27 March 2025
EMA/134905/2025
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Ryjunea

International non-proprietary name: atropine sulfate

Procedure No. EMEA/H/C/006324/0000

Note

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

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List of abbreviations

AE	Adverse event
AL	Axial length
BAK	Benzalkonium chloride
BCVA	Best corrected visual acuity
BFARM	Federal Institute for Drugs and Medical Devices
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
COVID-19	Coronavirus disease 2019
CRO	Contract Research Organisation
CSR	Clinical study report
D	Dioptre(s)
D20	Deuterium oxide
DC	Discontinuation
EMA	European Medicines Agency
eCRF	e-case report form
EoS	End of study
ET	Early termination
ETDRS	Early treatment diabetic retinopathy study
EU	European Union
FAS	Full analysis set
FDA	Food and Drug Administration
GCP	Good clinical practice
ICH	International Council for Harmonisation
IOP	Intraocular pressure
IVRS	Interactive voice response system
IWRS	Interactive web response system
MA	Marketing authorisation
MAA	Marketing authorisation application
MAR	Missing at random
MedDRA	Medical dictionary for Regulatory Activities
MMRM	Mixed model repeated measures
MNAR	Missing not at random

MPA	Swedish Medical Products Agency
OC	Observed case
OE	Ophthalmological examination
OrthoK	Orthokeratology
PIP	Paediatric investigation plans
PPS	Per-protocol set
PT	Preferred term
QOL	Quality of life questionnaire
SAF	Safety analysis set
SAP	Statistical analysis plan
SD	Standard deviation
SE	Spherical equivalent
SOC	System organ class
TEAE	Treatment-emergent adverse event
US	United States

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Santen Oy submitted on 8 March 2024 an application for marketing authorisation to the European Medicines Agency (EMA) for Ryjunea, through the centralised procedure under Article 3(2)(b) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 26 April 2023. The eligibility to the centralised procedure under Article 3(2)(b) of Regulation (EC) No 726/2004 was based on demonstration of interest of patients at Community level.

The application concerns a hybrid medicinal product as defined in Article 10(3) of Directive 2001/83/EC and refers to a reference product, as defined in Article 10(2)(a) of Directive 2001/83/EC, for which a marketing authorisation is or has been granted in Germany on the basis of a complete dossier in accordance with Article 10a of Directive 2001/83/EC.

The applicant applied for the following indication:

Ryjunea is indicated for the treatment of progression of myopia in children aged 3 to 18 years.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Hybrid application (Article 10(3) of Directive No 2001/83/EC).

The application submitted is composed of administrative information, complete quality data, and appropriate non-clinical and clinical data.

The chosen reference product is:

Medicinal product which is or has been authorised in accordance with Union provisions in force for not less than 8 years in the EEA:

- Product name, strength, pharmaceutical form: Atropin-POS 0.5 mg/ml, eye drops, solution
- Marketing authorisation holder: URSAPHARM
- Date of authorisation: 25-04-2005
- Marketing authorisation granted by:
  - Member State (EEA): Germany
    - National procedure
- Marketing authorisation number: 6009202.00.00

Medicinal product authorised in the Union/Members State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: Atropin-POS 0.5 mg/ml, eye drops, solution
- Marketing authorisation holder: URSAPHARM
- Date of authorisation: 25-04-2005
- Marketing authorisation granted by:
  - Member State (EEA): Germany
    - National procedure
- Marketing authorisation number: 6009202.00.00

1.3. Information on paediatric requirements

Not applicable

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.5. Applicant's request(s) for consideration

1.5.1. Additional data exclusivity/marketing protection

The applicant requested consideration of one year data exclusivity in regards of its application for a treatment of progression of myopia in children aged 3 to 18 years in accordance with Article 10(5) of Directive 2001/83/EC.

During the assessment of the marketing authorisation application, the applicant withdrew the application for a 1-year data exclusivity for Ryjunea, atropine sulfate 0.1 mg/mL and 0.3 mg/mL eye drops solution.

1.6. 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
5 November 2018	EMEA/H/SA/4009/1/2018/PED/III	Mr Nicolas Beix and Dr Kerstin Wickström

The scientific advice pertained to the following quality, non-clinical, and clinical aspects:

- The proposed product release, drug product and raw material specifications; the proposed preservative in the drug product, and plan for manufacturing registration batches;
- The proposed 26-week rabbit ocular toxicity study to support the use of deuterium oxide as new excipient, the safety of tropic acid degradant in the SYD-101 commercial product, and to support an MAA along with the additional available safety information;
- The acceptability of a single, phase 3 controlled study (SYD-101-001) to establish efficacy and safety; the proposed primary and secondary efficacy endpoints; the safety endpoints to characterise the safety profile of SYD-101; the proposed eligibility criteria and the definition of the target population; the schedule of visits and procedures; the proposed re-randomisation and submission of the MAA based on the Month 24 primary endpoint results.

1.7. Steps taken for the assessment of the product

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

Rapporteur: Jean-Michel Race Co-Rapporteur: Christian Gartner

The application was received by the EMA on	8 March 2024
The procedure started on	28 March 2024
The CHMP Rapporteur's first assessment report was circulated to all CHMP and PRAC members on	18 June 2024
The PRAC Rapporteur's first assessment report was circulated to all PRAC and CHMP members on	25 June 2024
The CHMP agreed on the consolidated list of questions to be sent to the applicant during the meeting on	25 July 2024
The applicant submitted the responses to the CHMP consolidated list of questions on	10 October 2024
The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs joint assessment report on the applicant's responses to the list of questions to all CHMP members on	19 November 2024
The PRAC agreed on the PRAC assessment overview and advice to CHMP during the meeting on	28 November 2024
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	12 December 2024
The applicant submitted the responses to the CHMP consolidated list of outstanding issues on	28 January 2025
The CHMP Rapporteur 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	13 February 2025
The applicant submitted the responses to the CHMP consolidated list of outstanding issues on	06 March 2025
The CHMP Rapporteur 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	12 March 2025
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Ryjunea on	27 March 2025

2. Scientific discussion

2.1. Introduction

Ryjunea (STN1012701, atropine sulfate 0.1 mg/mL [0.01%] eye drops, solution, MD) was intended to be indicated for the treatment of progression of myopia in children aged 3 to 18 years. Ryjunea 0.3 mg/mL presentation was withdrawn during the application assessment.

2.1.1. Epidemiology

The prevalence of myopia varies greatly between different populations and ethnic groups but is increasing worldwide. It was estimated to affect 30% to 34% of the overall population in 2020, and this number is anticipated to increase to 50% by 2050 (Holden, 2016).

2.1.2. Aetiology and pathogenesis

Myopia, or near-sightedness, appears during childhood and progress with age. Myopia is clinically defined as a refractive error of –0.50 dioptres (D) or worse (WHO, 2015). High myopia, defined as a refractive error of -6.00 D or worse, is associated with a significant risk of pathologic changes including glaucoma, cataract, retinal detachment, choroidal degeneration, choroidal neovascularisation, and retinoschisis, all of which can cause irreversible loss of vision (Wong et al., 2014). Depending on the degree of ocular elongation of the axial length (AL), and the existence of other anomalies, diverse type of myopia are to be distinguished. Among them and particularly in children the most common observed myopia is axile, which presents an increase of AL, and refractive or accommodative myopia. Axile myopia is often associated with ocular complications such as cataract, retinal detachment, macular hole, retinal atrophy. Furthermore, it is understood that myopia appears to be a multifactorial disease with an incidence of ethnicity, iris colour and even lifestyle (indoor/outdoor activities).

2.1.3. Clinical presentation, diagnosis and prognosis

The diagnosis is made through patient history combined with standard comprehensive eye and vision examination including assessments for visual acuity, refraction, accommodation, strabismus/amblyopia, binocularity and ocular health (American Optometric Association, 2016). The main symptom is constant blurred distance vision, however, younger children will mainly complain of other symptoms such as headaches or tired eyes, sitting close to the TV or classroom blackboard and problems with hand eye coordination.

2.1.4. Management

There is no current treatment to prevent myopia, however it is of importance to early detect myopia in children with routine eye examination in order to focus on treatment aimed to slow/control its progression. Correcting vision and maintaining good ocular health are also desired and spending outdoor times highly recommended. There are currently several treatment options available such as:

Optical Correction

Vision in myopic children may be corrected using ordinary adapted spectacles or contact lenses. Spectacles are often the first line of treatment, especially in young children as they provide clear distance vision, with little to no side effects. Contact lenses are usually reserved for older children since

they are more difficult to use, require a greater level of care and are associated with an increased potential for side effects such as eye redness, pain or vision loss due to ulcers (Walline et al., 2011). However, optical correction does not provide myopia control unlike multifocal spectacles/lenses.

Orthokeratology

Orthokeratology involves patients wearing reverse geometry contact lenses overnight, which results in temporary flattening of the cornea and provides clear vision during the day without any glasses or contact lenses. Reduction in myopia is achieved by central corneal epithelial thinning, midperipheral epithelial, and stromal thickening. However, orthokeratology is associated with an increased risk of ocular side effects.

Atropine

Currently there is a marketing authorisation (MA) in Australia under the name of Eikance 0.01% Eye Drops in order to slow the progression of myopia in children aged from 4 to 14 years. Atropine treatment may be initiated in children when myopia progresses ≥-1.0 D per year.

In addition, in France there is current use of atropine in children with myopia without defined criteria (prior to treatment range of progression) and without a marketing authorisation.

2.2. About the product

Atropine acts as a competitive antagonist of the muscarinic receptors. Atropine does not distinguish among the M1, M2, M3, M4 and M5 subgroups of muscarinic receptors. The mechanism through which atropine retards myopia progression is not fully understood. Atropine is reported to stimulate extracellular matrix biosynthesis in scleral fibroblast cells. This results in thickening of scleral tissue and a reduction in its elasticity and tendency to elongate. Additionally, atropine may decrease extracellular matrix in other tissues such as choroidal fibroblasts thus improving scleral blood perfusion through the choroid. Atropine has also been shown to increase choroidal thickness, which was correlated with slowing myopia progression.

2.3. The development programme/compliance with guidance/scientific advice

The applicant submitted a hybrid application under Article 10(3) of Directive 2001/83/EC for the proposed medicinal product atropine sulfate 0.1 mg/mL eye drops, solution in multi-dose container (identified as STN1012701, Syd-101, Ryjunea® throughout the report) for treatment of progression of myopia in children aged 3-18 years. The reference product for this hybrid application is the product Atropin-POS® 0.5% eyedrops, solution which has been marketed in Germany by URSAPHARM since 25 April 2005. Ryjunea was proposed for different concentrations (0.01%) and for a different therapeutic indication than the reference product, however, both products have the same route of administration (ocular use) and same pharmaceutical form (eye drops, solution).

The applicant has conducted a single pivotal clinical Phase 3 (study SYD-101-001; STAR-trial) trial in 847 children with myopia of –0.50 D to –6.00 D to support the intended indication in EU and US. This is an ongoing, randomised, double-masked, vehicle-controlled study of 48 months, comprising a primary treatment period of 36 months and a re-randomised withdrawal period of 12 months.

Additionally, the applicant provided an extensive review of the relevant published literature describing the use of atropine in paediatric patients when used for the treatment of progression of myopia in children in a range of doses between 0.01% and <1.0%.

There is no guideline in the claimed myopia indication.

The applicant did not submit a PIP since the legal basis of the application is hybrid.

The submission strategy of a hybrid application has been discussed with CHMP within a scientific advice procedure (EMEA/H/SA/4009/1/2018/PED/III).

The applicant has conducted a single pivotal clinical Phase III trial in children (study SYD-101-001) to establish efficacy and safety for both Ryjunea doses in the new indication. The total study duration is 48 months, comprising a primary treatment period of 36 months and a randomised withdrawal period of 12 months. The 24-month data were submitted in this marketing authorisation application. The 36-month data were provided in the responses during the procedure.

The application is also supported by an extensive review of the relevant published literature describing the use of atropine in paediatric patients with myopia to provide information supportive of the efficacy of low dose atropine sulphate eye drops when used for the treatment of progression of myopia in children in a range of doses between 0.01% and less than 1.0%.

Scientific advice was sought from the Medical Products Agency (MPA), Sweden (2018), from the EMA (2019), and BfArM, Germany (2022). A follow-up meeting was held with MPA in 2022. Discussions focussed on the appropriateness of the formulation, acceptability of the 26-week GLP ocular toxicity study in rabbits to support the application, and acceptability of the proposed design of the single pivotal study in children to support registration. Outcomes are discussed in the appropriate sections of this document.

2.4. General comments on compliance with GMP, GLP, GCP

A routine inspection in specific areas (except data management and laboratory/laboratory samples) was conducted by the Austrian health authority in July 2021 and concluded that the trial is conducted in accordance with Good Clinical Practice (ICH-GCP).

One exploratory PK study (Pharmacokinetic Study of STN1012701 and Atropine Sulfate 1% Following Acute Ocular Administration to Dutch Belted Rabbits, Study No 2698-002) was performed non-GLP-compliant. However, another definitive PK-study was performed to evaluate the local and systemic toxicity of the test article, in male pigmented Dutch Belted rabbits after daily ophthalmic administration for 26 weeks and to evaluate reversibility, persistence, or progression of any observed changes following a 1-month recovery period. This second and pivotal PK-study, which includes a toxicokinetic part, was conducted GLP-compliant.

2.5. Type of application and other comments on the submitted dossier

The legal basis for this application refers to: Article 10(3) of Directive 2001/83/EC – hybrid

The reference product is Atropin-POS® 0.5% eyedrops, solution which has been marketed in Germany by URSAPHARM since 25 April 2005.

The applicant did not conduct any clinical studies against the reference product, which was acceptable because of the differences in the strength, indication and composition (D20 instead of H2O). The application for Ryjunea only referred in certain areas to the RefMP, in particular to non-clinical data and the SmPC. In all these areas there is no need for bioequivalence or comparable bioavailability studies to the reference product. Clinical data were generated by the applicant to support the safe use of Ryjunea 0.01% in the proposed indication. For these reasons, it can be agreed that no clinical studies against the reference product are necessary. The information/justification provided by the

applicant is sufficient to allow relying/cross-reference to the data from the RefMP named above. Ryjunea 0.3 mg/mL presentation was withdrawn during the application assessment.

2.6. Quality aspects

2.6.1. Introduction

The finished product is presented as an eye drops solution containing 0.1 mg/mL of atropine sulfate as active substance. The product contains the monohydrate form of atropine sulfate.

Other ingredients are citric acid (E330), sodium citrate (E331), sodium chloride, benzalkonium chloride, sodium hydroxide (E524)/hydrochloric acid (E507) (for pH adjustment) and deuterium oxide, as described in section 6.1 of the SmPC.

The product is available in white low-density polyethylene (LDPE) bottles with white LDPE tips and red high-density polyethylene (HDPE) screw caps with a protective tamper-evident ring, as described in section 6.5 of the SmPC.

2.6.2. Active substance

2.6.2.1. General Information

The chemical name of the active substance is Bis[(1R,3r,5S)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl-(2RS)-3-hydroxy-2-phenylpropanoate] sulfate monohydrate corresponding to the molecular formula $(C_{17}H_{23}NO_3)\cdot 2H_2SO_4 \cdot H_2O$. It has a relative molecular mass of 694.83 and the following structure:

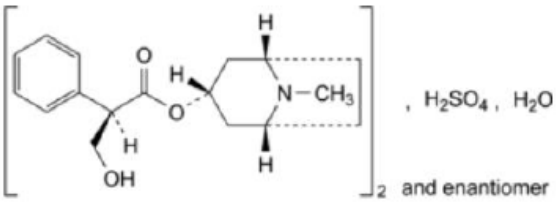


Figure 1: Active substance structure

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.

Atropine sulfate (INN) is a white to almost white hygroscopic crystalline powder or colourless crystals. The active substance is very soluble in water and a 2% solution in water has a pH of 4.5-6.2.

Atropine sulfate exhibits isomerism due to the presence of 4 asymmetric centres, and is obtained as a racemic mixture.

Polymorphism is not relevant since the active substance is dissolved in the finished product.

2.6.2.2. Manufacture, characterisation and process controls

The information related to active substance (AS) manufacturer, manufacture, characterisation, process controls and packaging of the AS has been assessed by the EDQM before issuing the Certificate of

Suitability.

2.6.2.3. Specifications

The active substance specification includes tests for: description (Ph. Eur.), identification (Ph. Eur.), identification E (Ph. Eur.), pH (Ph. Eur.), water content (Ph. Eur.), sulphated ash (Ph. Eur.), related substances (Ph. Eur.), assay (Ph. Eur.), residual solvents (Ph. Eur.), paraformaldehyde (HPLC), microbial enumeration tests (Ph. Eur.).

The specifications comply with the monograph of the Ph. Eur. supplemented by additional tests in line with the CEP and are suitably justified. All additional methods have been adequately validated and described according to ICH Q2.

The AS is intended to be used in a sterile medicinal product (eye drops solution); the specifications include tests for microbial enumeration in line with the Ph. Eur. The corresponding method has been suitably validated.

The same analytical methods as the ones applied by the active substance manufacturer are used by the finished product manufacturer for these tests. Ph. Eur. Reference standard is appropriately used for the control of the AS.

Batch analysis data were presented for 3 active substance batches and results comply with the proposed specifications.

2.6.2.4. Stability

Stability data from three batches of AS from the proposed manufacturer, packaged in the same container as described in the CEP, stored for up to 36 months under long term conditions (5 ± 3°C) and for up to six months under accelerated conditions (25 ± 2°C/60 ± 5% RH) according to the ICH guidelines were provided.

The stability-indicating parameters from the AS specifications are tested using the same analytical methods as the ones used at release. The following parameters were tested*:* description, identification pH, water content, related substances, assay. The analytical methods used were the same as for release and were stability indicating. Results comply with the specifications; no significant change is observed.

Forced degradation studies have been performed on one commercial scale batch. The AS in solution was subjected to elevated heat, acidic, alkaline and oxidative conditions; in solid state it was subjected to elevated temperature and UV irradiation. Results showed different degradations pathways and varied degree of degradation depending on the stress conditions. It was also demonstrated that the HPLC method used to control the API is stability-indicating.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 36 months at 2 – 8°C in the proposed container.

2.6.3. Finished medicinal product

2.6.3.1. Description of the product and Pharmaceutical development

The finished product (FP) is a clear and colourless, sterile preserved eye drops solution with a pH of 5.4 and an osmolality of 280 mOsm/kg, containing 0.1 mg/mL of atropine sulphate, with a nominal fill volume of 2.5 mL into 5 mL bottle with tip and cap. The composition of the FP contains atropine sulfate, citric acid (E330), sodium citrate (E331), sodium chloride, benzalkonium chloride, sodium hydroxide (E524)/hydrochloric acid (E507) (for pH adjustment) and deuterium oxide, as described in section 6.1 of the SmPC.

No overage has been added.

In the initial application a higher strength 0.3 mg/mL was also proposed. The higher strength was developed in parallel to the 0.1 mg/mL strength. However, it was withdrawn during the procedure.

The excipients were selected on the basis of their well-established use in eye preparations and are compendial, except deuterated water (deuterium oxide (D_2O)), which is classified as a novel excipient.

Benzalkonium chloride (BAK) is used as a preservative. The choice of BAK was mainly based on the literature. Ophthalmic preparations without preservatives are strongly recommended for use in paediatric patients notably by PDCO coordinator in 2019 and long-term treatment of BAK-containing eye drops in children needs to be thoroughly justified. In this regard the CHMP raised a Major Objection enquiring the strategies that have been considered to develop a preservative-free formulation, additional justifications for the choice of BAK and additional data on the achieved preservative efficacy, covering shelf life and a 28 days simulated in-use period.

In response to the MO, a discussion on the feasibility of optimising the formulation with regards to the preservative has been presented. In this context, a quality recommendation (REC) regarding optimisation of the finished product was recommended by the CHMP.

In their response the applicant also presented results of additional preservative efficacy testing (PET). Based on the results and discussion around them and considering that the BAK concentration used in the formulation remains in a range usually accepted, these responses were considered acceptable. In addition, based on the available results from the 12-month time point as well as the development data using reduced BAK levels, there is little risk for physico-chemical degradation or microbial proliferation during the in-use period of aged samples. Consequently, it is accepted to fix an in-use stability of 4 weeks.

Regarding other compounds, the selection of buffer, solvent have been sufficiently justified.

The choice of D_2O as an excipient was not sufficiently justified thus the CHMP raised a Major Objection in this regard. The applicant provided comparative stability results in long term and in accelerated conditions showing a significant improvement in stability when deuterated water is used instead of purified water. From a pharmaceutical quality point of view the use of the novel excipient purified deuterium oxide is justified.

Initially the level of information for the novel excipient in the dossier was not satisfactory and the CHMP raised an MO in this respect. The MO was related to the production of D_2O under GMP, details of manufacture, control of D_2O quality, storage and transportation of D_2O, and interactions of D_2O with the AS, impurities and excipients. The applicant updated the dossier accordingly in a satisfactory manner. Sufficient information on the manufacture, characterisation and controls of the novel excipient were included in the dossier.

The development approach is based on the knowledge that atropine degrades by hydrolysis which is slowed when pH decreases. CQAs such as pH, appearance, osmolality, assay of AS and BAK as well as degradation of drug substance have been taken into consideration in setting the FP specifications.

Minor differences in the way in which the pH was adjusted were noted during the three campaigns of pivotal P3 clinical study. Differences between the manufacturing process and equipment used to produce batches for pivotal clinical trials and the process were described in the dossier. In addition, all batches used in the pivotal study SYD-101-001 are representative of the FP allowing to show the slight difference from the formulation in the third clinical campaign and registration batches did not have any impact.

The manufacturing process was focused on the following main steps - the preparation of the bulk solution, sterile filtration, and aseptic filling. The choice of sterile filtration and aseptic filling as sterilisation method has been considered as sufficiently justified as it has been shown that terminal sterilisation is not possible due to the heat liability of the AS and the proposed container.

The primary container closure system of the FP is a multi-dose eye drop container made of white low-density polyethylene (LDPE) bottle with white LDPE nozzle and red high-density polyethylene (HDPE) cap. All the component of the finished products' primary packaging are stated to comply with the monograph 3.1.5 'Polyethylene with additives for containers for parenteral preparations and for ophthalmic preparations' of the Ph. Eur. The validation results for the primary packaging sterilisation have been adequately and sufficiently detailed. Interactions of the packaging components with the FP and drop size have also been properly investigated. In addition, this container closure system is considered suitable to prevent microbial ingress.

Novel excipient – Deuterated water (D_2O)

General information

Deuterated water or deuterium oxide is the form of water that contains two atoms of the hydrogen isotope with a mass double that of ordinary hydrogen (D). Its IUPAC name is ($^2H_2$) Water. Its structure has been elucidated bi IR spectroscopy.

It is a colourless and odourless liquid with a density of 1.107 g/mL (at 25°C) and a viscosity of 1.25mPa s (at 20ºC). It has a LogP value of -1.38 and a pH of 5.5 - 6.0.

Manufacture, characterisation and process controls

Deuterium oxide manufacture, characterisation and process controls have been evaluated by EMA. Deuterium oxide naturally is present in water at very low levels. It is possible to concentrate deuterium using the Girdler-Sulphide process. The resulting water can be then further enriched to produce "enriched" deuterium oxide with a high content of deuterium. Enriched deuterium oxide is a common commodity used in different industries. The enriched deuterium oxide is commercially available. The supplier of enriched deuterium oxide is stated in the dossier.

The enriched deuterium oxide is used as the starting material in the manufacture of the novel excipient, purified deuterium oxide. The manufacturer of the novel excipient deuterium oxide is stated in the dossier. The production of purified deuterium oxide is subject to GMP inspection surveillance.

The manufacturing processes of deuterium oxide (purification) was satisfactorily described and the batch size has been indicated. No critical steps are identified. Possible impurities in deuterium oxide have been discussed and are included in the specification. The carry-over of impurities during deuterium oxide's manufacturing process is suitably discussed.

Purified deuterium oxide container closure system was described and is acceptable.

Specification

The release specifications used by the manufacturers of purified deuterium oxide include test and limits for isotopic concentration, (FTIR), identification (IR), conductivity (Ph. Eur.), total organic carbon (Ph. Eur.), tritium (scintillation counter), nitrates (Ph. Eur.) and bioburden (Ph. Eur.).

The specifications, control strategy, specification, analytical methods, validation, and justification for specification for a novel excipient have been presented and are acceptable.

Stability

Stability of the novel excipient has been adequately demonstrated. Given that no chemical degradation can occur, no stability data has been generated, and the assignment of a re-test period is not proposed. Instead, purified deuterium oxide is stored at room temperature and analysed for bioburden content prior to use in the drug product manufacturing process.

One commercial batch of deuterium oxide was studied as it was being stored in a container under specified conditions and was tested against its specification (except identification) at each timepoint. All results met the specifications.

The proposed storage period for deuterium oxide prior to use in the finished product manufacturing process in the proposed container and the proposed storage conditions is acceptable.

2.6.3.1. Manufacture of the product and process controls

The FP manufacturer is stated on the dossier.

The FP manufacturing process consists of three main steps: dissolution of different compounds followed by a sterilizing filtration and an aseptic filling and closing into the pre-sterilised primary packaging. The process is considered to be a non-standard manufacturing process.

Critical steps consist of sterilising filtration, integrity testing of the 0.2 µm sterilising filters, aseptic filling of solution and microbiological environmental monitoring to assure the sterility of the FP.

In-process controls (IPCs) used during the preparation and filling of the FP were presented in the dossier and are acceptable and adequate for this type of manufacturing process and pharmaceutical form.

No intermediate products are involved in the manufacturing process of the FP. Maximum processing times and shipping conditions have been defined and adequately justified.

Process validation data for 3 batches has been provided. Validation data have also been presented for filter validation, and aseptic processing validation. Overall, it has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner.

2.6.3.2. Product specifications

The finished product release and shelf life specifications include appropriate tests for this kind of dosage form: appearance (visual), pH (Ph. Eur.), osmolality (USP), identification of atropine sulfate (HPLC), assay of atropine sulfate (HPLC), degradation products (HPLC), identification of BAK (HPLC), assay of BAK (HPLC), sterility (Ph. Eur.).

The proposed tests and limits are acceptable. Based on stability data and validation studies' results, the tightened acceptance criteria for atropine sulfate assay as well as the upper limit of the BAK assay at shelf life are justified. The lower limit for BAK assay is supported by microbial studies. The sterility test is performed in line with the Ph. Eur., and it has been suitably demonstrated that the FP does not inhibit microbial growth.

The proposed limit for tropic acid and thus corresponding tropine has been toxicologically qualified (see the non-clinical report) and are acceptable. The proposed limit for individual unidentified degradation product at release and at shelf life comply with ICH Q3B. The provided information on potential degradation products is provided and supports the proposed control strategy.

The potential presence of elemental impurities in the finished product has been assessed on a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. All potential sources of elemental impurities have been considered (AS, excipients, packaging and manufacturing equipment) and it has been suitably demonstrated that the absence of control for elemental impurities in the drug product is acceptable. Batch analysis data on a number of batches using a validated MS method was provided, demonstrating that each relevant elemental impurity was not detected above 30% of the respective PDE. Based on the risk assessment and the presented batch 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 regarding the potential formation of nitrosamine impurities is provided 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). 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.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for the AS and BAK testing has been presented.

Batch analysis data are presented for 3 industrial batches. Results comply with the proposed specifications confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

2.6.3.3. Stability of the product

Stability data from three commercial scale batches stored for up to 24 months under long term conditions (25°C/40% RH) and for up to 6 months under accelerated conditions (40°C/20% RH) according to the ICH guidelines were provided. The main stability batches are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested according to stability specifications. The analytical procedures used are the same as those used in the specification and are stability indicating.

Overall, results remain well within the specification limit during the stability studies up to 24 months under long term storage conditions and up to 6 months at accelerated conditions for all batches.

Supportive stability data was also provided from one engineering and four clinical batches . These batches are considered representative and support the proposed shelf life.

Photostability study as per ICH Q1B has been performed on one finished product main stability batch. The test results of the control samples and the test samples were within the stability specifications, and there were no significant differences between those samples.

In-use stability studies have been performed for 4 weeks at the long-term condition on one lot after 12 months storage. Results comply with the specifications; no significant degradation is observed. The proposed shelf life after first opening (SmPC sections 6.3) is thus justified.

Furthermore, freeze-thaw and photostability studies (ICH photostability guideline Q1B) have been performed on one finished product batch. No significant change has been observed; therefore, the finished product does not require a special storage instruction.

Based on the available stability data, the proposed shelf-life of 24 months and that the medicinal product does not require any special storage condition as stated in the SmPC (sections 6.3 and 6.4) are acceptable.

2.6.3.4. Post approval change management protocols

Not applicable.

2.6.3.5. Adventitious agents

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

2.6.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. A novel excipient is used in the finished product for which sufficient information about its manufacture and control has been provided.

During the procedure, three Major Objections were raised in relation to the use of BAK as preservative, the selection of the novel excipient deuterium oxide and the supporting documentation submitted for the same. All three MOs were resolved by the applicant’s responses with the provision of additional information as requested.

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.

At the time of the CHMP opinion, a minor unresolved quality issue related to the investigation of feasibility for optimising the formulation with regards to the preservative, having no impact on the benefit-risk balance of the product, was recommended to be submitted post marketing.

2.6.5. Conclusions on the chemical, pharmaceutical and biological aspects

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

2.6.6. Recommendation for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress,

the CHMP issued a recommendation to the applicant to investigate the feasibility of optimising the formulation with regards to the preservative and inform the CHMP within 3 years.

2.7. Non-clinical aspects

2.7.1. Introduction

In this hybrid application Atropin-POS® 0.5% eye drops are used as a reference product, and an abridged preclinical development programme evaluating systemic absorption of atropine after single ocular dose of STN1012701 0.1 mg/mL, qualification of a method for plasma atropinesterase activity in rabbit plasma, validation of a bioanalytical method for analysis of atropine in rabbit plasma, and a 26-week ocular toxicity study with STN1012701 0.1 mg/mL after once daily and three times daily dosing, including toxicokinetics, after single and multiple dosing were deemed sufficient to support registration of STN1012701.

2.7.2. Pharmacology

Atropine is a tertiary amine antimuscarinic alkaloid with both central and peripheral actions and is a well-known substance.

No pharmacology studies were conducted with STN1012701.

Atropin-POS® 0.5% eye drops are used as a reference product in this hybrid application. Relevant publications on animal studies are referred to. This is in line with regulatory guidance pertaining to hybrid applications.

An in vitro study showed that atropine acts as a competitive antagonist in muscarinic receptors.

In vivo, atropine was shown to inhibit myopia progression in several animal models.

The mechanism through which atropine slows down myopia progression is not fully understood. Atropine is reported to thicken scleral tissue and lead to a reduction in its elasticity and tendency to elongate. Atropine has also been shown to increase choroidal thickness correlated with slowing myopia progression.

Bibliographical references provided on pharmacology are considered in accordance with the proposed indication.

No safety pharmacology studies have been performed with STN1012701 which is acceptable for this hybrid MAA application. The safety pharmacological characteristics of atropine are well known.

Drug interactions have been described in the SmPC of the ocular medicinal products containing atropine, which is acceptable.

2.7.3. Pharmacokinetics

Non-clinical pharmacokinetics studies conducted in support of registration of STN1012701 are limited to a bioanalytical method qualification study for tropic acid in rabbit plasma, a bioanalytical method validation study for atropine in rabbit plasma, and an absorption study conducted in pigmented rabbits after administration of single dose of STN1012701 0.1 mg/mL (0.01%) topically, via eye drop. In addition, relevant publications on animal and human studies are referred to in the following sections.

An exploratory study was conducted to determine plasma concentrations of atropine following single-dose ocular administration of STN1012701 0.1 mg/mL (atropine sulfate 0.01% solution) or atropine sulphate ophthalmic solution 10 mg/mL (1%) to pigmented rabbits.

The results showed that in animals administered STN1012701 0.1 mg/mL, atropine was detectable in plasma up to 30 minutes post-dose; maximum plasma atropine concentrations (Tmax) occurred at 5 minutes post-dose. At 1-, 2- and 4-hours post-dose, plasma atropine concentrations were below the lower limit of quantitation (0.250 ng/mL).

The penetration and distribution of topical atropine in animal ocular tissues was studied by several authors. Results of one rabbit study showed that radioactivity was observed in all ocular tissues at 1, 2 and 4 hours after instillation. The radioactivity level was: cornea >> sclera > iris ciliary body ≈aqueous humour ≈ choroid > retina > vitreous humour.

Atropine has been shown to bind to melanin pigment of the iris and thus affect the duration but not the onset of the mydriatic effect in rabbit. It was measured that 96 hours after the administration of 3H atropine there was about eight times higher concentration of 3H-atropine in pigmented iris compared to non-pigmented iris.

An *in vitro* study showed that plasma in atropinesterase-positive rabbits possessed a capacity to breakdown large quantities of atropine, but plasma of other species, such as dogs, goats, guinea pigs, humans, pigs and rhesus monkeys possessed a capacity of only non-specific breakdown

No published data on excretion are available. No drug-drug interaction studies have been performed.

The pharmacokinetics section is acceptable for this type of hybrid application.

2.7.4. Toxicology

2.7.4.1. Single dose toxicity

Single dose studies in mice and rabbit by intravenous and intramuscular routes are reported, which is not deemed relevant as it is not the same route of administration than for STN1012701 0.1 mg/mL.

2.7.4.2. Repeat dose toxicity

The toxicity of STN1012701 0.1 mg/mL (atropine sulfate 0.01% solution) was studied in the rabbit in a 26-week ocular toxicity study followed by 4-week treatment-free recovery period.

There was no test article-related mortality/moribundity. There were no STN1012701 0.1 mg/mL-related or atropine 10 mg/mL-related clinical observations or effects on body weight. Similarly, there were no STN1012701 0.1 mg/mL-related or atropine 10 mg/mL-related ophthalmology, ERG or IOP findings at any assessment interval and no effects on clinical pathology analytes. No test article-related gross findings or organ weight changes were noted at either the terminal or recovery necropsies.

At the terminal necropsy, in animals administered STN1012701 0.1 mg/mL three times per day, minimal focal hyperkeratosis of the epidermis was noted in two animals in the left eyelid and in one animal in the right eyelid, affecting either the upper or lower eyelids, but not both. This finding was considered of uncertain relationship to test article administration based on unilateral and focal distribution, minimal severity grade, and its presence as a background finding in pigmented rabbits. This finding was unlikely to be procedure- or vehicle-related as similar findings were not noted in animals administered the negative or placebo control articles three times per day. The absence of similar findings in animals administered the atropine sulfate ophthalmic solution 10 mg/mL comparator

agent once per day suggests that the finding is not atropine related. Eyelid hyperkeratosis was not observed in either animal in this group at the Day 211 recovery necropsy.

Ryjunea sought approval for strength 0.01% (0.1 mg/ml) using the reference product Atropin-POS 0.5%. In the 26-week repeated-dose toxicity study in male Dutch Belted pigmented rabbit, Ryjunea strength (0.01%) was assessed. In this study, a comparator (atropine sulphate 1% - 10 mg/ml) different and with a 2-fold higher strength from the reference product, was used. The same holds true also for the exploratory single dose PK study in pigmented rabbit.

The applicant explained that when the study was initiated, the 0.01% atropine sulphate concentration was planned to be used in the clinical study. The atropine sulfate concentration of 1% was used as a comparator to confirm the local and systemic safety of atropine sulfate itself.

Concerning the single-dose PK study conducted with the Atropine sulfate 1% solution, it was carried out to establish the bioanalytical method for atropine in K2EDTA rabbit plasma fortified with acetonitrile to be validated in Study No. 2698-004. In toxicokinetic study in rabbit, the exposure to atropine after the first or third dosing of Ryjunea 0.01% can be found in the plasma up to 5 minutes. With the atropine 1% solution the exposure in the plasma was found up 2 hours. The Cmax in plasma was about 50 and 10 times higher with Atropine sulfate 1% compared to Ryjunea 0.01% on Days 1 and 182 respectively.

