest size (+ ~0.3 mm for the 0.01% dose). It was unclear to what extent the increased pupil size impacts visual performance or patient's their eyes' health; but this was not further of concern as no significant effect on IOP was observed in CHAMP.

Thus, there were no notable safety concerns over the 4 years evaluated in CHAMP. There was no indication that the safety profile changes the years thereafter, also considering that pupil size remained stable after Month 6. It was also not expected that, in case there are rare safety issues associated with Atropine Sulfate FGK 0.01%, that they can be picked up by a decades-long safety study. Routine evaluation in the form of PSURs were considered by CHMP more appropriate in this regard; however, this is not further applicable in light of the CHMP conclusion on the benefit/risk profile of Atropine FGK, as detailed in section 4 of this AR. Further, there were no evident safety signals from long-term use of magistral preparations of atropine 0.01% in the EEA. Altogether, it was considered that there was no direct concern that warrants further specific studies on safety.

Other comments

Atropine eye drops is a preservative-free ophthalmic formulation. From a safety perspective, this constituted a favourable point since many preservatives are known to be associated with ocular AEs.

Additional expert consultations

Not applicable.

2.6.10 Conclusions on the clinical safety

A reliable safety dataset comprising primarily four completed double-blind placebo-controlled studies was provided. In CHAMP, based on the number of TEAEs overall good tolerance to atropine 0.01% was observed with a profile comparable to Vehicle.

The type of AEs reported for atropine 0.01% in CHAMP were generally in line with what is known for atropine eye drops: mydriasis and vision blurred appeared dose-dependent. The frequency with which they were observed in CHAMP and MOSAIC were lower than what is generally known, but also much lower than in MTS1. As the proactive AE reporting frequency was limited, it was unclear if AEs in CHAMP may have been underreported.

Based on data provided and the well-known safety profile of atropine, no important identified risks or important potential risks were included in the drafted Risk Management Plan (RMP) proposed by the applicant in the framework of this initial MAA.

2.7 Risk Management Plan

The CHMP, having considered the data submitted in the application was of the opinion that due to the concerns identified with this application, the RMP cannot be agreed at this stage.

2.8 Pharmacovigilance

2.8.1 Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfilled the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2 Periodic Safety Update Reports submission requirements

Not applicable.

2.9 Product information

In light of the negative CHMP recommendation (see section 5 of this AR) on this initial MAA, a satisfactory summary of product characteristics, labelling and package leaflet cannot be agreed at this stage.

2.9.1 User consultation

The results of the user consultation with target patient groups on the proposed package leaflet submitted by the applicant showed that the package leaflet met the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3. Benefit-risk balance

3.1. Therapeutic context

3.1.1. Disease or condition

The (last) indication claimed by the applicant during MAA assessment for Atropine sulfate FGK (0.01%) is to slow myopia progression in children aged 6 to 10 years with spherical equivalent refraction (SER) in the range of -0.50 to -6.00 diopter (D).

Myopia, also called near-sightedness, is an eye disease that results from an increase of the axial length of the eye, or issues related to the cornea or lens.

Onset usually occurs during childhood. On average, myopia stabilizes by ~15 years of age, with 95% of patients with myopia stabilizing by age 24 (Nemeth et al., 2021). Myopia progression varies widely between individuals, but generally occurs at a rate of 0.50 to 1.00 D per year during childhood (Gifford, 2019; Walline, 2011; Walline, 2020).

High myopia places affected patients at increased risk for other ocular diseases and is defined as a refractive error of ≤−5 D by the World Health Organization (WHO; 2015) although more recently ≤−6 D has been proposed by the International Myopia Institute (IMI, 2020). These include glaucoma, cataract, retinal tears which may lead to detachment, and myopic maculopathy or macular degeneration (Williams and Hammond, 2019). More severe myopia resulted in an earlier onset of complications (Haarman et al., 2020).

It is anticipated that by 2050 approximately 50% of the world's population will be affected and 56% in Europe specifically (Holden, 2016; Morgan, 2021). Prevalence of myopia within EU children aged 6-10 years is estimated at approximately 10-20% (Hönekopp 2024; Matamoros 2015).

Myopia is diagnosed and monitored through examination of patient history and eye examinations, which may include assessment of cycloplegic refraction and eye length.

3.1.2. Available therapies and unmet medical need

There is currently no product approved in the EU to prevent or treat myopia. Ryjunea (atropine sulfate) (0.1 mg/ml eye drops, solution) received a positive CHMP opinion on 27 March 2025 for 'slowing the progression of myopia in paediatric patients. Treatment may be initiated in children aged 3-14 years with a progression rate of 0.5 D or more per year and a severity of -0.5 D to -6.0 D.'

Non-pharmacological approaches

Options in the EU include ordinary optical correction (spectacles, contact lenses), and interventional contact lenses: multifocal contact lenses and orthokeratology. Spectacles are generally the preferred option for young children with lenses reserved for older children as they are more challenging to use.

Aside from spectacles and contact lenses used only for correction of refraction error, the main non-pharmacological interventions for controlling myopia include public health (lifestyle) interventions for optimization of environmental influences. Surgical interventions are not considered first line treatment modalities and combination treatments are under investigation.

Atropine

The European Society of Ophthalmology in cooperation with International Myopia Institute as well as the American Academy of Ophthalmology concluded on a benefit of atropine for the treatment of myopia progression and management of at-risk pre-myopic children. There were, however, uncertainties on the optimal concentration of atropine to be used (Németh J et al. EJO 2021).

In the EU, magistral preparations are used for treating myopia and included in many (inter)national guidelines. E.g., atropine 0.01% has been proposed to have an appropriate benefit-risk ratio by the clinical field (World Society of Paediatric Ophthalmology and Strabismus myopia consensus statement, 2016).

A treatment that could prevent myopia would be highly welcomed; as such there is a medical need. However, as myopia in general is neither life threatening nor disabling there is no urgency or pressure. As such there is no unmet medical need as defined in the regulatory context.

3.1.3. Main clinical studies

The primary source of efficacy is **CHAMP** (CP-NVK002-0001; n=576), a randomized (2:2:3), double-blind, placebo-controlled, parallel-design two-stage study performed by the applicant. CHAMP tested Vehicle (n=165), Atropine Sulfate FGK 0.01% (n=164) and Atropine Sulfate FGK 0.02% (n=247) dosed once daily at bedtime in subjects aged 3 to ≤17 years with myopia (SER -0.50 to -6.00 D). Stage 1 was the 36-month primary analysis period; Stage 2 a 12-month re-randomized phase (1:1:1:1) to evaluate maintenance of effect and rebound effects of atropine.

Further evidence is from **MOSAIC** (n=250) and **MTS1** (n=187). Their design is comparable to CHAMP except that subjects were randomized 2:1 to Atropine Sulfate FGK 0.01% or Vehicle, had a primary analysis period of 24 months and were performed by independent investigators. MOSAIC ran exclusively in Ireland and had a tapering period of 12 months; MTS1 ran exclusively in the USA and had a follow-up of 6 months.

Two other studies (**mini-CHAMP** (n=526) and **China-CHAMP** (n=777)) alike CHAMP were conducted with Vehicle, Atropine Sulfate FGK 0.01% and 0.02% by a partner of the applicant exclusively in China. They are not considered decisive for the benefit-risk for the following reasons. Mini-CHAMP had a treatment duration up to 1 year which is without clear relevance to later timepoints. E.g., in CHAMP at 1-year the results for 0.01% and 0.02% were still similar yet divergence was seen at Month 24 and 36. The results of China-CHAMP were from preliminary analyses. Further, both studies showed treatment differences smaller than in CHAMP, which was already of questionable relevance. Moreover, the representativeness of data of Chinese children from studies *exclusively performed in China* for this EU MAA remains unclear as differences for Asian vs non-Asian patients have been suggested in terms of myopia progression (e.g., Brennan et al., 2024) and atropine effects (e.g., Lawrenson et al., 2025; Li et al., 2014). Mini-CHAMP and China-CHAMP results are therefore not further discussed in the Benefit-Risk section.

3.2. Favourable effects

In CHAMP, the primary analysis was conducted in mITT (ITT subgroup aged 6-10 years). In Round 2 the age limits of the target population were aligned with mITT. The primary endpoint was the between-treatment group difference for Atropine Sulfate 0.02% versus Vehicle in the proportion of subjects' eyes in mITT that showed <-0.50 D myopia progression (SER) at the Month 36 visit. No statistically significant effect was observed (proportion of responding eyes <0.5D Atropine 0.02% vs Vehicle: 22.1% vs 17.5%; absolute risk difference of 1.56; 95% CI: 0.55, 6.260; p=0.38). A secondary

endpoint assessed the between-treatment group difference for Atropine Sulfate 0.01% versus Vehicle, which was nominally significant (Atropine 0.01% vs Vehicle: 28.5% vs 17.5%; absolute risk difference: 11%; 95% WALD CI: 3.3%; 18.9%; nominal p=0.01).

In CHAMP, Change-in-SER was evaluated as secondary/tertiary endpoints. In mITT the treatment difference was nominally significant for atropine 0.01% but not 0.02% (Month 36, atropine 0.02% vs Vehicle: LSM difference of 0.099 D; 95% CI: -0.02; 0.22; p=0.1 and atropine 0.01% vs Vehicle: LSM difference of 0.24 D; 95% CI 0.106; 0.374; nominal p<0.001).

The change-from-baseline for axial elongation was also evaluated as secondary/tertiary endpoints and were nominally significant for both doses (in mITT at Month 36, atropine 0.02% vs Vehicle: LSM difference of -0.077 mm; 95% CI -0.131, -0.024; p=0.005 and for atropine 0.01% vs Vehicle: -0.13 mm; 95% CI -0.191, -0.069; nominal p<0.001).

In MOSAIC and MTS1, the primary endpoint was change in SER from baseline to the 24-month visit. In both studies no significant treatment difference for Atropine Sulfate 0.01% versus placebo was observed. In MOSAIC, the treatment difference (standard error) for atropine 0.01% vs placebo was 0.12 D (0.07), p=0.07. In MTS1, this treatment difference (95% CI) was −0.02 D (−0.19, 0.15D; p=0.83).

Axial elongation was assessed as secondary endpoint in MOSAIC and MTS1. In MOSAIC, a nominal significant treatment difference for atropine 0.01% vs Vehicle was shown (in ITT at Month 24: mean [standard error]: -0.07 mm [0.03], p <0.009). In MTS1, this treatment difference at Month 24 was −0.002 mm (95% CI −0.106 to 0.102; nominal p-value not provided).

3.3. Uncertainties and limitations about favourable effects

Methodological uncertainties

In CHAMP, the primary endpoint, which was limited to testing the 0.02% dose, was not met. MOSAIC and MTS1 also did not meet their primary endpoints. Formally these three ≥24 month studies did not meet their success criterion and are considered failed studies. The statistical testing that was performed after the primary endpoints were not met, is methodologically not allowed. The hierarchical test procedure accounting for multiplicity stopped after the primary endpoint analysis did not reach statistical significance. Hence, the statistical results that followed after the primary analyses cannot be readily interpreted.

The primary analysis presented for CHAMP by the applicant was based on the eye as analysis unit instead of the subject. During the PIP compliance check of the PDCO, the applicant committed to also provide the primary analysis based on the initial SAP at MAA, but this was not performed (EMA/PDCO/40253/2024 p.36 of 39). A retrieved drop-out analysis on subject level was therefore requested by CHMP and provided by the applicant in Round 2. This analysis consistently showed smaller effects for both doses and across all three endpoints:

- for the responder analysis at eye level, the treatment difference was not nominally significant for either dose (Month 36 in mITT, atropine 0.02% vs Vehicle: 3.7%; 95% WALD CI: -3.8%, 11.2% *p*=0.3 and atropine 0.01% vs Vehicle: 7.6%; 95% WALD CI: -1.4%, 16.5%, *p*=0.1).
- for the change-in-SER-from-baseline endpoint the treatment difference was not nominally significant for either dose (Month 36, atropine 0.02% vs Vehicle: LSM difference of 0.048 D; 95% CI: -0.10; 0.20; p=0.53 and atropine 0.01% vs Vehicle: LSM difference of 0.146 D; 95% CI -0.04; 0.34; p=0.13).

- for the change-in-AL-from-baseline endpoint the treatment difference was nominally significant for atropine 0.01% but not 0.02% (Month 36, atropine 0.02% vs Vehicle: LSM difference of -0.061 mm; 95% CI -0.125, 0.002; p=0.06 and for atropine 0.01% vs Vehicle: -0.098 mm; 95% CI -0.175, -0.02; p=0.01).

These results support the concern that the initial analysis overestimated the treatment effect, and consequently support the concerns on the credibility and clinical relevance of the results.

Uncertainties related to observed effect

The absence of dose-dependent, or at least similar effects in CHAMP for 0.01% and 0.02% support the concern that the result for atropine 0.01% may be a spurious finding.

The clinical relevance of the observed effect size for atropine 0.01% is uncertain. In the initial <0.5 D responder analysis, the treatment difference at Month 36 (atropine 0.01% vs vehicle) was 11% (n=13) in the mITT, this was 7.6% in the retrieved drop-out analysis. In the sample size calculations, the applicant expected a difference of 18% in responder rate, which was not met.

The 6-year projection that was provided in Round 2 did not cover the expected treatment duration (9 years), was too optimistic as it did not take CHAMP stage 2 results into account, and consequently did not show that there is a benefit of continuing using atropine 0.01%.

3.4. Unfavourable effects

Overall, the safety profile of Atropine FGK is comparable to what is known for low concentration atropine eye drops. The proportion of subjects with TEAEs for atropine 0.01% was similar and not dose-dependent to Vehicle and atropine 0.02%.

In CHAMP, there were four subjects who discontinued due to an AE (1x Vehicle; 3x atropine 0.02%). There were no deaths or ocular SAEs that were at least possibly related to atropine 0.01% or 0.02%.

Ocular TEAEs

Ocular TEAEs (CHAMP stage 1) were more reported in the Vehicle group (40.7%) than under atropine 0.02% (33.2%) and atropine 0.01% (25.6%). The majority of ocular TEAEs was judged at least possibly treatment-related. Severity was comparable across treatment groups; most TEAEs were mild. One subject that received atropine 0.02% had a treatment-related severe ocular TEAE (administration site pain) which resulted in study drug discontinuation. Most frequent TEAEs where (vehicle, atropine 0.01% atropine 0.02%, respectively): photophobia (3.1% vs 2.4% vs 4.5%); conjunctivitis allergic (3.1% vs 1.8% vs 4.5%), mydriasis (0% vs 1.2% vs 1.6%) and blurred vision (0% vs 1.2% vs 1.6%).

Similar overall observations apply to Stage 2. A curiosity is the observation of lattice degeneration in the atropine 0.01%: 1.9%; atropine 0.02%: 0.6%) and conjunctivitis which appeared dose-dependent (Vehicle: 0; atropine 0.01%: 0.6%; atropine 0.02%: 1.9%). One subject that received atropine 0.02% had a treatment-related severe ocular TEAE (eye irritation) which resulted in study drug discontinuation.

In MOSAIC, during the primary treatment period of 24-months, seven AEs were possibly/probably related to atropine 0.01%: eye discomfort (n = 3), temporary blurred vision at near (n = 1), temporary pupil dilation (n = 1), and rash on the eyelid (n = 2). There were no severe TEAEs.

In MTS1, ocular AEs were prevalent and with comparable incidence between groups: they included eye irritation at time of instillation (atropine 72%; placebo 82%), photophobia (atropine 26%; placebo n=27%) and blurred vision (atropine 14%; placebo 16%). Two subjects had severe ocular TEAEs and received atropine 0.01% (1x burning in both eyes after drug instillation; 1x pain in both eyes).

Non ocular TEAEs

In CHAMP Stage 1, non-ocular TEAEs were reported in 55.7% of subjects, most commonly in the infections and infestations SOC and most often in the Vehicle group (41.4%; atropine 0.01%: 27.4%; atropine 0.02%: 33.6%). COVID-19 TEAE and nasopharyngitis were the most reported TEAE in this SOC. Headache, a known systemic AE of atropine, was reported comparably between treatments (Vehicle: 8.6%, atropine 0.01%: 8.5%, atropine 0.02%: 9.3%). Similar observations apply to Stage 2 albeit TEAEs were reported with lower incidence. AEs related to heart-rate variability, also suggestive of systemic atropine exposure, were reported in three subjects (1x Vehicle; 2x atropine 0.02%).

No trends in the subgroups age, sex or race were observed for atropine 0.01% that raised concerns.

In subgroup analysis, in the atropine 0.01% group, eye disorder TEAEs were more reported in Asian (20.7%) and White/Caucasian (17.9%) subjects compared to Black/African American subjects (4.3%).

3.5. Uncertainties and limitations about unfavourable effects

Safety evaluation was primarily based on AE reporting and ophthalmologic assessment. Frequency of AE evaluation varied and may have resulted in underreporting. Specifically, in CHAMP proactive AE reporting was in Year 1 during office visits every 3 months and telephone checks ± 2 weeks, but reduced after Year 1 to once every 3 months in the remaining 3 years. In MOSAIC the frequency was every 6 months and in MTS1 every 3 months. CHAMP, MOSAIC and MTS1 were performed during the COVID-19 pandemic which resulted in that part of the physical site visits were cancelled.

3.6. Effects table

Table 59. Effects table for Atropine sulfate FGK 0.01% eye drops

Effect	Short Description	Unit	Treatment (Atropine 0.01% and 0.02%)	Control (Vehicle)	Uncertainties/ Strength of evidence	References
Favourable Effects						
Proportion of Subjects' Eyes That Showed Less than 0.5 D Myopia Progression at **Month 36** in **mITT**	Responder analysis (<0.5D)	n of eyes (%)	**Atropine 0.02%: 81 (22.1%)** Atropine 0.01%: 57 (28.5%)	44 (17.5%)	**-Primary endpoint*** of CHAMP not met -Effect not dose-dependent, nor at least similar -Analysis on eye-level -Effect not consistent across age and severity subgroups -Effect lower in preferred retrieved dropout analysis / Difference atropine 0.02% vs Vehicle: 4.6% ;*p=0.37* (95% confidence)** Difference atropine 0.01% vs Vehicle: 11%;*p=0.03*(unadjusted;95% confidence)** **Retrieved-dropout analysis** (mITT; atropine 0.01% vs Vehicle): 7.6%; 95% WALD CI: -1.4%,16.5%, p=0.1	CHAMP CSR Stage 1, Table 20

Effect	Short Description	Unit	Treatment (Atropine 0.01% and 0.02%)	Control (Vehicle)	Uncertainties/ Strength of evidence	References
Results for change from Baseline in SER at **Month 24** in **ITT**	Comparison results for mean change-from-baseline in normalized SER	D D D	CHAMP at M24 atropine 0.01%: -0.691* MOSAIC atropine 0.01%: -0.53 MTS1 atropine 0.01%: -0.78	CHAMP at M24: -0.932 MOSAIC: -0.63 MTS1: -0.74	**-Primary endpoint** of MOSAIC and MTS1 not met -Effect not dose-dependent, nor at least similar -Effect not consistent across age and severity subgroups in CHAMP -Effect lower in preferred retrieved dropout analysis / Difference atropine 0.01% vs Vehicle: -CHAMP at **M24**: 0.247 D (95% CI: 0.122,0.373; p<.001; unadjusted) -CHAMP at **M36**: 0.253 D (atropine 0.01%: -0.925 D; vehicle: -1.206 D; 95% CI: 0.129,0.377; p<.001; unadjusted) **Retrieved-dropout analysis** (mITT; M36; atropine 0.01% vs Vehicle): LSM difference 0.146 D; 95% CI -0.04; 0.34; p<0.13 -MOSAIC: 0.12 D [0.07]; p=0.07)*** -MTS1: -0.02 D (95% CI: -0.19,0.15;p=0.83)****	CHAMP CSR Stage 1, Table 14.2.2.1.4 MOSAIC and MTS1: Module 5.3.5.

Effect	Short Description	Unit	Treatment (Atropine 0.01% and 0.02%)	Control (Vehicle)	Uncertainties/ Strength of evidence	References
Axial elongation at **Month 36 in ITT**	Change-from-baseline in axial length	LSM in mm (95% CI)	Atropine 0.02%: 0.697 (0.660-0.734) Atropine 0.01%: 0.652 (0.607-0.698)	0.780 (0.735-0.825)	-Secondary endpoint. -Effect not dose-dependent. -Effect lower in preferred retrieved dropout analysis / Difference atropine 0.02% vs Vehicle: -0.083 (-0.14,-0.027; p=0.004; unadjusted) Difference atropine 0.01% vs Vehicle: -0.128 (-0.19,-0.065; p<0.001; unadjusted) **Retrieved-dropout analysis** (mITT; M36; atropine 0.01% vs Vehicle): LSM difference 0.146 D; 95% CI -0.04; 0.34; p<0.13 *Treatment difference for atropine 0.01% vs Vehicle at Month 24 for:* MOSAIC: -0.07 mm [0.03], p <0.009; unadjusted*** MTS1: −0.002 mm (95% CI −0.106 to 0.102; nominal p-value not provided).	CHAMP CSR Stage 1, Table 14.2.2.2.4
Unfavourable Effects						
Ocular TEAEs	Photophobia (CHAMP stage 1)	%	Atropine 0.02%: 3.6 Atropine 0.01%: 1.2	2.5	-Potentially underreported -AE duration unclear -Not dose-dependent / -Known ADR of atropine eye drops -Incidence low	CHAMP CSR Stage 1; 12.2.
	Mydriasis (CHAMP stage 1)	%	Atropine 0.02%: 1.6 Atropine 0.01%: 1.2	0	-Potentially underreported -AE duration unclear / -Dose-dependent -Known ADR of atropine eye drops. -Incidence low	CHAMP CSR Stage 1; 12.2.

Effect	Short Description	Unit	Treatment (Atropine 0.01% and 0.02%)	Control (Vehicle)	Uncertainties/ Strength of evidence	References
	Vision blurred (CHAMP stage 1)	%	Atropine 0.02%: 1.6 Atropine 0.01%: 1.2	0	Potentially underreported -AE duration unclear / -Dose-dependent -Known ADR of atropine eye drops -Incidence low	CHAMP CSR Stage 1; 12.2.

*Abbreviations: D: diopter; KSEP: key secondary endpoint; LSM: least square mean; mm: millimetre; n: number; PEP: primary endpoint; SER: spherical equivalent refraction; yo: years old. *: primary comparison was proportion of responding eyes for atropine 0.02% vs Vehicle. **: The primary endpoint was reported as odds ratios which is not agreed as they may exaggerate the effect size. Hence, instead the absolute % difference in responders and corresponding p-value are reported in the Effects Table. ***: Group differences are the difference [standard error] in the estimated marginal means for atropine 0.01% vs Vehicle, derived from the linear mixed model and are adjusted for the baseline value of the outcome. ****: Adjusted mean change in SER-from-baseline at Month 24 was -0.82 D vs -0.80 D in atropine and placebo groups, respectively (Repka et al., 2023)*

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Efficacy is not considered demonstrated as there are serious concerns on the overall credibility of the results and their clinical relevance.

The credibility of the provided results is uncertain as:

- Formally the three key studies submitted (CHAMP, MOSAIC and MTS1) did not meet their primary objective i.e., are failed studies.
- At least it would have been expected that the 0.02% strength performed comparably to the 0.01% strength, but this was not the case. The fact that the result for 0.02% strength was not statistically significant, bears on the credibility of 0.01% results, i.e., it remains of question if the atropine 0.01% result is not a spurious finding.
- The treatment effect in CHAMP has been inflated by using the eye as analysis unit instead of the subject. During the PIP compliance check of the PDCO, the applicant committed to also provide the primary analysis based on the initial SAP at MAA, but this was not performed (EMA/PDCO/40253/2024 p.36 of 39). A retrieved drop-out analysis on subject level was therefore requested by CHMP and provided by the applicant in Round 2. In the responder analysis, evidently lower and no longer nominally significant treatment differences were observed for both doses (0.02% vs Vehicle; 0.01% vs Vehicle). Even if the influence of the confounding therapies is taken into account the actual effect likely is closer (or in-between) the non-nominally significant result of the drop-out analysis vs the initial analysis.

In addition, the clinical relevance of the findings was not shown:

- It is agreed with the applicant that primarily prevention of progression to high myopia (<-6.0D) is key. However, no treatment difference was seen in patients progressing to that subgroup;
- Another clinically relevant result would be for patients to achieve stable myopia. However, there were only 11% (primary analysis) or 7.6% (retrieved drop-out analysis) more patients with stable myopia under atropine 0.01% vs Vehicle (i.e., a change of <0.5D/3y). Differences in responder analysis in MOSAIC and MTS1 were even lower (for 0.01% vs vehicle, in MOSAIC <0.75D/2y: 7.2%; in MTS1 <0.5D/2y: 2%).
- Also for the change-from-baseline SER results, relevance is questioned. LS means difference for atropine 0.01% vs Vehicle at Month 36 is 0.24 D (mITT; initial eye level analysis), or 0.25 D (mITT; retrieved drop-out analysis at subject level). Similar effects were also observed for change-in-axial length.
- Likewise, no difference between treatment groups in progression of the -0.5;-3D group to the -3.01;-6.0D group was observed when considering the proportional disbalance between vehicle and the atropine 0.01% group.

In terms of unfavourable effects, the type of AEs reported for atropine 0.01% were in line with the known safety profile for atropine eye drops. Atropine 0.01% and higher concentrations are often used and considered safe.

The frequency with which TEAEs were observed in CHAMP and MOSAIC appear lower than what is generally known, but also much lower than in MTS1. It is uncertain if AEs may have been

underreported. Even so, it is not expected that moderate and severe AEs were notably underreported as they usually are followed-up on by caregivers and/or tending physicians. Altogether, the safety profile of Atropine Sulfate FGK 0.01% was considered benign, comparable to what is known for low concentration atropine eye drops, and no new risks were identified.

3.7.2. Balance of benefits and risks

In CHAMP, in the initial analysis a nominally significant effect of atropine 0.01% versus Vehicle at Month 36 was observed. The effect was consistent on the proportion responder, change-from-SER and change-in-axial length endpoints. The safety profile of atropine 0.01% was considered benign and no new risks for atropine eye drops were identified.

However, inadequate evidence has been provided to support this MAA. CHAMP failed to meet its primary endpoint (superiority of 0.02% over vehicle at Month 36), rendering all subsequent statistical analyses not credible. Even more so as two 24-months studies (MOSAIC and MTS1) also failed to meet their primary endpoint (superiority of 0.01% over vehicle). That 0.02% and 0.01% results in CHAMP were not at least comparable, further bears on the credibility of results for atropine 0.01%. Moreover, clinical relevance of findings remained questionable. Efficacy has not been demonstrated, and this is weighed against the burden of years of treatment at young age.

3.8. Conclusions

The overall benefit/risk balance of Atropine Sulfate FGK 0.1 mg/ml eye drops, solution in single-dose container, is negative.

4. Recommendations

Based on the CHMP review of data on quality, safety and efficacy for Atropine sulfate FGK, in the treatment to slow myopia progression in children aged 6 to 10 years with spherical equivalent refraction (SER) in the range of -0.50 to -6.00 diopter (D), the CHMP considers by consensus that the efficacy of the above-mentioned medicinal product is not sufficiently demonstrated and, therefore recommends the refusal of the granting of the paediatric use marketing authorisation for Atropine sulfate FGK.

The CHMP considers that:

- Efficacy of Atropine sulfate FGK has not been established regarding the three main studies (CHAMP, MOSAIC and MTS1). These studies did not meet their primary objective and are formally failed studies. Thus, clinical relevance was not substantiated in the proposed indication.

Therefore, it is the opinion of the CHMP that the benefit-risk balance of Atropine Sulfate FGK 0.01% is negative.

Due to the aforementioned concerns a satisfactory summary of product characteristics, labelling, package leaflet, pharmacovigilance system, risk management plan cannot be agreed.

5. Re-examination of the CHMP opinion of 22 May 2025

Following the CHMP conclusion that Atropine sulfate FGK was not approvable, as efficacy had not been established regarding the three main studies CHAMP, MOSAIC and MTS1 and, consequently, clinical relevance had not been substantiated in the proposed indication, on 2 June 2025 the applicant sent a letter requesting re-examination of the CHMP opinion. In addition, the applicant requested an Ad Hoc Expert Group (AHEG) meeting to support the re-examination request.

On 21 July 2025, the applicant submitted the detailed grounds for the re-examination request.

It is noted that the grounds for refusal referenced by the applicant in the grounds for re-examination document do not fully reflect the wording of the actual grounds for refusal included in the CHMP opinion adopted on 22 May 2025, but rather include additional points from the initial CHMP assessment. In the re-examination assessment, the CHMP reviewed each ground for re-examination as submitted by the applicant.

Detailed grounds for re-examination submitted by the applicant

Following a request from the applicant at the time of the re-examination, on 3 September 2025 the CHMP convened an AHEG meeting inviting the experts to provide their views on the CHMP grounds for refusal, taking into account the applicant's response.

The applicant presented in writing and at an oral explanation (OE) its position.

5.1. Ground #1

Efficacy of Atropine Sulfate FGK has not been established regarding the three main studies (CHAMP, MOSAIC and MTS1). These studies did not meet their primary objective and are formally failed studies. The statistical testing for 0.01% vs Vehicle that followed, is methodologically not allowed.

Grounds for re-examination

The applicant would like to point out that not meeting a primary endpoint should not disqualify the assessment of other endpoints, as exemplified in a prior CHMP assessment (Group variations including extension of indication assessment report, EMA/44020/2023 [Eylea]). In the case of EMA/44020/2023 for a new indication of retinopathy of prematurity, subsequent statistical analyses were allowed despite the fact that the core study's primary endpoint was not met. The process of assessment in EMA/44020/2023 was based on the context, totality of evidence, consistency across endpoints, support of evidence synthesis and credibility of the mechanism. Because of the precedent of positive opinion of other MAA's with formally failed studies (such as EMA/44020/2023 and EMA/93332/2024 [Qalsody]), it is not reasonable to allow subsequent analyses in other assessments but not in the assessment of the current MAA.

Following the assessment precedent of EMA/44020/2023, the context of Atropine Sulfate FGK efficacy is that all pre-specified Atropine Sulfate FGK (0.01%) endpoints were nominally significant (Figure 2; CHAMP CSR Table 22, Table 23; Table 24; Table 29). The results in Figure 14 show that when considering all pre-specified endpoints of 0.01% Atropine Sulfate FGK, the totality of evidence is credible, and the consistency across all endpoints is clear. No *post hoc* analysis was needed to establish the efficacy of Atropine Sulfate FGK (0.01%). These results demonstrate a clear efficacy profile with 36 months of treatment of 0.01% Atropine Sulfate FGK.