The volume of each drop administered to rabbit eyes has been indicated in order to know the amount (mcg) of test article or BAK 0.01% in contact with the eye and to calculate safety margins. Totally, rabbits received 6 µg or 18 µg of atropine sulfate per day, after once or three times a day dosing in both eyes, respectively. In clinical situation the drop size is the same as in the 26-week ocular toxicity study i.e. 30 µL. The comparator solution which has been used in 26-week ocular toxicity study contains 10 mg/mL (1%) of atropine sulfate,

Concerning the BAK excipient, the amount in Ryjunea 0.1 mg/mL eye drops is 0.1 mg/mL which means there is 3 µg BAK in one eye drop per eye. Ryjunea and the comparator atropine sulphate contain 0.1 mg/mL (0.01%) BAK. Considering that the amount of the comparator is at most 50 µL, the amount of BAK is at most 5 µg in one drop.

In conclusion, the volume of each drop administered to rabbit eyes and the amount (mcg) of test article or BAK 0.01% in contact with the eye have been clearly detailed. It allowed to calculate safety margins. Those safety margins are considered acceptable.

Therefore, the hyperkeratosis of eyelid observed in 26-week rabbit study is not considered a safety concerns in clinical use.

Dutch Belted pigmented male rabbits were chosen as irises of human are pigmented and atropine is known to bind to melanin pigment of the iris. Moreover, as a long clinical experience showed no gender difference for atropine, the use of male rabbit only is considered sufficient by the applicant. This is also in an agreement with 3R principles followed in animal research.

Concerning the male reproductive organs, no histopathological examination was carried out in the 26 week study. However, no gross findings or organ weight changes were observed. Moreover, it was reported in a previous study in the literature that male rats receiving atropine for 16-17 days at 125 mg/kg/day showed testicular weight decrease but did not show histopathological changes in the testes or epididymis.

Atropine can pass the brain-blood barrier and its effects on the central nervous system are well known; no dependence study have been conducted and this is acceptable in view of the low systemic exposure.

2.7.4.3. Genotoxicity

Bibliographical references showed that atropine was not mutagenic in Ames assays.

2.7.4.4. Carcinogenicity

Carcinogenicity potential has not been evaluated with STN1012701.

Atropine has not been found to be carcinogenic in a study carried out in juvenile rats.

Reference product Atropin-POS® 0.5% is reported to have no evidence of tumorigenic effects.

2.7.4.5. Reproduction toxicity and developmental toxicity

In male rats treated orally with atropine for one week prior to mating to untreated female rats, a dose-related decrease in fertility index was noted (95%, 80%, 61% at 0, 62.5, and 125 mg/kg/day, respectively). A further study confirmed the results at the dose of 125 mg/kg/day, and it was suggested that this was related to pharmacologically-induced inhibition of contraction of vas deferens and seminal vesicle during emission, resulting in decreased sperm volume and altered composition of the ejaculate. The applicant relies on published clinical data showing systemic bioavailability of atropine after ocular application of atropine 1%. The current application is for an ophthalmic solution containing 0.01% atropine, i.e. 100-fold lower than the concentration in formulation containing 1% atropine or in the reference product Atropin-POS® 0.5%, therefore any systemic exposure to atropine after administration is expected to be much lower. In addition, the lowest dose showing effects on male rat fertility (62.5 mg/kg) is ~33,600-fold higher than the MRHD corresponding to 18 µg atropine per day on a mg/m^2 basis. It is therefore reasonable to consider these effects as of unlikely clinical relevance in line with ICH S5(R3), although a no observed effect level was not identified. The nonclinical data pertaining to potential effects on male fertility is reported in SmPC 5.3 with a statement that this was shown at high exposures indicating little relevance to clinical use. A published study reported effects on oestrous cycle (prolonged dioestrus) and various uterine findings in rats after intraperitoneal administration of atropine for 30 days at doses well in excess (700- to 200-fold) of the maximal human dose. No preclinical study is available to address effects on female fertility as mentioned in SmPC section 4.6.

As regards embryo-fetal development, the applicant relies on the results of one study published in 1973 with s.c. administration of atropine sulphate at 50 mg/kg to mice on either GD8 or GD9, with 6 litters per group. One case of exencephaly and one case of axial skeletal fusion were noted in fetuses of dams exposed on GD8 and GD9, respectively. Inclusion of these data in SmPC 5.3 is not supported in line with the conclusions of the authors that atropine injection alone resulted in the production of no significant anomalies and taking into consideration that this study was not conducted according to GLP (at least due to the time of study conduct), and has some limitations such as e.g. low number of animals. In addition, these malformations were seen in isolated fetuses with the use of only one dose level precluding the evaluation of any dose-effect. It is also relied on additional data (rat, chicken egg) which were not available for review. Overall, it is considered that there are no conventional embryo-fetal development study available with atropine in a rodent and non-rodent species. Accordingly, SmPC section 4.6 indicates that animal studies are insufficient with respect to reproductive toxicity.

No juvenile animal studies were conducted by the applicant. This is acceptable as no atropine related toxicity was observed in the literature at the dose levels used in STN1012701 or in the 26-week ocular toxicity study performed by the applicant, there are already human safety data in children available also with higher atropine concentrations than 0.1 mg/mL (0.01%) and the human eye is morphologically fully developed at the age of three years old. There are data on clinical studies

available which show the safety of the use of atropine after topical ocular dosing with concentrations up to 10 mg/mL (1%) for several years in children.

2.7.4.6. Toxicokinetic data

Blood samples for toxicokinetic evaluation of atropine in plasma were collected in the 26 week ocular study in rabbit from all available animals in all experimental groups on Days 1 and 182 at 1, 5, 30, 60 and 120 minutes after the first or third daily dose. Following once daily or three times daily ophthalmic administration of STN1012701 0.1 mg/mL, atropine was measurable in plasma of most animals up to 5 minutes post-dose on both Days 1 and 182; atropine plasma concentrations at the 30 minutes, 1 and 2 hour post-dose time points were below the assay limit of quantitation (<0.250 ng/mL).

Therefore, only systemic exposure (AUC) data from animals administered the atropine sulfate ophthalmic solution 10 mg/mL comparator agent were able to be generated. In male rabbits administered atropine 10 mg/mL once daily for 6 months, atropine was measurable in the plasma of the majority of animals at all time points evaluated (up to 2 hours post-dose) on both Days 1 and 182. In these animals, mean Cmax and AUC0-2h values were 14.7 ng/mL and 6.89 h*ng/mL, respectively, on Day 1 and 5.29 ng/mL and 5.04 h*ng/mL, respectively, on Day 182.

2.7.4.7. Local tolerance

The local tolerance was tested in the 26-week toxicity study in rabbits performed by the applicant. Results showed that STN1012701 was well tolerated after ocular administration.

2.7.4.8. Other toxicity studies

No other studies were conducted.

A novel excipient deuterated water D2O is used as a vehicle in STN1012701, instead of H2O. As all the other excipients are well-known and commonly used, only literature review for the safety of D2O was performed, which is acceptable.

D2O is similar to normal water except that it contains the deuterium isotope (2H) instead of hydrogen. D2O is denser and slightly more viscous. Deuterium (C-D) bonds in D2O are about 10 times stronger than the hydrogen (CH) bonds in water and are more resistant to chemical or enzyme cleavage.

Toxicity arises when high concentrations of D2O replace a large percentage (>20%) of body water. High systemic concentrations have been shown to be highly toxic or lethal in animals, likely due to disturbances in the rates of enzymatic reactions throughout the body.

D2O was not considered to be related to any kind of toxicity when dosed for 26 weeks once a day or three times per day in STN1012701 0.1 mg/mL formulation or three times per day in placebo control article in the 26 weeks ocular study in rabbit.

Water is naturally comprised of 0.015% D2O, which translates into approximately 1.6 g to 5.25 g total D2O for a 15-to 50-kg individual (assumes 70% of body weight in children is water), the approximate weight range of the 3 to 12 years old children. The total daily dose of D2O administered in STN1012701 will be approximately 70 µL or 0.08 g which represents 0.0008% amount of water content of 15 kg child. If all of the daily dose were absorbed systemically, D2O in body fluids would temporarily increase from normal amount of 0.015% to 0.016% (from 1.6 g to 1.68 g). However, as not all the dose is absorbed systemically this D2O increase is in practice smaller.

The use of the excipient D2O to replace H2O in the product Ryjunea (atropine sulphate, 0.1 mg/mL eye drops, solution) is not considered to present a risk in the recommended conditions of use.

2.7.5. Ecotoxicity/environmental risk assessment

$PEC_{surfacewater}$ for atropine sulfate contained in Ryjunea 0.01% is below the action limit of 0.01 µg/L and atropine sulfate is not a PBT substance as log Dow does not exceed 4.5.

The medicinal product Ryjunea does not present a risk to the environment.

STN1012701 does not require special disposal measures and in the package leaflet the following general statement was included: "Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to dispose of medicines you no longer use. These measures will help to protect the environment.".

2.7.6. Discussion on non-clinical aspects

As this is a hybrid application it is acceptable to refer to the reference product and literature when no own data are available. The non-clinical testing strategy is designed to be consistent with a hybrid application. A non-clinical overview has been provided, which is based on up-to-date and adequate scientific literature. The bibliographic references are well documented.

After a thorough assessment of the provided literature, the overview justifies the omission of additional non-clinical pharmacodynamic study data. In the eye, atropine acts on the iris sphincter muscle and the ciliary muscle causing mydriasis and cycloplegia and is used as a mydriatic and cycloplegic in ophthalmology. Atropine has also been shown to slow the rate of myopia progression in children in several clinical trials. The mechanism through which atropine slows down myopia progression is not fully understood. Sclera and choroid are considered to be involved in the mechanism of action.

Pharmacokinetic studies conducted in support of the registration of STN1012701 are limited to a bioanalytical method qualification study for tropic acid in rabbit plasma, a bioanalytical method validation study for atropine in rabbit plasma, and an absorption study conducted in pigmented rabbits administered single or multiple doses of STN1012701 0.1 mg/mL topically, via eye drop.

An LC-MS/MS method for the quantitation of tropic acid concentrations in rabbit plasma with K2EDT A has been successfully qualified. The calibration range of the method was 100 to 100,000 ng/mL for tropic acid using a 50 µL sample aliquot.

A non-GLP compliant pharmacokinetic study was performed to determine the plasma concentration of atropine in tested atropinesterase negative rabbits after single topical ocular dosing of STN1012701 0.1 mg/mL or atropine sulfate ophthalmic solution 10 mg/mL.

Plasma atropine concentrations were analysed (by the qualified LC-MS/MS method) with a lower limit of quantification of 0.250 ng/mL. Atropine was detectable in plasma up to 30 minutes post-dose after STN1012701 0.1 mg/mL and maximum plasma atropine concentrations occurred at 5 minutes post-dose. In animals administered atropine sulfate ophthalmic solution 10 mg/mL, atropine was detectable in plasma up to 4 hours post-dose and maximum plasma atropine concentrations occurred between 5 minutes and 15 minutes post-dose.

Results of the single-dose pharmacokinetic study were considered adequate to support selection of applicable toxicokinetic sampling time points for the definitive chronic (26-week) rabbit ocular toxicity study.

In this application Atropin-POS® 0.5% eye drops are used as a reference product, and an abridged preclinical development programme evaluating systemic absorption of atropine after single ocular dose of STN1012701 0.1 mg/mL, qualification of a method for plasma atropinesterase activity in rabbit plasma, validation of a bioanalytical method for analysis of atropine in rabbit plasma, and a 26-week ocular toxicity study with STN1012701 0.1 mg/mL, including toxicokinetics, after single and multiple dosing were deemed sufficient to support registration of STN1012701.

The applicant has performed a 26-week ocular toxicity study followed by 4-week treatment-free recovery period with STN1012701 0.1 mg/mL in rabbit to investigate the ocular and systemic safety of STN1012701 0.1 mg/mL administered once or three times a day. Commercial atropine sulfate ophthalmic solution 10 mg/mL administered once a day was used as a comparator agent. In the 26-week ocular toxicity study blood samples were taken for toxicokinetics analysis and analysed by the validated LC-MS/MS method. Following once daily or three times daily dosing of STN1012701 0.1 mg/mL, the majority of atropine plasma concentrations were below the quantification limit (< 0.250 ng/mL). Following once a day dosing of atropine sulfate ophthalmic solution 10 mg/mL mean Cmax and AUC0-2h values were 14.7 ng/mL and 6.89 ng*h/mL, respectively, on Day 1 and were 5.29 ng/mL and 5.04 ng*h/mL, respectively, on Day 182.

The toxicity of STN1012701 0.1 mg/mL (atropine sulfate 0.01% solution) was studied in the rabbit in a 26-week ocular toxicity study followed by 4-week treatment-free recovery period. The atropine sulfate concentration of 1% was used as a comparator to confirm the local and systemic safety of atropine sulfate itself.

Under the conditions of the study, STN1012701 0.1 mg/mL was considered to be well tolerated when given once or three times daily for 6 months to male rabbits via ophthalmic administration. Ocular findings were limited to minimal focal hyperkeratosis of the eyelid observed at the terminal necropsy in three of four rabbits administered STN1012701 0.1 mg/mL three times daily. This finding was considered of uncertain relationship to STN1012701 0.1 mg/mL administration. Observations noted were within limits of variation commonly encountered in animals of this sex, age, and strain.

Bibliographical references showed that atropine was not mutagenic in Ames assays. Carcinogenicity studies have not been conducted by the applicant which is acceptable.

As regards developmental and reproductive toxicity, the applicant conducted a review of literature data. This is considered as acceptable for the present application. In male rats, a pharmacologically related reduction fertility was observed at oral exposures considered sufficiently in excess of the maximal recommended human dose, indicating little relevance to clinical use. No data is available to evaluate any effect on female fertility. No conventional embryo-fetal development study was available with atropine. No juvenile toxicity study was conducted to support the current application, which is acceptable for this hybrid application considering the timing of eye development in humans (morphologically fully developed at the age of three years old) as well as the available nonclinical and clinical data.

One impurity, tropic acid, is above the identification and qualification threshold of 1.0% as determined in the ICH guideline Q3B(R2). The safety of tropic acid up to 8% has been confirmed in a 26-week ocular toxicity study in rabbits and it covers the upper limit approved in specification of the product. The amount of all other individual related substances is below the identification and qualification threshold of 1.0%.

A novel excipient, deuterated water D2O is used as a vehicle, instead of H2O. D2O is similar to normal water except that it contains the deuterium isotope (2H) instead of hydrogen. A broad literature review of the potential toxicity of D2O was summarised in the MAA dossier to justify the use of D2O. Toxicity arises when high concentrations of D2O replace a large percentage (>20%) of body water. High systemic concentrations have been shown to be highly toxic or lethal in animals. The use of the excipient D2O to

replace H2O in the product Ryjunea (atropine sulphate, 0.1 mg/mL eye drops, solution) is not considered to present a risk in the recommended conditions of use.

The impurity profile of STN1012701 has been discussed in detail and was considered acceptable. D2O was not considered to be related to any kind of toxicity when dosed for 26 weeks once a day or three times per day in STN1012701 0.1 mg/mL formulation or three times per day in placebo control article in this study.

Environment risk assessment was performed according to the guideline. The medicinal product Ryjunea does not present a risk to the environment.

Published literature data on the pharmacology and non-clinical safety of atropine, together with a safety profile of D2O, and the nonclinical studies performed with STN1012701 provide adequate data to the reference product Atropine-POS® 0.5%. Furthermore, the results of the GLP compliant 26-week chronic ocular toxicity study conducted in pigmented Dutch Belted rabbits supports the local (ocular) safety of deuterated water (which is a novel excipient) and tropic acid (a degradant) in STN1012701.

2.7.7. Conclusion on the non-clinical aspects

Scientific advice was sought from MPA in 2018 and from EMA in 2019 (EMA/CHMP/SAWP/123291/2019) for the non-clinical testing strategy by Sydnexis, and for acceptance of the reference product from BfArM in 2022 by Santen.

Both, CHMP (EMA) and MPA agreed that in the absence of any unexpected findings or safety concerns in a 26-week ocular toxicity study with STN1012701 0.1 mg/mL, in the context of a hybrid application, no additional studies are needed. Furthermore, it was confirmed that the pivotal 26-week ocular toxicity study, without any safety issues, qualifies the use of the new D2O excipient as well as the use of tropic acid degradant up to 8%.

Overall, the primary pharmacodynamic bibliographic references provided adequate evidence that supports the therapeutic indication.

From the pharmacokinetic point of view, bibliographic data provided as well as the absorption pharmacokinetic study are acceptable.

The Scientific Advice was followed by the applicant and ocular toxicity of STN1012701 has been investigated in the 26-week ocular toxicity study with STN1012701 0.1 mg/mL in pigmented rabbit. In this study the placebo control article was included in addition to test formulation, positive control article and negative control article. Placebo control article consisted of deuterated water containing 0.01% benzalkonium chloride. D2O was included in test formulation STN1012701 0.1 mg/mL dosed once a day and three times per day, and placebo control article dosed three times per day. There was no test article related or placebo control article related findings during this study.

The registration of STN1012701, filed as a hybrid application under Article 10(3) of Directive 2001/83/EC, is supported by the non-clinical studies conducted by the applicant and provided in the context of this marketing authorisation application.

There are no objections to approval of atropine sulfate eye drops solution from a non-clinical point of view.

2.8. Clinical aspects

2.8.1. Introduction

This is an application for Ryjunea 0.01% eye drops solution containing atropine sulfate.

The applicant provided a clinical overview outlining the pharmacokinetics and pharmacodynamics as well as efficacy and safety of atropine based on published literature. The SmPC is accordingly in line with the SmPC of the reference product.

CHMP scientific advice pertinent to the clinical development was given for this medicinal product.

There is no Guideline in the claimed myopia indication. For the clinical assessment the Annex of the European Commission guideline 'Excipients in the labelling and package leaflet of medicinal products for human use' (EMA/CHMP/302620/2017) and Guideline on excipients in the dossier for application for marketing authorisation of a medicinal product – Rev.2 EMEA/CHMP/QWP/396951/2006 on was considered.

GCP aspect

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

The applicant has 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.

Tabular overview of clinical studies

To support the application, the applicant has submitted one efficacy and safety study SYD-101-001.

Table 1: Clinical study

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
SYD-101-001	Total: 852 - STN1012701 0.1 mg/mL: 284 - STN1012701 0.3 mg/mL: 285 - Vehicle: 283	Multicentre, randomised (1:1:1) double-masked, vehicle-controlled	1 drop in each eye at bedtime over 48 months of either Vehicle, STN1012701 0.1 mg/mL or 0.3 mg/mL	3–14 years old, inclusive with myopia of -0.50 D to -6.00 D (inclusive); astigmatism ≤1.50 D; anisometropia ≤1.00 D

2.8.2. Clinical pharmacology

No clinical pharmacology studies were conducted with Ryjunea. The submission includes a non-clinical PK study which investigated ocular administration of Ryjunea (0.01%) or 1% atropine in Dutch Belted rabbits.
The development programme (quality, non-clinical, clinical) was discussed during an EMA-SA procedure (EMA/CHMP/SAWP/123291/2019). The PK/PD aspects were, however, not specifically discussed.

Atropine is a well-known substance and already marketed for use by IV and ocular routes of administration. Full PK characterisation is not required in the context of the application under review.

The applicant performed a literature search and summarised PK and PD of atropine after topical (ophthalmic) administration. The individual data sources are though not discussed in depth regarding their shortcomings and regarding the robustness of the data. However, the estimation of the systemic exposure to atropine with the claimed modality of use would be of interest to mitigate the systemic tolerability of the drug. As no data are available on systemic tolerability of Ryjunea should rely on clinical observations only.

It should be noted that the RefMP Atropin-POS 0.5% contains a 50 times higher atropine concentration compared to Ryjunea 0.01%. Ophthalmic solutions with 1% atropine (=100 times higher dosed than Ryjunea) are authorised in certain European countries and this higher strength was also available for the RefMP (in Germany). The RefMP can be administered three times per day (in contrast to once daily for Ryjunea) and includes indications for longer-term use, such as iritis.

2.8.2.1. Pharmacokinetics

Absorption

Ryjunea is intended for ocular local use. No investigation of absorption is formally requested as the drug is already marketed by IV and ocular routes and the claimed dose is much lower than that already approved. However, the estimation of systemic exposure to atropine is useful to support the assessment of systemic tolerability of Ryjunea.

As stated above, no clinical PK (absolute or relative bioavailability) investigation has been performed with the drug product under review. Considering that a similar product (Atropine-POS 0.5% eye drop) is already approved and that the claimed dose is 50-fold lower than the dose of the reference product. However, the applicant provided a compilation of published literature. Among the published literature, two references are in relation with the investigation of atropine absorption following ocular administration: (Kaila et al.,1999; Lahdes et al., 1988).

Kaila et al. (1999):
In this publication the outcome of a study conducted in 6 healthy adult volunteers (1 male and 5 females; 24-29 years old). The participants received a single dose of topical atropine sulfate administered as 30 µL of 1% atropine sulfate ophthalmic solution. The absolute bioavailability of atropine following topical ocular administration of 30 µL of 1% atropine sulfate ophthalmic solution and the same (0.3 mg) dose of IV atropine sulphate is approximately 64 ± 29% (range 19% to 95%). The mean (± SD) AUC after ocular administration was 1020 pg/h/mL. The mean (± SD) time to maximum plasma concentration (Tmax) was approximately 28 ± 27 minutes (range 3 to 60 minutes), and the mean (±SD) peak plasma concentration (Cmax) of l-hyoscyamine was 288 ± 73 pg/mL. The mean (±SD) plasma half-life was reported to be approximately 2.5 ± 0.8 hours. Once absorbed into the systemic circulation, topically administered atropine, the active moiety STN1012701, is distributed, metabolised, and excreted in a manner consistent with that described for atropine sulfate IV solution.

Lahdes et al. (1988):

In this publication the outcome of a study conducted in 16 hospitalised patients (38-74 years old) undergoing ophthalmic surgery who received 40 µL of a 1% atropine solution (0.4 mg) is reported. Participants received either a single, topical ocular 0.4 mg dose of atropine sulfate administered as 40 µL of the 1% ophthalmic solution into the operated eye, or placebo (salt solution) eye drop.

Following ocular administration, atropine was rapidly absorbed and peak concentrations of l-hyoscyamine of 860 ± 402 pg/mL were reached within 8 minutes in all patients. At 1 hour, more than 40% of the peak concentration was still detectable in plasma. The area under the plasma

concentration-time curve from time zero (0) to 90 minutes (AUC0-90 min) for atropine ranged from 2350 pg×min/mL to 77163 pg×min/mL with a mean of 43245 ± 24064 pg×min/mL.

Of note, while the study from Kaila et al. included blood samples until 8 hours after administration, Lahdes et al. only sampled until 90 minutes after administration, and a considerable proportion of l-hyoscyamine was still present at the last sampling time point of the latter study. Both studies used radioreceptor binding assays (detection limit Kaila et al.: 20 pg/mL; Lahdes et al.: 50 pg/mL).

PK parameters vary drastically between the two studies (doses: 30 vs. 40 µl 1% atropine; mean tmax: 27.6 vs. 8 min; mean cmax: 288.3 vs. 860 pg/ml). These differences may have been caused by factors such as the different sampling time points, differences in age of recruited participants, healthy subjects versus patients with eye diseases, the low number of participants in both studies, and potential differences between the used assays.

Due to the lack of data, the systemic exposure of Ryjunea in children is not known and could only be roughly estimated based on the 33-100 times lower dose compared to the studies described above. Of note, according to a publicly available FDA Clinical Pharmacology Review (FDA 2013), the mean elimination half-life after intramuscular atropine administration in children over 2 years of age seems to be similar to individuals 16-58 years of age. Only younger (< 2 years of age) and older individuals seem to have a prolonged elimination half-life (FDA 2013).

Considering that Ryjunea is expected to exert its effect locally, the systemic PK is mainly relevant from a safety perspective. The only non-ocular treatment-emergent adverse event which was considered related by the Investigator and occurred more than once was headache (see Clinical Safety section), suggesting that systemic exposures may be of limited relevance for the safety of Ryjunea. Besides expected ocular reactions, the Investigational product was overall well tolerated. However, potential rare adverse reactions cannot be excluded.

As discussed in more detail in the **non-clinical** section, administration of Ryjunea (0.1 mg/mL = 0.01%) to **Dutch Belted rabbits** led to rapid absorption into the systemic circulation. 0.01% atropine sulfate was only briefly detectable in plasma (up to a maximum of 30 minutes). In contrast, 1% atropine was detectable in plasma for up to 4 hours.

Local/ocular tissue absorption:

The applicant further summarised two non-clinical studies which investigated tissue concentrations after topical administration, since absorption or tissue distribution studies in human tissue were not identified in the literature. Wang et al., 2019 found both transcorneal and transconjunctival-scleral routes, and Mori et al., 2019 described a periocular-scleral route from the anterior to the posterior region.

Regarding the ocular resorption/systemic exposure, the applicant was requested to justify how the data extracted from Kaila et al. (1999) and Lahdes et al. (1988) (even inconsistent) could be considered relevant to Ryjunea and implemented in the SmPC. Data on systemic exposure in paediatric patients is still critically lacking. However, it is agreed that inserting information on systemic exposure in adult subjects treated with higher doses is better that no information at all.

Distribution

As mentioned above, no investigation was performed with Ryjunea and this is acceptable as atropine is already marketed by ocular and IV routes.

The volume of distribution after intravenous administration was comparable and high between two studies from literature (210-230.79 L; Hinderling et al, 1985, Adams et al., 1982). No PopPK model

was employed. Plasma protein and/or extensive tissue binding were not discussed further. Since the doses used in literature (1 mg; 1.35 mg and 2.15 mg) were much higher than in Ryjunea (3 µg or 9 µg in 1 drop of Ryjunea 0.01% or 0.03%, respectively), bridging to the low-dose atropine formulations is hardly possible with the information provided.

Elimination/ Metabolism

As mentioned above, no investigation was performed with Ryjunea and this is acceptable as atropine is already marketed by ocular and IV routes.

No information regarding Distribution/Metabolism and Elimination pattern of atropine was provided in the proposed SmPC, the applicant was requested to make a proposal, knowing that once absorbed, the Distribution/Metabolism and Elimination properties is expected to be similar to the IV route (already approved).

Main metabolites and elimination were briefly discussed by the applicant based on literature data. A study by Van der Meer et al. 1986 describes noratropine (24%), atropine-N-oxide (15%), tropine (2%) and tropic acid (3%) as main metabolites, while 50% of administered dose is excreted as unchanged atropine, potentially due to stereoselective metabolism (i.e., (-)-hyoscyamine enantiomer is selectively metabolised while the biologically inactive (+)-hyoscyamine enantiomer is excreted). According to Hinderling et al. 1985, urinary excretion of unchanged drug was 57% of the dose. Renal plasma clearance was 660 mL/min, which suggests significant tubular secretion. The renal clearance of atropine depended on urine flow. Urinary excretion of tropine (metabolite) amounted to 29% of the dose. Kaila et al. 1999 describe that ocular administration does not affect the elimination kinetics, as the terminal half-life was comparable between intravenous injection (2.97 ± 1.22 h) and topically administration as eye drops (2.45 ± 0.76 h).

Overall, the Pharmacokinetics part of the dossier is very limited. Several characteristics of the Pharmacokinetic profile of atropine have not been addressed, like in vitro and ex vivo protein binding of parent drug and pharmacologically active metabolites, contribution of main metabolites (potentially relevant for safety), concentration-dependence of protein binding, the risk of cumulation (mean volume of distribution of approximately 210–230 L, but only determined for much higher dose levels), in vivo interconversion of hyoscyamine enantiomers and potential effects on efficacy, intra- and inter-individual variability of PK parameters, or PK consequences if polymorphically expressed enzymes (e.g. cytochromes, transporters, etc.) are involved in the (non)ocular metabolism. Besides, the discrepancy in literature data mentioned in Q-71, these data were collected in different groups of subjects/patients: literature data were collected in healthy adult subjects and patients with other eye diseases undergoing surgery while Ryjunea is intended for children with myopia. Hence, the applicant was asked to argue and justify the complete lack of paediatric clinical PK data for Ryjunea. While it is understood that data are scarce, the applicant was asked to discuss which concentration range of atropine in plasma could potentially occur resp. ruled out in children after once daily administration, based on information in the literature and the available non-clinical data. The applicant did neither justify the lack of paediatric clinical PK data nor provided non-clinical literature data. Nevertheless, the applicant provided an estimate for a hypothetical atropine plasma concentration after administration of 100 µl of atropine 0.3 mg/ml (50 µl in each eye) which would result in a topical exposure with 30 ng atropine (or 15 ng l-hyoscyamine). The applicability of the Berjersten study is highly hypothetical since ocular and rectal bioavailability might differ. Furthermore, plasma concentrations for children with lower weight (up to 15 kg; e.g., relevant for children 3 years of age) was different compared to children ≥15 kg. The lack of clinical PK data in young children from 3 years of age is, therefore, still critically noted. Nevertheless, since the risk of considerable systemic concentrations is assumed to be relatively low and the safety profile of Ryjunea appears manageable in SYD-101-001, dedicated PK studies are not deemed necessary for the moment.

2.8.2.2. Pharmacodynamics

Mechanism of action

While no dedicated PD studies were conducted by the applicant, the applicant provided data from literature. The applicant summarised that "The mechanism through which atropine retards myopia progression is not fully understood, as both its primary site and full mechanism of action in this indication are not clearly established. The actual mechanism may be a combination of the effects observed." This is acknowledged.

Primary and Secondary pharmacology

Primary Pharmacology

The primary endpoint "change in spherical equivalent" is regarded an established and relevant clinical endpoint which is further discussed in the efficacy section. Moreover, evidence indicates that progressive myopia in children is the result of excessive elongation of the anterior/posterior axis of the eye (biomarker: axial length), which is assessed as secondary endpoint in study SYD-101-001. This is in line with a Cochrane review (Lawrenson et al. 2023), describing that "there is a broad consensus that the primary endpoints for judging efficacy in clinical trials of myopia control interventions should include change in axial length, in addition to change in refractive error".

Choroidal thickness seems to correlate with the degree of myopia (Muhiddin et al 2022). Some publications have reported an effect on choroidal thickness, but this seems to be less clear for the doses included in Ryjunea (e.g., Shi et al 2020, Zhao et al 2020, Li et al 2020, Yam et al 2022, Wu et al 2023, Kobia-Acquah 2023). Choroidal thickness was not investigated during Study SYD-101-001.

For investigated atropine dose levels (0.01%), no significant change in axial length was noted during the phase 3 trial. A Cochrane review describes an effect of higher doses of atropine on axial length (Lawrenson et al. 2023), but divergent outcomes were reported by recent studies which investigated the lower dose level included in Ryjunea (0.01%). For example, Repka et al. 2023 did not detect any effect on axial length, while a statistically significant difference to placebo was reported by Loughman et al. 2023. This unclear picture is further complicated by the results of a study by Zadnik et al 2023, which only showed a statistically significant effect for the 0.01% dose but not for a 0.02% dose. The data update from the ongoing phase 3 trial of Ryjunea is awaited (see efficacy discussion).

Secondary pharmacology

The applicant provided an extensive summary of literature on the mydriatic and cycloplegic effects of atropine, two of the pharmacologic effects for which 0.5-1% atropine is indicated (e.g., the RefMP). For Ryjunea, nevertheless, mydriasis and cycloplegia are regarded as side effects and listed as TEAEs in study SYD-101-001. Provided literature studies show that the mydriatic and cycloplegic effect of atropine is well characterised and, in principle, consistent with safety findings of study SYD-101-001 (see also Safety section).

The ATOM2 study (investigated the mydriatic and cycloplegic effects of different concentrations of atropine [0.01%, 0.1%, and 0.5%] in children aged 6-12 years old) found that accommodation amplitude and near visual acuity were reduced with atropine, albeit to a smaller extent with lower atropine concentrations (Chia et al 2012). While pupil size and near visual acuity seemed to have recovered in all groups, recovery was quicker and more complete in 0.01% eyes, during a 12-month washout period (Chia et al 2014). Due to the lack of a placebo arm, the loss in accommodative amplitude cannot be extrapolated with confidence from the ATOM2 study. Also, treatment effect and

side effect persistence are not clear. As the applicant reflects in the Summary of Clinical Pharmacology, "the diminished accommodative amplitude after the 1-year washout in all 3 groups raises some concern regarding a potential for a permanent decrement of accommodative ability. Data indicated that such an effect may be greatest with higher doses of atropine; however, a longer follow-up period is necessary to determine the true long-term effects." Therefore, the applicant was requested to discuss the potential of permanent effects on accommodative amplitude and near visual acuity based on a summary of available studies in the literature which included washout phases. According to the literature, there seems to be only a negligible non-reversible effect on near visual acuity and potentially a small negative effect on accommodative amplitude.

Of note, intraocular pressure (IOP) was analysed, although the current representation does not yet allow detailed assessment (see safety discussion of the present overview).

Genetic differences and patient maturation

No discussion of literature data was provided by the applicant. The applicant provided a literature review of age on myopia progression. The decrease in the magnitude of the treatment effect (e.g., no statistically significant difference to vehicle in participants aged 12–14 years) seems to be consistent with the decrease of myopia progression with increasing age, before myopia seems to stabilise around the age of 15 years. These data and the results from study SYD-101-001 indicate that atropine treatment should be initiated early.

Differences in treatment effect due to the age of patients/maturations is further discussed below in the efficacy section.

Product information

In SmPC section 5.1 Pharmacodynamic properties, the applicant describes the unspecific and competitive antagonistic nature of atropine and the unknown MoA of the inhibition of myopia progression. Considering available bibliographical data showing no consistency as regards to the effect of atropine on axial elongation (AL) and even if results from the SYD-101-001 rely on less than 50% of the patients, these data are considered of relevance for the prescribers. The inclusion of a brief description of AL results in section 5.1 of the SmPC is acknowledged. No discussion of literature data on potential drug-drug interactions that may affect PK or PD of atropine was provided by the applicant. Atropine is a competitive antagonist of the muscarinic receptors and considering that it is absorbed systemically, there is a potential for drug interactions such as potentiation of anticholinergic effects with drugs like amantadine, antihistamines, tricyclic antidepressants, or antiarrhythmics. However, due to the low dose included in Ryjunea and non-clinical data showing that atropine sulfate ophthalmic solution administered at a dose of 0.1 mg/mL is rapidly absorbed into the systemic circulation and is only briefly (up to a maximum of 30 minutes) detectable in plasma, it is agreed with the applicant that the risk for drug-drug interactions can be considered acceptably low.

2.8.3. Discussion on clinical pharmacology

Atropine is a well-known substance and already marketed for use by IV and ocular routes of administration. No clinical PK/PD studies with Ryjunea were performed, and the Clinical Pharmacology part of the dossier completely relies on information from the literature. The applicant only performed a non-clinical PK study with Ryjunea in Dutch Belted rabbits.

In the literature, the clinical PK data for topical administration of atropine are very sparse and only available for a higher dose level in adults. Many PK aspects that are usually relevant for clinical assessment (as described in the discussion above) are not covered by the literature.

The exact mechanism of action in slowing the progression of myopia is not known and besides effects on reduction of axial length and increase of choroidal thickness, which according to the literature were reported to be more pronounced and with a higher level of evidence at doses higher than those included in Ryjunea, a plethora of other potential mechanisms that may contribute to the effect have been hypothesised in the literature.

2.8.4. Conclusions on clinical pharmacology

Ryjunea contains atropine concentrations that are substantially lower compared to the RefMP. The RefMP also includes indications for use of up to 3 times daily administration of a 0.5 % atropine solution (duration determined by the practitioner). In addition, atropine is a well-known substance which is used since over 100 years. Regarding the potential influence on the progression of myopia, it is considered to exert its effect locally, while systemic concentrations may be more relevant from a safety perspective. Considering all this and in addition the availability of the phase 3 efficacy & safety study, a benefit/risk assessment can be made even in the absence of dedicated PK/PD studies with Ryjunea.

2.8.5. Clinical efficacy

The proposed indication is supported by efficacy and safety results from multicentre, randomised, double-masked, vehicle-controlled pivotal study in paediatric patients with myopia (Study SYD-101-001).