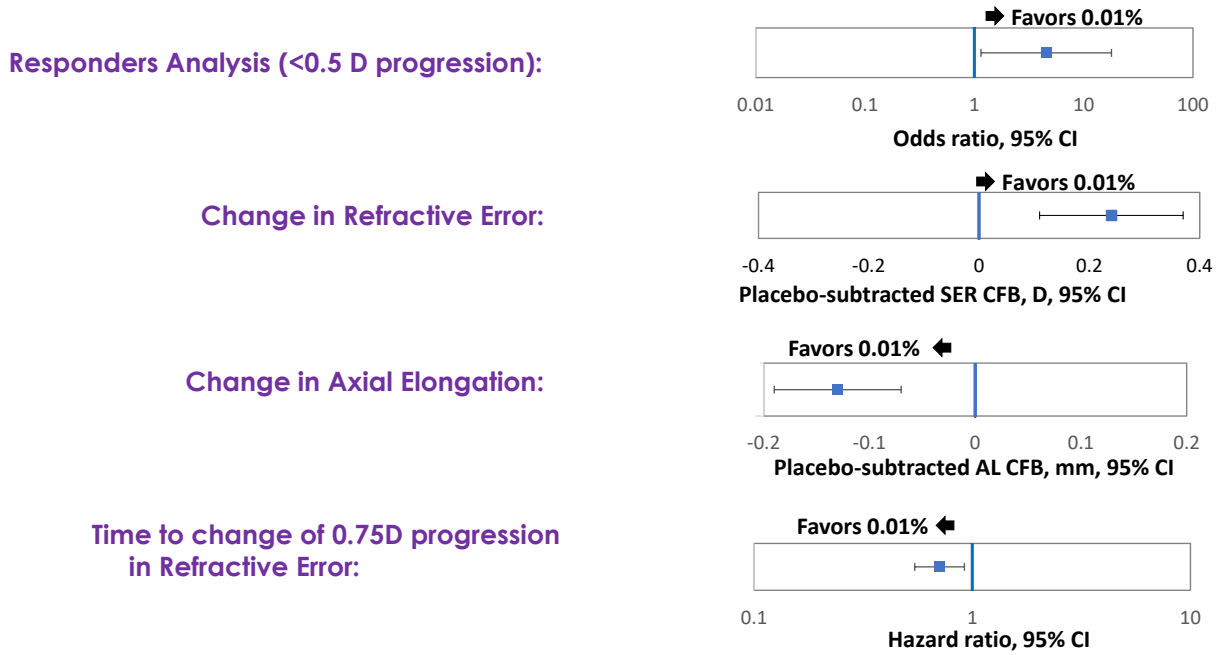


Figure 14. Forest plot summarizing 3 major pre-specified endpoints at Month 36 (top 3 endpoints) and a key supportive pre-specified endpoint (time to event endpoint at bottom) for Atropine Sulfate FGK 0.01% compared to placebo. CFB, change from baseline. SER, spherical equivalent refractive error. AL, axial length

In addition, the applicant would like to point out that the MOSAIC study (Loughman 2024) and the MTS1 study (Repka 2023) showed very different outcomes that warrant separate evaluations instead of treating both studies as the same. While both studies' primary endpoint was SER change from baseline at Month 24, the MOSAIC study outcomes were qualitatively consistent with those of CHAMP and many other published randomized placebo-controlled trials (RCT). As shown in Figure 15, the point estimate and 95% CI of Month 24 vehicle-subtracted SER change from baseline in MOSAIC were similar to those of CHAMP at Month 24, albeit the MOSAIC primary endpoint was associated with p = 0.07. The secondary endpoint of AL change from baseline in MOSAIC was nominally significant (p=0.009), and similar to that of CHAMP at 2-year. Comparing the MOSAIC SER and AL endpoints to other RCT's evaluating 0.01% atropine (Figure 16), the results from MOSAIC at Month 24 were consistent with other RCT's. The totality of evidence from MOSAIC indicates that the MOSAIC study was consistent with the efficacy conclusion of CHAMP.

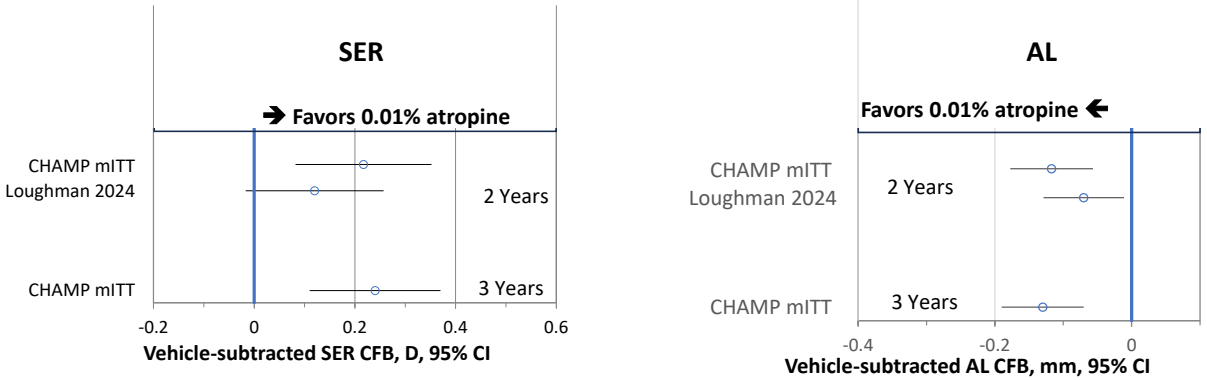


Figure 15. Comparison of MOSAIC Month24 endpoints with those of CHAMP. CFB, change from baseline

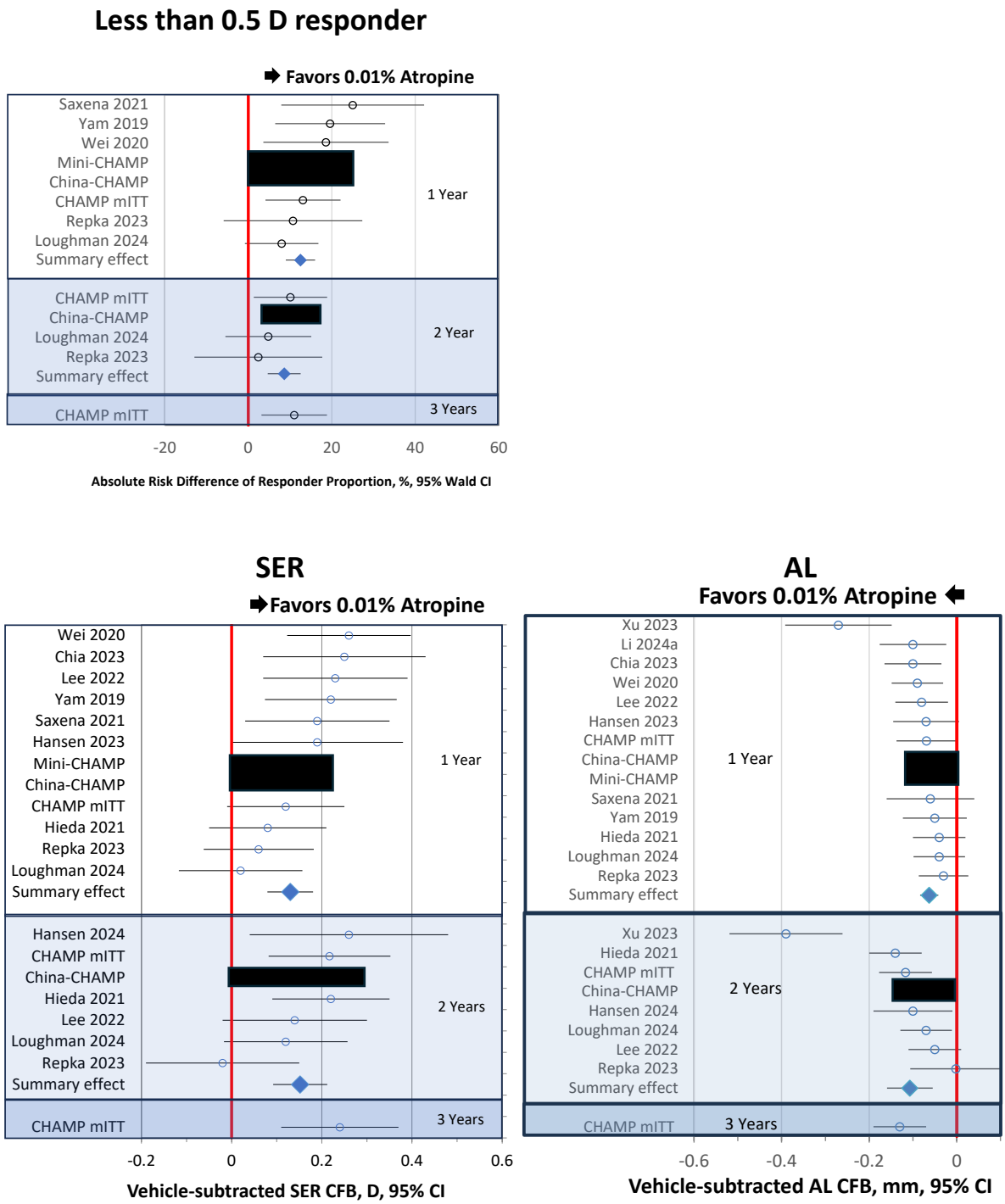


Figure 16. Meta-analysis of atropine 0.01% efficacy

(Top) Absolute risk difference in responder proportion (0.01% - placebo/vehicle) of less than 0.5 D progression. (Bottom left) Vehicle-subtracted SER change from baseline (CFB). (Bottom right) Vehicle-subtracted AL change from baseline (CFB).

In contrast, the MTS1 Month 24 result is the only outlier among all RCT's evaluating atropine 0.01%. As shown in Figure 16, at Month 24, the point estimate of MTS1's primary endpoint (SER) was the only one on the left side of the no effect vertical line. The point estimate of MTS1's secondary endpoint (AL) was the only one on the no effect vertical line. The MTS1 24-month results were clearly not

qualitatively consistent with all other RCT's, and it was likely due to study execution issues outlined below:

1) Randomization did not balance baseline characteristics across the dose arms.

   a) The Atropine Sulfate 0.01% group was assigned a higher percentage of children from 9 to 11 years old (40%) than the placebo group (32%)

   b) The placebo group was assigned more older children from 11 to 13 years old (42% vs 33%).

   c) More children in the atropine group entered the study with a higher baseline level of myopia (18% with more than -4.00 dioptres compared with 10% of the placebo).

2) Adherence measures: While the MTS1 study authors reported good patient retention at month 24, this does not equate to adherence to treatment.

   a) Participants without ampoule count were assumed to be 100% compliant (Repka 2023, supplement 3).

   b) Participants who missed visits were asked to recall their compliance (Repka 2023, supplement 3), a notoriously unreliable assessment.

   c) Adherence was based on subjective calendar logs instead of objective measurement.

3) Missing data in MTS1 was high (30% of Month 12 and Month 24 office visits were missed and without ophthalmic data) (Repka, 2023).

4) There is no biological evidence that participants took medication. No pupillometry data were collected, although the MTS1 paper cites an insignificant treatment group difference in near point accommodation at 6 months (0.68 cm, 95% CI [-0.29, 1.65]) as its measure of biological activity (Repka 2023, Supplemental materials).

In addition, the applicant has conducted an evidence synthesis using a meta-analysis approach to provide a more accurate summary effect (Peto 1987) of the efficacy results from 14 RCT's evaluating 0.01% atropine. As shown in Figure 4, considering all available placebo-controlled RCT's on 0.01% atropine (either Atropine Sulfate FGK or other atropine preparations), at both 1-year and 2-year, the vast majority of RCT's showed that 0.01% atropine increased the proportion of subjects or eyes with myopia progression less than 0.5 D, decreased the magnitude of SER progression, and decreased the magnitude of AL elongation. The favourable effect of 0.01% atropine is indicated by both the point estimate and the 95% CI. The Repka 2023 result at 2-year is the only outlier with its point estimate being unfavourable for 0.01% (SER endpoint at 2-year) or on the vertical no effect line (AL endpoint at 2-year). The meta-analysis in Figure 4 is an objective analysis of all available RCT's without unjustified exclusion, and including the Repka 2023 study in the meta-analysis still led to the conclusion that the summary effect of 0.01% atropine is favourable. The between-study variability in Figure 4 is consistent with the expectation that 0.01% atropine is in the minimum effective concentration range for slowing myopia progression, and the expectation of systematic review of RCT's (Peto 1987).

Finally, the credibility of the atropine efficacy is supported by 13 of 14 RCT's evaluating 0.01% atropine (Figure 4), with MTS1 being the only outlier at Month 24. The credibility of the atropine effect is consistent with the wide support in the ophthalmology community for the use of 0.01% atropine as the minimum effective concentration to treat myopia progression in children (Buzzonetti 2025; Dahlmann-Noor 2024; Diaz-Llopis 2018; Joachimsen 2019; Kaymak 2021; Moriche-Carretero 2023; Navarra 2025; Németh 2021; Perez-Flores 2023; Sacchi 2019).

In summary, because of the precedent set previously on proceeding to subsequent analyses despite the primary endpoint not being met in prior CHMP assessment (Group variations including extension of indication assessment report, EMA/44020/2023), it is unreasonable to dismiss the assessment of Atropine Sulfate FGK. It is important to note that the primary end in the CHAMP study is not on 0.01%,

hence the rationale to assess the endpoints of 0.01% is stronger than that of EMA/44020/2023. When all pre-specified endpoints for Atropine Sulfate FGK (0.01%) were considered, along with 13 other RCT's evaluating atropine 0.01% (4 of the 13 studies evaluating Atropine Sulfate FGK), the totality of evidence supports a credible and consistent efficacy of Atropine Sulfate FGK (0.01%).

CHMP position on the applicant´s claims

The precedents of marketing authorisations (MA) discussed by the applicant are acknowledged, however it should be noted that every MA application is assessed on its own merit, based on the totality of the data presented in the application, in support of the claimed indication. There are multiple factors affecting the benefit-risk evaluation for each application. It is the totality of data which is taken into account in every individual dossier.

The grounds for refusal relate to the lack of demonstrated efficacy for Atropine sulfate FGK, as evidenced by the failure of the three main studies (CHAMP, MOSAIC and MTS1) to meet their primary endpoints. Consequently, also clinical relevance of the effect estimates in the proposed indication remains unsubstantiated. The primary endpoint of CHAMP had been restricted to evaluate the 0.02% dose against vehicle and was not met. The lower strength (0.01%) was apparently proposed on the basis of nominally significant effects versus vehicle at month 36, only. This approach is however not acceptable, as the hierarchical testing procedure - which included the comparison of 0.01% versus vehicle as third step - was already halted following the non-significant primary endpoint result. Though the comparison of 0.01% atropine versus vehicle was prespecified in the protocol as secondary endpoint, nominal significance in such is not sufficient to conclude on a demonstrated treatment effect. For confirmatory demonstration of a treatment effect it is necessary, that (primary) endpoints to which alpha is allocated to can be declared statistically significant, so that the study-wise error of incorrect conclusions on efficacy is controlled. Consequently, efficacy of atropine sulfate FGK 0.01% could not be established in the CHAMP study.

MOSAIC and MTS1 both failed in meeting their primary endpoint (change from baseline in SER at month 24) and the differences between atropine 0.01% and vehicle were even smaller compared to CHAMP, substantiating that efficacy of atropine sulfate FGK is not demonstrated.

The applicant states possible reasons for the poor performance of atropine 0.01% in MTS1, where the point estimate was even in favour of placebo, including imbalances in baseline characteristics, lack of adherence to treatment, a high rate of missing data as well as lack of PD measurements. Altogether, while it is acknowledged that some points or deficiencies of the study apply, it is not accepted that they sufficiently account for the negative outcome of the study, nor can such deficiencies provide support for demonstration of efficacy. Moreover, some of the identified issues may at least partly relate to tolerability, treatment burden and/or acceptability in children. These aspects must be taken into account when establishing the overall benefit-risk balance. Even if MTS1 would be disregarded due to the stated deficiencies, also MOSAIC reported a lower and non-significant treatment difference than CHAMP, and it would not change the overall conclusion that efficacy has not been demonstrated.

Although the applicant – as in the initial assessment - refers to the relevance of efficacy results from 14 RCT's evaluating 0.01% atropine (Fig. 4), the deficiencies and limitations seen in the previous assessment remain: as the main studies CHAMP, MOSAIC and MTS1 did not meet their primary endpoint a meta-analysis with these failed studies is insufficient and not convincing to establish efficacy. Furthermore, many of these studies enrolled only patients from Asian regions, and moreover and relevantly different atropine formulations were used, which limits the adequacy of use of those studies and their generalisability to demonstration of efficacy of Atropine sulfate FGK 0.01% in the EU. CHAMP is the only study with data of up to 3-years, the others were of 2 years or even only one year duration. Overall, these data represent supportive background information and cannot substitute product-specific, alpha-controlled evidence at the target timepoints in an EU-relevant population. Also of note, during the oral explanation (OE) held in front of the CHMP on 16 September, the applicant made reference to Ryjunea.

Conclusion

Ground #1 not resolved.

5.2. Ground #2

It was expected that at the least Atropine Sulfate FGK 0.02% would perform comparably to Atropine Sulfate FGK 0.01%. This, however, was not the case: all point estimates for 0.02% vs Vehicle were lower than for 0.01% vs Vehicle.

Grounds for re-examination

The applicant would like to point out that atropine 0.02% did perform comparably to Atropine Sulfate FGK 0.01% when evaluating both the point estimate and 95% CI. It is inappropriate to use only point estimates for pair-wise comparison, and one must consider the 95% CI before drawing any conclusion (Akobeng 2008). For the responder proportion of less than 0.5 D progression at Month 36, a pair-wise comparison between 0.01% and 0.02% showed a p value of 0.127 for the difference between 0.01% and 0.02% in the responder proportion (CHAMP CSR Table 60). The similarity between the efficacy of the 2 concentrations is illustrated in Figure 17 where the extensive overlap of 95% CI's between the 2 concentrations is evident at 1-year, 2-year or 3-year. The point estimates and their 95% CI's in Figure 17 indicate that both 0.01% and 0.02% produced qualitatively similar effects, and a difference between the 2 point estimates of 0.01% and 0.02% is not a ground for the opinion that 0.01% and 0.02% are not similar.

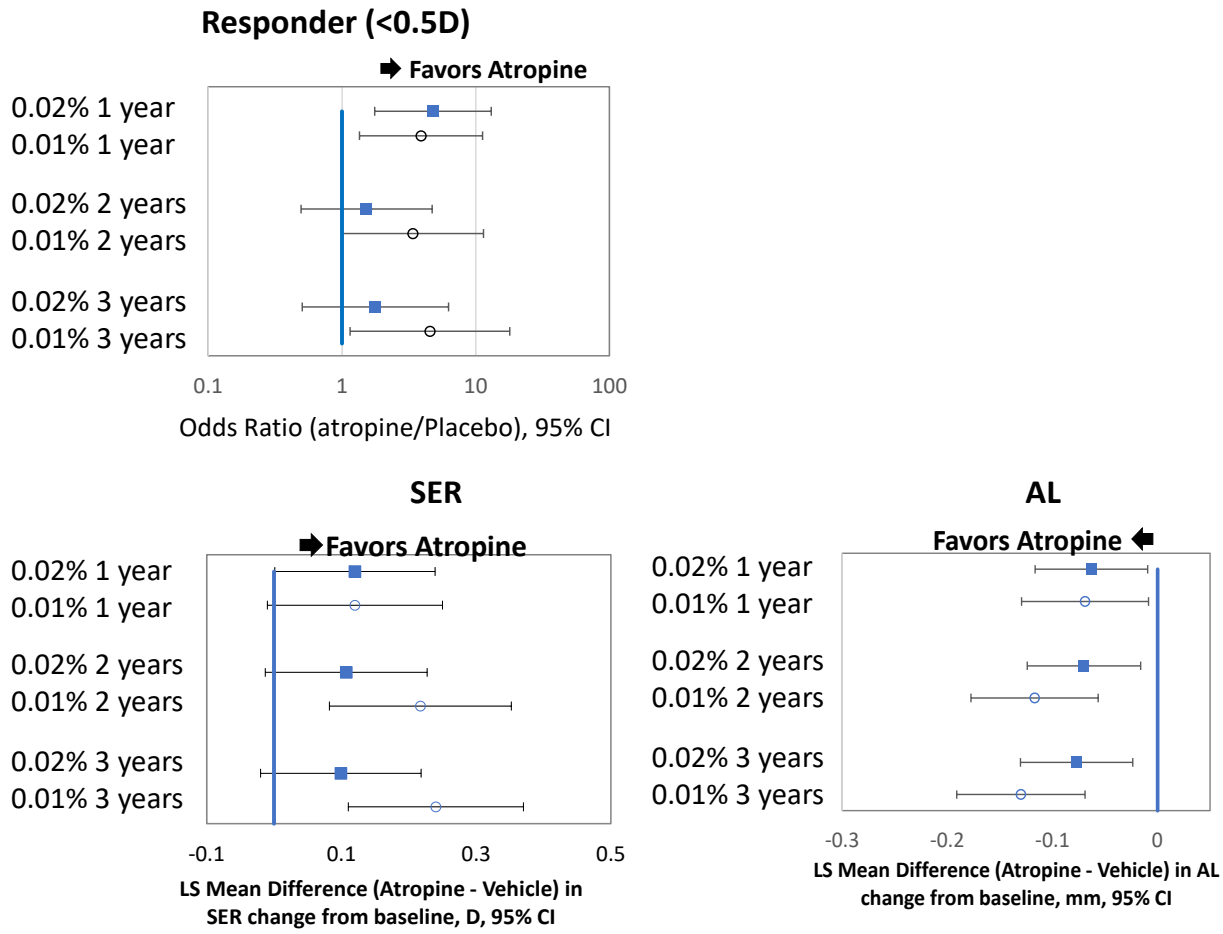


Figure 17. Comparison of 0.01% and 0.02% efficacy in the CHAMP study at various time points. (Top) Responder (less than 0.5 D progression) analysis. (Bottom left) SER change from baseline. (Bottom right) AL change from baseline

In addition, the time-to-event analysis is particularly useful in handling drop-outs who had not reached the progression cut-off criterion and provides another comprehensive view of the observed treatment effect of 0.01% and 0.02%. As shown in CHAMP CSR Table 29, 0.01% and 0.02% had similar hazard ratios for the time to change from baseline in SER of -0.75 D.

Consistent with the applicant's assessment of Figure 5, CHMP also concluded in the D156 Joint Assessment Report-Clinical (p.17) that "it is accepted that the trial was not meant to comparatively test between 0.01% and 0.02%", and "this uncertainty is therefore not pursued". Hence, there is no support for the opinion that 0.01% and 0.02% are not at least similar in the CHAMP study.

CHMP position on the applicant´s claims

It is agreed with the applicant that the results from the CHAMP study should not be interpreted as evidence for different efficacy of the two doses 0.01% and 0.02%. In this regard, it can be agreed a more balanced wording in comparison to the text included in the initial assessment. However, this does not change at all the conclusion on the lack of demonstrated efficacy, as drawn in the previous assessment, which is still supported.

In fact, the post-hoc selection of the lower dose is not only counterintuitive, but it may in fact mean that the estimate for the treatment effect is biased; thus, the effect size of the lower dose is overestimated.

Conclusion

Ground #2 not resolved.

5.3. Ground #3

Both Mini-CHAMP and China-CHAMP studies showed treatment differences smaller than in CHAMP. The representativeness of data from Chinese children of studies exclusively performed in China for EU MAA remains unclear as differences for Asian vs non-Asian patients have been suggested in terms of myopia progression (e.g., Brennan 2024) and atropine effects (e.g., Lawrenson 2025; Li 2014). Mini-CHAMP and China-CHAMP results are of limited importance in the context of CHAMP, MOSAIC and MTS1. Mini-CHAMP had a treatment duration up to 1 year which is without clear relevance to later timepoints.

Grounds for re-examination:

First, regarding the statement of "both Mini-CHAMP and China-CHAMP studies showed treatment differences smaller than in CHAMP", it is inappropriate to base a conclusion on point estimates per se (see Gound #2). While it is true that the point estimates of Mini-CHAMP and China-CHAMP are smaller than those of CHAMP, the 95% CI from the 3 studies clearly show that Atropine Sulfate FGK had similar effects in all 3 studies at 1-year or in CHAMP and China-CHAMP at 2-year (Figure 18).

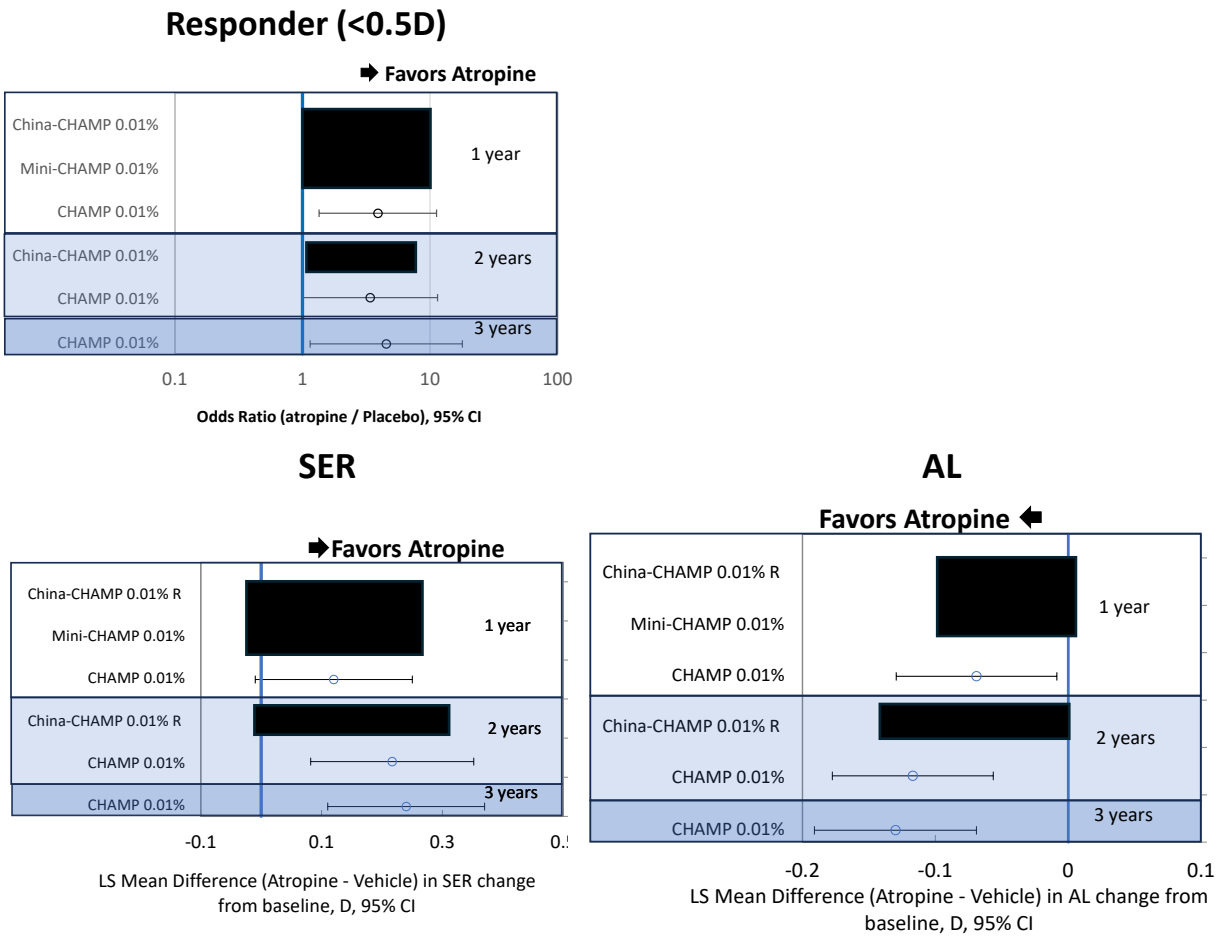


Figure 18. Comparison of Atropine Sulfate FGK 0.01% efficacy in CHAMP, Mini-CHAMP and China-CHAMP at various time points. (Top) Responder (less than 0.5 D progression) analysis. (Bottom left) SER change from baseline endpoint. (Bottom right) AL change from baseline endpoint

Second, regarding whether there is evidence to support a difference in atropine treatment effect in Asians vs non-Asians, Brennan 2024 evaluated race on myopia progression, but not race on the treatment effect of atropine. Whether race affects myopia progression and atropine treatment effect are two different questions. Regardless of whether race affects myopia progression, the relationship between race and progression does not predict the relationship between race and treatment effect. CHMP cited 2 references (Lawrenson et al., 2025; Li 2014) as support of race affecting atropine treatment effect. In Lawrenson 2025, the Asian vs non-Asian comparison was based on mixing results from all doses of atropine (0.01% to 0.05%) together (CHAMP; Yam 2019; Zhang 2024; Zhu 2023) in the subgroup analysis. Mixing different doses in meta-analysis to evaluate the treatment effect of 0.01% is inappropriate. In addition, some of the Asian studies in the Asian subgroup in Lawrenson 2025 were not placebo-controlled, and 2 unmasked Asian studies without placebo control (Ren 2017; Xia 2023) reported a treatment effect (compared to optical devices) in AL elongation substantially larger than those of randomized placebo-controlled Asian studies testing 0.01%.

In Li 2014, the meta-analysis was based on non-randomized observational cohort studies in white children, because in 2014, there was no randomized placebo-controlled trials of atropine in white children or in a heterogenous population. It is unreasonable to rely on non-randomized observational cohort studies when many randomized placebo-controlled trial results are available today, because of the inherent bias in non-randomized trials (Peto 1987). In contrast to Li 2014, the applicant's meta-analysis (Figure 4) relies on 14 randomized placebo-controlled trials of 0.01% atropine, and the results from Chinese children exclusively performed in China (Mini-CHAMP, China-CHAMP) are within the range

of results from studies conducted in countries other than China. Hence, available data indicate that the 0.01% atropine treatment effect is not dependent on race or geographical region. Similarly, a published meta-analysis of 6 of the 14 studies in Figure 4 concluded that the efficacy of individual myopia control treatments is largely independent of race (Bullimore 2023). Another published meta-analysis of 10 of the 14 studies in Figure 4 plus a study in children with myopia and intermittent exotropia found no difference in 0.01% atropine efficacy between Southeast Asian populations and populations in various other countries (Navarra 2025).

It should be noted that in addition to the above discussion that there are no data to support a race effect on atropine treatment effect size, there is also no biological rationale to suggest that myopia aetiology or myopia progression or atropine treatment effect could be dependent on race. For this discussion, all studies should be evaluated based on the relevant data available. The totality of evidence is important in assessing efficacy and safety, and hence it is important not to dismiss the Mini-CHAMP study in efficacy assessment unless there is a scientific ground. Since there is no biological reason to suggest Asian eyes would develop axial myopia differently compared to non-Asian eyes, there is no support for a hypothesis that race may affect atropine treatment effect size.

Furthermore, the between-study comparison of AL endpoint (Figure 6; Bullimore 2023; Navarra 2025) is consistent with the within-study CHAMP subgroup analysis on AL endpoint (Figure 7), indicating that in CHAMP or comparing CHAMP vs China-CHAMP vs Mini-CHAMP, the atropine treatment effect on the AL change from baseline are similar in Asians and non-Asians. In summary, all available mechanistic (i.e., AL) data indicate there is no difference in atropine treatment effect size in Asians vs non-Asians.