Table 2: Clinical study SYD-101-001

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
SYD-101-001	Total: 852 - STN1012701 0.1 mg/mL: 284 - STN1012701 0.3 mg/mL: 285 - Vehicle: 283	Multicentre, randomised (1:1:1) double-masked, vehicle-controlled	1 drop in each eye at bedtime over 48 months of either Vehicle, STN1012701 0.1 mg/mL or 0.3 mg/mL	3–14 years old, inclusive with myopia of -0.50 D to -6.00 D (inclusive); astigmatism ≤1.50 D; anisometropia ≤1.00 D

The applicant's clinical development was discussed; in several scientific advice where a second pivotal study was recommended but a single one with stronger statistical plan and robust efficacy data was acceptable. Also, bibliographic data is submitted in order to support MAA's claim.

2.8.5.1. Dose response study(ies)

The LAMP study in 438 myopic children directly compared concentrations of 0.01%, 0.025%, and 0.05% atropine over 1 year. There was a reduction of spherical equivalent (SE) progression of 27%, 43%, and 67%, and a slowing of AL growth of 12%, 29%, and 51%, at the respective concentrations. Overall, the effect on SE refraction was larger than that on AL (Yam et al., 2019). Dose-related responses have also been noted in other clinical studies and numerous meta-analyses have commented on an observed dose-response with respect to atropine dose and impact on myopia progression (Hou et al., 2023; Long et al., 2023). The incidence of side-effects including photophobia

and blurred vision is also consistently observed to be dose-related, with increase tolerability for the lowest doses. Similar conclusions apply to rebound effect. Prior to LAMP, other assessments of the effect of low-dose atropine were conducted but studies were limited by small sample sizes and/or sub-optimal design. For example, Cooper et al, 2013 suggested that atropine 0.025% is the highest concentration that does not produce significant clinical symptoms from accommodation paresis or pupillary dilation (Cooper et al., 2013). However, the study included only 12 subjects between the ages of 8 and 16 years who received increasing doses of atropine for no more than 1 week. All patients tested with 0.025% had minimal complaints of blurred vision and light sensitivity. Later, larger, well designed, long term randomised controlled studies such as LAMP have observed that the symptoms of photophobia and reduced near vision decrease or resolve over time (Fu et al., 2020; Yam et al., 2019).

The American Academy of Ophthalmology recommends the use of 0.01% of atropine for myopia control (Pineles et al., 2017). However, individual responses to 0.01% atropine can vary. Investigators have noted the potential for factors such as dark iris colour, parental myopia, and rapid progression of myopia to lessen a child's response to low-dose atropine (Chaurasia et al., 2022; Lee et al., 2022a; Li et al., 2014; Shih et al., 2001; Sun et al., 2022). In summary, the available clinical data did not allow concluding on the optimum dose for atropine for myopia control in the entire paediatric population. Therefore, the 0.3 mg/mL (0.03%) atropine formulation, as well as the 0.1 mg/mL (0.01%) dosage were selected to be investigated by the applicant to allow identifying appropriate options for a broader paediatric population, including those in whom additional benefit may be achieved using a slightly higher concentration of atropine. The risks associated with atropine 0.01% and, based on the data with 0.025%, anticipated with atropine 0.03% eyedrops are minimal and reversible upon treatment withdrawal (Chia et al., 2012).

Overall, no dose response/dose finding studies have been performed. The lower dose was selected as it appears to be the dose that provides the optimal benefit with the least amount of adverse events based on published dose-response data for the atropine 0.1 mg/ml (0.01%) and efficacy and safety data were extrapolated from 0.025% to the intended atropine' dosage of 0.3 mg/ml (0.03%). Moreover, published data tend to demonstrate a dose-related efficacy of atropine.

2.8.5.2. Main study(ies)

SYD-101-001

Table 3: Study identifiers

Study code	SYD-101-001
EU CT number	2018-004775-13
NCT number	NCT03918915
ISRCT number	Not applicable
Other identifier(s)	Not applicable
Location in eCTD	2.5, 2.7.3. and 5.3.5.

Methods

This Phase 3, multicentre, randomised, double-masked, vehicle-controlled study was planned to assess the efficacy and safety of SYD-101 (provided as SYD-101 0.01% and SYD-101 0.03%) eye drops in male and female children between 3 and 14 years of age (inclusive at baseline) with myopia of -0.50 D to -6.00 D (inclusive at baseline) compared with placebo (vehicle of SYD-101) eye drops. The treatment is administered each night at bedtime in each eye.

In Part 1 (from baseline), patients were randomised in a 1:1:1 ratio to receive either SYD-101 0.01% (0.1 mg/mL), SYD-101 0.03% (0.3 mg/mL), or Vehicle during Part 1 (Primary Treatment Period).

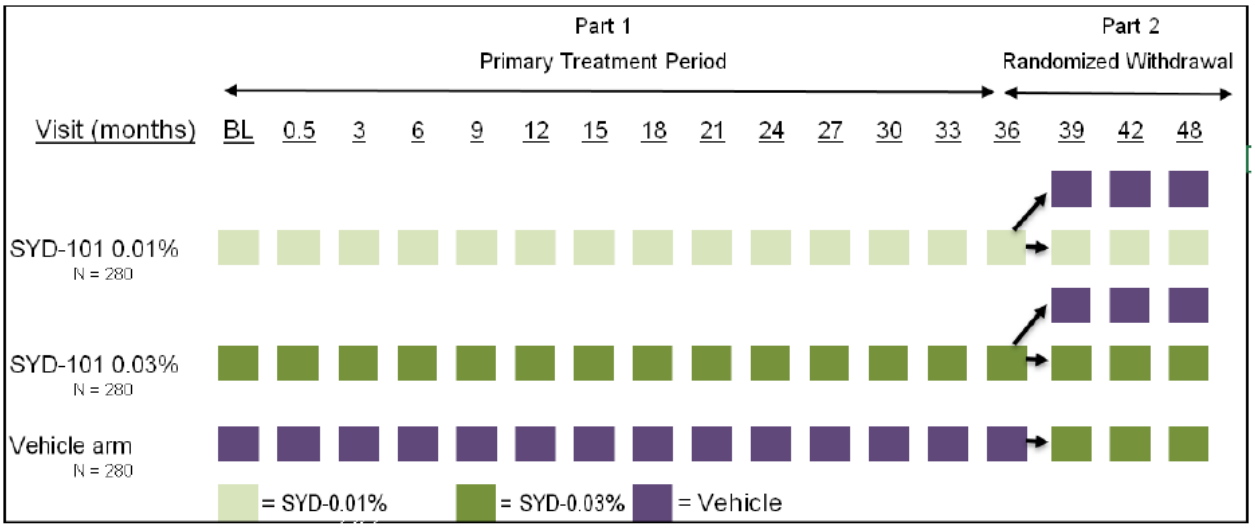
In Part 2 (from month 36), patients were re-randomised in a 1:1:1 ratio to the following dose groups:

- Those initially assigned to the SYD-101 0.01% arm were to be re-randomised in a 1:1 ratio to receive either (masked) SYD-101 0.01% (0.1 mg/mL) or Vehicle

- Those initially assigned to the SYD-101 0.03% arm were to be re-randomised in a 1:1 ratio to receive either (masked) SYD-101 0.03% (0.3 mg/mL) or Vehicle

- Those initially assigned to the Vehicle arm –not on escape medication- were to be re-randomised to receive (masked) SYD-101 0.03%

Clinic visits (with an investigator) were planned at Screening, Baseline (Day 1), Month 3, Month 6, and every 6 months thereafter until Month 48 or Early Termination (ET). A telephone visit with the study coordinator was to occur at Week 2 and between clinic visits, from Months 9 through 39 and no medications dispensed during or after the Month 48/End of Study (EOS) visit.



Abbreviation: BL, baseline.

Figure 2: Study schema

Some patients are non-responders and this was stated with a proper definition.

Study Participants

Participants were recruited from 41 sites in the United States, 3 sites in Austria, and 3 sites in Slovakia.

Main **inclusion criteria** are:

1. Participant is male or female between 3 and 14 years of age (inclusive) at the time of Screening

A question was raised regarding puberty onset considering that the subjects enrolled before the puberty could have had slower progression of myopia as compared to subjects already in pubertal development. The applicant clarified that the onset of puberty of the subjects was not part of the data collection in the SYD-101-001 study, thus were not captured. With available data, the applicant extrapolated age of onset of puberty (11 years in females and 12 years in males) to be able to discuss the impact of pubertal development on myopia. Additionally, other measures of puberty, including

height spurts, Tanner staging, menarche, break of voice (BOV), were discussed based on published data but also not captured in the trial. This was not pursued.

2. Participant is in good general health, with no clinically significant findings based on medical history and vital signs, as determined by the investigator at the time of Screening

Inclusion criteria #3 through #7 were required for both eyes:

3. Refractive error by cycloplegic autorefraction at the baseline visit:

a) Myopia of -0.50 D to -6.00 D (inclusive)

b) Astigmatism ≤1.50 D

c) Anisometropia ≤1.00 D

4. If the baseline myopia (SE) is better than -0.75 D, participant must have a history of myopia progression of -0.50 D in the previous 6 to 12 months

5. If baseline myopia (SE) is -0.75 D or worse, participant must be wearing refractive correction (single vision eyeglasses or soft, daily-wear, single-vision contact lenses) that meets the following criteria:

a) Myopia (SE) corrected to within ±0.50 D of the investigator's cycloplegic measurement of refractive error

b) Cylinder power must be within ±0.50 D of the investigator's standard refraction technique, which can be based on a cycloplegic or non-cycloplegic refraction

c) Cylinder axis must be within ±5 degrees of the axis found on the investigator's standard refraction when cylinder power is ≥1.00 D or within ±15 degrees when the cylinder power is <1.00 D

6. Best-corrected visual acuity (BCVA) of 75 letters (Snellen equivalent 20/32) or better

7. Normal intraocular pressure (IOP) <21 mmHg

Main **exclusion criteria** are:

1. Participant is a female who was pregnant, lactating, or intending to become pregnant within next 4 years

2. Participant has a known allergy or hypersensitivity to atropine or any of the components of SYD-101

3. Participant has history or current evidence of a medical condition predisposing the participant to degenerative myopia (e.g., Marfan syndrome, Stickler syndrome) or a condition that may affect visual function or development (e.g., diabetes mellitus, chromosome anomaly)

The applicant did not further discuss risks related to children having history of cardiovascular or central nervous system disease, or Down's syndrome. Instead, the applicant is referring to the SmPC section 4.4, where susceptibility to atropine in these patient populations is already included as a warning.

4. One or more biological parents with a history of myopia -9.00 D or worse

The applicant confirmed that parents of the subjects were asked to confirm their refractive error if they were myopic, which is considered acceptable. Additionally, the applicant justified the threshold of -9 dioptres based on literature (Flitcroft 2012).

5. Current use of a monoamine oxidase inhibitor

6. History of, or currently receiving treatment for, any systemic infection or autoimmune disease considered serious by the investigator

7. Participation in an investigational drug or device study within 30 days prior to Screening

8. Evidence of any ocular inflammation or infection in either eye, including blepharitis, conjunctivitis, keratitis, and scleritis

9. History or evidence of the following in either eye:

a) Retinopathy of prematurity

b) Abnormal refractive anatomy (e.g., keratoconus, lenticonus, spherophakia)

c) Amblyopia, manifest strabismus, or nystagmus

10. Use of any of the following (previously, currently, or plans to do so in the future):

a) Orthokeratology (orthoK), rigid gas-permeable, bifocal, progressive-addition, multi-focal, or other lenses to reduce myopia progression

b) Use of atropine, pirenzepine, or other anti-muscarinic agent for myopia

11. History or evidence of any ocular surgery or planned future ocular surgery in either eye

12. History or current evidence of ocular disease in the either eye that, in the opinion of the investigator, may confound assessment of visual acuity and/or refraction

13. Unwillingness or inability to comply with study requirements and restrictions, including but not limited to those specified in Section 5.3 of the protocol (e.g., required conversion from extended wear lenses to daily wear lenses, full-time use of contact lenses or spectacles).

Treatments

The active study treatment, SYD-101, is a sterile topical ophthalmic solution of atropine sulfate (0.01% and 0.03%) with HCl/NaOH, D2O, citric acid (as excipients) and Benzalkonium chloride (as preservative). To maintain masking when study treatments were administered, vehicle of SYD-101 containing H_2O instead of D_20 was administrated (Table 4).

One drop was to be administered to each eye nightly without a precision regarding the duration of the treatment.

Table 4: Summary of study drug components

Component	SYD-101 0.01%	SYD-101 0.03%	Vehicle
Atropine sulfate monohydrate	0.01%	0.03%	0%
Excipients	HCl/NaOH, D_2O, citric acid	HCl/NaOH, D_2O, citric acid	HCl/NaOH, H_2O, citric acid
Benzalkonium chloride (preservative)	0.01%	0.01%	0.01%

Abbreviations: D_2O, deuterium oxide; HCl= hydrochloric chloride; H_2O, water; NaOH, sodium hydroxide.

Responses to questions regarding study drug compliance were to be collected via a phone questionnaire or web-based application, first weekly for the first 6 months, then monthly.

In order to assess a clear allocation of potential safety events to D2O or the active treatment an additional vehicle arm containing D2O would have been needed. This is addressed in the Clinical safety section and considered as uncertainty in the B/R.

Prior and Concomitant Therapy

Medication considered necessary for the participant's welfare was to be given at the discretion of the investigator. Participants were instructed to maintain a stable dose of chronic medications during the study whenever possible. All concurrent medications (prescription, over the counter, and supplements), adjunct therapies, and concurrent procedures were to be recorded on the appropriate eCRF page.

Topical drops for examination procedures, such as anaesthetics, dilating agents, and fluorescein were permitted. Acute use of eye drops for allergies or anti-infective eye drops for treatment of bacterial or viral conjunctivitis was permitted; however, administration of any such treatment had to precede that of the study drug by 15 minutes.

1% Cyclopentolate was to be used for cycloplegic autorefraction measurements in this study.

Prohibited therapy

Due to the potential for drug-drug interactions, monoamine oxidase inhibitors were prohibited.

During the study, participants were prohibited to use any of the following:

☐ Any lenses to reduce myopia progression, including but not limited to orthokeratology, rigid gas-permeable, bifocal, progressive-addition, and multi-focal lenses

☐ Any anti-muscarinic agent for myopia, including but not limited to atropine and pirenzepine

Escape medication

For participants with measured myopia progression worse than or equal to -2.00 D from baseline in SE at a visit occurring between Month 18 and Month 36 (inclusive), and myopia progression confirmed 6 months later at the next scheduled visit (i.e., visit between Month 24 and Month 42 [inclusive]), treatment with escape medication (active SYD-101 0.03% on an open-labelled basis) could be initiated at the confirmatory visit and continued until Month 48. Participants on escape medication should adhere to the same visit schedule. As with masked study treatment, open-label SYD-101 0.03% (escape medication) was planned to be provided by the sponsor, managed and tracked using IVRS/IWRS, and dispensed to participants by the study coordinator.

Objectives

Overall objective

To evaluate the efficacy of SYD-101 for slowing the progression of myopia in children

Statistical hypothesis:

• H0: The mean annual progression rate through Month 24 is equal between Vehicle and SYD-101.

• H 1: The mean annual progression rate through Month 24 is different between Vehicle and SYD-101.

The primary efficacy analysis was tested at alpha=0.05 (2-sided) level of significance. Each dose of SYD-101, 0.01% and 0.03%, were independently compared to Vehicle. A truncated Hochberg adjustment with truncation parameter $\gamma = 0.80$ was performed to establish significance for comparisons of each of the active doses to Vehicle whilst controlling the overall type I error. For the primary efficacy endpoint, using the truncated Hochberg approach with a truncation parameter $\gamma = 0.80$, statistical significance at the 0.05 level was considered achieved for both dose comparisons if both comparisons had p-values < 0.045 $[(\alpha \times (1+\gamma)/2)]$. If one dose comparison had as p-value ≥ 0.045, then the other dose comparison p-value had to be less than 0.025 $[\alpha/2]$ to be significant.

The hypothesis testing of **secondary endpoints** will be conducted using a gatekeeping procedure based on a closed fixed-sequence test, provided the primary endpoint comparison is statistically significant. Additionally, the truncated Hochberg adjustment (γ=0.80) will be utilised to control for potential multiple dose comparisons for each endpoint. This procedure controls the study-wise type I error at the 0.05 significance level as described below.

In order to evaluate a dose comparison at each step, all preceding comparisons are to be statistically significant in favour of SYD-101 for that dose, i.e., for a given endpoint, comparisons will only be performed for the SYD-101 dose(s) that are statistically significant for the prior endpoint assessed. If both SYD-101 dose comparisons are statistically significant for the prior endpoint, the truncated Hochberg adjustment (γ=0.80) will be used to control type I error between the two doses for the given endpoint. Based on the truncated Hochberg adjustment with truncation parameter γ=0.80, if both dose comparisons were significant in the prior step, alpha of 0.05 is retained to the next step.

In that step the truncated Hochberg adjustment will again be applied if there are two dose comparisons for the given step. However, if in the prior comparison, only one dose comparison of two comparisons was significant, then alpha of 0.005 is retained and the one dose comparison must yield a P-value <0.005 to be significant.

For the EMA submission, the SYD treatment arms will be combined and compared to vehicle for endpoints assessed on subset of fast progressors. For those endpoints, the one comparison will be assessed at the alpha level retained from the prior comparison (either 0.05 if both dose comparisons were significant for both doses for all prior endpoints assessed or 0.005 if only one dose comparison was significant for the prior endpoint assessed).

Table 5: Order of testing efficacy endpoint for EMA analyses

Endpoint	EMA
1. Primary Efficacy Endpoint	Mean annual progression rate of myopia through month 24 Truncated Hochberg to control alpha for the two pairwise SYD to Vehicle comparisons
2. Key Secondary Efficacy Endpoint	Proportion of participants with myopic progression >0.75 D at or before Month 24 Truncated Hochberg to control alpha for the two pairwise SYD to Vehicle comparisons
Other Secondary Efficacy Endpoints	
3.	Proportion of participants with annual myopia progression rate through Month 24 ≤0.50 D/year Truncated Hochberg to control alpha for the two pairwise SYD to Vehicle comparisons

4.	Proportion of participants with annual myopia progression rate through Month 24 ≤0.25 D/year Truncated Hochberg to control alpha for the two pairwise SYD to Vehicle comparisons
5.	Proportion of participants with increase of myopia of >0.50 D at or before Month 24 Truncated Hochberg to control alpha for the two pairwise SYD to Vehicle comparisons
6.	Time to progression of myopia of >0.75 D through Month 24 Truncated Hochberg to control alpha for the two pairwise SYD to Vehicle comparisons
7.	Mean annual progression rate using Month 24 data on Subgroup of participants with refractive history of progression ≥ 0.5D If both dose comparisons are significant for prior endpoint, the SYD-101 0.01% and 0.03% arms will be combined for single comparison to vehicle at alpha retained from prior step. Otherwise, if only one treatment comparison is significant, then only that dose will be compared to vehicle using alpha retained from prior comparison
8.	Mean annual progression rate using Month 24 data on Subgroup of participants with refractive history of progression ≥ 0.75D If both dose comparisons are significant for time to progression endpoint and the pooled dose comparison for prior endpoint was significant, the SYD-101 0.01% and 0.03% arms will be combined for single comparison to vehicle at alpha retained from prior step
9.	Mean change from baseline in axial length at Month 24 (at sites with the requisite equipment; at least 50% of participants) Hochberg to control alpha for the two pairwise SYD to Vehicle comparisons

If the comparison is not statistically significant at any step, then remaining comparisons in the stated hierarchy will be considered nominal, descriptive, and exploratory. The study-wise type I error will be

maintained with the above closed procedure. No type I error adjustment is required for the different primary endpoints between regulatory agencies as efficacy will be assessed independently in each submission.

Outcomes/endpoints

Primary efficacy endpoint

The annual progression rate of myopia through Month 24.

Regarding, the measure of cycloplegic autorefraction (primary endpoint), discrepancies can be highly variable between individual autorefractor models, thus the applicant was advised in the CHMP scientific advice (EMA/CHMP/SAWP/123291/2019) to use an appropriate standardised device across study sites.

Primary and secondary efficacy endpoint selection was previously discussed during Scientific Advice procedure (MEA/H/SA/4009/1/2018/PED/III) and are principally acceptable. However, the following concerns were addressed:

The applicant clarified that different autorefractors were used at different sites. Each site applied their own autorefractor that was used in clinical practice. The same autorefractor was to be used for the patient throughout the duration of the study. If an autorefractor was replaced, it had to measure within 0.1D of the previous autorefractor measurements. This is principally endorsed. However, the number of different autorefractors and their characteristics in terms of precision (spherical equivalent measurement) were not provided. The applicant was not able to provide the information of the precision of each model of autorefractor used in this study but neither provided the list/number of different autorefractors used. However, the applicant further explains that the variety of autorefractors used by the clinical sites in the SYD-101-001 study reflects real-world clinical practice, in addition the analysis was based on changes in measurement values rather than absolute measurement values and that consistency of measurement was maintained Still, the impact of this source of variability due to different models of autorefractors used among the sites on the consistency of study results is not known.

The applicant explained that since the needed correction for initial BCVA was performed at screening using standard manual refraction (cycloplegic) measurements rather than cycloplegic autorefraction measurements, the applicant is not able to provide a discussion on the consistency between the patient-reported BCVA measures and cycloplegic autorefraction measurements. At least, based on the provided data in the response document (*Summary of Change from Baseline in BCVA (LogMar), Full Analysis Set*) it appears that BCVA remains stable within each treatment group (vehicle, 0.1 mg/mL atropine, 0.3 mg/mL atropine). Hence, a sudden vision loss in the atropine groups despite correction can be excluded.

The applicant clarified that study participants who missed the 3 to 28 days unscheduled visit to confirm progression were confirmed during the next scheduled visit (Month 30 for EMA) if myopia progression was >0.75D, while the recording date was the initial visit when Myopia was measured >0.75D. This is considered acceptable. The applicant failed to provide the requested number of subjects who missed unscheduled visits but as the handling of missed confirmation visits is considered acceptable, the number of missed visits is not considered relevant anymore.

In a post hoc analysis, the applicant evaluated the most severe eye of the participants in the study to compare the results with the previous analyses using both eyes. At M24 Months, analyses (most severe eye and both eyes) showed consistent differences in change from baseline SE between the STN1012701 doses and vehicle. Issue considered resolved.

Primary Efficacy Estimand

Table 6: Summary of estimand for EMA

Estimand Label	EMA Primary
Estimand Description	Difference in the mean annual progression rate of myopia based on 24 months of follow-up assuming no use of prohibited or escape medication or dosing interruptions/discontinuations due to logistical issues. For discontinuations due to tolerability issues (ie, due to a related AE), it is assumed that the effect in those participants is similar to that in participants receiving vehicle without escape medication or prohibited treatments
Target Population	Pediatric population of myopic children between 3 and 14 years of age at the time of screening that meet study criteria with parental/guardian consent
Endpoint	The annual progression rate of myopia through Month 24
Treatment Condition	Test: SYD-101 0.01% Test: SYD-101 0.03% Reference: Vehicle All without use of escape therapy for myopia control
Population-Level Summaries	Difference in mean annual progression rate of myopia through Month 24 between SYD-101 0.01% and Vehicle
	Difference in mean annual progression rate of myopia through Month 24 between SYD-101 0.03% and Vehicle

Table 7: Summary of intercurrent event handling for primary estimand

Intercurrent Event	Strategy for Primary Estimands	Justification
Intermittent Missing Data	Hypothetical • Intermittent missing data will be multiply imputed assuming data is missing at random (MAR)	Intermittent missing data are expected to be missing at random/due to logistical issues
Prohibited Treatment	EMA Endpoint: While on Treatment • MMRM using observed data until receipt of prohibited treatment (no multiple imputation) FDA Endpoint: Composite • Participants who receive prohibited treatment will be considered non-responders (eg, have progressed)	Prohibited treatments include therapies that have known efficacy for slowing myopia progression (e.g., MiSight multifocal contact lenses, Ortho-K lenses, compounded atropine, etc.) and use may be uneven between the groups, and this could distort the treatment effect of SYD to Vehicle
Escape Therapy	EMA Endpoint: While on Treatment • MMRM using observed data until receipt of prohibited treatment (no multiple imputation) FDA Endpoint: Composite • Participants who receive escape medication will be considered non-responders (eg, have progressed)	The American Academy of Ophthalmology recommends low dose atropine to reduce myopia progression. As escape medication use may be uneven between the groups, this could distort the treatment effect of SYD to Vehicle If escape medication is initiated per protocol, it is not to be given until after the 2-year EMA endpoint. Additionally, escape criterion of 2.0 D progression is larger than the FDA endpoint defined progression > 0.75 D. However, if sites should choose to treat participants prior to the defined escape criteria being met, that would indicate a belief that participants have progressed

Treatment Discontinuation	EMA Endpoint: Hypothetical • Observations after DC due to a related AE will be multiply imputed assuming missing not at random (MNAR) using a sequential vehicle-based pattern regression • Observations after Treatment DC for other reasons will be multiply imputed assuming MAR FDA Endpoint: Composite • Participants with discontinuation (DC) due to a related AE are non-responders • Observations after DC for other reasons will be multiply imputed assuming MAR	Discontinuation due to related AE are labelled non-responders is a conservative strategy as the discontinuation is related to treatment. Other reasons for discontinuation will be considered to occur at random Treatment policy will be used as a sensitivity analysis as this will reflect real world use including potential rebound effect when participants discontinue treatment
Study Discontinuation	EMA Endpoint: Hypothetical • Observations after DC due to a related AE will be multiply imputed assuming MNAR using a sequential vehicle-based pattern regression • Observations after Treatment DC for other reasons will be multiply imputed assuming MAR FDA Endpoint: Composite • Participants with DC due to a related AE are non-responders • Observations after DC for other reasons will be multiply imputed assuming MAR	This study was enrolling, and a large portion of participant follow-up was during the ongoing COVID-19 pandemic. The majority of study discontinuations are logistical due to withdrawal of consent. Discontinuation due to related AE are labelled non-responders and is a conservative strategy as the discontinuation is related to treatment. Other reasons for discontinuation will be considered to occur at random.
Invalid SE Values	Treatment Policy • Invalid SE values will be used	Given the age of children in participants, in clinical practice it would be expected to have non-ideal auto-refraction assessments.

The primary estimand was the difference in the mean annual progression rate of myopia based on 24 months of follow-up assuming no use of prohibited or escape medication or dosing interruptions/discontinuations due to logistical issues. For discontinuations due to tolerability issues (i.e., due to a related AE), it was assumed that the effect in those participants was similar to that in participants receiving vehicle without escape medication or prohibited treatments. As presented in Table 3.8, the intercurrent events prohibited treatment and escape therapy were planned to be targeted by a while on treatment strategy, treatment or study discontinuation by hypothetical strategies and invalid SE values by a treatment policy strategy.

The while-on-treatment strategy for prohibited and escape medication was implemented by omitting observations after the intercurrent event in the MMRM, which is equivalent to using multiple imputation assuming MAR for the values after the intercurrent event, rather targeting a hypothetical or treatment policy strategy than a while on treatment strategy. This is acceptable as there were only 6 patients who received escape medication (5 patients in the vehicle group and 1 patient in the 0.3 mg/mL atropine group, Table 5 in CSR) and apparently no patient used prohibited treatment (as SAP states "taking prohibited medications or treatment listed in protocol" as a reason to be interpreted as a major protocol deviation and Table 6 of CSR lists no such patient). The choice of the strategy for the intercurrent events prohibited treatment and escape therapy might however become more relevant when the updated data are presented, where more patients are expected to have received escape

medication. Then, Supplementary Analysis 4, which used multiple imputation informed by the vehicle arm for observations after prohibited or escape therapy, might give additional insight and was requested for the updated data as part of a concern raised in the results section.

Observations post study or treatment discontinuation not due to a related AE were multiply imputed assuming missing at random (MAR) and observations after treatment or study discontinuation due to a related AE were multiply imputed assuming missing not at random (MNAR). If study or treatment discontinuation for other reasons than being related to an AE was indeed solely logistically motivated, using multiple imputation assuming MAR might be adequate. As it is expected that some of the patients discontinued also for reasons related to the study drug, imputing the data after discontinuation based on the vehicle arm might give a more realistic picture. This was incorporated in Supplementary Analysis 4, which yielded less pronounced but similar results as the primary analysis. Thus, no further concern is raised. For the sake of consistency, it is noted that Supplementary Analysis 4 is understood to target not only treatment discontinuation but also study discontinuation by a treatment policy strategy, although the protocol claims that study discontinuation was handled by a hypothetical strategy. Indeed, using vehicle based imputation after study discontinuation is assumed to approximate the unobserved values after discontinuation. In order to avoid this confusion, in the following often the analysis strategy (e.g. vehicle based imputation) rather than the intercurrent event strategy (e.g. treatment policy strategy) will be described when discussing for instance supplementary analyses.

Handling of invalid SE values by the treatment policy strategy using observed data is considered appropriate.

The study protocol additionally lists intermittent missing data as intercurrent event but while missing data often occur as consequence of intercurrent events they should not be considered intercurrent events themselves. However, as the handling of intermittent missing data using multiple imputation assuming MAR is considered appropriate, no concerns are raised.

Table 5 in the CSR lists, among others, subject numbers who received escape medication, discontinued study or treatment together with corresponding reasons for study discontinuation. No data was found about the number of subjects with intermittent missing data or invalid SE values. The applicant was asked to provide information about how often the patients had intermittent missing data or invalid SE values, if it was not already provided, to facilitate decision-making about their impact on the primary analysis as well as secondary analyses. The applicant clarified that 11 visits with invalid SE values had been identified of which only 3 scheduled visits. As the number is low, no further concern regarding invalid SE values is raised. Information on number of missed assessments, a description of the observed pattern of missingness and reason for missingness were also requested. The pattern is discussed to be intermittent, and the reason for missingness was not collected unless the subject had discontinued the study, according to the applicant. The amount of missing data was not provided, however according to Listing 16.2.10.2 the number of missing visits seems to be limited. Thus, no further concern is raised.

The estimand for the key secondary endpoint confirmed myopic progression worse than 0.75 D until month 24 was defined similarly as the estimand for the primary endpoint but used a composite strategy for the handling of the intercurrent events prohibited and escape medication. Again, Supplementary Analysis 4 (vehicle-based imputation for study discontinuation, prohibited and escape medication; analysis of observations after treatment discontinuation as observed) is considered a plausible alternative to the primary analysis of the key secondary endpoint and hence no issues are raised in this context.

Key secondary efficacy endpoint

Proportion of participants with myopic progression >0.75 D at or before Month 24.

The key secondary endpoint confirmed myopic progression (>0.75D) at or before month 24 was analysed using Cochran-Mantel-Haenszel tests, which is considered adequate.

Other secondary efficacy endpoint

- Proportion of participants with annual myopia progression rate through Month 24 ≤0.50 D/year

- Proportion of participants with annual myopia progression rate through Month 24 ≤0.25 D/year

- Proportion of participants with increase of myopia of >0.50 D at or before Month 24

- Time to progression of myopia of >0.75 D through Month 24

- Mean annual progression rate using Month 24 data on Subgroup of participants with refractive history of progression ≥ 0.5D

- Mean annual progression rate using Month 24 data on Subgroup of participants with refractive history of progression ≥ 0.75D

- Mean change from baseline in axial length at Month 24 (at sites with the requisite equipment; at least 50% of participants).

Sample size

Sample size determination took into consideration both EMA and FDA primary endpoints.

For the EMA related primary endpoint, group sample sizes of 280 per treatment arm achieve >90% power to detect a reduction of 0.18 D or more in the annual progression rate between SYD-101 and Vehicle, assuming a common standard deviation (SD) of 0.60 D. Power calculations are based on a 2-sample t-test evaluated at the 0.025 significance level.

The sample size calculations can be followed from the technical perspective. Of note, for the sample size calculations a difference in the annual progression rate between the atropine groups and vehicle of at least 0.18 dioptres was assumed, which is larger by about 50% than the actually estimated difference of 0.12 dioptres for the 0.3 mg/mL atropine group and 0.13 dioptres for the 0.1 mg/mL atropine group. Group sample sizes of 280 in each treatment arm was to achieve at least 90% power to detect a difference in the percentage of participants with myopic progression (worse than -0.75 D) of at least 15% between a SYD-101 arm and Vehicle (FDA related primary endpoint). Power calculations are based on the Chi-squared test at a 2-sided significance level of 0.025.

Group sample sizes of 280 in each treatment arm will achieve at least 90% power to detect a difference in the percentage of participants with myopic progression (>0.75 D) of at least 15% between a SYD-101 arm and Vehicle. Power calculations presented in Figure 3 are based on the Chi-squared test at a 2-sided significance level of 0.025.

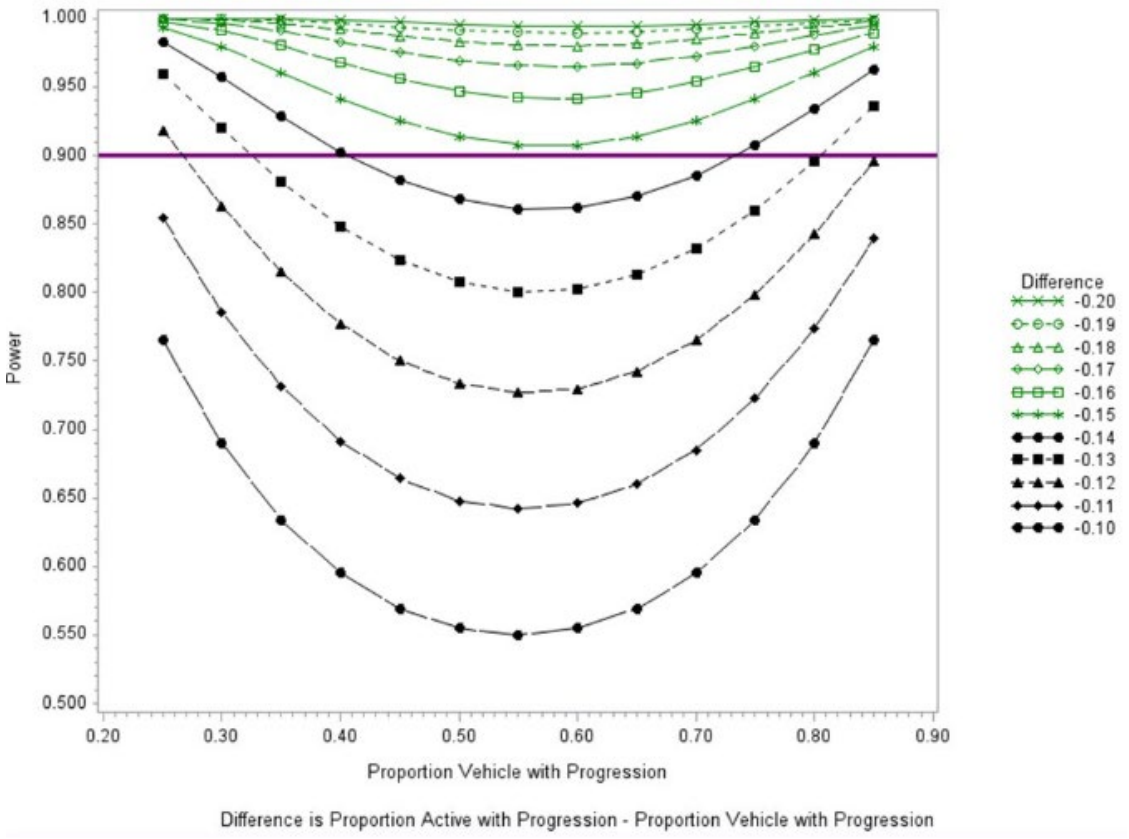


Figure 3: Power for 2-sided Chi-Square test evaluated at alpha=0.025 for proportion responders when 280 participants per arm

Additionally, group sample sizes of 280 per treatment arm achieves >90% power to detect a reduction of 0.18 D or more in the annual progression rate between SYD-101 and Vehicle, assuming a common SD of 0.60 D. Power calculations presented in Figure 4 are based on a 2-sample t-test evaluated at the 0.025 significance level.