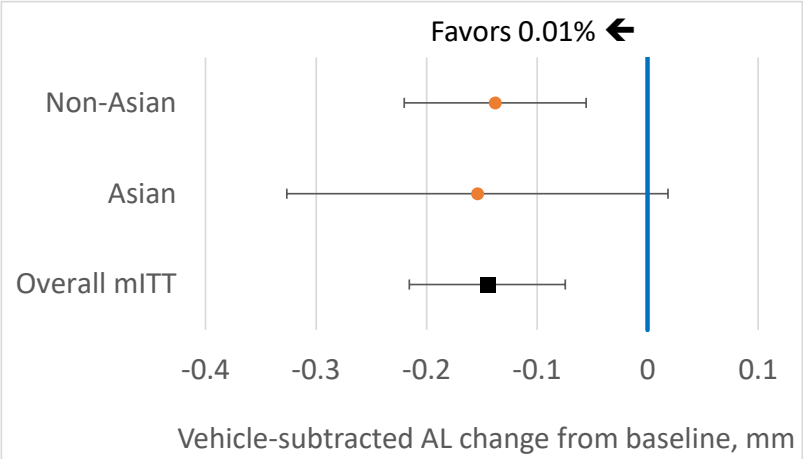


Figure 19. Race subgroup summary statistics of AL endpoint at Month 36 (CHAMP mITT). Unadjusted difference in mean AL change from baseline between 0.01% and vehicle is shown with 95% CI

Third, regarding the CHMP opinion that "Mini-CHAMP and China-CHAMP results are of limited importance in the context of CHAMP, MOSAIC and MTS1", the discussion above and Figure 6 and Figure 7 indicate that there is no biological basis nor credible evidence to hypothesize Asian myopia is different from non-Asian myopia or atropine treatment effect is different in Asians vs non-Asians. Furthermore, from the safety perspective in the D120 LOQ Question 98, CHMP requested to include ADRs from Mini-CHAMP in the proposed SmPC. The fact that ADRs from an Asian study are requested to be included in the proposed SmPC further supports that efficacy from Mini-CHAMP should be evaluated, too, and the inclusion of Mini-CHAMP ADR in SmPC directly contradicts the opinion that mini-CHAMP and China-CHAMP results are of limited importance in the context of CHAMP, MOSAIC and MTS1. Including safety results from Mini-CHAMP while excluding efficacy results from Mini-CHAMP is an unjustified selective reporting to fit an unsubstantiated opinion.

Lastly, regarding the CHMP statement of "mini-CHAMP had a treatment duration up to 1 year which is without clear relevance to later timepoints", the applicant would like to point out that the above statement is a misunderstanding of the mini-CHAMP, China-CHAMP and CHAMP data. As shown in Figure 6, 1-year efficacy in Mini-CHAMP is consistent with 2-year (China-CHAMP and CHAMP) or 3-year efficacy (CHAMP). More importantly, the meta-analysis (Figure 4) also indicates that 1-year efficacy is consistent with 2-year efficacy. Similarly, another published meta-analysis of 10 of the 14 studies in Figure 4 plus a study in children with myopia and intermittent exotropia concluded that the efficacy of 0.01% atropine eyedrops vs. placebo was maintained in a subpopulation of subjects after 24 months of treatment (Navarra 2025). In other words, there is no credible evidence to suggest tachyphylaxis when patients continue to receive treatment, and all available evidence indicates that 1-year efficacy is maintained in the second year (CHAMP and literature) and the third year (CHAMP).

In summary, assessment of all available data indicate that it is unreasonable to conclude mini-CHAMP and China-CHAMP results are of limited importance in the context of CHAMP, MOSAIC and MTS1.

CHMP position on the applicant´s claims

The applicant's criticism, that the observation made in the initial assessment that both the Mini-CHAMP and China-CHAMP studies showed treatment differences of a smaller magnitude compared to those reported in the CHAMP study is inappropriate, cannot be followed. The term 'treatment differences' is not to be understood as treatment effects, but as estimated treatment effects in the individual studies, which of course can be compared between studies.

Regarding the discussion of whether the atropine treatment effect is different or not in an Asian vs non-Asian region, it is noted that the sole question is whether efficacy of Atropine FGK 0.01% has been demonstrated for the EU population. The applicant's criticism of the studies cited during earlier assessment (Lawrenson et al., 2025 and Li 2014) is acknowledged. Irrespective of this discussion nevertheless, it is agreed with the earlier assessment that studies performed in the EU or US such as CHAMP, Mosaic and MTS1 are of greater relevance for this European Union marketing authorization application than the other studies discussed in this section by the applicant:

The B/R assessment of atropine sulfate FGK is based on the totality of evidence. The inclusion of safety results is not considered contradictory, as all available data are taken into account in the benefit-risk evaluation. Accordingly, the efficacy results from the mini-CHAMP and China CHAMP studies have not been excluded per se. However, there are multiple reasons why these were not considered as main studies and are of limited relevance, including treatment duration of just one year for mini-CHAMP, results from only preliminary top-line analyses - which cannot reach and outweigh the value of results from a comprehensive CSR - from China-CHAMP, an unclear rationale for representativeness of the data for an EU population, as both studies were performed in an Asian region (while CHAMP, MOSAIC and MTS1 included also European patients) and, most importantly, that these studies presented with even smaller observed treatment differences than those observed in CHAMP, already of highly questionable clinical relevance and which in fact formally failed to demonstrate efficacy. These points remain substantiated; therefore, these studies continue to provide little contribution to demonstration of efficacy in the totality of evidence.

Conclusion

Ground #3 not resolved.

5.4. Ground #4

Clinical relevance was not substantiated in the proposed indication. The efficacy of the above mentioned medicinal product is not properly or sufficiently demonstrated.

Grounds for re-examination:

Clinical relevance should be assessed from 2 perspectives: an individual patient perspective and a population-level summary perspective. From a patient perspective, achieving stable myopia (less than 0.5 D SER progression) is the ideal benefit. The fact that 11% more eyes (an absolute risk difference, not to be confused with proportion of subjects achieving stable myopia) in the 0.01% treatment group than the vehicle group achieved stable myopia is an undeniable clinical benefit. Similarly at subject level, the absolute risk difference is 10.5% without imputation (Response to D120 LOQ Q77). There is no scientific justification to deny this clinical relevance. This clinical relevance of responder analysis is illustrated in Figure 8. Atropine Sulfate FGK treatment shifted the cumulative distribution curve of SER change from baseline to the right, with 29% subjects achieving stable myopia in the 0.01% group. For those who had not achieved stable myopia, the treatment group had less SER progression on average compared to the vehicle treated group (see Table 2 later).

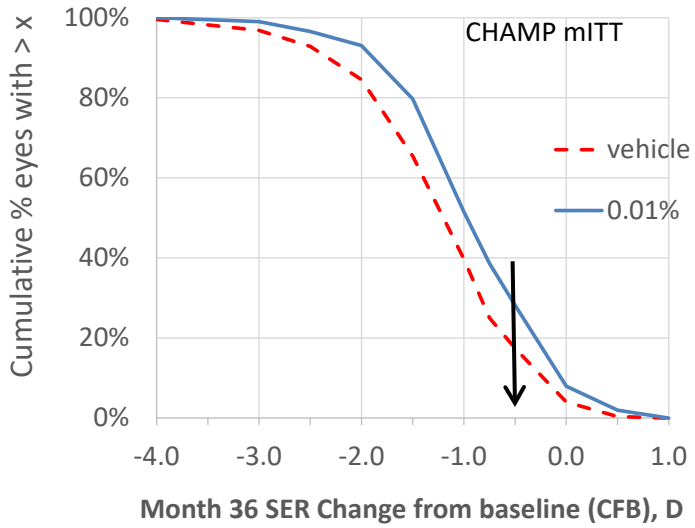


Figure 20. Cumulative distribution of Month 36 SER chang from baseline. Data on the right of -0.5 D on the x-axis (arrow) represent responders with less than 0.5 D progression

From the population-level summary perspective, it is important to remember that not every patient is expected to achieve stable myopia after 3 years of treatment (Figure 8). To fully characterize the clinical relevance of atropine treatment in the proposed population, one needs to evaluate both the binary responder analysis and the SER progression in the atropine treated group vs the vehicle group. In the binary responder analysis, "responder" and "non-responder" are analytical terms. "Non-responder" should not be confused with no clinical response. In addition, dichotomisation in responder analysis masks the distinction between non-responders who had a slower progression (e.g., SER change from baseline of – 0.6 D over 3 years) and non-responders who had a faster progression (e.g., SER change from baseline of – 3 D over 3 years) (Figure 8). For those patients who had not achieved stable myopia, the treatment effect of Atropine Sulfate FGK 0.01% vs vehicle (between-group difference in mean SER change from baseline at Month 36) is 0.24 D (Table 2). This treatment effect size is similar to that of the whole mITT set (0.24 D in CHAMP CSR Table 23).

Table 60. Mean SER change from baseline in either the responder subgroup or non-responder subgroup at subject level (mITT) (CHAMP)

		Vehicle	0.01%	0.01% vs vehicle p value
Less than 0.5 D progression over 3 years		Average of both eyes		
Yes (responder)	n	19	25	--
	Mean SER change from baseline, D	-0.09	-0.18	0.42
	SD	0.407	0.315	--
No (non-responder)	n	99	67	--
	Mean SER change from baseline, D	-1.48	-1.24	0.009
	SD	0.684	0.498	--

Source: CHAMP CSR Listing 16.2.6.1

The 22May2025 Assessment Report has misunderstood the meaning of 0.24 D (mean difference in SER change from baseline between 0.01% group and vehicle group), and arbitrarily called the 0.24 D difference too small. On p.158 of D180 List of Outstanding Issues and p. 111 of D195 Assessment Report Overview, it was stated that "a difference on 0.25 D is too small to substantially reduce the strength of optical correction needed, let alone resolve the need for optical correction itself". This is a misunderstanding of what the between-group difference of 0.24 or 0.25 D represents. Even though the applicant has pointed out this misunderstanding in the Response to D120 LOQ and the 23 April 2025 Oral Examination, the misunderstanding persisted in the D195 Assessment Report Overview and 22May2025 Assessment Report. The 0.24 D is the difference in mean SER change from baseline between 0.01% group and vehicle group (Table 2; Figure 9), and it is not related optical correction or the strength of optical correction for any individual. To know what optical correction strength one would need, one must look at the individual SER value (Figure 10). As illustrated in Figure 8, Figure 9 and Table 2, the 0.24D is the difference of 2 group means. For the 0.01% group, for example, the group mean SER change from baseline is – 1.24 D (Table 2), and this mean value encompasses the whole spectrum progression ranging from no change from baseline over 3 years (i.e., less than 0.5D progression) to a – 4.0 D progression over 3 years (Figure 8). Nonetheless, everyone still needs optical correction at all times, including those achieving stable myopia. Atropine can only slow or halt the progression of myopia, it will never reduce the strength of optical correction (Nemeth, 2021; Figure 10). The 0.24 D difference of 2 group means is not a strength of optical correction or reduction in strength of optical correction for any individual. Because atropine can only slow or halt myopia progression, the clinical outcome of atropine treatment is either stable myopia or a slower progression. If one achieves stable myopia, one's optical correction strength does not change but still need to have optical correction at all times (e.g., subject in Figure 10). If one achieves slower progression, one will need less frequent increase in optical correction strength but the correction strength cannot be decreased (e.g., subject Figure 10). As shown in Table 2, even for those who had not achieved stable myopia after 3 years of atropine treatment, the absolute value of the mean SER progression of the 0.01% group was less than that of the vehicle group, indicating the clinical benefit of Atropine Sulfate FGK.

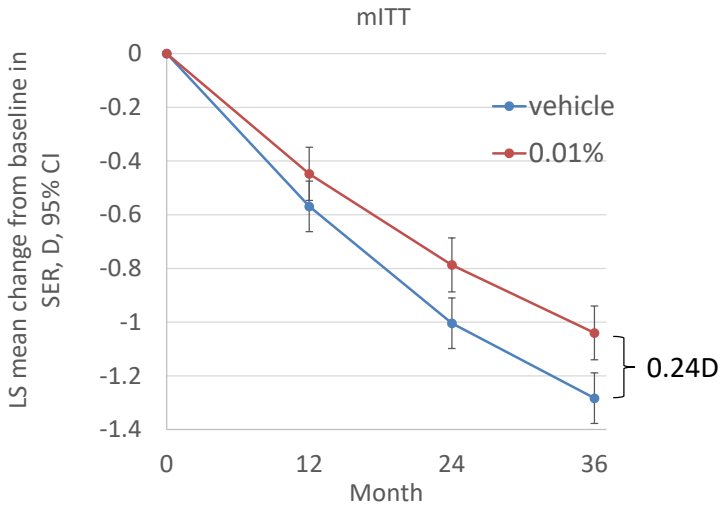


Figure 21. Least square mean change from baseline in SER (CHAMP mITT set) for the Atropine Sulfate FGK group and the vehicle group

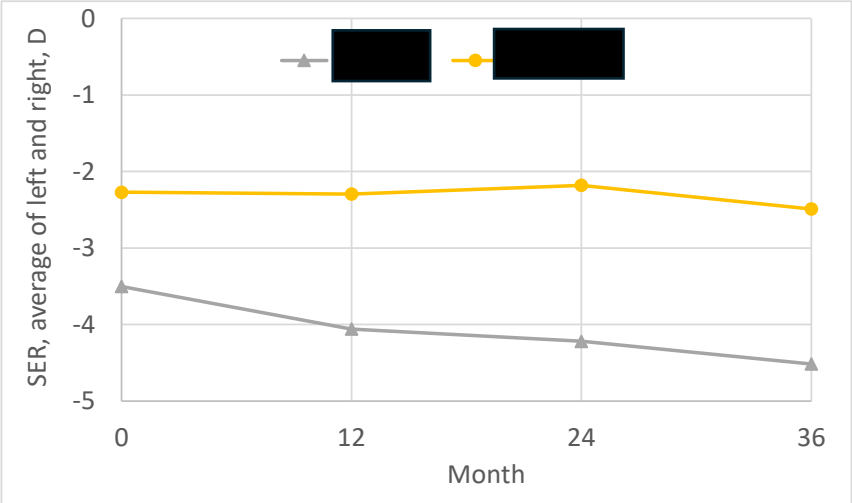


Figure 22. Examples of optical correction needed for a subject who achieved stable myopia and a subject who did not achieve stable myopia over 3 years (). Both subjects were on Atropine Sulfate FGK 0.01%

CHMP also requested a revised analysis with subject as the experimental unit and using retrieved dropout to impute missing data. Analyses using subject as experimental unit have confirmed analyses using eyes as experimental unit (Response to D120 LOQ Q77). However, missing data imputation using retrieved dropout (a missing not at random assumption) should not be used to override the original analyses for the CHAMP study or analyses at subject level without imputation. Missing data imputation by retrieved dropouts could have been more useful if the retrieved dropout information were to represent the progression of the patient without the impact of further therapeutic intervention (Guideline on Missing Data in Confirmatory Clinical Trials, EMA/CPMP/EWP/1776/99 Rev. 1). As discussed in the CHAMP CSR Section 11.4.2.6.2, approximately half of the retrieved dropouts used confounding therapies (orthokeratology, multifocal contact lens and/or compounded atropine) after discontinuing study medication. Hence, half of the retrieved dropout information in CHAMP does not fall in the category of useful information for missing data imputation. Even considering the limitation and assumption of the retrieved dropout imputation, it did not qualitatively change the conclusion of the subject level analysis without imputation (Response to D120 LOQ Q77).

On p.109 of the 22May2025 Assessment Report, it was stated that "the applicant claimed benefit on …. b) atropine 0.01% slowed myopia progression in those that did not achieve stable myopia, which was supported by a projection of treatment effect over 6 years". This is a misunderstanding of Applicant's response (see Response to D120 LOQ Q81). The applicant needs to point out that the statement "b) atropine 0.01% slowed myopia progression in those that did not achieve stable myopia" is not related to the projection over 6 years and does not require support from 6-year projection. The projection was a response to the D120 LOQ Q79b (Response to D120 LOQ Q79b), not related whether 0.01% slowed myopia progression in those who did not achieve stable myopia in 3 years. Instead, the conclusion of "b) atropine 0.01% slowed myopia progression in those that did not achieve stable myopia" is supported by results from the CHAMP study without any projection (Table 2).

Finally, the clinical relevance is further supported by the efficacy of Atropine Sulfate FGK in reducing AL elongation. It is well recognised that excessive AL elongation is the biological basis of axial myopia, and AL measurement is an important anatomic endpoint in addition to functional endpoint such as SER in clinical trials of myopia control (Mackey 2024; Jonas 2023; Tideman 2018a). As shown in Figure 5, Atropine Sulfate FGK reduced AL elongation compared to vehicle at 1-years, 2-year and 3- year, providing a sound biological basis for the observed refractive error endpoints.

In summary, clinical relevance is substantiated by the absolute risk difference (11%) of patients achieving stable myopia, and the slower myopia progression (either SER progression or AL elongation) in Atropine Sulfate FGK treated patients compared to vehicle treated patients. Atropine Sulfate FGK contains 0.01% atropine which is in the minimum effective concentration range. The treatment effect size of Atropine Sulfate FGK in slowing SER progression is consistent with that of other 0.01% atropine drug product approved in the EU or in the published literature. Both halting myopia progression and slowing myopia progression are clinically relevant because there is no safe level of myopia severity, and a reduction in the ultimate stabilized myopia severity will reduce the risk of myopia-related complications later in life (Tideman 2016; Haarman 2020).

CHMP position on the applicant´s claims

The adopted ground for refusal states that the three main studies are formally failed studies and thus, clinical relevance was not substantiated in the proposed indication. In the grounds for re-examination, the applicant attempts to demonstrate clinical relevance of the CHMAP study results by discussing the size of the estimated treatment effect for the 0.01% dose. However, discussing the clinical relevance of point estimates is irrelevant for the assessment as long as the endpoint for that dose cannot be considered statistically significant.

The applicant points out that the revised analysis with subject as experimental unit and using retrieved dropout to impute missing data, which was requested during the previous assessment, 'should not be used to override the original analyses for the CHAMP study or analyses at subject level without imputation'. First, it should be noted that even the originally presented analysis without imputation did not demonstrate statistical significance and the requested analysis resulted in an even smaller treatment effect estimate only, while remaining insignificant. Thus, it is irrelevant for the assessment of the grounds for re-examination to discuss whether the requested analysis using retrieved dropout data to impute missing data is useful or not. For the sake of completeness, it is added that using retrieved dropout data might indeed be a sensible way to implement a treatment policy strategy, which is of interest from a regulatory view.

Furthermore, the applicant elaborated on whether the claim that atropine 0.01% slowed myopia progression in those that did not achieve stable myopia is based on the projection of a treatment effect over 6 years as was previously commented. This discussion does not address the main issue that the main analyses did not demonstrate efficacy, and is therefore not considered relevant.

Conclusion

Ground #4 not resolved.

5.5. Ground #5

Other inaccurate statements in the 22May2025 Assessment Report are addressed below.

Grounds for re-examination:

Combined analysis of 3 endpoints in CHAMP
CHMP opinion:

On p.113 of the 22May2025 Assessment Report, it was stated that combined analysis cannot compensate for the fact that the individual studies failed to meet their primary endpoint.

The 22May2025 Assessment Report statement is a misunderstanding of the purpose of the combined assessment. The combined analysis is to address the scientific question of what is the probability of 0.01% efficacy due to chance in the CHAMP study. It is not related to the primary endpoint in CHAMP (0.02% responder), nor individual studies failing to meet their primary endpoint. The combined analysis was on the secondary endpoints (0.01%) of CHAMP. As a part of the assessment based on totality of evidence, it is a fair scientific question to ask what is the probability of 0.01% efficacy due to chance. In fact, CHMP asked the question in D120 LOQ Q78, "why the nominal effect seen for atropine 0.01% in CHAMP is not a spurious finding". As explained in the Response to D120 Q78, the combined assessment of the 3 key efficacy endpoints of 0.01% addressed specifically the question CHMP asked. This assessment starts with the assumption that the null hypothesis is true. By permutating the subjects between the atropine 0.01% and placebo arms 1500 times, the probability of observing the 3 endpoints that are equal to or more extreme than what CHAMP observed is 0.004. The combined assessment did not permute the outcomes, hence correlation between SER and AL does not impact the combined assessment (see Li 2020 for methodological details). This combined assessment provides a clear indication that the positive outcomes of 0.01% efficacy in CHAMP are unlikely due to chance (Stage 1 Report of Additional analyses V2.0, Section 5.4).

Progression to high myopia

CHMP opinion:

On p.151 of the 22May2025 Assessment Report, it was stated that "it is agreed with the applicant that primarily prevention of progression to high myopia (<-6.0D) is key".

Applicant Response:

The 22May2025 Assessment Report statement is a misunderstanding of the MAA or the objective of the CHAMP study. The CHAMP study was not designed to assess primarily prevention of progression to high myopia (<-6.0D). There is no mention of progression to high myopia in either primary endpoint or secondary endpoints. Instead, the SAP specified the progression to high myopia as a tertiary endpoint. Given the mean baseline SER of -2.49 D (mITT set) and the mean SER change from baseline of – 1.24 D at Month 36 (mITT vehicle group), the CHAMP study confirmed that there was not enough patients progressing to high myopia (< - 6.0 D) that would be suitable for a statistical analysis of between-group difference in the proportion of progression to high myopia (CHAMP CSR Section 11.4.1.3.4). A recent review confirmed the applicant's view that it is impractical to conduct a RCT with the objective of preventing high myopia (Eppenberger 2024).

CHMP position on the applicant´s claims

The applicant's claim that a combined analysis from three individual secondary endpoints in CHAMP 'provides clear indication that the positive outcomes of 0.01% efficacy in CHAMP are unlikely due to chance' is not agreed to. A post-hoc analysis which is by nature not multiplicity adjusted is considered of little value for the demonstration of efficacy. Moreover, as the endpoints are collected on the same subjects, it should not be a huge surprise that these endpoints are correlated.

The previous AR states that primarily prevention of progression to high myopia is key. According to the applicant this is a misunderstanding of the MAA or the objective of the CHAMP study. It is understood that the CHAMP study was not designed for demonstrating a benefit on the prevention of progression as pointed out by the applicant, but this was not suggested by the previous AR nor was it required. It is considered legitimate to discuss that prevention of progression to high myopia is an important objective in the treatment of myopia and to which extent the studies provided evidence for a benefit of Atropine sulfate FGK with regard to this objective.

Conclusion

Ground #5 not resolved.

5.6. Overall conclusion on the grounds for re-examination -applicant's position

Significant bias and misunderstanding of the nature of myopia progression have been identified in the 22May2025 Assessment Report and 22May2025 Opinion.

First, the Assessment Report did not allow the applicant to proceed to subsequent statistical analyses, but failed to acknowledge that CHMP in the past has allowed other applications to proceed to subsequent statistical analyses despite its primary endpoint not being met. This is an inconsistent and biased refusal. To fairly assess the efficacy of Atropine Sulfate FGK, assessment should be based on the context, totality of evidence, consistency across endpoints, support of evidence synthesis and credibility of efficacy in the same manner as other applications in which the primary endpoint was not met.

Second, the Assessment Report's conclusion that the effect of 0.01% and 0.02% were not comparable is in direct contradiction of the CHAMP results.

Third, the Assessment Report's conclusions that (1) the atropine effects in Mini-CHAMP and China-CHAMP were smaller than those in CHAMP, (2) there is a difference in atropine effect in Asians vs non-Asians, and (3) Mini-CHAMP and China-CHAMP are of limited importance are in direct contradiction of the CHAMP results. Comparison cannot be based on point estimates alone. One must consider both point estimates and 95% CI. The CHAMP results and the meta-analysis of 14 RCT's on 0.01% atropine showed that there is no evidence to suggest the atropine treatment effect could be different in Asians vs non-Asians. It is unreasonable to conclude Mini-CHAMP and China-CHAMP efficacy are of limited importance while contradictorily requesting Mini-CHAMP ADR's be included in the SmPC.

Fourth, the Assessment Report misunderstood the meaning of the absolute risk difference between 0.01% and vehicle (11%) and the meaning of the difference in mean SER change from baseline between 0.01% and vehicle (0.24 D). The Report erroneously concluded that 11% more patients achieving stable myopia is not relevant and 0.24 D is too small to substantially reduce the strength of optical correction needed. Achieving stable myopia is an undeniable clinical benefit. Atropine can only halt or slow myopia progression, one should not expect the strength of optical correction to be reduced. Any patient achieving stable myopia is an ideal clinical response, and it is unreasonable to expect all or most patients would have an ideal clinical response. For patients who had not achieved stable myopia, slowed progression should be recognized as beneficial because it reduces the ultimate severity of myopia and therefore reduces the risk of myopia-related complications later in life.

Lastly, other misunderstandings contributed to the negative opinion in the Assessment Report (22 May 2025), including the misunderstanding of the combined assessment of 3 endpoints and the misunderstanding of progression to high myopia as a key endpoint in CHAMP.

In summary, the Opinion and Assessment Report contain bias, misunderstanding of the CHAMP/Mini-CHAMP/China-CHAMP study results and misunderstanding of the nature of myopia progression, which warrant a re-examination. An *ad hoc* Expert Group consultation is necessary to help CHMP better understand the nature of myopia progression and holistically assess the benefit-risk balance of Atropine Sulfate FGK.

5.7. Report from the AHEG

The following questions were raised to the AHEG in view of the grounds for re-examination:

1) According to the assessment of the CHMP none of the three pivotal studies (CHAMP, MOSAIC and MTS1) did meet their primary objective, all are formally failed studies, and thereby efficacy of Atropine sulfate FGK is not demonstrated.

a) The experts are asked to comment and present their view on the results of these pivotal studies.

To address the question, firstly the experts conveyed that atropine can be effective in slowing myopia progression. An optimal dose concentration, balancing efficacy and safety (and potential rebound effect), and the exact mechanism of action are not (yet) established.

Different (magistral) preparations / formulations of atropine (e.g. eye drops) are available in the (EU) market. Atropine use was also noted in combination with e.g. spectacles.

Myopia tends to stabilise when the patient gets older. The experts agreed that, when attempting to slow progression of myopia, it is clinically more important to minimise the probability of patients experiencing higher myopia or structural eye damage rather than focusing on specific final diopter(s) (D) reduction.

Axial Length (AL) was noted as the best parameter to establish atropine efficacy in slowing myopia progression.

Experts also concurred that different concentrations of atropine are needed for different populations and, on this aspect, there is a variability of factors to consider (e.g. race, ethnicity, phenotypes, etc).

Lower side effects or risks would be expected with lower atropine dose concentration(s).

Different medicinal products containing atropine 0.01% have been approved. However, these products can't validate Atropine sulfate FGK 0.01% because active substances and medicinal products are different concepts (e.g. type of formulation, other factors should be taken into account as equally important).

While the active substance atropine can be effective for EU children, a key question remains on whether Atropine sulfate FGK 0.01 %, based on the results of the randomised clinical trials (RTCs) conducted by the applicant, is also effective.

Different problems in CHAMP, MOSAIC and MTS1 studies were mentioned by the experts (bias as triggered e.g. by effects of behavioural interventions not always reported or taken into account; heterogeneity e.g. in patient's subgroups and study results; methodological issues or [perhaps] issues within the applicant's development programme; impact of genetic variability which might alter the response to treatment; treatment's compliance's issues; etc.) aside for all these three studies not reaching their primary objective.

Concern was also expressed on the fact that the applicant ultimately claims efficacy of Atropine sulfate FGK 0.01% with post-hoc analyses after the pre-specified primary endpoints of the pivotal studies CHAMP, MOSAIC and MTS1 had not been meet.

From a patient's perspective, child's discomfort caused by the method of administration as eye drops, daily at bedtime, and for a prolonged period of time, aside from potential errors of (dose) administration, triggered by the administration procedure itself, are also areas of concern.

In summary, having noted the results of the pivotal studies CHAMP, MOSAIC and MTS1, specifically the key endpoints of efficacy assessment for Atropine sulfate FGK, the experts agreed that:

- Response less than 0.5 D (specifically: 0.25 D) after 3 years of treatment was not considered clinically relevant;

- Spherical Equivalent Refraction (SER) was not considered clinically relevant.

In addition:

- Axial Length (AL) difference (change from baseline) was the only endpoint considered *per se* a reliable and relevant measurement that showed some efficacy of Atropine sulfate FGK 0.01%. However, the experts could not agree on whether this result of AL difference of only 0.13 mm is clinically significant.

b) In addition, the experts are asked to present their view on the fact that there are external studies indicating efficacy of the drug substance atropine sulfate, while efficacy could not be established in the three pivotal studies investigating the proposed drug product Atropine sulfate FGK.

The experts noted that the external studies focused on non-EU patients.

Different responses to treatment for the active substance atropine sulfate have been noted in literature, e.g. depending on race. For example, it is known that Asian patients have predominantly dark eyes (thus, a higher concentration of melanin pigment in the iris) and, in comparison to EU patients, are affected by faster myopia progression. In addition, in comparison to Europeans, Asians may respond differently to the drug substance atropine sulfate. Of note, melanin concentration in the iris varies depending on e.g. age, race, region, eye's colour and this might affect the response to treatment.

The experts agreed that CHAMP and MOSAIC studies could offer a picture of what would typically be expected in an EU population treated to slow myopia progression.

One participant expressed that a study in an EU population, better defined in terms of patient's sub-groups with common characteristics, would have been helpful to (better) identify a (sub)population where Atropine sulfate FGK might have been more effective, if effective *per se*.

According to the experts a direct comparison of the three RTCs investigating Atropine sulfate FGK with external studies not representative of the European population (for which a marketing authorisation application has been sought) is not possible. This is due to demographic differences (e.g. composition of enrolled populations); diverse formulations of atropine, study's durations (e.g. CHAMP was considerably longer, with a 3-year duration as opposed to 1 or 2 years in other studies), measurements and methods to evaluate results, etc.

In the experts' view, there are enough compelling reasons for discrepancies between the applicant's pivotal RTCs and the external studies. These discrepancies in efficacy or safety results could possible be due to dose-exposure mismatch. Other factors could be: the formulation (e.g. atropine's ocular bioavailability can be impacted by excipients, viscosity, pH, preservatives, tonicity, etc.), treatment's

regimen, phenotype, ethnicity, age (range), baseline progression, if a study was multi-center or conducted just in one country. Adherence to treatment's compliance was also mentioned, together with (diverse) methods described to measure such adherence.

In summary, in the context of establishing efficacy of the drug substance Atropine sulfate FGK, external studies in non-EU patients should not be regarded as relevant as CHAMP (conducted, aside for US, in Hungary, Ireland, Netherlands, Spain and UK) and MOSAIC (conducted in Ireland) as their results may not clearly correlate to (or replicate the results in) the EU population where Atropine sulfate FGK would be used. On the contrary, CHAMP and MOSAIC tested Atropine sulfate FGK in the intended EU patient population for which a MA has been sought.

2) In the experts' view, would they have expected a differential response in the pivotal study CHAMP for the two investigated dose concentrations (0.02% and 0.01%) of Atropine sulfate FGK?

The experts would have expected a better efficacy response to the higher dose concentration of Atropine sulfate FGK 0.02%.

A completely satisfactory explanation was not identified. Perhaps, the higher dose concentration of Atropine sulfate FGK 0.02% loses more effect over time than the 0.01%.

Looking at data in the CHAMP study, after 1 year the difference in spherical error between 0.02% and 0.01% dose concentration is bigger and the difference in AL is the same, but the response diminishes in the 2nd and 3rd year. A potential explanation might be that Atropine sulfate FGK 0.02% loses some effect in the 2nd and 3rd year of treatment. However, looking at a response of 0.25 D, over time a response difference between 0,02% and 0.01% dose concentrations would be very small and not statistically relevant.