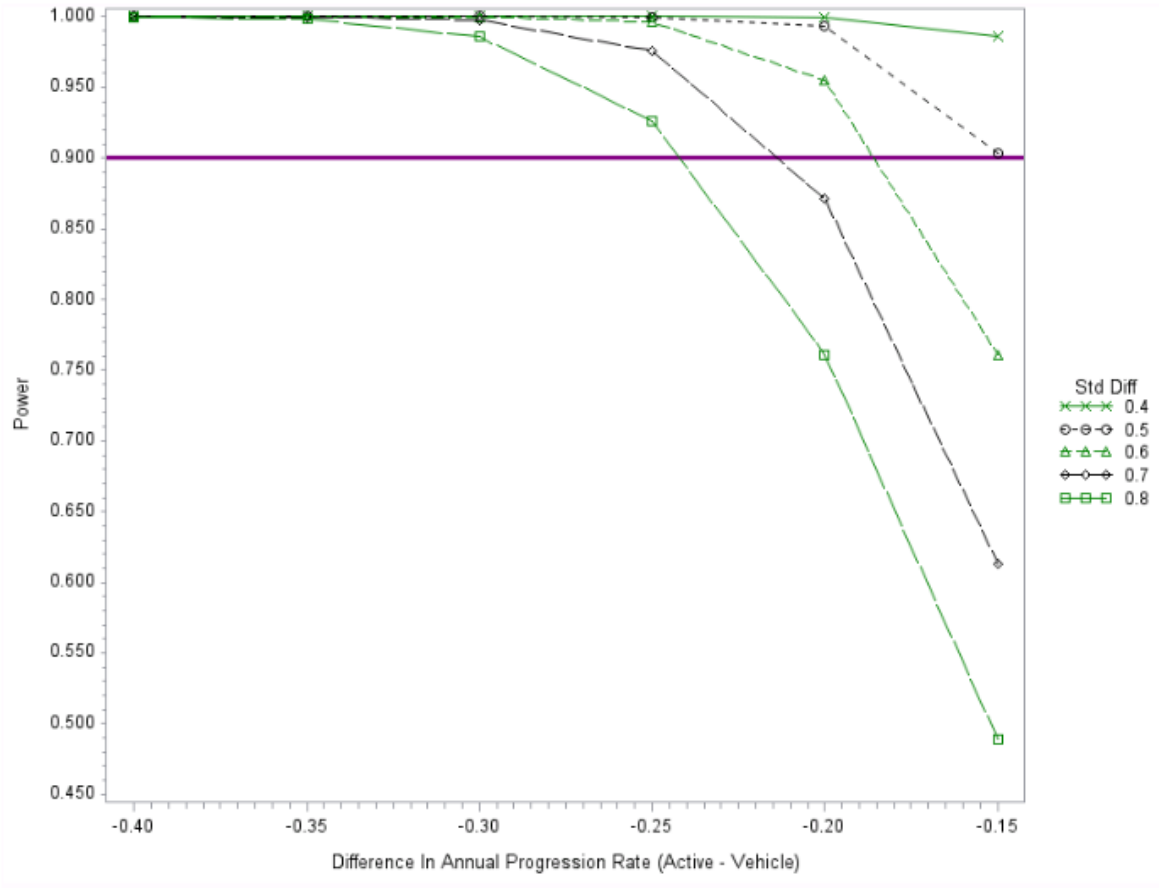


Figure 4: Power for 2-sided T-Test evaluated at alpha=0.025 for annual progression rate when 280 participants per arm

Calculations were performed using SAS® 9.3 Software (SAS Institute, Inc, Cary, North Carolina).

This study plans to continue follow-up for all enrolled participants through Month 48, regardless of early discontinuation of study treatment or receipt of escape medication/prohibited therapy. All participants will be included in analyses based on their observed data. Because the effect size estimates have already taken into consideration the impact of no therapy/escape medication, enrolment of additional participants beyond 280 participants per treatment arm has not been planned.

The sample size is endorsed and covers with a somewhat high power (> 90%) the objectives targeted in the two investigated geographical regions (EU and USA). It should be noted that to anticipate the possibility of claiming either active dose, there was a correction for multiple comparisons of doses with the vehicle, leading to a calculation of the sample size based on a two-sided type-1 error of 0.025, in agreement with the Hochberg procedure described in section Primary objective above.

Randomisation and blinding (masking)

Method of Assigning Patients to Treatment Groups

Prior to baseline randomisation (PART 1), the participant or parent/guardian administered 1 drop of an artificial tear to each eye to demonstrate cooperation and performance with eye drop instillation. Once study entry procedures have been completed, the investigator's designee obtained the randomisation assignment and drug kit number from the Interactive Voice Response System (IVRS)/Interactive Web Response System (IWRS) and provided training to the participant or parent/guardian in the correct administration.

Randomisation and Masking

The masking procedure is considered adequate.

Allocation to study treatment was to occur in a double-masked manner on 2 occasions: initial randomisation at Baseline (for Primary Treatment Period [Part 1]) and re-randomisation at Month 36 (for Randomised Withdrawal Period [Part 2]).

For Part 1, prior to initiation of study treatment, randomisation occurred by site staff via the IVRS/IWRS once it was confirmed that the participant met the final study entry criteria. The IVRS/IWRS provided the participant identification number used on all study documents and was used to manage the randomisation and treatment assignment based on a stratified randomisation scheme prepared by Sydnexis' designee. Initial randomisation was in a 1:1:1 ratio of SYD-101 0.01%: SYD-101 0.03%: Vehicle and stratified by baseline SE (-0.50 D to -3.0 D and worse than -3.0 D to -6.0 D) and age (3 years to <6 years, 6 years to <9 years, 9 years to <12 years, and 12 years to 14 years).

For Part 2, to maintain treatment masking, sites are to contact the IVRS/IWRS at Month 36 for all participants. At Month 36, participants who were initially assigned (at Baseline) to SYD-101 0.01% were to be re-randomised in a 1:1 ratio to masked SYD-101 0.01% or Vehicle; participants initially assigned (at Baseline) to SYD-101 0.03% were to be re-randomised in a 1:1 ratio to masked SYD-101 0.03% or Vehicle. The re-randomisation of SYD-101 participants was not stratified. All participants who were initially assigned (at Baseline) to Vehicle were to be re-randomised to masked SYD-101 0.03% at Month 36.

Sites were also to contact the IVRS/IWRS at the time a participant qualifies to initiate treatment with escape medication (i.e., at confirmatory visit when measurements confirm progression of myopia worse than or equal to -2.00 D in SE from baseline) for any participant who had qualified for and desired to use escape medication.

Study drugs were labelled with medication kit numbers, and the IVRS/IWRS provided each site with the specific medication kit (each kit containing 3 bottles) number(s) for each randomised participant at the time of randomisation and any required drug resupply visit. Additionally, to maintain study masking, the IVRS/IWRS is programmed to assign a new medication kit for all participants at any timepoints study treatments might switch based on study design (i.e., the rerandomisation at Month 36, at escape for confirmed progression worse than or equal to -2.00 D), even if the new medication kit was to be of the same treatment type of the medication kit currently assigned. Sites were to dispense study drug according to the IVRS/IWRS instructions. Sites were to receive the IVRS/IWRS confirmation notifications for each transaction. All notifications were to be maintained with the study source documents.

Masking of individual participant treatment assignments was planned to be maintained throughout the study for all participants and required site staff until the database is locked for the end of study (EOS) analysis at Month 48. If it is necessary for the safety and appropriate treatment of a participant, the treatment assignment can be unmasked by the site via the IVRS/IWRS. When possible, the medical monitor was to be notified prior to the unmasking, and the reason for breaking the mask documented in the source documentation. The investigator was requested to inform the medical monitor of the unmasking if there was no notification prior to the unmasking. The treatment assignment for the participant was determined by designated site staff calling into the IVRS/IWRS via password-protected access. The reason for breaking the code was to be recorded in the participant's source documents and electronic case report form (eCRF).

To minimise bias, results of the Month 24 analyses for EU submission were neither made public, nor shared with any Sydnexis personnel until after completion of the Month 36 analysis and with CRO personnel, study monitors, or study sites until after completion of the Month 48 analysis. All data and

correspondence on data obtained after database lock were to be processed by other independent stakeholders, with a strict wall with sites, and personnel involved in the FDA.

Baseline randomisation was stratified by baseline spherical equivalent and age but would also have been expected to be stratified by centre or region. However, since only patients from the US and Europe were included and the relative frequencies of patients from Europe were quite similar across the arms (8.5%, 6.7% and 9.5% for vehicle, 0.1 mg/mL atropine group and 0.3 mg/mL atropine group, respectively), no further concern is raised. It is not understood why re-randomisation was not stratified since the number of patients per arm seems to be high enough to allow for consideration of at least a limited number of strata, but this discussion is pointless after initiation of the study. Data after re-randomisation, which are not yet available, will be more easily interpretable if the numbers are balanced within important prognostic groups.

Statistical methods

Statistical Analysis Sets

Efficacy Analysis

The analysis of the primary endpoint was based on the FAS. The analysis grouped participants according to initial randomised treatment regardless of the status of escape medication. As supplementary analyses, an analysis was repeated for the PPS and for the FAS using other intercurrent event policies. All secondary endpoints were primarily analysed for the FAS and repeated for the PPS as supplementary analyses. Supplementary analyses using other intercurrent event policies were performed for the key secondary efficacy endpoints for the FAS.

The key secondary endpoint confirmed myopic progression (>0.75D) at or before month 24 was analysed using Cochran-Mantel-Haenszel tests, which is considered adequate.

The confirmatory testing scheme based on a gatekeeping procedure using truncated Hochberg adjustment for each family comprised the primary, the key secondary and all seven other "secondary" endpoints, as defined by the applicant. One difference to the gatekeeping procedure described by Dmitrienko and Tamhane (Dmitrienko, A., Tamhane, A.C., & Bretz, F. Eds. 2009). Multiple Testing Problems in Pharmaceutical Statistics (1st ed. Chapman and Hall/CRC) is that if only one dose comparison was considered significant within a family consisting of two dose comparisons for a certain endpoint only that dose was to be tested for all subsequent endpoints. Moreover, for the secondary endpoints mean annual progression rate in the patients with refractive history of progression worse than 0.5 D/year (Fast Progressor Subgroup 1) or worse than 075 D/year (Fast Progressor Subgroup 2), the two atropine groups were to be pooled if both dose comparisons were statistically significant for all endpoints higher in the testing hierarchy. Thus, it is not clear whether the designed procedure indeed controls the familywise error rate at the 0.05 level. However, since for all but the last endpoint (mean change in axial length) in the testing scheme both dose comparisons were found significant, the proposed gatekeeping procedure and the published one (with pooling of atropine arms for Fast Progressor Subgroups 1 and 2) come to identical conclusions and it is agreed that all secondary efficacy endpoints besides of axial length can be claimed statistically significant.

<u>Supplementary Analyses</u>

All the seven 'sensitivity' analyses provided for the primary and key secondary endpoint are in fact considered to be supplementary analyses, i.e. targeting different estimands than the primary analyses following ICH E9 (R1) terminology. Thus, in this assessment we will refer to 'Sensitivity Analysis' 1-7 as "Supplementary Analysis" 1-7.

The list of supplementary analyses is presented below. Supplementary Analysis 6 was conducted for the confirmed progression -0.75 D or worse endpoint only, while Supplementary Analysis 7 was conducted for the annual progression rate primary endpoint only.

1. Supplementary Analysis 1 (PPS While on Treatment/Hypothetical)

2. Supplementary Analysis 2 (FAS Treatment Policy for Prohibited Treatment, Escape Therapy and Treatment Discontinuation)

3. Supplementary Analysis 3 (FAS MAR Tipping Point)

4. Supplementary Analysis 4 (FAS MNAR exclude Prohibited and Escape Observations)

5. Supplementary Analysis 5 (FAS MNAR include Vehicle post Prohibited and Escape Observations)

6. Supplementary Analysis 6 (confirmed progression endpoint only – all missing considered progression)

7. Supplementary Analysis 7 (annual progression rate endpoint only - MMRM no imputations)

Other Analysis

Allocation to the treatment groups was stratified by baseline SE (-0.50 D to -3.0 D and worse than -3.0 D to -6.0 D) and age (3 years to <6 years, 6 years to <9 years, 9 years to <12 years, and 12 years to 14 years). Subgroups were defined based on baseline age category as described above and also 3 years to < 12 years, 6-14 years, and baseline SE category as per stratification. Additional subgroups were parental history of myopia, ocular medical history (progression of SE vs. no progression of SE) within past 12 months, iris colour (dark vs light), region (EU vs US), race, sex, average time outdoors, average time near work. The primary efficacy endpoints were analysed separately for these subgroups using the FAS. The study was not powered for subgroup analysis; these analyses are considered descriptive only. The subgroup analyses were performed using the same multiply imputed data as for the primary efficacy analyses.

Quality of Life (QOL) Questionnaire

The investigator's designee was to administer a questionnaire to participants (or parents/guardians) to assess potential impact of treatment on the participant's QOL. Responses were to be marked as strongly agree, agree, neither agree or disagree, disagree, strongly disagree. There were eight questions in all. Questions 2 to 7 were to be scored from 5 for strongly agree to 1 for strongly disagree and questions 1 and 8 were to be reversed scored from 1 for strongly agree to 5 for strongly disagree so that higher values consistently indicate a "worse" outcome for the participant. Summary statistics presented for each question as well as for the per participant average of the 8 questions. Participants were to be included in the analysis of average question score if they had at least 4 non-missing question responses. For the average question score, missing question responses were to be imputed from the mean of the available question responses. Additionally, a Wilcoxon Rank Sum test and frequency tables were presented summarizing results and individual participant's responses were listed. The Wilcoxon Rank Sum test was performed in a pairwise manner comparing each treatment dose (SYD-101 0.01%, SYD-101 0.03%) to vehicle. No adjustment for type 1 error were planned to be made for the multiple dose comparisons or multiple timepoints.

Safety Analysis

Safety was assessed through summaries of AEs and changes in vital signs, BCVA, biomicroscopy, IOP, and ophthalmoscopy abnormalities. Safety data was summarised by treatment group using the Safety Set. In general, for ocular assessments, safety was summarised using the average of both eyes' averages, with a few exceptions where presenting data for the eye with the worst response for the

given assessment. Percentages, if applicable, were calculated based on the number of participants in the Safety Set. For analysis of event data, participants were counted once for given event if the event occurs in at least one eye. For safety analyses from baseline to Month 24, the baseline was considered the start of study prior to administration of any study medication.

Planned subgroup analyses

Additionally, special subsets were defined to identify participants with a history of fast progression based historical refraction data.

☐ Fast Progressor Subgroup 1: FAS participants with progression of -0.50 D/year or worse based on historical refraction for any of the 3 history time intervals

☐ Fast Progressor Subgroup 2: FAS participants with progression of -0.75 D/year or worse based on historical refraction for any of the 3 history time intervals

For all statistical tests, unless otherwise stated, a two-sided type I error rate of 5% was used, with corresponding 95% confidence intervals (CIs) and associated p-values provided as appropriate.

All efficacy endpoints are summarised by treatment group and visit. Individual participant listings for each efficacy endpoint are provided to support the summary tables.

Note: In the event that a site was identified as having significant improper investigator oversight, the primary and secondary efficacy analyses were to be performed both with and without this site's data to assess its significance.

The analysis of the primary efficacy endpoint mean annual progression rate of myopia through 24 months used a MMRM model adjusted for baseline age category, categorical visit, the treatment by visit interaction and the baseline SE value (average of both eyes) employing fixed effects, which is considered appropriate. Data from all visits through Month 24 were included in the model, with the primary comparison at the Month 24 visit. Based on the protocol, the FAS including all randomised subjects who received at least 1 drop of study drug, was the population used for the primary efficacy analyses which is considered adequate.

The treatment effect of the primary efficacy endpoint is only described by estimates (within and between arms) from the MMRM. In order to gain a better understanding of the analysis approach including the missing data handling strategy, the applicant was asked to present descriptive statistics of the raw data for the primary efficacy endpoint and the key secondary efficacy endpoint. In particular, the annual progression rate of myopia within each treatment arm (before imputation) should be described by the number of available observations, mean, standard deviation, minimum and maximum value for the time periods baseline to month 6, 12, 18 and 24 and if feasible to month 36 and 48.

Similarly, the number of patients with confirmed progression at or before month 6, 12, 18 and 24 and if feasible at or before month 36 and 48 needed to be described. The provided raw data show smaller mean progression rates for all treatment arms and time points. For instance, at month 24 the mean progression rate based on raw data was -0.36 D/yr in the vehicle group and -0.24 D/yr in the 0.1 mg/mL atropine group, while the MMRM model based on imputed data gave estimated mean progression rates of -0.44 D/yr for the vehicle group and -0.31 D/yr for the 0.1 mg/mL atropine group. Moreover, while the MMRM resulted in an estimated difference in the annual progression rates until month 24 of 0.132 D/yr (95% CI 0.061, 0.204) between the 0.1 mg/mL atropine group and the vehicle group, this difference was only 0.118 D/yr based on the raw data. In order to understand the reason for these differences, the applicant was asked to provide the code and data for reproducing the primary analysis including the imputation model. These data and a comparison of the imputed and observed values provided by the applicant indicate that the difference between imputed and observed

values is not large enough to explain the differences between the MMRM model results and the raw data described above. However, the provided code suggests that the MMRM model was applied without using the OBSMARGIN statement, even though the applicant's response in an earlier assessment round was understood differently. It is conceivable that assuming a balanced distribution for the categorical covariate age when estimating the LSMEANS from the MMRM model, which is the default behaviour when not using OBSMARGIN, might have resulted in the observed differences between mixed model results and the raw data. The applicant provided results based on the OBSMARGIN statement for all analyses that are included in the SmPC where estimates within study arms are shown.

In addition, as requested, the applicant provided an MMRM analysis for change from baseline (CfB) in spherical equivalent mimicking the primary analysis of the primary endpoint annual progression rate (CfB per year). According to this analysis the change from baseline until month 24 was -0.72 D in the vehicle group and -0.49 D in the 0.1 mg/mL atropine group, corresponding to a treatment difference of 0.238 D with 95% confidence interval of (0.131, 0.345). These numbers translate into an annual progression rate of -0.36 D/yr for the vehicle group and -0.245 D/yr in the 0.1 mg/mL atropine group, while the originally presented primary MMRM analysis of the annual progression rate estimated an annual progression rate until month 24 of -0.44 D/yr for the vehicle group and of -0.31 D/yr for the 0.1 mg/mL atropine group. These differences are unexpected as it is assumed that performing an MMRM on the CfB values and translating the estimated CfB values to the annual rate scale (CfB/year) should give similar results to performing an MMRM directly on the annual progression rate values. It is understood that in both analyses multiple imputation was performed on the level of average SE values (over both eyes), which does not explain the differences either. The applicant has provided a revised MMRM analysis of change from baseline, where intercurrent events are handled in the same way as in the primary analysis of annual progression rates. The estimates are aligned, with the estimated difference in change from baseline divided by the respective time interval being similar to the estimated difference in annualised progression rate. Moreover, the applicant has provided the requested code for performing the MMRM for change from baseline in spherical equivalent. Moreover, the applicant clarified that 11 visits with invalid SE values had been identified of which only 3 scheduled visits. As the number is low, no further concern regarding invalid SE values is raised. Information on number of missed assessments, a description of the observed pattern of missingness and reason for missingness were also requested. The pattern is discussed to be intermittent, and the reason for missingness was not collected unless the subject had discontinued the study, according to the applicant. The amount of missing data was not provided, however according to listing provided, the number of missing visits seems to be limited. Thus, no further concern is raised.

Error probabilities, adjustment for multiplicity and interim analyses

The absence of correction for multiplicity regarding geographical different primary endpoints is fully agreed upon as long as there will be no claim in the failed geographical region (if so) that would be based on the primary endpoint results of the successful geographical region.

Results

Participant flow

The overall disposition of participants is presented in Table 8 and a simplified CONSORT diagram is presented in Figure 5.

The main reasons for discontinuation were lost to follow-up (58 participants [6.8%] overall), withdrawal by parents or guardians (44 participants [5.2%] overall), and withdrawal by subject (38 participants [4.5%] overall). Five (1.8%) participants in SYD-101 0.03% group discontinued the study

due to an AE, compared with no participants in the other groups. The percentage of drop-outs across the three arms (18.7% in vehicle group vs 19.7% in atropine 0.01% and 18.6% in atropine 0.03%) were taken into account for the efficacy results (multiple imputations, sensitivity analysis). The applicant precise the most common reasons for discontinuation at Month 36 across groups: lost to follow-up, withdrawal by subjects, and withdrawal by parents or guardians. Furthermore, 1.2% of the drop-outs were AEs related up to 36 months (2, 1 and 8 patients in vehicle, SYD-101 0.01%, and SYD-101 0.03% groups respectively).

Table 8: Participant disposition - informed consent participants

	Vehicle N (%)	SYD-101 0.01% N (%)	SYD-101 0.03% N (%)	Total N (%)
Informed consent [1]				1035
Screen failure				181
Randomized	283	284	285	852
Dosed	282	282	283	847
Completed Month 24	232 (82.0)	228 (80.3)	231 (81.1)	691 (81.1)
Received escape medication	5 (1.8)	0 (0.0)	1 (0.4)	6 (0.7)
Discontinued study	48 (17.0)	52 (18.3)	51 (17.9)	151 (17.7)
Discontinued study treatment	53 (18.7)	56 (19.7)	53 (18.6)	162 (19.0)
Primary reason for study discontinuation				
Adverse event	0 (0.0)	0 (0.0)	5 (1.8)	5 (0.6)
Withdrawal by Subject	14 (4.9)	14 (4.9)	10 (3.5)	38 (4.5)
Withdrawal by Parent or Guardian	12 (4.2)	16 (5.6)	16 (5.6)	44 (5.2)
Lost to Follow-up	18 (6.4)	22 (7.7)	18 (6.3)	58 (6.8)
Physician Decision	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.1)
Other	3 (1.1)	0 (0.0)	2 (0.7)	5 (0.6)

Note: Percentages are based on the number of participants randomized.

[1] The number of patients who provided informed consent also includes screen failures.

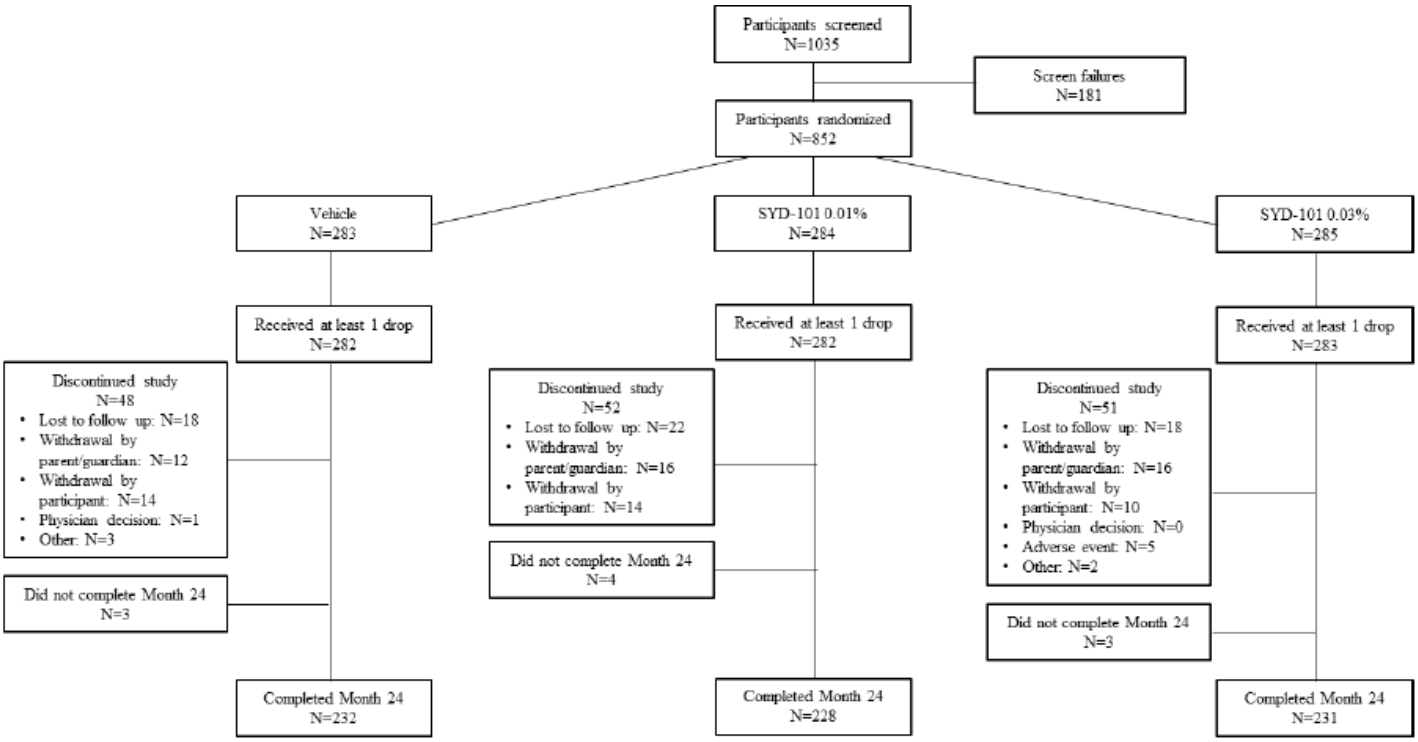


Figure 5: Participant flow

Recruitment

The start of the study: 24 April 2019

End of trial: ongoing study, data lock-point 21 July 2023 (24 month)

The study was conducted in 3 countries: the US (41 active sites), Austria (3 sites) and Slovakia (3 sites).

As requested, the applicant discussed the representativity of the trial population (91.7% of patients were from US) with regard to the intended marketing authorisation in European population (8.3% of trial' patients). The applicant indicated that Atropine pharmacology is not likely to be affected by ethnicity. There are no intrinsic or extrinsic ethnic factors that will preclude the extrapolation of the results of the US population to the EU. Moreover, the diagnosis and treatment of myopia are similar in the US and EU. In addition, the conduct of clinical trials in the US and EU are generally the same and the study was conducted following internationally accepted good clinical practice (GCP) requirements (ICH E5 R1 guidance).

Intrinsic factors include genetic polymorphism, age, gender, height, weight, lean body mass, body composition, and organ dysfunction and were mostly assessed within the subgroup analyses of the primary endpoint, for which results were in line with the results in the FAS. Extrinsic factors include the social and cultural aspects of a region, such as medical practice, diet, use of tobacco, and use of alcohol. Additionally, the applicant provided baseline characteristics presented by population (EU vs US) for each groups including intrinsic/extrinsic factors. Generally, baseline characteristics are considered similar across groups, except for racial and ethnic background.

As well, efficacy results from Study SYD-101-001 were provided by region for the primary endpoint in FAS.

In European participants, the annual myopic progression was -0.47D and -0.40D in the vehicle, and SYD-101 0.01% groups, respectively. Difference to vehicle (LS mean rates) in European patients was 0.066 D (95% CI [-0.219, 0.351]; p-value 0.6484) in SYD-101 0.01% group.

In US participants, the annual myopic progression was -0.44D and 0.30 D in the vehicle and atropine 0.1 mg/mL groups, respectively. Difference to vehicle (LS mean rates) in European patients was 0.135 D (95% CI [0.061, 0.209]; p-value 0.0004) in SYD-101 0.01% group.

Globally, the results of the subgroup analyses in US patients are in line with the primary endpoints results provided by the applicant. However, results in EU patients are not statistically significant although the difference with the vehicle is similar in US patients and clinical pertinence in SYD-101 0.01% group was questionable. Given, small population tested in the subgroup analyses, the issue is not pursued.

Conduct of the study

SYD-101-001 study started on 24th of April 2019 and is still ongoing. applicant amended the protocol two times. Amendments were in majority related to COVID, and following CHMP and FDA scientific advice. The applicant briefly clarified that the protocol amendments did not have an impact on the efficacy results as they were implemented to update and clarify statistical methods to allow for different requirements regarding primary and secondary endpoint assessment as requested by EMA and FDA.

Overall protocol deviation (PD) data are considered not sufficiently processed and summarised. As requested, the applicant provided a table including all protocol deviations (PDs) (as previously submitted for major PDs) for the three study arms. Since PDs are evenly distributed across study arms and no noticeable difference was detected between treatment groups. Further, the applicant clarified that no PD related to unblinding/unmasking occurred. Major protocol deviations through Month 24 concerned 28 patients (6 patients in the vehicle arm, 9 and 13 in SYD-101 0.01% and 0.03% arms respectively). A total of 29 major protocol deviations were related to selection criteria not being met, more particularly the two following inclusion criteria: "refractive error by cycloplegic autorefraction at the baseline visit", and "if the baseline myopia (SE) is better than -0.75 D, participant must have a history of myopia progression of -0.50 D in the previous 6 to 12 months". Patients with major PDs were excluded from the PPS but not from the FAS which is considered acceptable.

Baseline data

Baseline characteristics

Table 9: FAS – baseline characteristics

	Vehicle (N=282)	SYD-101 0.01% (N=282)	SYD-101 0.03% (N=283)	Total (N=847)
AGE (YEARS)				
n	282	282	283	847
MEAN (SD)	10.4 (2.42)	10.4 (2.44)	10.2 (2.46)	10.3 (2.44)
MEDIAN	11.0	11.0	10.0	10.0
MIN, MAX	4, 14	3, 14	3, 14	3, 14
PLANNED AGE CATEGORIES (YEARS) n (%)				
3 TO < 6	9 (3.2)	9 (3.2)	9 (3.2)	27 (3.2)
6 TO < 9	61 (21.6)	61 (21.6)	62 (21.9)	184 (21.7)
9 TO < 12	111 (39.4)	110 (39.0)	111 (39.2)	332 (39.2)
12 TO 14	101 (35.8)	102 (36.2)	101 (35.7)	304 (35.9)
ACTUAL AGE CATEGORIES (YEARS) n (%)				
3 TO < 6	9 (3.2)	8 (2.8)	9 (3.2)	26 (3.1)
6 TO < 9	61 (21.6)	62 (22.0)	62 (21.9)	185 (21.8)
9 TO < 12	110 (39.0)	110 (39.0)	111 (39.2)	331 (39.1)
12 TO 14	102 (36.2)	102 (36.2)	101 (35.7)	305 (36.0)
SEX n (%)				
MALE	133 (47.2)	115 (40.8)	127 (44.9)	375 (44.3)
FEMALE	149 (52.8)	167 (59.2)	156 (55.1)	472 (55.7)
HEIGHT (cm)				
n	280	282	283	845
MEAN (SD)	146.71 (15.890)	146.23 (15.888)	145.06 (16.099)	146.00 (15.955)
MEDIAN	148.90	147.30	147.10	147.30
MIN, MAX	103.0, 188.5	104.0, 177.8	100.3, 208.3	100.3, 208.3
WEIGHT (kg)				
n	280	282	283	845
MEAN (SD)	42.48 (15.580)	43.37 (16.468)	42.76 (17.704)	42.87 (16.595)
MEDIAN	39.90	40.40	39.90	39.90
MIN, MAX	15.4, 112.0	11.3, 111.6	15.4, 114.8	11.3, 114.8
RACE n (%)				
WHITE	198 (70.2)	190 (67.4)	192 (67.8)	580 (68.5)
BLACK OR AFRICAN AMERICAN	21 (7.4)	35 (12.4)	22 (7.8)	78 (9.2)
ASIAN	47 (16.7)	46 (16.3)	55 (19.4)	148 (17.5)
FROM INDIA	8 (2.8)	8 (2.8)	10 (3.5)	26 (3.1)
OTHER	39 (13.8)	38 (13.5)	45 (15.9)	122 (14.4)
AMERICAN INDIAN OR ALASKA NATIVE	4 (1.4)	2 (0.7)	3 (1.1)	9 (1.1)
NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDER	2 (0.7)	1 (0.4)	0	3 (0.4)
OTHER	5 (1.8)	4 (1.4)	2 (0.7)	11 (1.3)
MULTIPLE	4 (1.4)	4 (1.4)	8 (2.8)	16 (1.9)
ETHNICITY n (%)				
HISPANIC OR LATINO	81 (28.7)	74 (26.2)	71 (25.1)	226 (26.7)
NOT HISPANIC OR LATINO	201 (71.3)	208 (73.8)	212 (74.9)	621 (73.3)
REGION n (%)				
EUROPE	24 (8.5)	19 (6.7)	27 (9.5)	70 (8.3)
UNITED STATES	258 (91.5)	263 (93.3)	256 (90.5)	777 (91.7)
DEGREE OF PARENTAL MYOPIA - MOTHER				
MILD	84 (29.8)	87 (30.9)	90 (31.8)	261 (30.8)
MODERATE	65 (23.0)	79 (28.0)	68 (24.0)	212 (25.0)
HIGH	24 (8.5)	23 (8.2)	27 (9.5)	74 (8.7)
UNKNOWN	18 (6.4)	13 (4.6)	6 (2.1)	37 (4.4)
DEGREE OF PARENTAL MYOPIA - FATHER				
MILD	73 (25.9)	67 (23.8)	73 (25.8)	213 (25.1)
MODERATE	44 (15.6)	62 (22.0)	60 (21.2)	166 (19.6)
HIGH	19 (6.7)	14 (5.0)	14 (4.9)	47 (5.5)
UNKNOWN	33 (11.7)	25 (8.9)	18 (6.4)	76 (9.0)
BASELINE SE [1]				
n	282	282	283	847
MEAN (SD)	-2.70 (1.267)	-2.73 (1.374)	-2.65 (1.286)	-2.69 (1.309)
MEDIAN	-2.63	-2.50	-2.44	-2.50
MIN, MAX	-5.9, -0.1	-5.8, -0.5	-6.0, -0.6	-6.0, -0.1
PLANNED BASELINE SE CATEGORY - N (%)				
0.50 D to 3.0 D	173 (61.3)	176 (62.4)	175 (61.8)	524 (61.9)
>3.0 D to 6.0 D	109 (38.7)	106 (37.6)	108 (38.2)	323 (38.1)
UNASSIGNED	0	0	0	0
ACTUAL BASELINE SE CATEGORY - N (%)				
0.50 D to 3.0 D	170 (60.3)	176 (62.4)	177 (62.5)	523 (61.7)
>3.0 D to 6.0 D	111 (39.4)	106 (37.6)	106 (37.5)	323 (38.1)
>6.0 D or <0.5 D	1 (0.4)	0	0	1 (0.1)
NUMBER OF PARTICIPANTS WITH BASELINE MYOPIA(SE) <0.75 D - N (%)	3 (1.1)	4 (1.4)	7 (2.5)	14 (1.7)
NUMBER OF PARTICIPANTS WITH BASELINE MYOPIA(SE) >= 1.0 D - N (%)	265 (94.0)	258 (91.5)	261 (92.2)	784 (92.6)

ANNUAL MYOPIA PROGRESSION RATE PRIOR TO BASELINE				
n	161	156	169	486
MEAN (SD)	-0.62 (1.281)	-0.58 (1.177)	-0.58 (1.738)	-0.59 (1.425)
MEDIAN	-0.45	-0.55	-0.53	-0.51
MIN, MAX	-9.4, 4.1	-3.6, 7.6	-10.6, 7.7	-10.6, 7.7
HISTORY OF MYOPIA PROGRESSION - N (%) [2][3]				
NUMBER WITH HISTORY n	106 (37.6)	102 (36.2)	108 (38.2)	316 (37.3)
AT LEAST 0.50 D PROGRESSION				
YES	24 (22.6)	30 (29.4)	29 (26.9)	83 (26.3)
NO	82 (77.4)	72 (70.6)	79 (73.1)	233 (73.7)
AT LEAST 1.0 D PROGRESSION				
YES	12 (11.3)	11 (10.8)	8 (7.4)	31 (9.8)
NO	94 (88.7)	91 (89.2)	100 (92.6)	285 (90.2)
AXIAL LENGTH (mm) [4]				
n	173	172	179	524
MEAN (SD)	24.49 (0.886)	24.51 (0.953)	24.33 (0.927)	24.44 (0.924)
MEDIAN	24.42	24.51	24.23	24.40
MIN, MAX	22.2, 27.7	21.0, 27.1	22.5, 27.4	21.0, 27.7
BEST-CORRECTED VISUAL ACUITY (BCVA) LETTER SCORE				
n	272	271	274	817
MEAN (SD)	83.88 (3.816)	83.96 (3.652)	83.48 (3.858)	83.77 (3.778)
MEDIAN	84.00	84.50	84.00	84.50
MIN, MAX	75.0, 98.5	75.5, 93.0	75.0, 94.0	75.0, 98.5
BINOCULAR-NEAR BCVA (LOGMAR)				
n	278	280	282	840
MEAN (SD)	0.03 (0.072)	0.02 (0.055)	0.03 (0.057)	0.03 (0.062)
MEDIAN	0.00	0.00	0.00	0.00
MIN, MAX	0.0, 0.4	0.0, 0.3	0.0, 0.3	0.0, 0.4
PUPIL DIAMETER (mm)				
n	280	281	283	844
MEAN (SD)	5.18 (1.220)	5.12 (1.208)	5.16 (1.313)	5.16 (1.247)
MEDIAN	5.00	5.00	5.00	5.00
MIN, MAX	2.5, 8.3	2.0, 8.5	0.5, 9.0	0.5, 9.0
IOP (mmHg)				
n	280	282	281	843
MEAN (SD)	15.40 (2.802)	15.77 (2.491)	15.70 (2.717)	15.62 (2.674)
MEDIAN	15.50	16.00	16.00	16.00
MIN, MAX	7.5, 21.0	7.0, 21.0	7.0, 21.0	7.0, 21.0
CORNEAL ENDOTHELIAL CELL COUNT [5]				
n	48	47	48	143
MEAN (SD)	3081.69 (214.321)	3084.08 (155.886)	3022.41 (196.273)	3062.58 (191.436)
MEDIAN	3101.75	3105.17	3008.92	3083.33
MIN, MAX	2492.3, 3633.2	2582.3, 3322.5	2543.0, 3464.8	2492.3, 3633.2
IRIS COLOR CATEGORY - N (%) [6]				
DARK	204 (72.3)	184 (65.2)	199 (70.3)	587 (69.3)
LIGHT	78 (27.7)	98 (34.8)	84 (29.7)	260 (30.7)
AVERAGE TIME OUTDOORS - n (%)				
ABOVE MEDIAN (1.74)	131 (46.5)	137 (48.6)	146 (51.6)	414 (48.9)
LESS THAN EQUAL TO MEDIAN (1.74)	143 (50.7)	142 (50.4)	130 (45.9)	415 (49.0)
AVERAGE TIME NEAR WORK - n (%)				
ABOVE MEDIAN (2.73)	136 (48.2)	138 (48.9)	140 (49.5)	414 (48.9)
LESS THAN EQUAL TO MEDIAN (2.73)	138 (48.9)	141 (50.0)	136 (48.1)	415 (49.0)

Ocular assessments are summarized using the average of the right and left eye.
[1] SE will be measured 3 times per eye and averaged per eye prior to taking the average over both eyes for analysis.
[2] Percentages based on the number of participants with recorded history within the 12 months prior to baseline.
[3] History of myopia progression is based on the absolute progression in the past 12 months prior to the baseline visit calculated as the difference in SE (average of both eyes) between the earliest recorded refraction history within the past 12 months and the baseline refraction.
[4] Axial length is measured 3 times per eye and averaged per eye prior to taking the average over both eyes for analysis. Axial length is measured at a subset of sites.
[5] Corneal endothelial cell count is measured 3 times per eye and averaged per eye prior to taking the average over both eyes for analysis. Corneal endothelial cell count is measured at a subset of sites.
[6] Iris color will be summarized at the participant level. Blue, green, grey and hazel eyes will be categorized as light. Eyes that are black, brown, or other will be categorized as dark. If a participant has different colored eyes, the participant will be classified as having dark eyes if either eye is dark.