An expert suggested for the applicant to re-analyse CHAMP study results and, if those on Axial Length (AL) are measurable, maybe the effect above described could be ascertained. Aside for that tolerability and compliance issues might also provide an explanation: a higher dose concentration of 0.02% may cause e.g. more discomfort, more pupil dilation or accommodation issues that could impact compliance to the treatment, thus possibly reduce effectiveness (while potentially triggering more frequent or more severe side effects) despite the theoretical pharmacological superiority of the higher 0,02% dose concentration.

Ethnicity and iris' pigmentation were also mentioned as potential explanations. It was likewise considered that perhaps the lower dose concentration of Atropine sulfate FGK 0.01% nearly achieves the maximum therapeutic effect on muscarinic receptors. Therefore, the higher dose concentration of 0.02% may not trigger a proportionally higher benefit but increase the side effects. The experts concurred that more population-specific studies are needed to ascertain the above.

CHAMP study highlighted that dose selection(s) should be population-specific and Atropine sulfate FGK 0.01% dose concentration might offer an acceptable benefit-risk profile for Western children (due to genetic factors) whereas in the Asian population higher doses, for various reasons, could be more preferable. In addition, in future clinical studies the settings should be more precisely defined and more emphasis given to effect's modifiers' aspects (e.g. eye's colour, compliance to treatment, etc.).

In summary, uncertainty remains on the absence of a differential response in the pivotal study CHAMP for the two investigated dose concentrations (0.02% and 0.01%) of Atropine sulfate FGK. The experts considered that that 0.01% could be the ceiling dose concentration to treat myopia in the EU population due to specific eye's characteristics and genetic factors. A plausible worse treatment compliance for the higher dose concentration, caused by more severe or more frequent side effects

(i.e. photophobia, etc.), was also mentioned as potential explanation, together with higher patient's discomfort or a tapering effect after 2-3 years of treatment with Atropine sulfate FGK 0.02%.

EMA post-meeting note

During the AHEG meeting reference was made to the publication of Li Y. et al, available at pubmed.ncbi.nlm.nih.gov/38019503/.

A short summary is provided below:

The ATLAS study was a prospective, double-masked observational study of the ATOM1 and ATOM2 randomized clinical trials that took place at two single centers and included adults reviewed in 2021 through 2022 from the ATOM1 study (atropine 1% vs. placebo; 1999 through 2003) and the ATOM2 study (atropine 0.01% vs. 0.1% vs 0.5%; 2006 through 2012). In these cohorts, the use of short-term topical atropine eye drops, ranging from 0.01% to 1.0%, for two to four years, starting at approximately 9 years of age, with moderate myopia, was not associated with differences in final refractive errors 10 to 20 years after treatment. There was no increased incidence of treatment or myopia-related ocular complications in the 1% atropine-treated group vs. the placebo group.

The researchers wrote in their paper that "this study may support existing literature that atropine may be ineffective at reducing myopia progression, with this study specifically examining progress into adulthood through observation of outcomes over a 10- to 20-year period."

5.8. Oral explanation

The applicant was invited to present its position during an oral explanation (OE).

On 16 September 2025, a presentation to address the grounds for MA refusal was made at the CHMP plenary meeting.

Having also considered the views expressed by the AHEG on 3 September 2025, during the OE the applicant directed CHMP attention to the applicant's view on the key endpoints for Atropine sulfate FGK efficacy assessment, the totality, consistency and credibility of evidence from all presented studies(of which 5 RTC conducted on Atropine Sulfate FGK, all having at least a 1-year results, 4 out of 5 a 2-year results, 1 out of 5 [CHAMP], a 3-year results), focusing on Atropine sulfate FGK 0.01% concentration (for which the applicant is seeking MA in the EU), debated the effects of atropine in the Asian and an heterogeneous patient's population, the impact of retrieved dropouts imputation in the pivotal CHMP study, with reference to EMA guideline on missing data in confirmatory trials (EMA/CPMP/EWP/1776/99 Rev. 1), the clinical relevance of slowing of myopia progression in the context of the relative risk of retinal detachment (conveyed as approximately 3 folds higher in patients with myopia versus those without myopia).

Of note, as previously expressed (e.g. with reference to Ground #1), every MAA is assessed on its own merit, based on the totality of the data presented in the dedicated application for the medicinal product under evaluation, specifically Atropine sulfate FGK 0.01%) in support of the claimed indication in the EU population. In addition, the summary effect of a meta-analysis including external studies evaluating atropine 0.01% should not substitute or compensate for the failure of the Atropine sulfate FGK dedicated RTCs. Furthermore, sufficient evidence is required in the European population where the product would to be administered. The CHMP also conveyed that any data following treatment discontinuation should be collected and considered when interpreting and contextualising the analyses, particularly the frequency and timing of any further therapeutic intervention(s). In summary, after this OE, the Committee concluded that, given the concerns on lack of demonstration of efficacy of Atropine sulfate

FGK in CHAMP, MOSAIC and MTS1 studies, as expressed in the present assessment report (and further detailed e.g. in section 7), did not change the CHMP initial opinion on this MAA.

5.9. CHMP overall conclusion on the grounds for re-examination

The assessment for every MAA is conducted considering the totality and robustness of evidence, consistency across endpoints, and the plausibility of efficacy. Hence the assessment report adopted by the CHMP on 22 May 2025 was not seen as biased or in contradiction to other applications where e.g. the primary endpoint was not met.

The different arguments presented by the applicant (in writing and / or during the OE held in front of the CHMP on 16 September 2025), as above noted, did not change the outcome of the initial assessment on the ground for MA refusal. Ultimately, based on the totality of data pertaining to Atropine sulfate FGK presented in the dedicated MAA, the CHMP, by consensus, remained of the opinion that the efficacy of Atropine sulfate FGK in the claimed indication could not be sufficiently demonstrated.

5.10. Risk Management Plan

The CHMP, having considered the data submitted in the application, was of the opinion that due to the concerns identified, the risk management plan (RMP) cannot be agreed at this stage.

5.11. Pharmacovigilance

5.11.1. Pharmacovigilance system

Not applicable.

5.11.2. Periodic Safety Update Reports submission requirements

Not applicable.

5.12. Product information

The CHMP, having considered the data submitted in the application was of the opinion that due to the concerns identified, the product information cannot be agreed at this stage.

5.13. New active substance claim

Not applicable.

6. Benefit-risk balance following re-examination

6.1. Therapeutic context

6.1.1. Disease or condition

The indication claimed by the applicant during the MAA assessment for Atropine sulfate FGK (0.01%) is to slow myopia progression in children aged 6 to 10 years with spherical equivalent refraction (SER) in the range of -0.50 to -6.00 diopter (D).

Myopia, also called near-sightedness, is an eye disease that results from an increase of the axial length of the eye, or issues related to the cornea or lens.

Onset usually occurs during childhood. On average, myopia stabilizes by ~15 years of age, with 95% of patients with myopia stabilizing by age 24 (Nemeth et al., 2021). Myopia progression varies widely between individuals, but generally occurs at a rate of 0.50 to 1.00 D per year during childhood (Gifford, 2019; Walline, 2011; Walline, 2020).

High myopia places affected patients at increased risk for other ocular diseases and is defined as a refractive error of ≤−5 D by the World Health Organization (WHO; 2015) although more recently ≤−6 D has been proposed by the International Myopia Institute (IMI, 2020). These include glaucoma, cataract, retinal tears which may lead to detachment, and myopic maculopathy or macular degeneration (Williams and Hammond, 2019). More severe myopia resulted in an earlier onset of complications (Haarman et al., 2020).

It is anticipated that by 2050 approximately 50% of the world's population will be affected and 56% in Europe specifically (Holden, 2016; Morgan, 2021). Prevalence of myopia within EU children aged 6-10 years is estimated at approximately 10-20% (Hönekopp 2024; Matamoros 2015).

Myopia is diagnosed and monitored through examination of patient history and eye examinations, which may include assessment of cycloplegic refraction and eye length.

6.1.2. Available therapies and unmet medical need

In the EU Ryjunea (atropine sulfate) (0.1 mg/ml eye drops, solution) is approved for 'slowing the progression of myopia in paediatric patients. Treatment may be initiated in children aged 3-14 years with a progression rate of 0.5 D or more per year and a severity of -0.5 D to -6.0 D.'

Non-pharmacological approaches

Options in the EU include ordinary optical correction (spectacles, contact lenses), and interventional contact lenses: multifocal contact lenses and orthokeratology. Spectacles are generally the preferred option for young children with lenses reserved for older children as they are more challenging to use.

Aside from spectacles and contact lenses used only for correction of refraction error, the main non-pharmacological interventions for controlling myopia include public health (lifestyle) interventions for optimization of environmental influences. Surgical interventions are not considered first line treatment modalities and combination treatments are under investigation.

The European Society of Ophthalmology in cooperation with International Myopia Institute as well as the American Academy of Ophthalmology concluded on a benefit of atropine for the treatment of

myopia progression and management of at-risk pre-myopic children. There were, however, uncertainties on the optimal concentration of atropine to be used (Németh J et al. EJO 2021).

In the EU, magistral preparations are used for treating myopia and included in many (inter)national guidelines. E.g., atropine 0.01% has been proposed to have an appropriate benefit-risk ratio by the clinical field (World Society of Paediatric Ophthalmology and Strabismus myopia consensus statement, 2016).

A treatment that could prevent myopia would be highly welcomed; as such there is a medical need. However, as myopia in general is neither life threatening nor disabling there is no urgency or pressure. As such there is no unmet medical need as defined in the regulatory context.

6.1.3. Main clinical studies

The primary source of efficacy is CHAMP (CP-NVK002-0001; n=576), a randomized (2:2:3), double-blind, placebo-controlled, parallel-design two-stage study performed by the applicant. CHAMP tested Vehicle (n=165), Atropine Sulfate FGK 0.01% (n=164) and Atropine Sulfate FGK 0.02% (n=247) dosed once daily at bedtime in subjects aged 3 to ≤17 years with myopia (SER -0.50 to -6.00 D). Stage 1 was the 36-month primary analysis period; Stage 2 a 12-month re-randomized phase (1:1:1:1) to evaluate maintenance of effect and rebound effects of atropine.

Further relevant evidence comes from MOSAIC (n=250) and MTS1 (n=187). Their design is comparable to CHAMP except that subjects were randomized 2:1 to Atropine Sulfate FGK 0.01% or Vehicle, had a primary analysis period of 24 months and were performed by independent investigators. MOSAIC ran exclusively in Ireland and had a tapering period of 12 months; MTS1 ran exclusively in the USA and had a follow-up of 6 months.

Two other studies (mini-CHAMP (n=526) and China-CHAMP (n=777)) alike CHAMP were conducted with Vehicle, Atropine Sulfate FGK 0.01% and 0.02% by a partner of the applicant exclusively in China. Although the benefit/risk assessment of atropine sulfate FGK is based on the totality of evidence, the data from the mini-CHAMP and China-CHAMP are not considered decisive for the benefit-risk for the following reasons. Mini-CHAMP had a treatment duration up to 1 year only, a duration which is without clear relevance to later timepoints. E.g., in CHAMP at 1-year the results for 0.01% and 0.02% were still similar yet divergence was seen at Month 24 and 36. The results of China-CHAMP were from early and preliminary topline analyses, and no CSR is available. Further, both studies showed treatment differences smaller than in CHAMP, which was already of questionable relevance and which formally did not demonstrated efficacy. Moreover, the representativeness of data of Chinese children from studies exclusively performed in China for this EU MAA remains unclear as differences for Asian vs non-Asian patients have been suggested in terms of myopia progression (e.g., Brennan et al., 2024) and atropine effects (e.g., Lawrenson et al., 2025; Li et al., 2014). Mini-CHAMP and China-CHAMP results are therefore not further discussed in the Benefit-Risk section.

6.2. Favourable effects

In CHAMP, the primary analysis was conducted in mITT (ITT subgroup aged 6-10 years). Therefore the age limits of the target population were aligned with mITT. The primary endpoint was the between-treatment group difference for Atropine Sulfate 0.02% versus Vehicle in the proportion of subjects' eyes in mITT that showed <-0.50 D myopia progression (SER) at the Month 36 visit. No statistically significant effect was observed (proportion of responding eyes <0.5D Atropine 0.02% vs Vehicle: 22.1% vs 17.5%; absolute risk difference of 1.56; 95% CI: 0.55, 6.260; p=0.38). A secondary

endpoint assessed the between-treatment group difference for Atropine Sulfate 0.01% versus Vehicle, which was nominally significant (Atropine 0.01% vs Vehicle: 28.5% vs 17.5%; absolute risk difference: 11%; 95% WALD CI: 3.3%; 18.9%; nominal p=0.01).

In CHAMP, Change-in-SER was evaluated as secondary/tertiary endpoints. In mITT the treatment difference was nominally significant for atropine 0.01% but not for 0.02% (Month 36, atropine 0.02% vs Vehicle: LSM difference of 0.099 D; 95% CI: -0.02; 0.22; p=0.1 and atropine 0.01% vs Vehicle: LSM difference of 0.24 D; 95% CI 0.106; 0.374; nominal p<0.001).

The change-from-baseline for axial elongation was also evaluated as secondary/tertiary endpoints and were nominally significant for both doses (in mITT at Month 36, atropine 0.02% vs Vehicle: LSM difference of -0.077 mm; 95% CI -0.131, -0.024; p=0.005 and for atropine 0.01% vs Vehicle: -0.13 mm; 95% CI -0.191, -0.069; nominal p<0.001).

In MOSAIC and MTS1, the primary endpoint was change in SER from baseline to the 24-month visit. In both studies no significant treatment difference for Atropine Sulfate 0.01% versus placebo was observed. In MOSAIC, the treatment difference (standard error) for atropine 0.01% vs placebo was 0.12 D (0.07), p=0.07. In MTS1, this treatment difference (95% CI) was −0.02 D (−0.19, 0.15D; p=0.83).

Axial elongation was assessed as secondary endpoint in MOSAIC and MTS1. In MOSAIC, a nominal significant treatment difference for atropine 0.01% vs Vehicle was shown (in ITT at Month 24: mean [standard error]: -0.07 mm [0.03], p <0.009). In MTS1, this treatment difference at Month 24 was −0.002 mm (95% CI −0.106 to 0.102; nominal p-value not provided, but non-significant).

6.3. Uncertainties and limitations about favourable effects

None of the three main studies (CHAMP, MOSAIC, MTS1) achieved their respective success criteria, therefore they are considered formally failed studies.

In CHAMP, the primary objective (between-treatment group difference for 0.02% atropine sulfate FGK versus Vehicle in the proportion of subjects' eyes in mITT that showed <-0.50 D myopia progression (SER) at the Month 36 visit) was not met. MOSAIC and MTS1 also did not meet their primary objectives (between treatment group difference in change in SER from baseline to the 24-month visit between 0.01% atropine sulfate FGK and placebo). In CHAMP, the hierarchical testing procedure stopped after the primary analysis did not reach statistical significance, therefore none of the subsequent analyses can be declared as having demonstrated a statistically significant treatment effect.

The primary analysis presented for CHAMP was conducted on the eye as the unit of analysis rather than the subject. During the PIP compliance check of the PDCO, the applicant committed to also provide the primary analysis based on the initial SAP at MAA, but this was not performed (EMA/PDCO/40253/2024 p.36 of 39). A retrieved drop-out analysis on subject level was therefore requested by CHMP and provided by the applicant. This analysis consistently showed smaller effects for both doses and across all three endpoints:

- for the responder analysis at eye level, the treatment difference was not nominally significant for either dose (Month 36 in mITT, atropine 0.02% vs Vehicle: 3.7%; 95% WALD CI: -3.8%, 11.2% *p*=0.3 and atropine 0.01% vs Vehicle: 7.6%; 95% WALD CI: -1.4%, 16.5%, *p*=0.1).
- for the change-in-SER-from-baseline endpoint the treatment difference was not nominally significant for either dose (Month 36, atropine 0.02% vs Vehicle: LSM difference of 0.048 D; 95%

CI: -0.10; 0.20; p=0.53 and atropine 0.01% vs Vehicle: LSM difference of 0.146 D; 95% CI -0.04; 0.34; p=0.13).