The applicant discussed the imbalance observed at baseline and its impact on efficacy results regarding patient's sex, race (in particularly Asian, and non-Asian) and iris colour and stated that the imbalance are considered negligible. Demographics were collected based on Asian and further subdivided into Indian and non-Indian and subgroup analyses supports the primary analysis in FAS, which is taken into account. Demographic and baseline characteristics of the fast progressors subgroups 1 and 2 (1: progression -0.50 D/year or worse based on historical refraction; progression -0.75 D/year or worse based on historical refraction) are provided as a post hoc analysis. In general, demographic and baseline characteristics were similar in both fast progressor subgroups, and were similar to the overall population, with the exception of baseline SE which showed worse myopia in both subgroups than the

overall population. This appears plausible, assuming that those with a fast-progressing disease are already in a more advanced disease state.

Of note, in the fast progressor subgroup 1, a higher number of participants with light irises in the 0.1 mg/mL atropine group (32.6%) than the vehicle (29.0%) was included. This was not the case for the fast progressor subgroup 2 where proportions of subjects with light irises were rather balanced between groups.

Medical History

Regarding history of medical conditions, applicant states a similar frequency across groups with at least 1 medical history (the most frequently reported ocular medical history was retinal degeneration and the non-ocular medical history was seasonal allergy, followed by asthma, attention deficit, hyperactivity disorder and headache).

Prior and Concomitant Medications

Table 10: SAF – ocular concomitant medications through month 24

ATC level 1 term ATC level 2 term Preferred term	Vehicle (N=282) n (%)	SYD-101 0.01% (N=282) n (%)	SYD-101 0.03% (N=283) n (%)	Total (N=847) n (%)
Total number of concomitant medications	32	19	30	81
Number of participants with at least one concomitant medication	24 (8.5)	17 (6.0)	26 (9.2)	67 (7.9)
Sensory organs	24 (8.5)	17 (6.0)	26 (9.2)	67 (7.9)
Ophthalmologicals	24 (8.5)	17 (6.0)	26 (9.2)	67 (7.9)
Aciclovir	1 (0.4)	1 (0.4)	0	2 (0.2)

Artificial tears [umbrella term]	4 (1.4)	0	8 (2.8)	12 (1.4)
Bepotastine besilate	0	0	1 (0.4)	1 (0.1)
Betamethasone sodium phosphate;neomycin sulfate	0	0	1 (0.4)	1 (0.1)
Carmellose	1 (0.4)	0	0	1 (0.1)
Carmellose sodium;glycerol	0	0	1 (0.4)	1 (0.1)
Carmellose sodium;glycerol;polysorbate 80	1 (0.4)	0	0	1 (0.1)
Cetirizine	0	0	1 (0.4)	1 (0.1)
Ciprofloxacin	1 (0.4)	0	0	1 (0.1)
Cyclopentolate hydrochloride	1 (0.4)	1 (0.4)	0	2 (0.2)
Dexamethasone	1 (0.4)	0	0	1 (0.1)
Dexamethasone;neomycin sulfate;polymyxin b sulfate	1 (0.4)	0	0	1 (0.1)
Dexamethasone;tobramycin	0	1 (0.4)	0	1 (0.1)
Dextran 70; macrogol; povidone; tetryzoline hydrochloride	1 (0.4)	0	0	1 (0.1)
Emedastine fumarate	0	0	1 (0.4)	1 (0.1)
Erythromycin	1 (0.4)	4 (1.4)	1 (0.4)	6 (0.7)
Fluorescein sodium;oxybuprocaine hydrochloride	1 (0.4)	1 (0.4)	0	2 (0.2)
Fluorometholone	0	0	1 (0.4)	1 (0.1)
Gentamicin sulfate	1 (0.4)	0	0	1(0.1)
Glycerol;propylene glycol	0	1 (0.4)	0	1 (0.1)
Homatropine	1 (0.4)	0	0	1 (0.1)
Ketotifen	0	1 (0.4)	0	1 (0.1)
Ketotifen fumarate	2 (0.7)	0	2 (0.7)	4 (0.5)
Loteprednol etabonate;tobramycin	1 (0.4)	0	0	1 (0.1)
Loteprednol;tobramycin	0	0	1 (0.4)	1 (0.1)
Macrogol	2 (0.7)	0	0	2 (0.2)
Macrogol 400;propylene glycol	1 (0.4)	1 (0.4)	0	2 (0.2)
Moxifloxacin	1 (0.4)	1 (0.4)	1 (0.4)	3 (0.4)
Neomycin	0	0	1 (0.4)	1 (0.1)
Ofloxacin	1 (0.4)	0	0	1 (0.1)
Olopatadine	1 (0.4)	0	0	1 (0.1)
Olopatadine hydrochloride	2 (0.7)	4 (1.4)	5 (1.8)	11 (1.3)
Polymyxin b sulfate;trimethoprim	1 (0.4)	0	0	1 (0.1)
Polymyxin b;trimethoprim	2 (0.7)	0	0	2 (0.2)
Polyvinyl alcohol	0	1 (0.4)	2 (0.7)	3 (0.4)
Polyvinyl alcohol;povidone	0	1 (0.4)	0	1 (0.1)
Propylene glycol	0	0	1 (0.4)	1 (0.1)
Tetryzoline hydrochloride	0	1 (0.4)	0	1 (0.1)
Tobramycin	1 (0.4)	0	0	1 (0.1)

Note: A concomitant medication was any medication taken on or after the date of first dose of study treatment, including those that were initiated prior to the study. Within each level of participant summarization, a participant was counted once if the participant reported one or more medications.

Concomitant medications were coded with the WHO Drug dictionary dated March 2023.

Concomitant medications were summarized based on treatment received at the time when the concomitant medication was taken.

Non-Ocular Prior and Concomitant Medications

The application describes a total of 27 (3.2%) patients (9 (3.2%) in Vehicle group, 12 (4.3%) in SYD-101 0.01% and 6 (2.1%) in SYD-101 0.03% group) reported with at least 1 non-ocular prior medication. The most frequently reported medications were drugs for obstructive airway diseases and analgesics (each 4 (0.5%) participants overall).

Numbers analysed

The FAS and Safety Set were identical for all treatment groups and included a total of 847 participants; participants were excluded from the PPS if they had a major deviation (N=28) or had no post-baseline efficacy assessment (N=46) (Table 11).

A total of 291 and 225 participants were included in the fast progressor subgroups 1 and 2, respectively. Treatment compliance was above 97% in patients of 12-14 years in each groups (vehicle, SYD-101 0.01%) without evidence of a decrease over time in the study.

Table 11: Analysis sets - all randomised participants

	Vehicle (N=283) n (%)	SYD-101 0.01% (N=284) n (%)	SYD-101 0.03% (N=285) n (%)	Total (N=852) n (%)
Total number of participants [1]				
Randomized [2]	283 (100.0)	284 (100.0)	285 (100.0)	852 (100.0)
Full-analysis set [2]	282 (99.6)	282 (99.3)	283 (99.3)	847 (99.4)
Safety set [3]	282 (99.6)	282 (99.3)	283 (99.3)	847 (99.4)
Per protocol set – 24 months [3]	258 (91.2)	256 (90.1)	259 (90.9)	773 (90.7)
Fast progressor subgroup 1 [2] [4]	93 (32.9)	95 (33.5)	103 (36.1)	291 (34.2)
Fast progressor subgroup 2 [2] [5]	71 (25.1)	76 (26.8)	78 (27.4)	225 (26.4)

[1] Percentages are based on the number of participants randomized.

[2] Summarized by treatment assigned at original randomization and received at least 1 drop of study drug.

[3] Summarized by actual treatment received and received any amount of study drug.

[4] Summarized by all participants in FAS with a refractive history of progression -0.5 D/year or worse for any of the 3 history time intervals.

[5] Summarized by all participants in FAS with a refractive history of progression -0.75 D/year or worse for any of the 3 history time intervals.

Outcomes and estimation

Primary Efficacy Endpoint

A summary of analysis of annual progression rate of myopia at Month 36 is presented in Table 12.

Table 12: FAS – annual progression rate of myopia at month 36

Annual myopic progression rate (D/yr)	Vehicle (N=282)	STN1012701 0.1 mg/mL (N=282)
Baseline to Month 24		
LS Mean Rate	-0.44	-0.31
95% Confidence Interval [1]	(-0.50, -0.38)	(-0.37, -0.25)
Difference to Vehicle		
Difference in LS Mean Rates		0.132
95% Confidence Interval [1]		(0.061, 0.204)
P-Value [1]		0.0003
Baseline to Month 36		
LS Mean Rate	-0.38	-0.30
95% Confidence Interval [1]	(-0.42, -0.34)	(-0.34, -0.27)
Difference to Vehicle		
LS mean rates of the difference to Vehicle (% difference in slowing myopia progression)		0.079
95% Confidence Interval [1]		(0.038, 0.120)
p-Value [1]		0.0002

Note: Annual myopic progression rate is defined as the negative change in SE (averaged over both eyes) from baseline divided by the number of days since baseline * 365.25. Intermittent missing observations were multiply imputed assuming missing at random (MAR). Observations after use of escape/prohibited medications or treatments were censored for the Month 24 analysis or were multiply imputed assuming missing not at random (MNAR) using a sequential vehicle-based pattern regression for the Month 36 analysis. Observations after treatment or study discontinuation due to a related AE were multiply imputed assuming MNAR. All other observations after treatment or study discontinuation were multiply imputed assuming MAR. Invalid SE were analysed as observed.
[1] The 50 imputations are analysed using a REML-based Mixed Models Repeated Measures (MMRM) model with fixed effects for treatment group, baseline age category, categorical visit, visit by treatment interaction, with baseline SE as a covariate and compound symmetry covariance for the Month 24 analysis, or Unstructured Covariance for the Month 36 analysis. The results of these 50 analyses are combined to produce the LS means, difference of LS means, 95% CIs, and P-value.

Sensitivity Analysis

Results of the sensitivity analysis on the FAS applying multiple imputation to STN1012701 observations after receipt of a prohibited therapy or escape medication assuming missing not at random are summarised in Table 13, at the request of the CHMP.

Table 13: FAS – sensitivity analysis of the annual progression rate of myopia at month 36

Annual myopic progression rate (D/yr)	Vehicle (N=282)	STN1012701 0.1 mg/mL (N=282)
Baseline to Month 36		
LS Mean Rate	-0.38	-0.31
95% Confidence Interval [1]	(-0.42, -0.34)	(-0.35, -0.27)
Difference to Vehicle		
Difference in LS Mean Rates		0.073
95% Confidence Interval [1]		(0.032, 0.114)
p-Value [1]		0.0005

Note: Annual myopic progression rate is defined as the negative change in SE (averaged over both eyes) from baseline divided by the number of days since baseline * 365.25. Intermittent missing observations were multiply imputed assuming missing at random (MAR). Missing data after participant study discontinuation or escape/prohibited medication or treatment was multiply imputed assuming missing not at random (MNAR) using a sequential vehicle-based pattern regression. Participants who terminated study treatment early and who did not receive escape/prohibited medications or treatments but who continued study follow-up were included based on observed data. Invalid SE was analysed as observed.
[1] The 50 imputations are analysed using a REML-based Mixed Models Repeated Measures (MMRM) model with fixed effects for treatment group, baseline age category, categorical visit, visit by treatment interaction, with baseline SE as a covariate and Unstructured Covariance. The results of these 50 analyses are combined to produce the LS means, difference of LS means, 95% CIs, and P-value.

Subgroups Analyses

Age

Table 14: FAS – summary of the difference in annual myopic progression rate at month 24 by age

Annual myopic progression rate (D/yr)	Vehicle	SYD-101 0.01%	SYD-101 0.03%
3 to <6 years - N	9	9	9
Difference to Vehicle (LS mean rates)		0.594	0.362
95% Confidence Interval [1]		(0.040, 1.148)	(-0.195, 0.920)
Nominal p-value [1]		0.0354	0.2023
6 to <9 years - N	61	61	62
Difference to Vehicle (LS mean rates)		0.243	0.177
95% Confidence Interval [1]		(0.074, 0.412)	(0.007, 0.347)
Nominal p-value [1]		0.0048	0.0415
9 to <12 years - N	111	110	111
Difference to Vehicle (LS mean rates)		0.131	0.127
95% Confidence Interval [1]		(0.013, 0.249)	(0.010, 0.244)
Nominal p-value [1]		0.0290	0.0335
12 to 14 years - N	101	102	101
Difference to Vehicle (LS mean rates)		0.027	0.060
95% Confidence Interval [1]		(-0.073, 0.127)	(-0.040, 0.161)
Nominal p-value [1]		0.5998	0.2397
6 to 14 years – N	273	273	274
Difference to Vehicle (LS mean rates)		0.117	0.113
95% Confidence Interval [1]		(0.045, 0.188)	(0.041, 0.184)
Nominal p-value [1]		0.0014	0.0019
3 to <12 years – N	181	180	182
Difference to Vehicle (LS mean rates)		0.192	0.155
95% Confidence Interval [1]		(0.096, 0.288)	(0.059, 0.251)
Nominal p-value [1]		0.0001	0.0016

Annual myopic progression rate is defined as the negative change in SE (averaged over both eyes) from baseline divided by the number of days since baseline * 365.25. Intermittent missing observations were multiply imputed assuming missing at random (MAR). Observations after use of escape/prohibited medications or treatments were censored. Observations after treatment or study discontinuation due to a related AE were multiply imputed assuming missing not at random using a sequential vehicle-based pattern regression. All other observations after treatment or study discontinuation were multiply imputed assuming MAR. Invalid SE was analysed as observed.

[1] The 50 imputations were analysed using a REML-based Mixed Models Repeated Measures (MMRM) model with fixed effects for treatment group, baseline age category, categorical visit, visit by treatment interaction, with baseline SE as a covariate and Compound Symmetry Covariance. The results of these 50 analyses were combined to produce the difference of LS means, 95% CIs and p-value.

Table 15: FAS – summary of annual progression rate of children aged 3 to less than 6 years old over 36 months

APR (D/YR)	VEHICLE (N=9)	STN1012701 0.1 MG/ML (N=9)
BASELINE TO 24 MONTHS		
LS MEAN (CI)	-0.899 (-1.29, -0.51)	-0.305 (-0.70, 0.09)
DIFFERENCE TO VEHICLE (%)		0.594 (66%)
CI		(0.040, 1.148)
P-VALUE		0.0354
BASELINE TO 36 MONTHS		
LS MEAN (CI)	-0.726 (-0.99, -0.47)	-0.301 (-0.56, 0.05)
DIFFERENCE TO VEHICLE (%)		0.424 (58%)
CI		(0.059, 0.789)
P-VALUE		0.0227

Table 16: FAS – summary of annual progression rate of children aged 12 to 14 years old over 36 months

APR (D/YR)	VEHICLE (N=101)	STN1012701 0.1 MG/ML (N=102)
BASELINE TO 24 MONTHS		
LS MEAN (CI)	-0.185 (-0.26, -0.11)	-0.158 (-0.23, 0.09)
DIFFERENCE TO VEHICLE (%)		0.027 (15%)
CI		(-0.073, 0.127)
P-VALUE		0.5998
BASELINE TO 24 MONTHS		
LS MEAN (CI)	-0.163 (-0.20, -0.12)	-0.158 (-0.20, -0.12)
DIFFERENCE TO VEHICLE (%)		0.005 (3%)
CI		(-0.054, 0.064)
P-VALUE		0.8665

Baseline SE

Table 17: FAS – summary of the difference in annual myopic progression rate at month 24 by baseline spherical equivalent

Annual myopic progression rate (D/yr)	Vehicle	SYD-101 0.01%
From -0.5 D to -3.0 D - N	173	176
Difference to Vehicle (LS mean rates)		0.174
95% Confidence Interval [1]		(0.085, 0.262)
Nominal p-value [1]		0.0001
From worse than -3.0 D to -6.0 D - N	109	106
Difference to Vehicle (LS mean rates)		0.062
95% Confidence Interval [1]		(-0.058, 0.183)
Nominal p-value [1]		0.3110
-1.0 D or worse - N	265	258
Difference to Vehicle (LS mean rates)		0.128
95% Confidence Interval [1]		(0.053, 0.202)
Nominal p-value [1]		0.0008

Annual myopic progression rate is defined as the negative change in SE (averaged over both eyes) from baseline divided by the number of days since baseline * 365.25. Intermittent missing observations were multiply imputed assuming missing at random (MAR). Observations after use of escape/prohibited medications or treatments were censored. Observations after treatment or study discontinuation due to a related AE were multiply imputed assuming missing not at random using a sequential vehicle-based pattern regression. All other observations after treatment or study discontinuation were multiply imputed assuming MAR. Invalid SE was analysed as observed.

[1] The 50 imputations were analysed using a REML-based Mixed Models Repeated Measures (MMRM) model with fixed effects for treatment group, baseline age category, categorical visit, visit by treatment interaction, with baseline SE as a covariate and Compound Symmetry Covariance. The results of these 50 analyses were combined to produce the difference of LS means and 95% CIs, and p-value.

History of myopic progression

No marked difference between the SYD-101 groups and the Vehicle group was observed in the subgroups of participants with a history of myopic progression of -0.5 D or worse and -1.0 D or worse. Of note, the sample size of these subgroups was low (ranging from 8 to 30 per group).

Among participants with a history of progression of no more than -0.5 D, a difference was noted between the SYD-101 0.01% group and the Vehicle group (difference of 0.197 D, nominal p-value of 0.0043). A difference to Vehicle was also noted in both SYD-101 groups in the subgroup of participants without any recorded history of myopia progression: 0.095 D difference in favour of SYD-101 0.01% (nominal p-value of 0.0393).

Parental myopic history

No marked difference between the SYD-101 groups and the Vehicle group was observed in the subgroup of participants whose parents had no myopia, whereas a difference was observed in participants who had at least one myopic parent: 0.134 D difference in favour of SYD-101 0.01% (nominal p-value of 0.0018).

Iris colour

No marked difference between the SYD-101 groups and the Vehicle group was observed in the subgroup of participants who had light iris, whereas a difference was observed in participants with dark iris: 0.145 D difference in favour of SYD-101 0.01% (nominal p-value of 0.0013).

Region

No marked difference between the SYD-101 groups and the Vehicle group was observed in the subgroup of European participants, whereas a difference was observed in participants from the US: 0.135 D difference in favour of SYD-101 0.01% (nominal p-value of 0.0004). However, participants included in Europe represented only 8.3% of the overall population.

Race

No marked difference between the SYD-101 groups and the Vehicle group was observed in the subgroups of Asian and Indian participants, whereas a difference was observed in non-Asian and White participants. In non-Asian participants, a 0.137 D difference in favour of SYD-101 0.01% (nominal p-value of 0.0006) were observed. In White participants, a 0.145 D difference in favour of SYD-101 0.01% (nominal p-value of 0.0008) were observed. However, the numbers of Asian and Indian participants were low (ranging from 8 to 45 per group).

Sex

Both in males and females, a difference between the SYD-101 and the Vehicle groups was observed. The results were the following: in males, the difference between the Vehicle and SYD-101 0.01% groups was 0.126 D (nominal p-value of 0.0183). In females, the difference between the Vehicle and SYD-101 0.01% groups was 0.137 D (nominal p-value of 0.0063).

Average time outdoors

These subgroups were defined based on the median time spent outdoors in the overall population. In participants who spent on average the median time identified for the group or less outdoors, a difference in the annual myopic progression rate was observed between the SYD-101 and the Vehicle groups: a 0.119 D difference in favour of SYD-101 0.01% (nominal p-value of 0.0227) were observed. In participants who spent on average more than the median time identified for the group outdoors, a difference was observed only between the Vehicle group and the SYD-101 0.01% group (0.137 D, nominal p-value of 0.0088).

Average time near work

These subgroups were defined based on the median time spent doing near work in the overall population. In participants who spent on average the median time identified for the group or less doing near work, a difference in the annual myopic progression rate was observed between the SYD-101 and the Vehicle groups: a 0.134 D difference in favour of SYD-101 0.01% (nominal p-value of 0.0095) were observed. In participants who spent on average more than the median time identified for the group doing near work, a difference was observed between the SYD-101 and the Vehicle groups: a 0.114 D difference in favour of SYD-101 0.01% (nominal p-value of 0.0318) were observed.

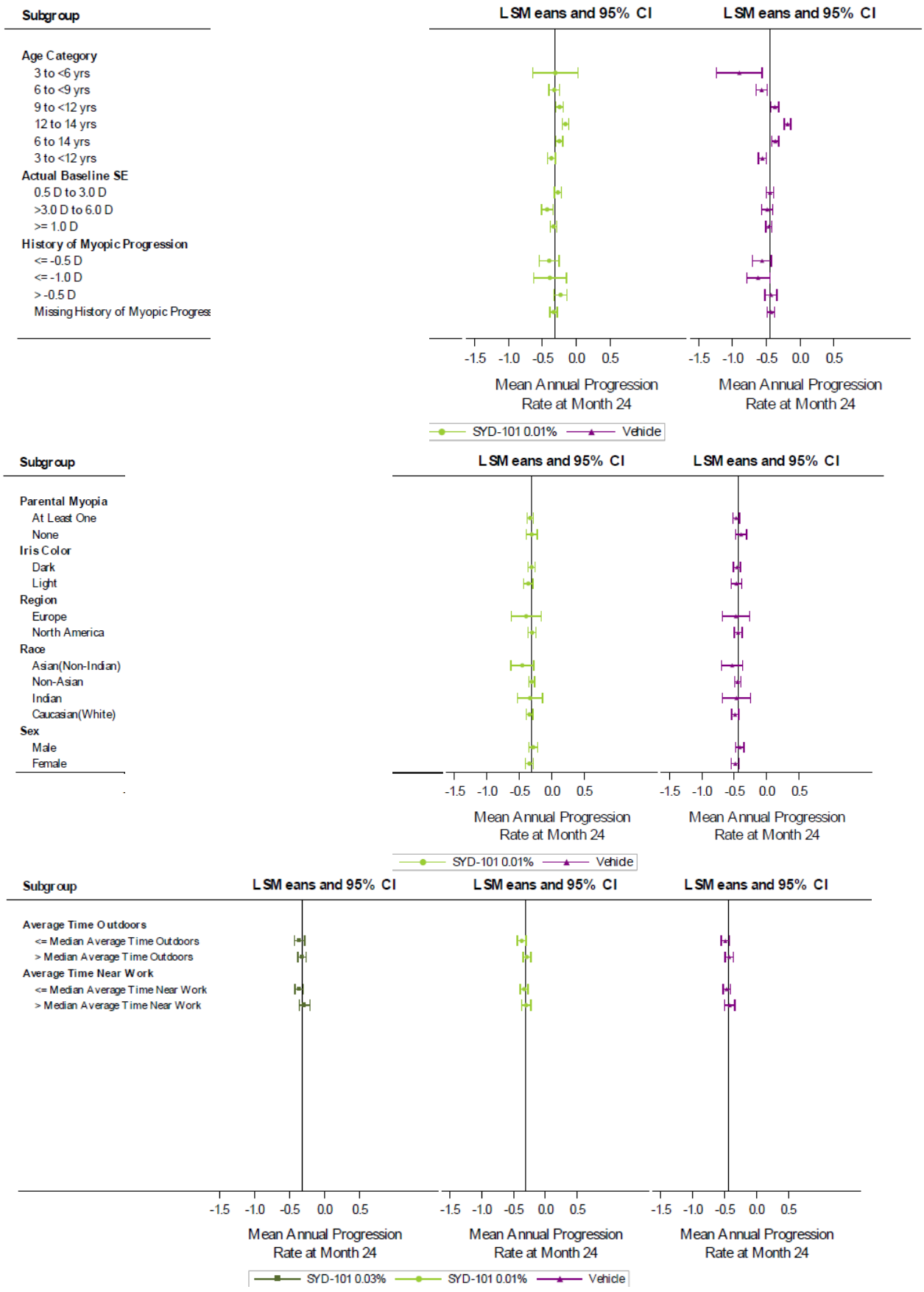


Figure 6: FAS – forest type plot of mean annual progression rate at month 24 by treatment and subgroups

According to the originally presented subgroup analyses for the individual factors age and myopia severity (baseline SE) a higher treatment effect was observed for subjects with lower age and for subjects with mild myopia. The intention behind the request on subgroup analysis in interactions of age and severity groups was to understand whether the difference in the treatment effect between patients with mild and moderate myopia might be explained by different age distributions. If so, then we should see a similar treatment effect for patients with mild and moderate myopia when restricting to a small age interval. However, the provided subgroup analyses do not allow for any conclusions of this type as the investigated age intervals are too broad. It is understood that the investigation of smaller age intervals is not feasible due to small sample numbers. In summary, the applicant has provided the requested analyses but they did not provide the expected insight.

Key Secondary Efficacy Endpoint

A summary of the analysis of the proportion of participants with confirmed myopia progression worse than -0.75 D at Month 36 is presented in Table 18.

Table 18: FAS - confirmed myopia progression at month 36

Confirmed progression	Vehicle (N=282)	STN1012701 0.1 mg/mL (N=282)
Participants with progression at or before Month 24 – n (%) [1]	100.7 (35.72)	72.0 (25.55)
95% CI	(29.8, 41.6)	(20.2, 30.9)
Difference to vehicle [2]		-10.0
95% CI of difference		(-17.49, -2.46)
P-value		0.0181
Participants with progression at or before Month 36 – n (%) [1]	138.9 (49.24)	111.4 (39.50)
95% CI	(43.0, 55.5)	(33.4, 45.6)
Difference to vehicle [2]		-9.6
95% CI of difference		(-17.91, -1.26)
P-value		0.0459

Note: Confirmed myopia progression was defined as a progression worse than -0.75 D (averaged over both eyes) at or before 24/36 months. Intermittent missing observations were multiply imputed assuming missing at random (MAR). Observations after use of escape/prohibited medications or treatments were imputed as having progressed. Observations after treatment or study discontinuation due to a related AE were multiply imputed assuming missing not at random using a sequential vehicle-based pattern regression for the Month 24 analysis, or as having progressed for the Month 36 analysis. All other observations after treatment or study discontinuation were multiply imputed assuming MAR. Invalid SE values were analysed as observed.

[1] The number of participants with progression are based on the averages from the 50 imputations. The proportion of participants with progression of -0.75 D or worse and ASE [sqrt (p(1-p)/n)] was calculated by imputation and the values combined to present the pooled estimate and corresponding 95% CI then converted to percentages as p*100.

[2] The Mantel-Haenszel common overall risk difference and 95% CI for that risk difference and the p-value based on Cochran-Mantel-Haenszel test with baseline SE and age category were calculated for each imputation and combined for the 50 imputations. Risk difference and 95% CI presented as a percentage.

Sensitivity analysis

Table 19: FAS – sensitivity analysis of confirmed myopia progression at month 36

Confirmed progression	Vehicle (N=282)	STN1012701 0.1 mg/mL (N=282)
Participants with progression at or before Month 36 – n (%) [1]	139.7 (49.55)	113.8 (40.37)
Difference to vehicle [2]		-9.1
95% CI of difference		(-17.11, -1.01)
P-value		0.0533

Note: Confirmed myopia progression is defined as a progression > 0.75 diopters (averaged over both eyes) at or before 36 months. Intermittent missing observations were multiply imputed assuming missing at random (MAR). Missing data after participant study discontinuation or escape/prohibited medication or treatment was multiply imputed assuming missing not at random (MNAR) using a sequential vehicle-based pattern regression. Participants who terminated study treatment early and who did not receive escape/prohibited medications or treatments but who continued study follow-up were included based on observed data. Invalid SE was analysed as observed.
[1] The number of participants with progression are based on the averages from the 50 imputations. The proportion of participants with > 0.75 D progression and ASE [sqrt (p(1-p)/n)] will be calculated by imputation and the values combined to present the pooled estimate and corresponding 95% CI then converted to percentages as p*100.
[2] The Mantel-Haenszel common overall risk difference and 95% CI for that risk difference and the p-value based on Cochran-Mantel-Haenszel test with baseline SE and age category will be calculated for each imputation and combined for the 50 imputations. Risk difference and 95% CI presented as a percentage.

Subgroups Analysis

Age

Table 20: FAS – summary of the difference in confirmed myopia progression at month 24 by age

Confirmed myopia progression (%)	Vehicle	SYD-101 0.01%
3 to <6 years - N	9	9
Difference to Vehicle		-38.2
95% Confidence Interval		(-84.67, 8.30)
Nominal p-value		0.2822
6 to <9 years - N	61	61
Difference to Vehicle		-24.2
95% Confidence Interval		(-42.59, -5.89)
Nominal p-value		0.0222
9 to <12 years - N	111	110
Difference to Vehicle		-9.6
95% Confidence Interval		(-22.29, 3.14)
Nominal p-value		0.2798
12 to 14 years - N	101	102
Difference to Vehicle		0.6
95% Confidence Interval		(-9.43, 10.64)
Nominal p-value		0.5764
6 to 14 years - N	273	273
Difference to Vehicle		-9.1
95% Confidence Interval		(-16.66, -1.47)
Nominal p-value		0.0370
3 to <12 years - N	181	180
Difference to Vehicle		-15.9
95% Confidence Interval		(-26.18, -5.69)
Nominal p-value		0.0053

Confirmed myopia progression was defined as a progression worse than -0.75 D (averaged over both eyes) at or before 24 months. Intermittent missing observations were multiply imputed assuming missing at random (MAR). Observations after use of escape/prohibited medications or treatments were imputed as having progressed. Observations after treatment or study discontinuation due to a related AE were multiply imputed assuming missing not at random using a sequential vehicle-based pattern regression. All other observations after treatment or study discontinuation were multiply imputed assuming MAR. Invalid SE values were analysed as observed.

The Mantel-Haenszel common overall risk difference and 95% CI for that risk difference based on Cochran-Mantel-Haenszel test with baseline SE and age category were calculated for each imputation and combined for the 50 imputations. Risk difference and 95% CI presented as a percentage.

Baseline SE

Table 21: FAS – summary of the difference in confirmed myopia progression at month 24 by baseline spherical equivalent

Confirmed myopia progression (%)	Vehicle	SYD-101 0.01%
From -0.5 D to -3.0 D - N	173	176
Difference to Vehicle		-13.2
95% Confidence Interval		(-22.50, -3.83)
Nominal p-value		0.0117
From worse than -3.0 D to -6.0 D - N	109	106
Difference to Vehicle		-4.8
95% Confidence Interval		(-17.61, 8.03)
Nominal p-value		0.9316
-1.0 D or worse - N	265	258
Difference to Vehicle		-8.4
95% Confidence Interval		(-16.32, -0.49)
Nominal p-value		0.0706

Confirmed myopia progression was defined as a progression worse than -0.75 D (averaged over both eyes) at or before 24 months. Intermittent missing observations were multiply imputed assuming missing at random (MAR). Observations after use of escape/prohibited medications or treatments were imputed as having progressed. Observations after treatment or study discontinuation due to a related AE were multiply imputed assuming missing not at random using a sequential vehicle-based pattern regression. All other observations after treatment or study discontinuation were multiply imputed assuming MAR. Invalid SE values were analysed as observed.

The Mantel-Haenszel common overall risk difference and 95% CI for that risk difference based on Cochran-Mantel-Haenszel test with baseline SE and age category were calculated for each imputation and combined for the 50 imputations. Risk difference and 95% CI presented as a percentage.

History of myopic progression

No relevant trends could be observed in relationship with the history of myopic progression. Isolated differences (nominal p-values < 0.05) were observed in some subgroups without a clear pattern.

Parental myopic history

No marked difference between the SYD-101 groups and the Vehicle group was observed in the subgroup of participants whose parents had no myopia, whereas a difference was observed in participants who had at least 1 myopic parent: the proportion of participants with confirmed myopia progression was 10.8% lower in the SYD-101 0.01% group than the Vehicle group (nominal p-value of 0.0253).

Iris colour

No relevant trends could be observed in relationship with the iris colour.

Region

No marked difference between the SYD-101 groups and the Vehicle group was observed in the subgroup of European participants, whereas a difference was observed in participants from the US: the proportion of participants with confirmed myopia progression was 10.2% lower in the SYD-101 0.01% group than the Vehicle group (nominal p-value of 0.0211). However, participants included in Europe represented only 8.3% of the overall population.

Race
No marked difference between the SYD-101 groups and the Vehicle group was observed in the subgroups of Asian and Indian participants, whereas a numerical difference was observed in non-Asian and White participants. In non-Asian participants, the proportion of participants with confirmed myopia progression was 11.1% lower in the SYD-101 0.01% than the Vehicle group (nominal p-value of 0.0171). In White participant, the proportion of participants with confirmed myopia progression was 10.9% lower in the SYD-101 0.01% than the Vehicle group (nominal p-value of 0.0350). However, the numbers of Asian and Indian participants were low (ranging from 8 to 45 per group).

Sex
No relevant trends could be observed in relationship with the gender.

Average time outdoors
These subgroups were defined based on the median time spent outdoors in the overall population. No relevant trends could be observed in relationship with the amount of time spent outdoors.

Average time near work
These subgroups were defined based on the median time spent doing near work in the overall population. No relevant trends could be observed in relationship with the amount of time spent outdoors.

Other Secondary Efficacy Endpoints

Categorised Myopic Progression

A summary of analysis of myopia progression based on different thresholds through Month 24 is presented in Table 22.

At Month 24, the proportion of participants with annual myopia progression rate no worse than -0.50 D/year was 70.23% in Vehicle group and 82.00% in SYD-101 0.01% group. The proportion of participants with annual myopia progression rate no worse than -0.50 D/year was 11.60% (95% CI: 4.40, 18.80) higher in the SYD-101 0.01% than the Vehicle group (p-value of 0.0034).

At Month 24, the proportion of participants with annual myopia progression rate no worse than -0.25 D/year was 41.79% in Vehicle group and 55.24% in SYD-101 0.01% group. The proportion of participants with annual myopia progression rate no worse than -0.25 D/year was 13.31% (95% CI: 4.97, 21.64) higher in the SYD-101 0.01% than the Vehicle group (p-value of 0.0039).

At Month 24, the proportion of participants with an increase in myopia worse than -0.5 D was 57.46% in Vehicle group, 44.72% in SYD-101 0.01% group. The proportion of participants with an increase in myopia worse than -0.5 D was 12.60% (95% CI: 4.24, 20.96) lower in the SYD-101 0.01% than the Vehicle group (p-value of 0.0066).

The secondary endpoints reached statistical significance, as each comparison yielded a p-value < 0.045.

Similar results were observed in the PPS (Table 23).

Table 22: FAS – summary of analysis of participants by categorised myopic progression

	Vehicle (N=282)	SYD-101 0.01% (N=282)
At or before Month 24		
Participants assessed - n	282	282
Annual progression rate no worse than -0.50 D/yr – n (%) [1]	198.0 (70.23)	231.2 (82.00)
Difference to Vehicle [2]		
Difference		11.60
95% CI percentage with progression		(4.40,18.80)
P-value		0.0034
Participants assessed - n	282	282
Annual progression rate no worse than -0.25 D/yr – n (%) [1]	117.8 (41.79)	155.8 (55.24)
Difference to Vehicle [2]		
Difference		13.31
95% CI percentage with progression		(4.97,21.64)
P-value		0.0039
Participants assessed - n	282	282
Increase in myopia worse than -0.50 D – n (%) [1]	162.0 (57.46)	126.1 (44.72)
Difference to Vehicle [2]		
Difference		-12.60
95% CI percentage with progression		(-20.96, -4.24)
P-value		0.0066

Note: Intermittent missing observations were multiply imputed assuming missing at random (MAR). Observations after use of escape/prohibited medications or treatments were multiply imputed assuming MAR.

Observations after treatment or study discontinuation due to a related AE were multiply imputed as missing not at random (MNAR) using a sequential vehicle-based pattern regression. All other observations after treatment or study discontinuation were multiply imputed assuming MAR. Invalid SE values were analyzed as observed.

[1] The number and proportion of participants with progression are based on the averages from the 50 imputations.

[2] The Mantel-Haenszel common overall risk difference and 95% CI for that risk difference and the p-value based on Cochran-Mantel-Haenszel test with baseline SE and age category were calculated for each imputation and combined for the 50 imputations. Risk difference and 95% CI presented as a percentage.

Table 23: PPS – summary of analysis of participants by categorised myopic progression

	Vehicle (N=258)	SYD-101 0.01% (N=256)
AT OR BEFORE MONTH 24		
PARTICIPANTS ASSESSED - n	258	256
ANNUAL PROGRESSION RATE <=0.50D/yr - n (%) [1]	183.9(71.26)	209.7(81.92)
DIFFERENCE TO VEHICLE [2]		
DIFFERENCE		10.63
95% CONFIDENCE INTERVAL		(3.36,17.91)
P-VALUE		0.0086
PARTICIPANTS ASSESSED - n	258	256
ANNUAL PROGRESSION RATE <=0.25D/yr - n (%) [1]	111.8(43.32)	142.8(55.77)
DIFFERENCE TO VEHICLE [2]		
DIFFERENCE		12.41
95% CONFIDENCE INTERVAL		(3.84,20.98)
P-VALUE		0.0097
PARTICIPANTS ASSESSED - n	258	256
INCREASE IN MYOPIA >0.50D - n (%) [1]	144.1(55.86)	113.2(44.23)
DIFFERENCE TO VEHICLE [2]		
DIFFERENCE		-11.61
95% CONFIDENCE INTERVAL		(-20.22,-3.00)
P-VALUE		0.0167

Note: Intermittent missing observations will be multiply imputed assuming missing at random (MAR). Observations after use of escape/prohibited medications or treatments will be multiply imputed assuming MAR. Observations after treatment or study discontinuation due to a related AE will be multiply imputed assuming missing not at random (MNAR) using a sequential vehicle-based pattern regression. All other observations after treatment or study discontinuation will be multiply imputed assuming MAR. IntermittentInvalid SE values will be multiply imputed assuming MAR.

[1] The number and proportion of participants with progression are based on the averages from the 50 imputations.

[2] The Mantel-Haenszel common overall risk difference in percentage and 95% CI for that risk difference and the p-value based on Cochran-Mantel-Haenszel test with baseline SE and age category will be calculated for each imputation and combined for the 50 imputations.

Time to Myopic Progression

A summary of time to myopic progression through Month 24 is presented in Table 24, and the Kaplan-Meier estimates are schematised in Figure 7.

The median time to progression of myopia could not be calculated in any treatment group. A quarter of the sample had myopic progression worse than -0.75 D from baseline after 549 days in the Vehicle group and 735 days in the SYD-101 0.01% group. The Kaplan-Meier analysis showed a separation of the Vehicle and each SYD-101 group curves from Month 12 to Month 24. The p values were 0.006 for the comparison of the SYD-101 0.01% group versus the Vehicle group at Month 24. This secondary endpoint reached statistical significance, as each comparison yielded a p-value <0.045.

Similar results were observed in the PPS (Table 25).

Table 24: FAS – summary of analysis of time to myopic progression through month 24

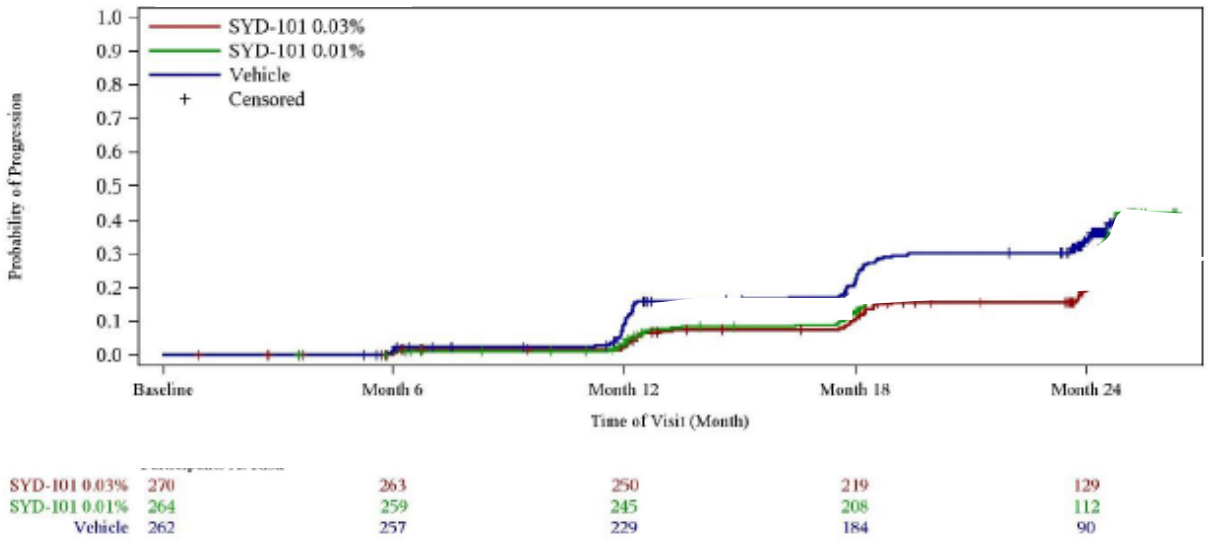
	Vehicle (N=282) n (%)	SYD-101 0.01% (N=282) n (%)
Number of participants assessed for time to progression	262	264
Number of events	84 (32.1)	64 (24.2)
Number censored	178 (67.9)	200 (75.8)
P-value (log-rank test)		0.006
Time to progression (days) (95% CI)		
25th percentile	549.0 (539.00, 588.00)	735.0 (568.00, 743.00)
Median	NC	NC (751.00, NC)
75th percentile	NC	NC

NC: not calculable

Note: Each dose of SYD-101 was compared to Vehicle for time to progression of myopia using the log-rank test stratified by the randomization stratification factors.

Progression was defined as an SE measurement that represents a worsening of -0.75 D or more from baseline. The quartiles and their 95% CI were obtained from Kaplan-Meier (KM) estimates.

Participants who did not experience myopic progression through or at 24 months or who had an early study discontinuation without a progression were censored at the date of their last SE assessment at or before Month 24. Participants who received a prohibited treatment or escape therapy prior to myopic progression were censored as of the date they first received the prohibited or escape therapy. Observations after treatment discontinuation were included as observed.



Note: Progression was defined as an SE measurement that represented a reduction of worse than -0.75 D from baseline. Participants who did not experience myopic progression through or at 24 months or who had an early study discontinuation without a progression were censored at the date of their last SE assessment at or before Month 24. Participants who received a prohibited treatment or escape therapy prior to myopic progression were censored as of the date they first received the prohibited or escape therapy. Observations after treatment discontinuation were included as observed.

Figure 7: FAS – Kaplan-Meier estimates of time to confirmed myopia progression through month 24

Table 25: PPS – summary of analysis of time to myopic progression through month 24

	Vehicle (N=258)	SYD-101 0.01% (N=256)
NUMBER OF PARTICIPANTS ASSESSED	258	256
FOR TIME TO PROGRESSION NUMBER OF EVENTS	82 (31.8)	64 (25.0)
NUMBER CENSORED	176 (68.2)	192 (75.0)
P-VALUE (LOG-RANK TEST)		0.017
TIME TO PROGRESSION (DAYS) (95% CI)		
25TH PERCENTILE	551.0(539.00,715.00)	731.0(562.00,740.00)
MEDIAN	NC	NC(751.00,NC)
75TH PERCENTILE	NC	NC

Note: Each dose of SYD-101 will be compared to Vehicle for time to progression of myopia using the log-rank test stratified by the randomization stratification factors.
Progression is defined as an SE measurement that represents a reduction of >0.75D from baseline. The quartiles and their 95% CI are obtained from Kaplan-Meier (KM) estimates.
Participants who do not experience myopic progression through or at 24 months or who have an early study discontinuation without a progression will be censored at the date of their last SE assessment at or before Month 24. Participants who receive a prohibited treatment or escape therapy prior to myopic progression will be censored as of the date they first received the prohibited or escape therapy. Observations after treatment discontinuation will be included as observed.
NC = Not Calculable.

Fast Progressor Subgroup Analyses

The annual myopia progression rate in the fast progressor subgroups is summarised in Table 26.

As all prior endpoints reached statistical significance, the SYD-101 groups were combined for the analyses in the fast progressor subgroup 1 as pre-specified, and the endpoint was to be analysed on the combined groups. In participants with refractive history of progression of -0.50 D/year or worse, the mean (least squares means) annual progression rate from baseline to Month 24 was -0.54 D (95% CI: -0.63, -0.45) in the Vehicle group -0.433 D (95% CI: -0.50, -0.37) in the Vehicle group and -0.226 D (95% CI: -0.29, -0.16) in the SYD-101 0.01% group. For both SYD-101 groups, statistically significant differences of 0.207 D (95% CI: 0.112, 0.302) in mean annual progression rate compared to Vehicle were shown for 0.01% group (p-value of <0.001).

As the endpoint reached statistical significance (p-value <0.05 for the comparison of the pooled SYD-101 groups and the Vehicle group), the analysis of the endpoint in the fast progressor subgroup 2 was also to be conducted combining both SYD-101 groups, as pre-specified. In participants with refractive history of progression of -0.75 D/year or worse, the mean (least squares means) annual progression rate from baseline to Month 24 was -0.435 D (95% CI: -0.51, -0.36) in Vehicle group and -0.249 D (95% CI: -0.33, -0.17) in the SYD-101 0.01% group. Statistically significant differences of 0.186 D (95% CI: 0.077, 0.296) in mean annual progression rate compared to Vehicle was shown for 0.01% group (p-value of 0.0009).

Table 26: FAS – annual myopic progression rate at month 24 in fast progressor subgroups

ANNUAL MYOPIC PROGRESSION RATE (D/yr)	Vehicle (N=93)	SYD-101 0.01% (N=95)
Fast progressor 1		
BASELINE TO MONTH 6		
LS MEAN RATE	-0.557	-0.193
95% CONFIDENCE INTERVAL [1]	(-0.68, -0.43)	(-0.32, -0.07)
DIFFERENCE TO VEHICLE		
DIFFERENCE IN LS MEAN RATES		0.365 (65%)
95% CONFIDENCE INTERVAL [1]		(0.186, 0.543)
P-VALUE [1]		0.0001
BASELINE TO MONTH 12		
LS MEAN RATE	-0.522	-0.231
95% CONFIDENCE INTERVAL [1]	(-0.62, -0.43)	(-0.33, -0.14)
DIFFERENCE TO VEHICLE		
DIFFERENCE IN LS MEAN RATES		0.291 (56%)
95% CONFIDENCE INTERVAL [1]		(0.158, 0.424)
P-VALUE [1]		<.0001
BASELINE TO MONTH 18		
LS MEAN RATE	-0.468	-0.223
95% CONFIDENCE INTERVAL [1]	(-0.54, -0.39)	(-0.30, -0.15)
DIFFERENCE TO VEHICLE		
DIFFERENCE IN LS MEAN RATES		0.245 (52%)
95% CONFIDENCE INTERVAL [1]		(0.137, 0.353)
P-VALUE [1]		<.0001
BASELINE TO MONTH 24		
LS MEAN RATE	-0.433	-0.226
95% CONFIDENCE INTERVAL [1]	(-0.50, -0.37)	(-0.29, -0.16)
DIFFERENCE TO VEHICLE		
DIFFERENCE IN LS MEAN RATES		0.207 (48%)
95% CONFIDENCE INTERVAL [1]		(0.112, 0.302)
P-VALUE [1]		<.0001

ANNUAL MYOPIC PROGRESSION RATE (D/yr)	Vehicle (N=71)	SYD-101 0.01% (N=76)	3%
Fast progressor subgroup 2			
BASELINE TO MONTH 6			
LS MEAN RATE	-0.510	-0.245	
95% CONFIDENCE INTERVAL [1]	(-0.65, -0.37)	(-0.38, -0.11)	5)
DIFFERENCE TO VEHICLE			
DIFFERENCE IN LS MEAN RATES		0.265 (52%)	)
95% CONFIDENCE INTERVAL [1]		(0.072, 0.459)	22)
P-VALUE [1]		0.0074	
BASELINE TO MONTH 12			
LS MEAN RATE	-0.530	-0.275	
95% CONFIDENCE INTERVAL [1]	(-0.64, -0.42)	(-0.38, -0.17)	17)
DIFFERENCE TO VEHICLE			
DIFFERENCE IN LS MEAN RATES		0.254 (48%)	)
95% CONFIDENCE INTERVAL [1]		(0.100, 0.409)	05)
P-VALUE [1]		0.0014	
BASELINE TO MONTH 18			
LS MEAN RATE	-0.472	-0.255	
95% CONFIDENCE INTERVAL [1]	(-0.56, -0.38)	(-0.34, -0.17)	23)
DIFFERENCE TO VEHICLE			
DIFFERENCE IN LS MEAN RATES		0.217 (46%)	)
95% CONFIDENCE INTERVAL [1]		(0.092, 0.341)	78)
P-VALUE [1]		0.0007	
BASELINE TO MONTH 24			
LS MEAN RATE	-0.435	-0.249	
95% CONFIDENCE INTERVAL [1]	(-0.51, -0.36)	(-0.33, -0.17)	24)
DIFFERENCE TO VEHICLE			
DIFFERENCE IN LS MEAN RATES		0.186 (43%)	)
95% CONFIDENCE INTERVAL [1]		(0.077, 0.296)	28)
P-VALUE [1]		0.0009	

Annual myopic progression rate (D/yr)	Vehicle	SYD-101 0.01%
Fast progressor subgroup 1	**N=93**	**N=95**
Baseline to Month 6		
LS Mean Rate	-0.66	-0.31
95% Confidence Interval [1]	(-0.75, -0.57)	(-0.40, -0.22)
Baseline to Month 12		
LS Mean Rate	-0.64	-0.35
95% Confidence Interval [1]	(-0.73, -0.55)	(-0.44, -0.26)
Baseline to Month 18		
LS Mean Rate	-0.58	-0.34
95% Confidence Interval [1]	(-0.67, -0.49)	(-0.43, -0.25)
Baseline to Month 24		
LS Mean Rate	-0.54	-0.34
95% Confidence Interval [1]	(-0.63, -0.45)	(-0.43, -0.25)
Difference to Vehicle		
Difference in LS Mean Rates		0.204
95% Confidence Interval [1]		(0.102, 0.306)
P-Value [1]		0.0001
Fast progressor subgroup 2	**N=71**	**N=76**
Baseline to Month 6		
LS Mean Rate	-0.60	-0.35
95% Confidence Interval [1]	(-0.70, -0.49)	(-0.45, -0.24)
Baseline to Month 12		
LS Mean Rate	-0.63	-0.38
95% Confidence Interval [1]	(-0.73, -0.52)	(-0.48, -0.27)
Baseline to Month 18		
LS Mean Rate	-0.57	-0.36
95% Confidence Interval [1]	(-0.67, -0.46)	(-0.47, -0.25)
Baseline to Month 24		
LS Mean Rate	-0.53	-0.35
95% Confidence Interval [1]	(-0.63, -0.42)	(-0.46, -0.24)
Difference to Vehicle		
Difference in LS Mean Rates		0.179
95% Confidence Interval [1]		(0.056, 0.301)
P-Value [1]		0.0044

Fast Progressor Subgroup 1: this subgroup included all randomised participants in the FAS, with a refractive history of progression of -0.5D /year or worse for any of the three history time intervals.

Fast Progressor Subgroup 2: this subgroup included all randomised participants in the FAS, with a refractive history of progression of -0.75D /year or worse for any of the three history time intervals.

Annual myopic progression rate was defined as the negative change in SE from baseline divided by the number of days since baseline * 365.25. Observations after use of escape/prohibited medications or treatments were censored. Observations after study discontinuation were not imputed. Participants who terminated study treatment early but who continued study follow-up were included based on observed data. Invalid was analysed as observed.

[1] LSMEANS, confidence intervals, and p-values based on a REML-based Mixed Models Repeated Measures (MMRM) model with fixed effects for treatment group, baseline age category, categorical visit, visit by treatment interaction, with baseline SE as a covariate and Unstructured Covariance.

Note: [1] LSMEANS, confidence intervals, and p-values based on a REML-based Mixed Models Repeated Measures (MMRM) model with fixed effects for treatment group, baseline age category, categorical visit, visit by treatment interaction, with baseline SE as a covariate and Unstructured Covariance.

Note: Percentage = Difference in LS Mean rates/LS Mean rate from Vehicle

Note: Update PROC MIXED with OBSMARGINS.

Table 27: Change from baseline in spherical equivalent (D) at months 36 in fast progressor subgroups 1

Change from baseline in spherical equivalent (D)	Vehicle	STN1012701 0.1 mg/mL
Fast Progressors Subgroup 1 and Baseline SE from -0.5 D to -3.0 D - N	47	46
Baseline to Month 24		
LS mean rates of the difference to Vehicle (% difference in slowing myopia progression)		0.617 (65%)
95% Confidence Interval [1]		(0.343, 0.892)
Nominal p-value [1]		<0.0001
Baseline to Month 36		
LS mean rates of the difference to Vehicle (% difference in slowing myopia progression)		0.669 (55%)
95% Confidence Interval [1]		(0.305, 1.032)
Nominal p-value [1]		0.0004
Fast Progressors Subgroup 1 and Baseline SE from worse than -3.0 D to -6.0 D - N	46	49
Baseline to Month 24		
LS mean rates of the difference to Vehicle (% difference in slowing myopia progression)		0.181 (22%)
95% Confidence Interval [1]		(-0.104, 0.465)
Nominal p-value [1]		0.2118
Baseline to Month 36		
LS mean rates of the difference to Vehicle (% difference in slowing myopia progression)		0.203 (20%)
95% Confidence Interval [1]		(-0.159, 0.564)
Nominal p-value [1]		0.2685

Fast Progressor Subgroup 1: This subgroup included all randomised participants in the FAS, with refractive annual progression history of -0.5D/year or worse for any of the three history time intervals.
[1] LSMEANS, confidence intervals, and p-values based on a REML-based Mixed Models Repeated Measures model with fixed effects for treatment group, baseline age category, categorical visit, visit by treatment interaction, with baseline SE as a covariate and Unstructured Covariance.

The results for fast progressors (FP, patients progressing 0.5D/year or more before enrolment) showed an increase in magnitude of treatment effect in terms of efficacy as compared to the FAS, at 24 and 36 months, for reduction of both annual progression rate (APR) and worsening of SE when looking at FP subgroups by myopia severity, the clinical relevance of treatment effect of Ryjunea 0.1 mg/mL in subjects with -3.0 to -6.0 D at baseline remained questionable. the following findings are shown for

change from baseline in SER (LS mean rates of the difference to vehicle) with consistent findings in the provided figures:

- -0.5 to -3.0 D: M24 0.617 (0.343, 0.892) nominal p<0.0001; M36 0.669 (0.305, 1.032) nominal p=0.0004;
- -3.0 to -6.0 D: M24 0.181 (-0.104, 0.465) nominal p=0.2118; M36 0.203 (-0.159, 0.564) nominal p=0.2685.

APR through Month 36 in fast progressors with higher myopia (-3.0 to -6.0 D) shows similar rates with 0.1 mg/mL and placebo. Considering all of the above, the applicant was asked to further discuss the study results and the clinical relevance for 0.1 mg/mL dose in case of initial myopia ranging -3.0 to -6.0 (which is also more at risk for myopia complications) in the target population. As discussed in a previous assessment round, it might be helpful to investigate the association between severity and treatment effect within age groups. While the numbers of patients within subgroups defined by age and severity may be too small to allow for informative subgroup analysis, a model including the three-way interaction between treatment, age (continuous, not subgroups) and baseline SE values could be investigated, which would allow to estimate the treatment effect for different combinations of age and severity values. Plotting the treatment effect versus severity conditioning on age (varying age in steps of 1 year in the age-range from 3-14 years) in the fast-progressing subgroup could allow to decide whether severity is a predictive factor or whether the observed association between myopia severity and the treatment effect is confounded by age. For simplicity, the model might be restricted to the annualised progression rate at 24 months instead of including data for all timepoints. Based on the results, the following statement was included in the SmPC section 5.1: *"Larger effect sizes were observed with younger ages."*.

Axial length

Axial length was measured only in a subset of sites with requisite equipment, therefore, it was measured in 139, 139, and 135 participants in the Vehicle, SYD-101 0.01% and SYD-101 0.03% groups, respectively, whereas the FAS included 282, 282, and 283 participants. A summary of change from baseline in axial length is presented in Table 28.

At Month 24, the change from baseline (least square means) in axial length was 0.40 (95% CI: 0.34, 0.47) mm in Vehicle group and 0.35 (95% CI: 0.29, 0.41) mm in SYD-101 0.01% group. For SYD-101 0.01% group, a difference of -0.05 (95% CI: -0.13, 0.02) in axial length compared to Vehicle was shown (p value of 0.1526). This endpoint did not reach statistical significance although axial length tended to increase less in the SYD-101 groups than the Vehicle group (Figure 8). Similar results were observed in the PPS (Table 29).

There is no significant difference between treatment groups and the vehicle control in the prespecified secondary EP in axial length, which is of concern. The inclusion of a brief description of AL results in section 5.1 of the SmPC is acknowledged.

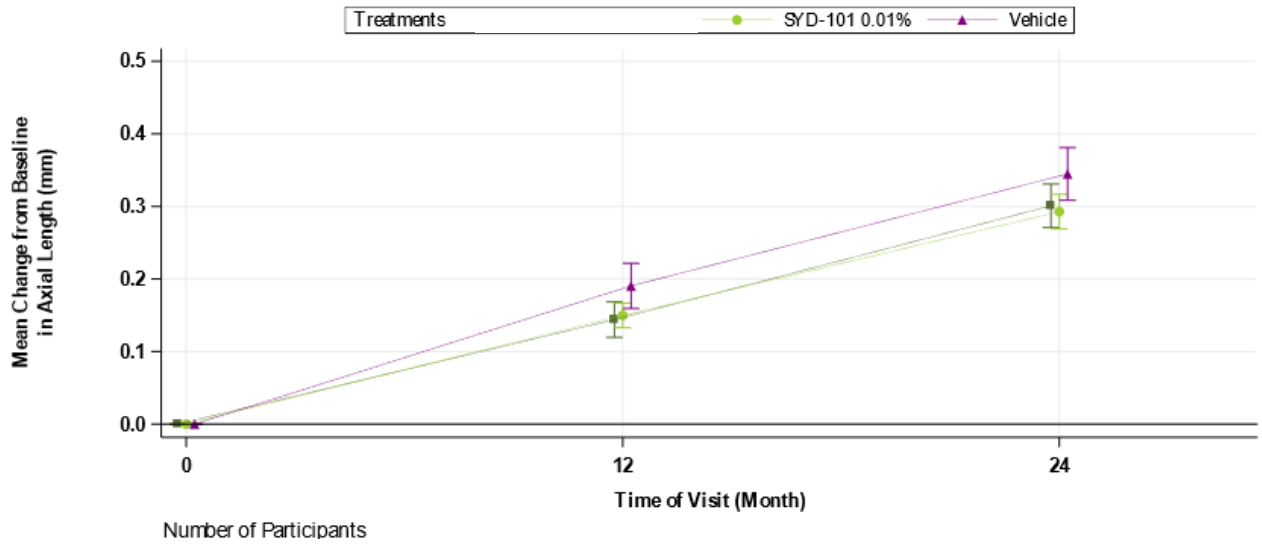
Table 28: FAS – summary of change from baseline in axial length (mm)

Visit	Vehicle (N=282)		SYD-101 0.01% (N=282)	
	Actual Value	Change from Baseline[1]	Actual Value	Change from Baseline[1]
Baseline				
n	173		172	
Mean (SD)	24.49 (0.886)		24.51 (0.953)	
Median	24.42		24.51	
Min, Max	22.2, 27.7		21.0, 27.1	
Month 12				
n	155	152	150	149
Mean (SD)	24.70 (0.851)	0.19 (0.384)	24.69 (0.989)	0.15 (0.207)
Median	24.63	0.18	24.70	0.14
Min, Max	22.4, 27.6	-3.2, 1.8	21.3, 27.2	-1.3, 0.9
Model-Adjusted Change From Baseline[2]				
LS Mean		0.25		0.20
SE of LS Mean		0.03		0.03
95% CI		(0.20, 0.31)		(0.15, 0.26)
Difference to Vehicle [2]				
Difference of LS Means				-0.05
95% CI				(-0.12, 0.02)
P-Value				0.1360
Month 24				
n	140	139	140	139
Mean (SD)	24.87 (0.876)	0.34 (0.428)	24.90 (1.025)	0.29 (0.281)
Median	24.83	0.29	24.93	0.24
Min, Max	22.4, 27.7	-2.6, 1.7	21.4, 27.2	-1.2, 1.1
Model-Adjusted Change From Baseline[2]				
LS Mean		0.40		0.35
SE of LS Mean		0.03		0.03
95% CI		(0.34, 0.47)		(0.29, 0.41)
Difference to Vehicle[2]				
Difference of LS Means				-0.05
95% CI				(-0.13, 0.02)
P-Value				0.1526

Note: Baseline is defined as last non-missing measurement prior to first dose. Observations after receipt of prohibited treatment or escape therapy were censored. Observations after treatment discontinuation were included as observed. Multiple imputation was not performed. A single average axial length for the right and left eyes was used for analysis.

[1] Change from baseline: Value at specified visit – baseline value. At each specified visit, only participants with a value at both baseline visit and specified visit are included.

[2] LS means, difference of LS means, 95% CIs, and P-values are obtained from a REML-based Mixed Models Repeated Measures (MMRM) model with fixed effects for treatment group, baseline age category, categorical visit, visit by treatment interaction, with baseline SE and baseline axial length as covariates and unstructured covariance.



Note: Baseline is defined as last non-mising measurement prior to first dose. Observations after receipt of prohibited treatment or escape therapy will be censored. Observations after treatment discontinatuion will included as observed. A single average axial length for the right and left eyes will be used for analysis.

Figure 8: FAS – mean (+/- SE) change from baseline in axial length (mm) during the study through month 24

Table 29: PPS – summary of change from baseline in axial length (mm)

	Vehicle (N=258)		SYD-101 0.01% (N=256)	
Visit	Actual Value	Change From Baseline [1]	Actual Value	Change From Baseline [1]
Baseline				
n	164		158	
MEAN (SD)	24.51 (0.873)		24.51 (0.980)	
MEDIAN	24.43		24.51	
MIN, MAX	22.4, 27.7		21.0, 27.1	
Month 12				
n	154	151	146	145
MEAN (SD)	24.70 (0.853)	0.19 (0.384)	24.69 (0.995)	0.15 (0.209)
MEDIAN	24.63	0.18	24.69	0.14
MIN, MAX	22.4, 27.6	-3.2, 1.8	21.3, 27.2	-1.3, 0.9
MODEL-ADJUSTED CHANGE FROM BASELINE [2]				
LS MEAN		0.25		0.21
95% CI		(0.19,0.31)		(0.15,0.26)
DIFFERENCE TO VEHICLE [2]				
DIFFERENCE OF LS MEANS				-0.05
95% CI				(-0.11,0.02)
P-VALUE				0.1777
Month 24				
n	139	138	137	136
MEAN (SD)	24.87 (0.879)	0.34 (0.427)	24.89 (1.035)	0.29 (0.284)
MEDIAN	24.83	0.28	24.93	0.24
MIN, MAX	22.4, 27.7	-2.6, 1.7	21.4, 27.2	-1.2, 1.1
MODEL-ADJUSTED CHANGE FROM BASELINE [2]				
LS MEAN		0.40		0.35
95% CI		(0.34,0.46)		(0.29,0.42)

DIFFERENCE TO VEHICLE [2]	
DIFFERENCE OF LS MEANS	-0.05
95% CI	(-0.12,0.03)
P-VALUE	0.2148

Note: Baseline is defined as last non-missing measurement prior to first dose. Observations after receipt of prohibited treatment or escape therapy will be censored. Observations after treatment discontinuation will be included as observed. Multiple imputation will not be performed. A single average axial length for the right and left eyes will be used for analysis.

[1] Change from baseline: Value at specified visit − baseline value. At each specified visit, only participants with a value at both baseline visit and specified visit are included.

[2] LS means, difference of LS means, 95% Cis, and P-value are obtained from a REML-based Mixed Models Repeated Measures (MMRM) model with fixed effects for treatment group, baseline age category, categorical visit, visit by treatment interaction, with baseline SE and baseline axial length as covariates and Unstructured Covariance.

Comparing the primary analysis of the key secondary endpoint on the FAS with Supplementary analysis 1 on the PPS (Table 14.2.2.3.1) suggests that 10.9 patients (average over imputed datasets) of the 24 patients in the vehicle group included in the FAS but excluded from the PPS were classified as progressors, while only 3.9 patients among 26 patients in the 0.1 mg/mL atropine group included in the FAS but excluded from the PPS were progressors were classified as progressors. Considering that 46 out of the 74 patients excluded from the PPS were excluded due to missing post-baseline efficacy assessments, which was handled by multiple imputation based on MAR in the primary analysis, the observed difference between study arms suggest that the imputation process might have given quite different results for the different study arms. The applicant has not provided any new information. Moreover, the table provided by the applicant describes the imputation rules for the primary endpoint while the question focuses on the key secondary endpoint of progression. Thus, it remained unclear, why the proportion of progressions was so much higher in the imputed values in the vehicle arm than in the imputed values in the active arms. The applicant's efforts to provide the software code and the data were acknowledged. However, the primary analysis for the key secondary endpoint could not be reproduced using the data. As the related concern regarding differences between imputed and observed data was resolved, this issue was not pursued further.

Exploratory Endpoint

Activity outcomes

Activity outcomes are summarised in Table 14.2-11.1a of the efficacy data summaries figures tables.

The mean time spent per day doing outdoor activities during daylight hours tended to be stable between Week 1 and Month 18, around 1.6-1.7 h in each treatment group. From Month 19 to Month 24, it tended to increase in all treatment groups to values close to 2 h.

The mean time spent per day doing near-work tasks remained around 2.6 h over time in all treatment groups.

QOL questionnaire

A summary of QOL questionnaire evaluated through Month 24 is presented in Table 14.2-12.1a of the efficacy data summaries figures tables.

Questions 2 to 7 were to be scored from 5 for strongly agree to 1 for strongly disagree and questions 1 and 8 were to be reversed scored from 1 for strongly agree to 5 for strongly disagree.

The mean score to Question 1 'Does not seem to mind using drops' was similar in all treatment groups over time and ranged between 1.355 and 1.516.

The mean score to Question 2 'Worry may miss out on fun activities' was similar in all treatment groups over time and ranged between 1.273 and 1.344.

The mean score to Question 3 'Using drops affects learning' was similar in all treatment groups over time and ranged between 1.270 and 1.356.

The mean score to Question 4 'Using drops makes it hard to be outside' was similar in all treatment groups over time and ranged between 1.311 and 1.581.

The mean score to Question 5 'Trouble putting drops in eyes' was similar in all treatment groups over time and ranged between 1.390 and 1.543.

The mean score to Question 6 'Difficult near vision activities' was similar in all treatment groups over time and ranged between 1.312 and 1.478.

The mean score to Question 7 'Worry will become injured when using drops' was similar in all treatment groups over time and ranged between 1.281 and 1.385.

The mean score to Question 8 'Can see well when using drops' was similar in all treatment groups over time and ranged between 1.621 and 1.754.

No marked differences in QOL between groups were observed.

Ancillary analyses

Not applicable.

Summary of main efficacy results

The 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).