- for the change-in-AL-from-baseline endpoint the treatment difference was nominally significant for atropine 0.01% but not 0.02% (Month 36, atropine 0.02% vs Vehicle: LSM difference of -0.061 mm; 95% CI -0.125, 0.002; p=0.06 and for atropine 0.01% vs Vehicle: -0.098 mm; 95% CI -0.175, -0.02; p=0.01).

These findings reinforce the concern that the initial analysis may have overestimated the treatment effect of atropine sulfate FGK, thereby raising further doubts about the credibility and clinical relevance of the results.
The post-hoc selection of the lower dose might indicate that the estimate observed in the CHAMP study for the treatment effect of atropine 0.01% is an overestimation of its true treatment effect and efficacy of this dose and its clinical relevance cannot be concluded.

Further the clinical relevance of the observed effect size for atropine 0.01% remains uncertain. In the initial <0.5 D responder analysis, the treatment difference at Month 36 (atropine 0.01% vs vehicle) was 11% (n=13) in the mITT, this was 7.6% in the retrieved drop-out analysis. In the sample size calculations, the applicant expected a difference of 18% in responder rate, which was not achieved.

6.4. Unfavourable effects

The safety profile of Atropine FGK is comparable to what is known for low concentration atropine eye drops. The proportion of subjects with TEAEs for atropine 0.01% was similar and not dose-dependent to Vehicle and atropine 0.02%.

Four subjects in CHAMP discontinued due to an AE (1x Vehicle; 3x atropine 0.02%). There were no deaths or ocular SAEs that were at least possibly related to atropine 0.01% or 0.02%.

Ocular TEAEs

Ocular TEAEs (CHAMP stage 1) were more frequently reported in the Vehicle group (40.7%) compared to atropine 0.02% (33.2%) and atropine 0.01% (25.6%) with the majority of ocular TEAEs at least possibly treatment-related. Severity was comparable across treatment groups with mostly mild TEAEs. In the atropine 0.02% group one subject experienced a treatment-related severe ocular TEAE (administration site pain) which resulted in study drug discontinuation. Most frequent TEAEs included (vehicle, atropine 0.01% atropine 0.02%, respectively): photophobia (3.1% vs 2.4% vs 4.5%); conjunctivitis allergic (3.1% vs 1.8% vs 4.5%), mydriasis (0% vs 1.2% vs 1.6%) and blurred vision (0% vs 1.2% vs 1.6%). Similar results were observed in Stage 2. In the atropine 0.02% group one subject experienced a treatment-related severe ocular TEAE (eye irritation) which resulted in study drug discontinuation.

In MOSAIC, during the primary treatment period of 24-months, seven AEs were possibly/probably related to atropine 0.01%: eye discomfort (n = 3), temporary blurred vision at near (n = 1), temporary pupil dilation (n = 1), and rash on the eyelid (n = 2). There were no severe TEAEs.

In MTS1, ocular AEs were prevalent and with comparable incidence between groups, including eye irritation at time of instillation (atropine 72%; placebo 82%), photophobia (atropine 26%; placebo n=27%) and blurred vision (atropine 14%; placebo 16%). Two subjects had severe ocular TEAEs and received atropine 0.01% (1x burning in both eyes after drug instillation; 1x pain in both eyes).

Non ocular TEAEs

In CHAMP Stage 1, non-ocular TEAEs were reported in 55.7% of subjects, most commonly in the infections and infestations SOC and more frequently in the Vehicle group (41.4%; atropine 0.01%: 27.4%; atropine 0.02%: 33.6%). COVID-19 TEAE and nasopharyngitis were the most reported TEAE in this SOC. The known systemic AE of atropine, headache, was reported between treatments with comparable frequency (Vehicle: 8.6%, atropine 0.01%: 8.5%, atropine 0.02%: 9.3%). Similar safety results were observed for Stage 2, however TEAEs were reported with lower incidence. AEs related to heart-rate variability, suggestive of systemic atropine exposure, were reported in three subjects (1x Vehicle; 2x atropine 0.02%).

No trends in the subgroups age, sex or race were observed for atropine 0.01% that raised concerns. In subgroup analysis, in the atropine 0.01% group, eye disorder TEAEs were more reported in Asian (20.7%) and White/Caucasian (17.9%) subjects compared to Black/African American subjects (4.3%).

6.5. Uncertainties and limitations about unfavourable effects

Safety assessments were primarily based on AE reporting and ophthalmologic evaluations. Variability in AE assessment frequency across studies may have contributed to potential underreporting. In CHAMP, proactive AE monitoring occurred during Year 1 via office visits every three months and telephone follow-ups within a ±2-week window; however, from Year 2 onward, monitoring was reduced to office visits every three months. In MOSAIC, AE evaluations were conducted biannually, while study MTS1 maintained quarterly assessments. All three studies were conducted during the COVID-19 pandemic, which led to cancellations of certain on-site visits and may have further impacted AE reporting consistency.

6.6. Effects table

Table 61. Effects table for Atropine sulfate FGK

Effect	Short Description	Unit	Treatment (Atropine 0.01% and 0.02%)	Control (Vehicle)	Uncertainties/ Strength of evidence	References
Favourable effects						

Effect	Short Description	Unit	Treatment (Atropine 0.01% and 0.02%)	Control (Vehicle)	Uncertainties/ Strength of evidence	References
Proportion of Subjects' Eyes That Showed Less than 0.5 D Myopia Progression at **Month 36** in **mITT**	Responder analysis (<0.5D)	n of eyes (%)	**Atropine 0.02%: 81 (22.1%)** Atropine 0.01%: 57 (28.5%)	44 (17.5%)	**-Primary endpoint*** of CHAMP not met -Effect not dose-dependent, nor at least similar -Analysis on eye-level -Effect not consistent across age and severity subgroups -Effect lower in preferred retrieved dropout analysis / Difference atropine 0.02% vs Vehicle: 4.6% ;*p=0.37* (95% confidence)** Difference atropine 0.01% vs Vehicle: 11%;*p=0.03*(unadjusted ;95% confidence)** **Retrieved-dropout analysis** (mITT; atropine 0.01% vs Vehicle): 7.6%; 95% WALD CI: -1.4%,16.5%, p=0.1	CHAMP CSR Stage 1, Table 20

Effect	Short Description	Unit	Treatment (Atropine 0.01% and 0.02%)	Control (Vehicle)	Uncertainties/ Strength of evidence	References
Results for change from Baseline in SER at **Month 24** in **ITT**	Comparison results for mean change-from-baseline in normalized SER	D D D	CHAMP at M24 atropine 0.01%: -0.691* MOSAIC atropine 0.01%: -0.53 MTS1 atropine 0.01%: -0.78	CHAMP at M24: -0.932 MOSAIC: -0.63 MTS1: -0.74	**-Primary endpoint** of MOSAIC and MTS1 not met -Effect not dose-dependent, nor at least similar -Effect not consistent across age and severity subgroups in CHAMP -Effect lower in preferred retrieved dropout analysis / Difference atropine 0.01% vs Vehicle: -CHAMP at **M24**: 0.247 D (95% CI: 0.122,0.373; p<.001; unadjusted) -CHAMP at **M36**: 0.253 D (atropine 0.01%: -0.925 D; vehicle: -1.206 D; 95% CI: 0.129,0.377; p<.001; unadjusted) **Retrieved-dropout analysis** (mITT; M36; atropine 0.01% vs Vehicle): LSM difference 0.146 D; 95% CI -0.04; 0.34; p<0.13 -MOSAIC: 0.12 D [0.07]; p=0.07)*** -MTS1: -0.02 D (95% CI: -0.19,0.15;p=0.83)****	CHAMP CSR Stage 1, Table 14.2.2.1.4 MOSAIC and MTS1: Module 5.3.5.

Effect	Short Description	Unit	Treatment (Atropine 0.01% and 0.02%)	Control (Vehicle)	Uncertainties/ Strength of evidence	References
Axial elongation at **Month 36 in ITT**	Change-from-baseline in axial length	LSM in mm (95% CI)	Atropine 0.02%: 0.697 (0.660-0.734) Atropine 0.01%: 0.652 (0.607-0.698)	0.780 (0.735-0.825)	-Secondary endpoint. -Effect not dose-dependent. -Effect lower in preferred retrieved dropout analysis / Difference atropine 0.02% vs Vehicle: -0.083 (-0.14,-0.027; p=0.004; unadjusted) Difference atropine 0.01% vs Vehicle: -0.128 (-0.19,-0.065; p<0.001; unadjusted) **Retrieved-dropout analysis** (mITT; M36; atropine 0.01% vs Vehicle): LSM difference 0.146 D; 95% CI -0.04; 0.34; p<0.13 *Treatment difference for atropine 0.01% vs Vehicle at Month 24 for:* MOSAIC: -0.07 mm [0.03], p <0.009; unadjusted*** MTS1: −0.002 mm (95% CI −0.106 to 0.102; nominal p-value not provided).	CHAMP CSR Stage 1, Table 14.2.2.2.4
Unfavourable effects						
Ocular TEAEs	Photophobia (CHAMP stage 1)	%	Atropine 0.02%: 3.6 Atropine 0.01%: 1.2	2.5	-Potentially underreported -AE duration unclear -Not dose-dependent / -Known ADR of atropine eye drops -Incidence low	CHAMP CSR Stage 1; 12.2.

Effect	Short Description	Unit	Treatment (Atropine 0.01% and 0.02%)	Control (Vehicle)	Uncertainties/ Strength of evidence	References
	Mydriasis (CHAMP stage 1)	%	Atropine 0.02%: 1.6 Atropine 0.01%: 1.2	0	-Potentially underreported -AE duration unclear / -Dose-dependent -Known ADR of atropine eye drops. -Incidence low	CHAMP CSR Stage 1; 12.2.
	Vision blurred (CHAMP stage 1)	%	Atropine 0.02%: 1.6 Atropine 0.01%: 1.2	0	Potentially underreported -AE duration unclear / -Dose-dependent -Known ADR of atropine eye drops -Incidence low	CHAMP CSR Stage 1; 12.2.

Abbreviations: *D: diopter; KSEP: key secondary endpoint; LSM: least square mean; mm: millimetre; n: number; PEP: primary endpoint; SER: spherical equivalent refraction; yo: years old. *: primary comparison was proportion of responding eyes for atropine 0.02% vs Vehicle. **: The primary endpoint was reported as odds ratios which is not agreed as they may exaggerate the effect size. Hence, instead the absolute % difference in responders and corresponding p-value are reported in the Effects Table. ***: Group differences are the difference [standard error] in the estimated marginal means for atropine 0.01% vs Vehicle, derived from the linear mixed model and are adjusted for the baseline value of the outcome. ****: Adjusted mean change in SER-from-baseline at Month 24 was -0.82 D vs -0.80 D in atropine and placebo groups, respectively (Repka et al., 2023)*

6.7. Benefit-risk assessment and discussion

6.7.1. Importance of favourable and unfavourable effects

Efficacy of atropine sulfate FGK could not be demonstrated. All three main studies failed in meeting their primary endpoint.

In CHAMP, the primary endpoint (between-treatment group difference for atropine sulfate 0.02% versus Vehicle in the proportion of subjects' eyes in mITT that showed <-0.50 D myopia progression (SER) at the Month 36 visit) was not met. The lower strength (0.01%) was proposed for marketing authorization, seemingly on the basis of nominally significant effects versus vehicle at month 36. From a methodological standpoint, this approach is not acceptable, as the hierarchical testing procedure which included the comparison of 0.01% versus vehicle with respect to progression as third step was halted following the non-significant primary endpoint result. Consequently, efficacy of atropine sulfate FGK 0.01% could not be demonstrated in the CHAMP study.

MOSAIC and MTS both failed in meeting their primary endpoint (change from baseline in SER at month 24) and differences between atropine 0.01% and vehicle were even smaller compared to CHAMP, substantiating that efficacy of atropine sulfate FGK is not demonstrated.

None of the results in the three main studies is considered clinically relevant as none of the results is statistically significant, i.e. there is no evidence that Atropine sulfate FGK has any treatment effect at all. In addition, the post-hoc selection of the lower dose might indicate that the estimate observed in the CHAMP study for the treatment effect of atropine 0.01% is an overestimation of its true treatment effect and efficacy of this dose and its clinical relevance cannot be concluded.

The handling of drop-outs in the primary analysis of the CHAMP study assuming missing-at-random might have resulted in an overly optimistic treatment effect. A sensitivity analysis based on retrieved drop-out data yielded smaller treatment effect estimates, which were no longer nominally significant for neither dose. Using retrieved drop-out data is considered to approximate a treatment policy strategy for the intercurrent event treatment discontinuation and is thus considered to define a relevant effect from a regulatory perspective. The influence of confounding therapies as proposed by the applicant does not change this conclusion.

In the primary analysis there were only 11% and in the retrieved drop-out analysis even just 7.6% more patients with stable myopia under atropine 0.01% vs Vehicle (i.e., a change of <0.5D/3y). Responder analysis in MOSAIC and MTS1 showed even lower differences (for 0.01% vs vehicle, in MOSAIC <0.75D/2y: 7.2%; in MTS1 <0.5D/2y: 2%).

Further the relevance of change-from-baseline SER results is not conclusively established. LS means difference for atropine 0.01% vs Vehicle at Month 36 is 0.24 D (mITT; initial eye level analysis), or 0.25 D (mITT; retrieved drop-out analysis at subject level). Similar effects were also observed for change-in-axial length. Correspondingly no difference between treatment groups in progression of the -0.5;-3D group to the -3.01;-6.0D group was observed between vehicle and the atropine 0.01% group, when taking into account the proportional disbalance between vehicle and the atropine 0.01% group at baseline.

The frequency of TEAEs observed in CHAMP and MOSAIC appear lower than what is generally known and it remains uncertain if AEs may have been underreported. Nonetheless, regarding the overall AEs for the atropine sulfate 0.01% concentration were consistent with the established safety profile of atropine eye drops. Notably, 0.01% atropine is frequently used and generally regarded as safe.

Overall, the safety profile of Atropine Sulfate FGK 0.01% is considered benign, comparable to what is known for low concentration atropine eye drops, and no new risks were identified.

6.7.2. Balance of benefits and risks

The ground for refusal relating to the lack of demonstrated efficacy for Atropine sulfate FGK, as evidenced by the failure of the three pivotal studies (CHAMP, MOSAIC and MTS1) to meet their primary endpoints remains unsolved.

Although atropine 0.01% exhibits a benign safety profile, the absence of demonstrated efficacy of 0.01% atropine sulfate FGK precludes a positive benefit-risk assessment. Based on the current evidence the overall benefit–risk balance is deemed unfavourable.

6.7.3. Additional considerations on the benefit-risk balance

Not applicable.

6.8. Conclusions

The overall benefit-risk balance of Atropine sulfate FGK is negative.

7. Recommendations following re-examination

Based on the arguments of the applicant and all the supporting data on quality, safety and efficacy,

the CHMP re-examined its initial opinion and in its final opinion concluded by consensus decision that the efficacy of Atropine sulfate FGK, in the treatment to slow myopia progression in children aged 6 to 10 years with spherical equivalent refraction (SER) in the range of -0.50 to -6.00 diopter (D), is not sufficiently demonstrated and, therefore recommends the refusal of the granting of the paediatric use marketing authorisation for Atropine sulfate FGK.

The CHMP considers that:

- Efficacy of Atropine sulfate FGK has not been established regarding the three main studies (CHAMP, MOSAIC and MTS1). These studies did not meet their primary objective and are formally failed studies. Thus, clinical relevance was not substantiated in the proposed indication.

Therefore, it is the opinion of the CHMP that the benefit-risk balance of Atropine Sulfate FGK 0.01% is negative.