Table 30: Summary of efficacy for trial SYD-101-001

Title: SYD-101-001		
Study identifier	SYD-101-001; 2018-004775-13; NCT03918915	
Design	This Phase 3, multicentre, randomised, double-masked, vehicle-controlled study was planned to assess the efficacy and safety of SYD-101 (provided as SYD-101 0.01% and SYD-101 0.03%) eye drops in male and female children between 3 and 14 years of age (inclusive at baseline) with myopia of -0.50 D to -6.00 D (inclusive at baseline) compared with placebo (vehicle of SYD-101) eye drops. The treatment is administered each night at bedtime in each eye.	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	48 months not applicable not applicable
Hypothesis	Superiority	
Treatments groups	SYD-101 0.01%, eyes drop, one drop administrated each night in each eyes.	SYD-101 0.01%, 36 or 48 month (depending on the re-randomisation), 284 patients randomised
	SYD-101 0.03%, eyes drop, one drop administrated each night in each eyes.	SYD-101 0.03%, 36 or 48 month (depending on the re-randomisation), 285 patients randomised
	Vehicle	Vehicle, 36 or 48 month (depending on the re-randomisation), 283 patients randomised

Title: SYD-101-001				
Study identifier	SYD-101-001; 2018-004775-13; NCT03918915			
Endpoints and definitions	Primary endpoint	The annual progression rate of myopia through Month 24	The annual progression rate of myopia through Month 24 based on SE.	
	Key Secondary	Proportion of participants with myopic progression >0.75 D at or before Month 24	Proportion of participants with myopic progression >0.75 D at or before Month 24	
Database lock	24 month			
Results and Analysis				
Analysis description	**Primary Analysis and Key secondary**			
Analysis population and time point description	FAS 24 months			
Descriptive statistics and estimate variability	Treatment group	Vehicle	SYD-101 0.01%	SYD-101 0.03%
	Number of subject	232	228	231
	The annual progression rate of myopia through Month 24 in LS mean rate SE	- 0.44 D	-0.31D	
	Proportion of participants with myopic progression >0.75 D at or before Month 24	35.72%	25.55%	

Effect estimate per comparison	Primary endpoint	Comparison groups	Vehicle vs SYD-101 0.01%
		Difference between groups	0.132 D in Vehicle vs SYD-101 0.01%
		95% CI	(0.061, 0.204) in Vehicle vs SYD-101 0.01%
		P-value	0.0003 in Vehicle vs SYD-101 0.01%
	Key Secondary	Comparison groups	Vehicle vs SYD-101 0.01%
		Difference between groups	10% in Vehicle vs SYD-101 0.01%
		95% CI	(2.46, 17.49) in Vehicle vs SYD-101 0.01%

Title: SYD-101-001			
Study identifier	SYD-101-001; 2018-004775-13; NCT03918915		
		P-value	0.0181 in Vehicle vs SYD-101 0.01%
Notes	Statistically significant for both endpoints.		

2.8.5.3. Clinical studies in special populations

Not applicable.

2.8.5.4. In vitro biomarker test for patient selection for efficacy

Not applicable.

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

Not applicable.

2.8.5.6. Supportive study

A multi-database literature search was undertaken to identify published clinical trials or meta-analyses of such studies describing the use of low dose topical atropine for the treatment of myopia in children. Results from the most pertinent randomised controlled trials (RCTs) describing efficacy data using low dose (defined as ≤0.5%) atropine in the target indication.

Overall, from the published data submitted by the MAA, it appears that there is a consensus on the atropine efficacy on slowing progression of myopia. However, robustness, study design, number of patients included and population included can differ from SYD-101-001 study and the relevance of some of the bibliographic data submitted can be questionable. In general, wide range of atropine dosage were assessed (0.005 to 1%), mostly in Asian population of 6-14 years, and effect on slowing progression of myopia (pupillary diameter, accommodative amplitude, AL elongation and SE elongation) was observed. Dose-effect relation is not always concluded and atropine 0.01% most often emerges as the dose with minimal rebound effect and few side effects. However, bibliographic data were not discussed in the submission.

2.8.6. Discussion on clinical efficacy

The applicant submitted a hybrid application under Article 10(3) of Directive 2001/83/EC for the proposed medicinal product atropine sulfate 0.1 mg/mL eye drops, solution in multi-dose container (identified as STN1012701, Syd-101, Ryjunea® throughout the report) for treatment of progression of myopia in children aged 3-18 years. The reference product for this hybrid application is the product Atropin-POS® 0.5% eyedrops, solution which has been marketed in Germany by URSAPHARM since 25 April 2005. Ryjunea is proposed for different concentration (0.01%) and for a different therapeutic indication than the reference product, however, both products have the same route of administration (ocular use) and same pharmaceutical form (eye drops, solution).

The hybrid application is supported by a single pivotal Phase III trial, in which efficacy of Ryjunea eye drops 0.1 mg/mL has been evaluated in patients with myopia aged 3 to 14 years. Clinical evidence of Ryjunea (0.01%) is primarily based on this single trial. Results from the trial are described as pivotal evidence of the effectiveness of Ryjunea eye drop solution in patients with myopia. Results from the

reference product Atropin-POS® 0.5% eyedrops and literature data gathered from the longstanding off-label use of compounded atropine ophthalmic solutions at various strengths (ranging from 0.01% - 1% atropine) for the treatment of myopia progression are considered as supportive evidence of the effectiveness.

The applicant did not conduct any clinical studies against the reference product, which is acceptable because of the differences in the strength, indication and composition (D20 instead of H2O). The application for Ryjunea only referred in certain areas to the RefMP, in particular to non-clinical data and clinical pharmacology data. In all these areas there is no need for bioequivalence or comparable bioavailability studies to the reference product. Clinical data were generated by the applicant to support the safe use of Ryjunea in the proposed indication. For these reasons, it can be agreed that no clinical studies against the reference product are necessary. The information/justification provided by the applicant is sufficient to allow relying/cross-reference to the data from the RefMP named above.

No dose response/dose finding studies have been performed. Both doses 0.1 mg/ml (0.01%) and 0.3 mg/ml (0.03%) atropine were selected based on literature data gathered from the off-label use of compounded atropine ophthalmic solutions for myopia control. The lower dose was selected as it appears to be the dose that provides the optimal benefit with the least amount of adverse events based on published dose-response data, which can be followed. The risks associated with atropine 0.01% based on existing data from literature appear minimal and reversible. Of note, the 0.03% dose was not applied before, hence no published data exists. The applicant assumed that based on the data with 0.025%, safety risks anticipated with atropine 0.03% eyedrops are potentially minimal and reversible upon treatment withdrawal. However, although very small, the study by Cooper (Optom Vis Sci, 2013) suggests that atropine 0.02% is the highest concentration that does not produce significant clinical symptoms from accommodation paresis or pupillary dilation. The higher dose was selected to allow identifying appropriate options for a broader paediatric population, including those in whom additional benefit may be achieved using a slightly higher concentration of atropine (e.g. children with dark iris colour and rapid progression of myopia). The applicant's rationale can principally be followed, and there was no objection against the investigation of two doses to allow for broader customised myopia control. However, 0.03% dose was withdrawn.

Design and conduct of clinical studies

The applicant's clinical development is based on a single pivotal study. SYD-101-001 is an ongoing, Phase 3, multicentre, randomised, double-masked, vehicle-controlled study assessing efficacy and safety of SYD-101 (atropine sulfate 0.01% and 0.03%) compared to placebo (vehicle of SYD-101) in male and female children between 3 and 14 years of age with myopia range from -0.50 D to -6.00 D. The treatment is administered each night at bedtime in each eye without a precision regarding defined criteria on treatment duration. Treatment compliance was collected via a phone questionnaire or web-based application, first weekly for the first 6 months, then monthly. Rescue medication (SYD-101 0.03%) on an open-label basis was permitted in case of myopia progression ≥-2.00 D from baseline in SE at a visit occurring between Month 18-36, and myopia progression confirmed 6 months later at the next scheduled visit (visit between Month 24-42).

SYD-101-001 study is composed of 2 parts. The first part intends to randomise patients in a 1:1:1 ratio in 3 arms (SYD-101 0.01%; SYD-101 0.03% and vehicle) during a period of 36 month. Thereafter, at month 36 (Part 2), patients will be re-randomised in a 1:1:1 ratio receiving SYD-101 0.01%, SYD-101 0.03% or vehicle treatment as follows: patients initially in the SYD-101 arm will be re-randomised in a 1:1 ratio to either continue with their initial atropine's dosage or vehicle, and patients initially in the vehicle arm will be re-randomised in a 1:1 ratio to either pursue the placebo treatment or SYD-101 0.03%.

The primary objective defined by the applicant is the assessment of the efficacy of SYD-101 for slowing the progression of myopia in children based on spherical equivalent (SE) measured by cycloplegic autorefraction through Month 24 and aims to demonstrate superiority over vehicle with a proposed truncated Hochberg adjustment for controlling the type-one error. It is to note that, SE can be also influenced by prior to treatment measure extrinsic factors (as outdoor activities), and the methods of measure itself, which can be different, in particular in young patients.

Primary and secondary efficacy endpoint selection was previously discussed during Scientific Advice procedure (MEA/H/SA/4009/1/2018/PED/III) and are principally acceptable.

The applicant clarified that different autorefractors were used at different sites. Each site applied their own autorefractor that was used in clinical practice. The same autorefractor was to be used for the patient throughout the duration of the study. If an autorefractor was replaced, it had to measure within 0.1D of the previous autorefractor measurements. This is principally endorsed. However, the number of different autorefractors and their characteristics in terms of precision (spherical equivalent measurement) were not provided. Hence the impact of this source of variability due to different models of autorefractors used among the sites on the consistency of study results is not known.

The applicant also explained that since the needed correction for initial BCVA was performed at screening using standard manual refraction (cycloplegic) measurements rather than cycloplegic autorefraction measurements, the applicant is not able to provide a discussion on the consistency between the patient-reported BCVA measures and cycloplegic autorefraction measurements. At least, based on the provided data (*Summary of Change from Baseline in BCVA (LogMar), Full Analysis Set*) it appears that BCVA remains stable within each treatment group (vehicle, 0.1 mg/mL atropine). Hence, a sudden vision loss in the atropine groups despite correction can be excluded.

The applicant clarified that study participants who missed the 3 to 28 days unscheduled visit to confirm progression were confirmed during the next scheduled visit (Month 30 for EMA) if myopia progression was >0.75D, while the recording date was the initial visit when Myopia was measured >0.75D. This is considered acceptable.

In a post hoc analysis, the applicant evaluated the most severe eye of the participants in the study to compare the results with the previous analyses using both eyes. At M24, analyses (most severe eye and both eyes) showed consistent differences in change from baseline SE between the STN1012701 doses and vehicle. Other secondary endpoints were assessed as the mean change in axial length from baseline to month 24, which is clinically relevant to better characterise atropine mechanism of action. Indeed, in this type of myopia, increase in axial length expose to ocular complications (e.g. cataract, retinal detachment, macular hole, retinal atrophy). Additionally, endpoints regarding subgroups of patients with refractive history of progression ≥0.5D or ≥0.75D/year were planned by the applicant in order to assess efficacy of SYD-101-001 0.01% in fast progressors patients.

The primary estimand was the difference in the mean annual progression rate of myopia based on 24 months of follow-up assuming no use of prohibited or escape medication or dosing interruptions/discontinuations due to logistical issues. For discontinuations due to tolerability issues (i.e., due to a related AE), it was assumed that the effect in those participants was similar to that in participants receiving vehicle without escape medication or prohibited treatments. As presented in table above, the intercurrent events prohibited treatment and escape therapy were planned to be targeted by a while on treatment strategy, treatment or study discontinuation by hypothetical strategies and invalid SE values by a treatment policy strategy.

The while on treatment strategy for prohibited and escape medication was implemented by omitting observations after the intercurrent event in the MMRM, which is equivalent to using multiple imputation assuming MAR for the values after the intercurrent event, rather targeting a hypothetical or treatment

policy strategy than a while on treatment strategy. This is acceptable as there were only 6 patients who received escape medication until M24 (5 patients in the vehicle group and 1 patient in the 0.3 mg/mL atropine group, table in CSR) and apparently no patient used prohibited treatment (as SAP states "taking prohibited medications or treatment listed in protocol" as a reason to be interpreted as a major protocol deviation and table of CSR lists no such patient). With more frequent use of prohibited or escape medication, Supplementary Analysis 4, which used multiple imputation informed by the vehicle arm for observations after prohibited or escape therapy, the choice of the strategy would have been considered more impactful.

Observations post study or treatment discontinuation not due to a related AE were multiply imputed assuming missing at random (MAR) and observations after treatment or study discontinuation due to a related AE were multiply imputed assuming missing not at random (MNAR). If study or treatment discontinuation for other reasons than being related to an AE was indeed solely logistically motivated, using multiple imputation assuming MAR might be adequate. As it is expected that some of the patients discontinued also for reasons related to the study drug, imputing the data after discontinuation based on the vehicle arm might give a more realistic picture. This was incorporated in Supplementary Analysis 4, which yielded less pronounced but similar results as the primary analysis. For the sake of consistency, it is noted that Supplementary Analysis 4 is understood to target not only treatment discontinuation but also study discontinuation by a treatment policy strategy, although the protocol claims that study discontinuation was handled by a hypothetical strategy. Indeed, using vehicle based imputation after study discontinuation is assumed to approximate the unobserved values after discontinuation. In order to avoid this confusion, in the following often the analysis strategy (e.g. vehicle based imputation) rather than the intercurrent event strategy (e.g. treatment policy strategy) will be described when discussing for instance supplementary analyses.

Handling of invalid SE values by the treatment policy strategy using observed data is considered appropriate.

Table 5 in the CSR lists, among others, subject numbers who received escape medication, discontinued study or treatment together with corresponding reasons for study discontinuation. After request, the applicant clarified that 11 visits with invalid SE values had been identified of which only 3 scheduled visits which is acceptable. The amount of missing data was not provided, however according to listing provided, the number of missing visits seems to be limited.

The estimand for the key secondary endpoint confirmed myopic progression worse than 0.75 D until month 24 was defined similarly as the estimand for the primary endpoint but used a composite strategy for the handling of the intercurrent events prohibited and escape medication. Again, Supplementary Analysis 4 (vehicle-based imputation for study discontinuation, prohibited and escape medication; analysis of observations after treatment discontinuation as observed) is considered a plausible alternative to the primary analysis of the key secondary endpoint and hence no issues are raised in this context.

The analysis of the primary efficacy endpoint mean annual progression rate of myopia through 24 months used a MMRM model adjusted for baseline age category, categorical visit, the treatment by visit interaction and the baseline SE value (average of both eyes) employing fixed effects, which is considered appropriate. Data from all visits through Month 24 were included in the model, with the primary comparison at the Month 24 visit. Based on the protocol, the FAS including all randomised subjects who received at least 1 drop of study drug, was the population used for the primary efficacy analyses which is considered adequate.

During the assessment it was clarified that an LSMEANS statement based on the default setting had been used to estimate the annual progression rate within treatment arms from the MMRM model. These estimates assume a population with balanced covariate distribution which is presently however

far from what was observed in the study population and what is expected in the proposed patient population. This is also reflected in a discrepancy observed between the LSMEANS estimates and descriptive statistics. Therefore, revised LSMEANS estimates using the OBSMARGIN option were provided upon request and were included into the SmPC.

Complementary to the analysis of the primary endpoint, the applicant was asked to provide an MMRM analysis of change from baseline (CfB) in spherical equivalent to be included in the SmPC. The results were well aligned with the results presented for the primary endpoint, in the sense that the annualised progression rate equals the change from baseline per year.

According to the Kaplan-Meier Analysis of time to confirmed myopia progression the probability of progression at month 25 seems to be higher for the 0.1 mg/mL atropine group than for the vehicle arm which is in contrast to the results for the key secondary endpoint. It is suspected that this apparent discrepancy is an artefact from the distribution of the actually observed follow-up times. Generally, the provided analysis of time to progression of myopia is not considered informative in addition to the analysis of the binary endpoint confirmed progression of myopia at months 6, 12, 18 and 24, as the progression status was assessed only at the mentioned four time points. Thus, the analysis of time to progression will not be taken into account in the benefit-risk assessment.

Study SYD-101-001 included male and female patients aged from 3 to 14 years old with myopia of -0.50 D to -6.00 D, astigmatism ≤1.50 D, anisometropia ≤1.00 D and Best-corrected visual acuity (BCVA) of 75 letters (Snellen equivalent 20/32) or better were included. Additionally, these patients had to present a myopia progression of -0.50 D in the previous 6 to 12 months if the baseline myopia (SE) was >-0.75 D or wear specified refractive correction (single vision eyeglasses or soft, daily-wear, single-vision contact lenses) if the baseline myopia (SE) was ≤-0.75 D. Also patients were excluded mainly in case of history, evidence or current medical condition predisposing the participant to degenerative myopia (e.g., Marfan syndrome, Stickler syndrome) or a condition that may affect visual function or development (e.g., diabetes mellitus, chromosome anomaly) as well as systemic infection or autoimmune disease, ocular inflammation or infection in either eye, retinopathy of prematurity, abnormal refractive anatomy (e.g., keratoconus, lenticonus, spherophakia), amblyopia, manifest strabismus, or nystagmus. As well, patients were excluded in case of previous, current, or future treatment with monoamine oxidase inhibitor, atropine, pirenzepine, or other anti-muscarinic agent for myopia, orthokeratology (orthoK), rigid gas-permeable, bifocal, progressive-addition, multi-focal, or other lenses to reduce myopia progression.

Family history of myopia ≤9 dioptres is a questionable exclusion criterion. As the ametropia value is rarely known to patients, it is impossible to accurately determine ametropia without examining the parents. In addition, the threshold of -9 dioptres is surprising since -6 dioptres is a commonly accepted threshold value to define high myopia increasing the risk of ocular complications. The applicant confirmed that parents of the subjects were asked to confirm their refractive error if they were myopic, which is considered acceptable. Additionally, the applicant justified the threshold of -9 dioptres based on literature (Flitcroft 2012). Furthermore, the applicant was requested to provide and discuss the number of subjects before vs after the onset of puberty both when enrolled and during the study, considering that the subjects enrolled before the puberty could have had slower progression of myopia as compared to subjects already in pubertal development. The applicant only declared that the onset of puberty is not available, however with available data, the applicant extrapolated age of onset of puberty (11 years in females and 12 years in males) to be able to discuss the impact of pubertal development on myopia. Additionally, other measures of puberty, including height spurts, Tanner staging, menarche, break of voice (BOV), were discussed based on published data but also not captured in the trial. The issue was not further pursued.

In the pivotal study SYD-101-001, only 3.1% of patients enrolled were below the age of 6 (less than 10 in each treatment arms) which may be understood due to the difficulty with recruiting such young patients. The applicant clarified that according to exclusion criteria, children, including those below 6 years of age (yoa), who had a history or current evidence of a medical condition predisposing them to degenerative myopia (e.g., Marfan syndrome, Stickler syndrome), or a condition that may affect visual function or development (e.g. diabetes mellitus, chromosome anomaly), were not included in study SYD-101-001. As requested, the applicant provided aetiologies/demographic and baseline characteristics of patients from 3 - <6 yoa, including underlying pathologies, medical history and degree of parental myopia (mother and father). Based on provided baseline characteristics it appears that this young age group is representative for the general myopia population and a more severe disease pattern appears to be unlikely. To further substantiate the validity of the observed results in the 3 - <6, the applicant focusses on the annual progression rate (APR) of myopia in this age group. Data up to M36 were provided in addition to M24 data that were already available at the initial submission. At M24 and M36, data in APR and SE demonstrate that atropine 0.1 mg/ml has a significant effect compared to the vehicle. The results indicate also that there were signals of a higher efficacy in this age group compared to other age groups: a difference from vehicle of 0.594 D/year (66%) in mean annual progression rate was observed at Month 24 in subjects receiving Ryjunea 0.1 mg/ml.

Based on the provided information within several assessment rounds, observed results in this very young population can indeed be considered to support the treatment of the age group 3 to <6 yrs and consequently inclusion of this age-group into the label is justified. A mention in section 4.4 to exclude progressive syndromic myopia of childhood, such as glaucoma, retinitis pigmentosa, congenital hemeralopia and myelinated nerve fibre syndrome have been provided since these severe conditions do not evolve similarly and should not be treated with atropine without further data**.**

As requested, the applicant provided age distribution using the age categories defined for stratification of randomisation within the two myopia severity groups (mild: 0.5-3.0 D vs. moderate: 3.0-6.0 D), to explore whether the observed differences in treatment effects between patients with mild and moderate myopia could be attributed to variations in age distribution. The percentage of patients younger than 9 years was 27.5% in the patients with mild myopia compared to only 20.7% in the patients with moderate myopia, i.e. patients with mild myopia tended to be younger than patients with moderate myopia. As younger age is known to be associated with higher treatment effects, the difference in the age distribution is considered to at least partially explain the observed differences in treatment effects between patients with mild and moderate myopia. The nature of this observation is therefore understood and no further action on this observation is deemed necessary.

During the assessment, the applicant changed the target population and proposed *Ryjunea treatment for paediatric patients with a progression rate of -0.5 D or more per year (fast progressors) with treatment initiation between 3-14 years.* To further characterise the subgroup of patients 12-14 years of age at treatment initiation and with a progression rate of 0.5 D or more per year, the applicant performed additional post-hoc analyses to elucidate effects in this specific subgroup. In general, a higher magnitude of treatment effect is estimated in the fast progressor subgroup (progression rate of 0.5 D or more per year) compared to the full study population. Considering the low rate of fast progressors in the 12-14 age category and the borderline effect size observed in this study, the medical need and the clinical benefit of treatment initiation with atropine 0.1 mg/ml in patients ≥12 years of age was questioned. Upon multiple requests the applicant provided sufficient information and data confirming reduced myopia progression in the pre-specified age subgroup (12-14 yoa) in patients with a history of progression of ≥0.5D/year compared to vehicle. Hence, inclusion of fast-progressing patients aged 12 to 14 into the label is justified.

However, as a better efficacy is observed in younger patients, a special mention has been added in SmPC section 5.1 to draw prescribers' attention to the reduced effect in older patients.

Efficacy data and additional analyses

The study was conducted in 3 countries: the US (41 active sites with 91.8% of patients included), Austria (3 sites) and Slovakia (3 sites). As requested, the applicant discussed the representativity of the trial population (91.7% of patients were from US) with regard to the intended marketing authorisation in European population (8.3% of trial' patients). The applicant indicated that Atropine pharmacology is not likely to be affected by ethnicity. There are no intrinsic or extrinsic ethnic factors that will preclude the extrapolation of the results of the US population to the EU. Moreover, the diagnosis and treatment of myopia are similar in the US and EU. In addition, the conduct of clinical trials in the US and EU are generally the same and the study was conducted following internationally accepted good clinical practice (GCP) requirements (ICH E5 R1 guidance).

Intrinsic factors include genetic polymorphism, age, gender, height, weight, lean body mass, body composition, and organ dysfunction and were mostly assessed within the subgroup analyses of the primary endpoint, for which results were in line with the results in the FAS. Extrinsic factors include the social and cultural aspects of a region, such as medical practice, diet, use of tobacco, and use of alcohol. Additionally, the applicant provided baseline characteristics presented by population (EU vs US) for each groups including intrinsic/extrinsic factors. Generally, baseline characteristics are considered similar across groups, except for racial and ethnic background.

As well, efficacy results from Study SYD-101-001 were provided by region for the primary endpoint in FAS. In European participants, the annual myopic progression was -0.47D and -0.40D -in the vehicle and SYD-101 0.01% groups, respectively. Difference to vehicle (LS mean rates) in European patients were 0.066 D (95% CI [-0.219, 0.351]; p-value 0.6484) in SYD-101 0.01% group. In US participants, the annual myopic progression was -0.44D and 0.30 D in the vehicle and atropine 0.1 mg/mL groups, respectively. Difference to vehicle (LS mean rates) in European patients were 0.135 D (95% CI [0.061, 0.209]; p-value 0.0004) in SYD-101 0.01% group.

Globally, the results of the subgroup analyses in US patients are in line with the primary endpoints results provided by the applicant.

Protocol was amended two times in SYD-101-001 study and mostly related to COVID-19, and following CHMP and FDA scientific advice. The applicant briefly clarified that the protocol amendments did not have an impact on the efficacy results as they were implemented to update and clarify statistical methods to allow for different requirements regarding primary and secondary endpoint assessment as requested by EMA and FDA. This was acknowledged.

Major protocol deviations were observed through Month 24 that concerned 28 patients (6 patients in the vehicle arm, 9 and 13 in SYD-101 0.01% and 0.03% arms respectively). The applicant indicated that patients with major PDs were excluded from the PPS but not from the FAS which is considered acceptable.

Overall, 1035 participants were screened, and 852 patients were randomised at baseline (283, 284 and 285 in Vehicle, SYD-101 0.01% and 0.03% arms, respectively) and 691 patients completed 24 month visits (232, 228 and 231 in Vehicle, SYD-101 0.01% and 0.03% arms, respectively). Treatment discontinuation through month 24, appears in similar proportions across treatment groups: 53 (18.7%) patients in the Vehicle group, 56 (19.7%) patients in the SYD-101 0.01% group, and 53 (18.6%) patients in the SYD-101 0.03% group. The main reasons for discontinuation were lost to follow-up (58 patients [6.8%] overall), withdrawal by parents or guardians (44 patients [5.2%] overall), withdrawal

by subject (38 patients [4.5%] overall) and 5 (1.8%) patients only in SYD-101 0.03% arm discontinued the study due to an AE. The applicant indicated that compliance was above 97% in patients of 12-14 years in each group (vehicle, SYD-101 0.01%, and SYD-101 0.03%) without evidence of a decrease over time in the study. This indicates that efficacy results in older patients are not impacted by the compliance rate. The following demographic characteristics at baseline were observed: more male patients were included in total (55.7%) than females (44.3%), mean age across groups was 10.3 ± 2.44 years, in majority patients were in aged range of 9 and <12 years (39.1%) or between 12 and 14 years (36.0%). Most participants were White (68.5%) and were not Hispanic or Latino (73.3%); Asian (non-Indian) participants accounted for 14.4% and are known to be well responders to atropine based on published data. Mean participants' baseline SE was -2.69 ± 1.309 D and was similar between the treatment groups. As well, mean annual myopia progression rate prior to baseline was -0.59 ± 1.425 D; 26.3% of participants had had a progression of at least -0.50 D in the past 12 months, with a trend towards a lower proportion of participants in the Vehicle group (22.6%) compared with the SYD-101 groups (29.4% and 26.9%). The mean axial length was 24.44 ± 0.924 mm and not considered balanced between groups, as a difference in 1 mm influences the dioptric' value by 2.5D, knowing that the baseline dioptre values are not provided in Table 3.12. Most participants (69.3%) had dark iris, with a slightly higher number of participants with light iris in the SYD-101 0.01% group (34.8%) than in the Vehicle (27.7%) and the SYD-101 0.03% groups (29.7%). However, some essential baseline characteristics do not appear to be similar across groups. The applicant discussed the imbalance observed at baseline and its impact on efficacy results regarding patient's sex, race (in particularly Asian, and non-Asian) and iris colour and stated that the imbalance is considered negligible. Demographics were collected based on Asian and further subdivided into Indian and non-Indian and subgroup analyses supports the primary analysis in FAS, which is taken into account. Therefore, the issue was not pursued.

Regarding history of medical conditions, the applicant stated a similar frequency across groups with at least 1 medical history (the most frequently reported ocular medical history was retinal degeneration and the non-ocular medical history was seasonal allergy, followed by asthma, attention deficit, hyperactivity disorder and headache). As well, applicant described a total of 27 (3.2%) patients (9 (3.2%) in Vehicle group, 12 (4.3%) in SYD-101 0.01% and 6 (2.1%) in SYD-101 0.03% group) reported with at least 1 non-ocular prior medication. The most frequently reported medications were drugs for obstructive airway diseases and analgesics (each 4 (0.5%) participants overall). Ocular concomitant medications were reported in a total of 67 (7.9%) patients (24 (8.5%), 17 (6.0%) and 26 (9.2%) patients in the Vehicle, SYD-101 0.01% and SYD-101 0.03% groups respectively). The most frequently reported were artificial tears in 12 (1.4%) patients in total (4 (1.4%), 0 and 8 (2.8%) patients in the Vehicle, SYD-101 0.01% and SYD-101 0.03% groups respectively) and olopatadine hydrochloride in 11 (1.3%) patients in total (2 (0.7%), 4 (1.4%), and 5 (1.8%) patients in the Vehicle, SYD-101 0.01% and SYD-101 0.03% groups respectively). Non-ocular concomitant medications were reported in a total of 505 (59.6%) patients (171 (60.6%), 157 (55.7%) and 177 (62.5%) patients in the Vehicle, SYD-101 0.01% and SYD-101 0.03% groups respectively). The most frequently non-ocular concomitant medication in the overall patients (> 5%) were: tozinameran (15.9%), followed by ibuprofen (12.5%), paracetamol (9.4%), vitamin NOS (7.7%) loratadine (5.3%), and cetirizine hydrochloride (5.1%).

The applicant performed 2 subgroups analyses for fast progressors:

- subgroup 1 - patients with history of progression -0.5D/years or worse for any of the 3 history time intervals: 291 (34.2%) patients in total (93 (32.9%) and 95 (33.5%) in vehicle and SYD-101 0.01%, respectively).

- subgroup 2 - patients with history of progression -0.75D/years or worse for any of the 3 history time intervals: 225 (26.4%) patients in total (71 (25.1%) and 76 (26.8%) in vehicle and SYD-101 0.01%, respectively).

Observed imbalance in fast progressor subgroup 1 (32.9% and 33.5% patients in Vehicle and SYD101 0.01 groups, respectively) and subgroup 2 (25.1% and 26.8% patients in Vehicle and SYD101 0.01 groups, respectively) are discussed by the applicant and impact on efficacy results across age groups is considered acceptable. Compliance was high and similar in all treatment groups (98.26% in the vehicle group and 97.92% in the 0.1 mg/mL atropine group). The overall mean duration of exposure was 682.1 (SD 158.95) days, without marked differences between groups. No concerns arise from treatment compliance or exposure.

The primary endpoint at 24 months was the difference in mean annual myopic progression rate compared to vehicle and was statistically significant in both treatment groups with a difference compared to Vehicle of: 0.132 D (95% CI: 0.061, 0.204; p-value of 0.0003) for SYD-101 0.01%. However, this difference is inferior to the one pre-specified in the sample size (0.18 D or more). A total of 6 supplementary analyses ("PPS Multiple Imputation", "FAS Treatment Policy for Prohibited Treatment, Escape Therapy and Treatment Discontinuation", "FAS MAR Tipping Point", "FAS MNAR exclude Prohibited and Escape Observations", "FAS MNAR include Vehicle post Prohibited and Escape Observations", "MMRM no imputations") were performed. Results of the supplementary analyses were in line with the FAS results, except for sensibility analysis 3 (FAS MAR Tipping Point) for which significant differences were observed for all C values ranging from 0 to -0.5 in SYD-101 0.01% group.

It is to note that even if statistical differences are observed in supplementary analyses, even lower differences are observed, as in the PPS analysis where the difference in mean annual myopic progression rate compared to vehicle is : 0.123 (95% CI: 0.049, 0.198; p-value of 0.0012) for SYD-101 0.01%.

Other analyses regarding the difference in annual myopic progression rate at Month 24 were performed by:

- Age-range (3 to <6 years, 6 to <9 years, 9 to <12 years and 12 to 14 years): the difference appears statistically met only in SYD-101 0.01% vs vehicle group in 3 to <6 years, 6 to <9 years.

- History of myopic progression (participants with history of myopic progression of -0.5 D or worse and -1.0 D or worse), parental myopic progression (participants whose parents had no myopia), iris colour (light colour), region (European), race (Asian and Indian), sex (males in SYD-101 0.03% group), average time outdoors (in SYD-101 0.03% group) showed no marked difference and subgroups analysis were performed for most of these subgroups in small sample size. The applicant was requested to investigate the effect of treatment on the primary efficacy endpoint within the subgroups obtained as intersections of the age and severity groups. If some of the groups are too small, it was suggested to pool age categories. According to the originally presented subgroup analyses for the individual factors age and myopia severity (baseline SE) a higher treatment effect was observed for subjects with lower age and for subjects with mild myopia. The intention behind the request on subgroup analysis in interactions of age and severity groups was to understand whether the difference in the treatment effect between patients with mild and moderate myopia might be explained by different age distributions. If so, a similar treatment effect should be seen for patients with mild and moderate myopia when restricting to a small age interval. However, the provided subgroup analyses do not allow for any conclusions of this type as the investigated age intervals are too broad. It is understood that the investigation of smaller age intervals is not feasible due to small sample numbers. In summary, the applicant has provided the requested analyses, but they did not provide the expected insight.

The key secondary endpoint was the proportion of participants with myopic progression >0.75 D at or before Month 24 and was statistically met in treatment group, with a difference compared to Vehicle of: 10% (95% CI: 2.46, 17.49; p-value of 0.0181) for SYD-101 0.01%. A total of 6 supplementary analysis ("PPS Multiple Imputation", "FAS Treatment Policy for Prohibited Treatment, Escape Therapy and Treatment Discontinuation", "FAS MAR Tipping Point", "FAS MNAR exclude Prohibited and Escape Observations", "FAS MNAR include Vehicle post Prohibited and Escape Observations", "all missing considered progression") were performed. Results of the supplementary analyses were in line with the FAS results except for sensibility analysis 3 (FAS MAR Tipping Point) for which significant differences were observed for all C values ranging from 0 to -0.2 in SYD-101 0.01% group and supplementary analyses 1 (PPS multiple imputation) and 6 (all missing considered progression) where a difference between vehicle and SYD-101 0.01% was not statistically significant.

As for the primary endpoint, other analyses regarding the difference in annual myopic progression rate at Month 24 with regard to the key secondary endpoint were performed by:

- Age-range (3 to <6 years, 6 to <9 years, 9 to <12 years and 12 to 14 years): the difference appears statistically met only in SYD-101 0.01% vs vehicle group in 3 to <6 years, 6 to <9 years.

- History of myopic progression, parental myopic progression (participants whose parents had no myopia), iris colour, region (European), race (Asian and Indian), sex, average time outdoors or near work showed no marked difference as stated by the applicant**.**

Additionally, other secondary endpoints provided following results:

- Categorised myopia progression rate (≤0.25 D/year, ≤0.50 D/year or >0.50 D) through Month 24. The difference observed appeared statistically met in both SYD-101 groups compared to vehicle. The proportion of participants with annual myopia progression rate no worse than -0.25 D/year was 13.31% (95% CI: 4.97, 21.64; p-value of 0.0039) higher in the SYD-101 0.01% than in the vehicle group. The proportion of participants with annual myopia progression rate no worse than -0.50 D/year was 11.60% (95% CI: 4.40, 18.80; p-value of 0.0034) higher in the SYD-101 0.01% than in the vehicle group. Finally, the proportion of participants with annual myopia progression rate worse than -0.50 D was 12.60% (95% CI: 4.24, 20.96; p-value of 0.0066) higher in the SYD-101 0.01% than in the vehicle group.

- Time to progression of myopia of >0.75 D through Month 24 appeared later in SYD-101 0.01% group after the first year compared to the vehicle group.

- Mean annual progression rate at 24 months on subgroups of patients with refractive history of progression ≥ 0.5D and ≥ 0.75D were significantly lower in SYD-101 0.01% group. In patients with refractive history of progression of -0.50 D/year or worse, the mean difference compared to vehicle in annual progression rate from baseline to Month 24 was 0.204 D (95% CI: 0.102, 0.306; p-value 0.0001) in SYD-101 0.01%. In patients with refractive history of progression of -0.75 D/year or worse, the mean difference with vehicle in annual progression rate from baseline to Month 24 was 0.179 D (95% CI: 0.056, 0.301; p-value 0.0044) in SYD-101 0.01%.

In the responses, the applicant provided further discussion on Annual Progression Rate of Myopia and Change from Baseline in Spherical Equivalent (Difference to vehicle) at 24M and 36M for Ryjunea 0.1 mg/ml in the Full Analysis Set and in patients progressing 0.5 D/year or more. The provided results show that, there are significant differences in the results for the FAS population and the fast progressors (FP1), concerning the APR and SE at 24 and 36 months. In the FAS, Ryjunea 0.1 mg/mL demonstrated a difference to vehicle of 0.132 D/year (30%, p=0.0003) at 24 months and 0.079 D/year (21%, p=0.0002) at 36 months in APR, and of 0.238 D (33%, p<0.0001) and 0.215 D (23%, p=0.0022) in SE, respectively. In FP1, Ryjunea 0.1 mg/ml demonstrated a difference to vehicle of 0.204 D/year (38%, p<0.0001) at 24 months and 0.154 D/year (33%, p=0,0002) at 36 months in

APR, and of 0.388D (43%, p=0.0001) and 0.425D (38%, p=0.0012) in SE, respectively. These results demonstrate an increase in magnitude of treatment effect in terms of efficacy for fast progressors compared to the FAS, at 24 and 36 months, for both APR and SE. For SE, these results show a reduction in myopia progression of 43% at 24 months and 38% at 36 months in the FP1 group compared to 33% and 23%, respectively, in the FAS. The results in the FP1 group are close to the threshold of 40% reduction in progression (in SE) over 3 years acknowledged as being clinically meaningful, according to Wolffsohn (2019). However, even if these data are significant, they indicate a decline in treatment effectiveness over time. Even if the threshold was achieved by Ryjunea 0.1 mg/ml only at Month 24 (43% reduction in progression), the results at Month 36 remained mostly sustained. In the study, it is observed that younger population exhibit faster progression. According to the effect of age on the treatment effect of Ryjunea 0.1 mg/ml the corresponding % Change from Vehicle at 24 months also increases over the clinical threshold of 40% as the population gets younger. An increase in the magnitude of treatment effect in fast progressors was observed with Ryjunea 0.1 mg/ml, and that this effect remains mostly sustained at Month 36. This population, at the highest risk of complications caused by myopia, is also the one expected to benefit the most. It is also acknowledged it corresponds to younger children, since they exhibit faster progression. Therefore, the target population defined for Ryjunea as patients with a progression rate of 0.5 D or more per year, as proposed by the applicant, is endorsed.

However, the results for fast progressors (FP, patients progressing 0.5 D/year or more before enrolment) showed an increase in magnitude of treatment effect in terms of efficacy as compared to the FAS, at 24 and 36 months, for reduction of both annual progression rate (APR) and worsening of SE. When looking at FP subgroups by myopia severity, the clinical relevance of treatment effect of Ryjunea 0.1 mg/mL in subjects with -3.0 to -6.0 D at baseline remained questionable. The following findings are shown for change from baseline in SER (LS mean rates of the difference to vehicle) with consistent findings in the provided figures in the provided responses:

- -0.5 to -3.0 D: M24 0.617 (0.343, 0.892) nominal p<0.0001; M36 0.669 (0.305, 1.032) nominal p=0.0004;
- -3.0 to -6.0 D: M24 0.181 (-0.104, 0.465) nominal p=0.2118; M36 0.203 (-0.159, 0.564) nominal p=0.2685.

APR through Month 36 in fast progressors with higher myopia (-3.0 to -6.0 D) shows similar rates with 0.1 mg/mL and placebo. Considering all the above, the applicant was asked to discuss the study results and the clinical relevance for 0.1 mg/mL dose in case of initial myopia ranging -3.0 to -6.0 (which is also more at risk for myopia complications) in the target population. As discussed, it might be helpful to investigate the association between severity and treatment effect within age groups. While the numbers of patients within subgroups defined by age and severity may be too small to allow for informative subgroup analysis, a model including the three-way interaction between treatment, age (continuous, not subgroups) and baseline SE values could be investigated, which could allow to estimate the treatment effect for different combinations of age and severity values. Plotting the treatment effect versus severity conditioning on age (varying age in steps of 1 year in the age-range from 3-14 years) in the fast-progressing subgroup would allow to decide whether severity is indeed a predictive factor or whether the observed association between myopia severity and the treatment effect is confounded by age. For simplicity, the model might be restricted to the annualised progression rate at 24 months instead of including data for all timepoints. Based on this model, the applicant described treatment effects with Ryjunea throughout age and myopia severity groups. This was questioned. It was stressed that this model was designed as a tool to investigate whether severity is a predictive factor or whether the observed association between myopia severity and the treatment effect is confounded by age, but does not allow to reliably estimate the treatment effect for specific age-severity combinations. The model is too simplistic, assuming only linear effects of age and

severity. Moreover, even estimates from a more flexible model would be considered highly exploratory and would need to be evaluated on independent data.

Provided results on rebound from the literature are of major concern regarding the loss of efficacy after treatment cessation. As discussed, literature shows that rebound effect may occur in some cases even at concentrations as low as 0.1 mg/mL. Recent systematic reviews/meta-analyses (Lee S-H et al., 2024; Sánchez-Tena et al., 2024) on the rebound effect after cessation of atropine showed that the treatment effect (measured as the difference in SE) does likely decrease after atropine cessation, even in a 0.1 mg/mL treatment regimen. In the recent WA-ATOM study (Lee SS-Y et al., 2024), the cumulative myopia progression since baseline was overlapping between the 0.1 mg/mL atropine and the placebo groups one year after cessation of treatment. Those results from the literature are of major concern regarding the loss of efficacy after treatment cessation, albeit less concerning for the 0.1 mg/ml dose. Any potential rebound effects after cessation of treatment are planned to be minimised by recommending that treatment should be continued until disease stabilisation has occurred and when stopping treatment to consider tapering. Respective recommendations are included in the SmPC and are in line with WHO recommendations. However, further recommendation of treatment duration and tapering, may be informed with the awaited 48-month data from study SYD-101-001. Since the rebound effect has not been fully characterised (which includes not just a loss of effectiveness but also a faster progression after treatment is stopped, compared to what would happen without treatment), the data, along with the planned treatment until stabilisation, will be important for determining any further label update. The applicant has considered assessment comments and has withdrawn the 0.3 mg/mL Ryjunea strength. The applicant committed to submit the M48 data as PAES (as Annex II.D condition) as soon as they are available.

Mean change from baseline in **axial length** at Month 24 were performed at sites with the requisite equipment in only 48.8% of patients (based on 139, 139, and 135 participants in the vehicle, 0.1 mg/mL and 0.3 mg/mL groups, respectively). Difference in change from baseline (least square means) in AL compared to vehicle were: -0.05 mm (95% CI: -0.13, 0.02; p value of 0.1526) in SYD-101 0.01%. An increase in AL is considered as the main PD effect that would explain an increase in myopia. But no effect in AL was observed, hence PD is not clear. It is known that eye elongation decreases with age. A child's eye is meant to have normal growth, from birth until around the age of 12. In school-aged children, this growth is around 0.1 - 0.2 mm per year, slowing down after age 10 to around 0.1 mm per year and ceasing by the early teens. This might explain the lower effects observed in older patients. There is no significant difference between treatment groups and the vehicle control in the prespecified secondary EP in axial length, which is of concern. According to the applicant, in post hoc analyses a significant difference in AL between treatment groups was observed in participants aged 9 to <12 years old. This data could give further insight in underlying PD effects. The applicant was requested to discuss PD effects (AL) in correlation with observed effects in myopia progression focussing on specific age groups. Since requested data were provided, the issue can be considered resolved. However, PD effects underlying atropine treatment specifically effects on AL elongation are still uncertain, which is largely in line with what was observed in literature. In literature there is no consistency as regards the effect of atropine on axial elongation. Key findings from meta-analyses with atropine doses ranging from 0.01% to 1% and from the most pertinent randomised controlled trials using low dose atropine (defined as ≤0.5%) in the target indication are varying. On the one hand, no dose dependant effects with doses ranging from 0.01%-1% (Ha et al., 2022) were reported; on the other hand, effects showing that higher doses slow overall axial elongation by approximately 0.5 mm over 2 years (Cochrane review – Lawrenson et al., 2023), and dose related effects (0.05%, 0.5% 1%) (Zhao et al., 2020) were reported. The same is true for data obtained from randomised controlled trials using low dose (≤0.5%) atropine. Results from meta-analyses focussing on 0.01% atropine are also pointing in different directions. There are reports suggesting that 0.01% atropine can effectively slow down the axial lengthening (Zhang et al., 2023), but others conclude that 0.01% atropine

treatment significantly inhibits myopia progression and axial elongation (Sun et al., 2022). Similar diverse results were obtained across most pertinent randomised controlled trials using low dose atropine (≤0.5%) in the target indication. In conclusion, the PD effects underlying myopic progression are not clear and constitute an uncertainty. A respective statement was included in the SmPC section 5.1.

Regarding the exploratory endpoints, the mean time spent per day doing outdoor activities during daylight hours tended to be stable between Week 1 and Month 18, and increased slightly afterwards, but was similar across the 3 groups. Answer to QOL questionnaires were overall similar across groups.

2.8.7. Conclusions on clinical efficacy

The overall benefit/risk balance of Ryjunea 0.01% atropine eye drops is considered positive 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".* In order to further characterise the effects of Ryjunea and the rebound effects and progression of myopia after treatment cessation, the MAH should submit the 48 months follow-up results from the study SYD-101-001with due date 30.06.2026. (Annex II.D condition).

2.8.8. Clinical safety

The submitted dossier includes safety data of STN1012701 0.1 mg/mL and 0.3 mg/mL which was evaluated in a single pivotal phase III randomised, double-masked vehicle-controlled study (SYD-101-001). Safety and tolerability were evaluated over a range of clinical outcomes. These included the incidence and severity of ocular and non-ocular AEs, best-corrected visual acuity (BCVA), pupil diameter, binocular accommodative amplitude, intraocular pressure (IOP), vital signs, slit lamp examination, and ophthalmoscopy and change from baseline in corneal endothelial cell. Moreover, a tolerability questionnaire was administered to participants (or parents/guardians) to specifically assess the potential AEs of blurred vision, burning/stinging, eye pain, grittiness in eye, sensitivity to light, and headache. Clinic visits (AEs, concomitant medications, and concurrent procedures; with an investigator) took place at Screening, Baseline (Day 1), Month 3, Month 6, and every 6 months thereafter until Month 48 or Early Termination. A telephone visit with the study coordinator occurred at Week 2 and between clinic visits, from Months 9 through 39.

The proposed safety evaluation is considered appropriate to assess the safety profile of atropine low-dose including patient burden. In study SYD-101-001, safety analyses were conducted for subgroups (age, gender, iris colour, race, fast progressor status) although these analyses will be solely descriptive, this is endorsed. The safety profile of atropine is well-known and consists commonly of ocular AEs such as blurred vision, photophobia, mydriasis and non-ocular AEs such as headache which in long-term use may have an impact on the patient's daily life. Atropine ophthalmic solutions at higher strengths (0.5%, 1%) are approved in the European Union for a number of indications. The label of the reference product Atropin-POS 0.5% includes use as a mydriatic agent prior to determination of the refractive index but for example also indications for chronic use in acute and chronic intraocular inflammation of the iris. From a safety perspective, it is of relevance to note that the label of the significantly higher dosed reference product recommends use of up to 3 times per day, while the SmPC of Ryjunea recommends once daily administration before bedtime.

The study arms of study SYD-101-001 consist of atropine 0.01%, atropine 0.03% and control (H20). However, literature suggests that atropine 0.02% is the highest concentration that does not produce significant clinical symptoms from accommodation paresis or pupillary dilation. The study duration of 48 months (36 months of exposure and 12 months of withdrawal) is endorsed from a safety aspect as

long-term implications for vision, ocular health and accommodation are unknown. It is not clear whether long-term use could cause premature presbyopia, predispose to cataracts, or even cause retinal light harm in case of a small long-term dilation of the pupil.

The formulation contains a novel excipient D20 which D2O is not a component of any approved topical ophthalmic drug products in Europe and thus is a novel excipient for eye drops. Aqueous solutions of atropine are relatively unstable, and it was shown that the concentration of compounded low-dose atropine eye drops may vary (Richdale et al. 2023). The deuterium isotope is endogenously present in the human body and the applicant describes that if all of the daily dose were absorbed systemically, D2O in body fluids would temporarily increase from a normal amount of 0.015% to 0.016% (from 1.6 g to 1.68 g). In the proposed formulation, the daily dose of D_2O (one drop per eye per day) remains lower than its toxic threshold (>20% of body water replaced by high concentrations of D2O). The applied product solution is expected to be washed out by the tears (about 0.5 - 1 ml produced per eye per day). Based on this information, it seems rather unlikely that the solvent would have a systemic effect although a potential local effect of D_2O cannot be excluded. The Vehicle (control) contains H2O instead of D2O to evaluate the safety of the D2O-formulation, this is supported. Although, for a clear allocation of potential safety events to D2O or the active treatment an additional vehicle arm containing D2O would have been needed. Non-clinical data showed that D2O was not considered to be related to any kind of toxicity when dosed for 26 weeks once a day or three times per day in STN1012701 0.1 mg/mL formulation or three times per day in placebo control article. The use of the excipient D2O to replace H2O in the product Ryjunea (atropine sulphate, 0.1 mg/mL eye drops solution) is not considered to present a risk and long-term safety of D2O will be monitored through routine pharmacovigilance.

Additionally, the proposed formulation is not preservative-free as it contains BAK at 0.01%, which is a crucial issue, known to provoke irritation and burns, thus impacting compliance, management in daily-life practice and safety. No safety issue arose from pre-clinical data based on the 26-week ocular toxicity study with STN1012701 0.1 mg/mL in pigmented rabbit. In study SYD-101-001, all arms contained BAK in their formulation thus, the methodology does not allow to assess the risk associated with BAK in comparison with atropine or D20, in particular risk of ocular surface toxicity, as BAK is known to cause eye irritation, symptoms of dry eyes and may affect the tear film and corneal surface. The long-term safety will be assessed through routine pharmacovigilance in the PSURs. Use of BAK is at risk in patients with concurrent disorders of the cornea. In the SmPC, there is a warning for BAK in section 4.4 Special warnings and precautions for use as BAK is considered as an excipient with known effect (Annex to the European Commission guideline on 'Excipients in the labelling and package leaflet of medicinal products for human use' SANTE-2017-11668). Furthermore, the CHMP has recommended to investigate the feasibility of optimising the formulation with regards to this preservative.

Supportive data are available from a literature review describing the use of atropine in children with myopia when used in a range of doses between 0.01% and 1.0%. Of note, compounded atropine ophthalmic solutions at different strengths are used off-label for slowing myopia progression. The applicant further submitted an unpublished manuscript draft of an investigator-sponsored open label, prospective, observational cohort study of 147 children with myopia who started treatment with 0.01% or 0.03% atropine compounded by a pharmacy. For the evaluation of safety data from the literature and the unpublished manuscript, it has to be considered that Ryjunea includes D_2O (deuterium oxide, new excipient) as solvent instead of water.

2.8.8.1. Patient exposure

The double masked, randomised pivotal study has 2 active treatment groups (atropine 0.1 mg/mL and 0.3 mg/mL) and one vehicle group. One drop of assigned masked study drug is administered each night into each eye. Of note, as agreed during an EMA scientific advice procedure (EMEA/H/SA/4009/1/2018/PED/III), the vehicle group contains H2O instead of D2O. The solutions used for all three treatment groups (vehicle, 0.1 mg/mL=0.01%, 0.3 mg/mL = 0.03%) contain Benzalkonium chloride as preservative.

In study SYD-101-001, 852 participants were randomised at baseline in study SYD-101-001 including 283, 284 and 285 in control group (H20), atropine 0.01% group and atropine 0.03% group respectively. The safety set includes a total of 847 participants (vehicle: N=282, 0.1 mg/mL: N=282, 0.3 mg/mL: N=283) which is not in line with a recommendation given during EMA SA. During the scientific advice, the number of included participants by treatment arms was considered to be actually too low to detect even a common adverse event (appear in ≥1/100) with sufficient precision and it was recommended that the sample size is increased to have "at least 300 evaluable subjects per treatment group at the end of the 2-year treatment period". Concern in particular was raised for the 0.03% atropine dosing regimen for which safety data from literature are sparse. The applicant justified that after re-randomisation 400-to-500 subjects will have received 0.03% SYD-101 for at least one year (up to 48 Month) and that pooling of the active arms will provide sufficient safety data of the vehicle in comparison to placebo provided that no unexpected adverse events will occur. As requested, the applicant provided safety data up to 36 months, patients who were receiving the vehicle up to this point will be re-randomised according to protocol to the SYD-101 0.03% while patient treated by SYD-101 0.01% and 0.03% will either remain treated by SYD-101 0.01% or 0.03% respectively or be re-randomised to receive the vehicle. At month 36, 221 patients were treated with the vehicle, which means that up to 48 months 414 subjects are expected to complete at least 1 year of treatment under 0.3 mg/ml. Regarding the SYD-101 0.01% arm, a total of 230 patients completed Month 24 and 210 patients completed Month 36. At this stage, data up to month 48 which will comprise data from the randomised withdrawal phase (between months 36 and 48) are not yet available. Nevertheless, month 48 data from efficacy PAES will also provide further long-term safety information.

Of note, up to Month 24 there was a rather significant dropout until the data cut-off, as only a total of 232 (82.0%) participants in vehicle group, 228 (80.3%) participants in the 0.1 mg/mL group and 231 (81.1%) participants in the 0.3 mg/mL group completed Month 24. It is however reassuring that the dropouts were relatively balanced between the groups. Still, 5 (1.8%) participants discontinued the study due to AEs in the 0.03% atropine group (but none in the 0.01% or vehicle groups).

Up to the data lock point (05 June 2024), a total of 221 patients (78.1%) participants in vehicle group, 210 (73.9%) in STN1012701 0.1 mg/mL and 219 (76.8%) in STN1012701 0.3 mg/mL completed Month 36.

	Vehicle (N=282)	STN1012701 0.1 mg/mL (N=282)	STN1012701 0.3 mg/mL (N=283)	Total (N=847)
Duration of exposure (days)				
N	272	278	276	826
Mean (SD)	682.2 (161.11)	680.1 (156.73)	684.1 (159.56)	682.1 (158.95)
Median	734.0	732.0	737.5	734.0
Min, max	2, 795	50, 797	12, 793	2, 797
Duration category – n (%)				
Missing	0	1 (0.4)	0	1 (0.1)
≤ 91	4 (1.4)	5 (1.8)	3 (1.1)	12 (1.4)
92 - 182	6 (2.1)	2 (0.7)	9 (3.2)	17 (2.0)
183 - 280	5 (1.8)	8 (2.8)	5 (1.8)	18 (2.1)
281 - 364	6 (2.1)	6 (2.1)	4 (1.4)	16 (1.9)
365 - 546	10 (3.5)	17 (6.0)	9 (3.2)	36 (4.3)
547 - 728	85 (30.1)	79 (28.0)	77 (27.2)	241 (28.5)
729 - 910	156 (55.3)	161 (57.1)	169 (59.7)	486 (57.4)
Compliance (%)				
N	272	279	276	827
Mean (SD)	98.26 (2.869)	97.92 (4.019)	97.55 (6.119)	97.91 (4.548)
Median	99.47	99.59	99.55	99.54
Min, max	84.8, 100.0	64.3, 100.0	31.9, 100.0	31.9, 100.0
Compliance category – n (%)				
≥ 90	262 (92.9)	265 (94.0)	258 (91.2)	785 (92.7)
≥ 70 - < 90	10 (3.5)	13 (4.6)	15 (5.3)	38 (4.5)
≥ 50 - < 70	0	1 (0.4)	2 (0.7)	3 (0.4)
≥ 30 - < 50	0	0	1 (0.4)	1 (0.1)
< 30	0	0	0	0
NC	0	0	0	0

Note: Duration of Exposure was calculated in days as the following algorithm: (date of last dose – date of Day 1 visit + 1). NC: Not calculable, SD: Standard Deviation.
Percent Compliance was calculated as the mean percent compliance from each of the reporting periods. For each of the reporting period, the compliance was calculated as (Duration of Exposure in a Week/Month – Number of Reported Missed Doses in a Week/Month)/(Duration of Exposure in a Week/Month) * 100.

Table 31: Summary of treatment exposure and compliance – safety set, study SYD – 101-001

Up to Month 24, treatment discontinuation although similar between treatment arms (18.7% in vehicle group vs 19.7% in atropine 0.01% and 18.6% in atropine 0.03%) is considered high. The main reasons for patient's discontinuation were lost to follow-up (6.4% control; 7.7% atropine 0.01% and 6.3% atropine 0.03%) followed by withdrawal by parent or guardian (4.2% in control, 5.6% in atropine 0.01% and 0.03%) and withdrawal by subjects (4,9% control; 4,9% atropine 0.01% and 3.5% atropine 0.03%). The mean duration of exposure (SD) was 682.1 (158.95) days and comparable between the groups with more than 80% of the patients in each arms being treated ≥ 547 days. The reported compliance was overall high (97.91%) and only slightly lower in the 0.3 mg/mL group (97.55%), compared to the vehicle group (98.26%) and the 0.1 mg/mL group (97.92%). However, the compliance was calculated based on the number of reported missed doses and it cannot be excluded that there may have been some underreporting of missed doses in this paediatric population.

Up to Month 36, the overall mean (SD) duration of exposure was 973.4 (284.05) days, without marked differences between groups. Compliance was high and comparable between groups (above 97 % in all groups; 98.04% in Vehicle group, 97.80% in STN1012701 0.1 mg/mL group, and 97.50% in STN1012701 0.3 mg/mL randomised group) with only one patient in the STN1012701 0.3 mg/mL having a compliance below 50%.

Patient's disposition and demographic characteristics are further described and discussed in *Efficacy section*. It is to be noted, that the overall mean age at baseline was 10.3 years (SD 2.44) and the mean baseline refractive error was -2.69 D (SD 1.3) spherical equivalents (SE). According to the protocol, children between 3 and 14 years of age (inclusive) and with myopia of 0.50 D to 6.00 D were allowed for inclusion in the trial. In children with baseline myopia <0.75 D, participants must have had a history of myopia progression of 0.50 D in the previous 6 to 12 months.

2.8.8.2. Adverse events

2.8.8.2.1. Common adverse events

In study SYD-101-001, up to Month 24, among the 847 participants in the safety set, 554 reported a total of 1545 treatment emergent adverse events. A higher incidence of any TEAEs was reported in the atropine 0.03% (70.0%) arm compared to atropine 0.01% (64.9%) arm and control (61.3%) arm, which is consistent with a dose-adverse effect correlation. This was driven by a clearly higher reported incidence of ocular TEAEs in the atropine 0.03% arm (55.5%), followed by atropine 0.01% (42.9%), and control (40.1%) arms, while non-ocular TEAEs were more reported in the control arm (47.5%), compared to atropine 0.03% (44.9%) and atropine 0.01% (39.4%) arms suggesting that the safety profile of Ryjunea is mainly characterised by local adverse reactions.

Serious TEAEs were reported in low proportions and in slightly higher incidence in atropine 0.03% (2.8%), while being comparable between atropine 0.01% (1.4%) and control (1.8%). Serious TEAEs were for the majority non-ocular TEAEs, and in slightly higher incidence in the atropine 0.03% arm (2.5%), compared to atropine 0.01% arm (1.1%) and control (1.8%).

Regarding TEAEs which were considered related by the investigator, a dose-related increase in incidences was noted for any related TEAEs (vehicle: 33%, 0.1 mg/mL: 35.8%, 0.3 mg/mL: 47%), any related ocular TEAEs (vehicle: 30.9%, 0.1 mg/mL: 34.8%, 0.3 mg/mL: 44.9%), and also any related non-ocular TEAEs but with considerably lower frequencies (vehicle: 4.6%, 0.1 mg/mL: 5.7%, 0.3 mg/mL: 11.3%). The same trend as described for subject incidences was also noted with respect to the actual numbers of reported related events. No serious TEAEs were assessed as drug related. TEAEs leading to study discontinuation were reported in similar proportions between atropine 0.01% and control (0.7%) arms while reported in higher proportion in the atropine 0.03% (2.5%).

In general, similar proportions of ocular and non-ocular TEAEs lead to study discontinuation in treatment arms (1.4% vs 1.1% and 0.4% vs 0.4% for atropine 0.03% and control group respectively), except for atropine 0.01% where solely ocular TEAEs lead to study drug discontinuation (0.7%). No TEAEs conducted to patient's death in all treatment arms. The data above are summarised in Table 32 as follows.

Table 32: Overall summary of treatment-emergency adverse events through month 24 – safety set

Number Of Participants With	Vehicle (N=282) n (%) [E]	SYD-101 0.01% (N=282) n (%) [E]	SYD-101 0.03% (N=283) n (%) [E]	Total (N=847) n (%) [E]
Any TEAE	183 (64.9) [555]	173 (61.3) [443]	198 (70.0) [547]	554 (65.4) [1545]
Ocular TEAE	113 (40.1) [215]	121 (42.9) [225]	157 (55.5) [314]	391 (46.2) [754]
Non-ocular TEAE	134 (47.5) [340]	111 (39.4) [218]	127 (44.9) [233]	372 (43.9) [791]
Any serious TEAE	5 (1.8) [7]	4 (1.4) [4]	8 (2.8) [10]	17 (2.0) [21]
Ocular TEAE	1 (0.4) [1]	1 (0.4) [1]	1 (0.4) [1]	3 (0.4) [3]
Non-ocular TEAE	5 (1.8) [6]	3 (1.1) [3]	7 (2.5) [9]	15 (1.8) [18]
Any study drug-related TEAE	93 (33.0) [146]	101 (35.8) [175]	133 (47.0) [267]	327 (38.6) [588]
Ocular TEAE	87 (30.9) [133]	98 (34.8) [157]	127 (44.9) [234]	312 (36.8) [524]
Non-ocular TEAE	13 (4.6) [13]	16 (5.7) [18]	32 (11.3) [33]	61 (7.2) [64]
Any study drug-related serious TEAE	0	0	0	0
Ocular TEAE	0	0	0	0
Non-ocular TEAE	0	0	0	0
Any TEAE leading to study drug discontinuation	2 (0.7) [2]	2 (0.7) [2]	7 (2.5) [8]	11 (1.3) [12]
Ocular TEAE	1 (0.4) [1]	2 (0.7) [2]	4 (1.4) [5]	7 (0.8) [8]
Non-ocular TEAE	1 (0.4) [1]	0	3 (1.1) [3]	4 (0.5) [4]
Any TEAE leading to death	0	0	0	0
Ocular TEAE	0	0	0	0
Non-ocular TEAE	0	0	0	0

TEAE: treatment-emergent adverse event

Note: TEAE Leading to Treatment Discontinuation are identified as AEs where the action taken with study drug is "Drug withdrawn" or "Caused treatment discontinuation" field is marked Yes. If the relationship to study drug for an AE is missing, the AE is reported as "Related". At each level of summarization, a participant is counted once if the participant reported one or more events. Events are summarized based on treatment received at the time of event.

n represents the number of participants at each level of summarization.

[E] represents the number of events at each level of summarization.

Adverse Events were coded using MedDRA v26.0.

Up to Month 36, a higher proportion of patients presented at least one TEAEs in the 0.3 mg/mL group (72.4%) compared to STN1012701 0.1 mg/mL group (64.9%) and vehicle group (68.8%) due to ocular TEAE (44.7% in vehicle, 44.7% % STN1012701 0.1 mg/mL group and 57.6% in STN1012701 0.3 mg/mL group) and TEAE study related (34.4% in vehicle, 38.3% STN1012701 0.1 mg/mL group and 48.8% in STN1012701 0.3 mg/mL group) which were mainly ocular TEAEs (32.6% in vehicle, 36.2% STN1012701 0.1 mg/mL group and 46.6% in STN1012701 0.3 mg/mL group). Serious TEAEs were reported in low proportions: 6 (2.1%) participants in the Vehicle group reported a total of 8 serious TEAEs, 4 (1.4%) participants in the STN1012701 0.1 mg/mL group reported a total of 4 serious TEAEs, and 8 (2.8%) participants in the STN1012701 0.3 mg/mL randomised group reported a total of 10 serious TEAEs. One serious ocular TEAEs was reported in one patient in each group. No serious ocular TEAEs were assessed as related to study treatment. TEAEs leading to study drug discontinuation were reported in 2 (0.7%) participants in the Vehicle group, 1 (0.4%) participant in the STN1012701 0.1 mg/mL group and 7 (2.5%) participants in the STN1012701 0.3 mg/mL randomised group. Non-ocular TEAEs were more reported in the vehicle group (52.5%) compared to STN1012701 0.1 mg/mL (46.8%) and STN1012701 0.3 mg/mL randomised group (50.2%). Non-ocular TEAEs considered as related to the study treatment were reported more frequently in the STN1012701 0.3 mg/mL randomised group (11.7% vs 6.7% in STN1012701 0.1 mg/mL group and 4.6% in the vehicle) and consisted solely of headache at Year 3. Serious non-ocular TEAEs were reported in low proportions in each treatment group (2.1% in the vehicle, 1.1% in STN1012701 0.1 mg/mL group and 2.5% in STN1012701 0.3 mg/mL group) and none were related to study treatment. Non-ocular TEAEs leading to study drug discontinuation were reported solely in the STN1012701 0.3 mg/mL randomised group (1.1%). No death was reported up to Month 36. The data above are summarised in Table 33 as follows.

Table 33: Overall summary of TEAEs through month 36 – safety set, study SYD-101-001

Number Of Participants With	Vehicle (N=282) n (%) [E]	STN1012701 0.1 mg/mL (N=282) n (%) [E]	STN1012701 0.3 mg/mL			Total (N=847) n (%) [E]
			STN1012701 0.3 mg/mL (N=283) n (%) [E]	Escape (N=35) n (%) [E]	0.3 mg/mL Total (N=307) n (%) [E]	
Any TEAE	**194 (68.8) [721]**	**183 (64.9) [560]**	**205 (72.4) [656]**	**7 (20.0) [19]**	**210 (68.4) [675]**	**584 (68.9) [1956]**
Ocular TEAE	126 (44.7) [253]	126 (44.7) [260]	163 (57.6) [344]	5 (14.3) [12]	168 (54.7) [356]	418 (49.4) [869]
Non-ocular TEAE	148 (52.5) [468]	132 (46.8) [300]	142 (50.2) [312]	6 (17.1) [7]	146 (47.6) [319]	424 (50.1) [1087]
Any serious TEAE	**6 (2.1) [8]**	**4 (1.4) [4]**	**8 (2.8) [10]**	**0**	**8 (2.6) [10]**	**18 (2.1) [22]**
Ocular TEAE	1 (0.4) [1]	1 (0.4) [1]	1 (0.4) [1]	0	1 (0.3) [1]	3 (0.4) [3]
Non-ocular TEAE	6 (2.1) [7]	3 (1.1) [3]	7 (2.5) [9]	0	7 (2.3) [9]	16 (1.9) [19]
Any study drug-related TEAE	**97 (34.4) [166]**	**108 (38.3) [193]**	**138 (48.8) [290]**	**4 (11.4) [10]**	**142 (46.3) [300]**	**346 (40.9) [659]**
Ocular TEAE	92 (32.6) [152]	102 (36.2) [172]	132 (46.6) [256]	4 (11.4) [9]	136 (44.3) [265]	329 (38.8) [589]
Non-ocular TEAE	13 (4.6) [14]	19 (6.7) [21]	33 (11.7) [34]	1 (2.9) [1]	34 (11.1) [35]	66 (7.8) [70]
Any study drug-related serious TEAE	**0**	**0**	**0**	**0**	**0**	**0**
Ocular TEAE	0	0	0	0	0	0
Non-ocular TEAE	0	0	0	0	0	0
Any TEAE leading to study drug discontinuation	**2 (0.7) [2]**	**1 (0.4) [1]**	**7 (2.5) [8]**	**1 (2.9) [2]**	**8 (2.6) [10]**	**11 (1.3) [13]**
Ocular TEAE	2 (0.7) [2]	1 (0.4) [1]	4 (1.4) [5]	1 (2.9) [2]	5 (1.6) [7]	8 (0.9) [10]
Non-ocular TEAE	0	0	3 (1.1) [3]	0	3 (1.0) [3]	3 (0.4) [3]
Any TEAE leading to death	**0**	**0**	**0**	**0**	**0**	**0**
Ocular TEAE	0	0	0	0	0	0
Non-ocular TEAE	0	0	0	0	0	0

Abbreviations: AE = Adverse Event; MedDRA = Medical Dictionary For Regulatory Activities; TEAE = Treatment-Emergent Adverse Event.

Note: TEAE Leading to Treatment Discontinuation are identified as AEs where the action taken with study drug is "Drug withdrawn" or "Caused treatment discontinuation" field is marked as "Yes". Related events include those reported as 'Possibly Related' or 'Related' or with missing relationship. At each level of summarisation, a participant is counted once if the participant reported one or more events. Events are summarised based on treatment received at the time of event.

2.8.8.2.2. Ocular adverse events

Up to month 24, in study SYD-101-001, the imbalances with respect to ocular TEAEs were driven by three particular events, namely photophobia (vehicle: 16.7%, 0.1 mg/mL: 24.1%, 0.3 mg/mL: 30.4%), vision blurred (vehicle: 8.2%, 0.1 mg/mL: 10.3%, 0.3 mg/mL: 18%), and mydriasis (vehicle: 0.4%, 0.1 mg/mL: 1.8%, 0.3 mg/mL: 7.1%). These adverse events are in line with the mechanism of action of atropine as well as the administration site and a high proportion of these events were also considered related by the Investigator. Other ocular events such as Eye irritation, Eye pain, Instillation site pain, Instillation site Irritation, Foreign body sensation were either more reported in the control arm or observed in similar frequency between control and treatment groups, except for the AE of conjunctival papillae. The data above are summarised in Table 34 as follows.

Table 34: Summary of frequency ocular TEAEs with 1% or greater incidence through month 24 – safety set, study SYD-101-001

System Organ Class Preferred Term	Vehicle (N=282) n (%) [E]	STN1012701 0.1 mg/mL (N=282) n (%) [E]	STN1012701 0.3 mg/mL (N=283) n (%) [E]	Total (N=847) n (%) [E]
All ocular TEAE	**113 (40.1) [215]**	**121 (42.9) [225]**	**157 (55.5) [314]**	**391 (46.2) [754]**
Eye Disorders	**92 (32.6) [165]**	**114 (40.4) [188]**	**145 (51.2) [275]**	**351 (41.4) [628]**
Conjunctival Papillae	2 (0.7) [2]	7 (2.5) [7]	3 (1.1) [4]	12 (1.4) [13]
Eye Irritation	10 (3.5) [12]	8 (2.8) [8]	6 (2.1) [6]	24 (2.8) [26]
Eye Pain	14 (5.0) [17]	8 (2.8) [10]	11 (3.9) [11]	33 (3.9) [38]
Foreign Body Sensation in Eyes	17 (6.0) [20]	18 (6.4) [19]	17 (6.0) [18]	52 (6.1) [57]
Mydriasis	1 (0.4) [1]	5 (1.8) [6]	20 (7.1) [22]	26 (3.1) [29]
Photophobia	47 (16.7) [52]	68 (24.1) [72]	86 (30.4) [101]	201 (23.7) [225]
Vision Blurred	23 (8.2) [25]	29 (10.3) [31]	51 (18.0) [59]	103 (12.2) [115]
General Disorders and Administration Site Conditions	**29 (10.3) [33]**	**26 (9.2) [27]**	**28 (9.9) [32]**	**83 (9.8) [92]**
Instillation Site Irritation	17 (6.0) [20]	19 (6.7) [20]	18 (6.4) [21]	54 (6.4) [61]
Instillation Site Pain	12 (4.3) [13]	7 (2.5) [7]	10 (3.5) [10]	29 (3.4) [30]

TEAE: treatment-emergent adverse event

Note: At each level of participant summarisation, a participant was counted once if the participant reported one or more events. Events are summarised based on treatment received at the time of event.

n represents the number of participants at each level of summarisation.

[E] represents the number of events at each level of summarisation.

Adverse Events were coded using MedDRA, V26.0

Similar findings were observed up to Month 36. Through Month 36, the most frequently (≥10%) reported ocular TEAEs included photophobia (25.6%) and vision blurred (13.1%). Other frequent (≥1%) ocular TEAEs included instillation site irritation (9.6%), foreign body sensation in eyes (6.6%), eye pain (4.0%), mydriasis (3.7%), eye irritation (3.2%), conjunctival papillae (1.5%), conjunctivitis (1.2%), conjunctivitis allergic (1.1%), dry eye (1.1%), and punctate keratitis (1.1%). Photophobia, vision blurred and mydriasis were clearly more frequently reported in the STN1012701 0.3 mg/mL group. The data above are summarised in Table 35 as follows.

Table 35: Summary of frequency ocular TEAEs with 1% or greater incidence through month 26 – safety set, study SYD-101-001

System Organ Class Preferred Term	Vehicle (N=282) n (%) [E]	STN1012701 0.1 mg/mL (N=282) n (%) [E]	STN1012701 0.3 mg/mL			Total (N=847) n (%) [E]
			STN1012701 0.3 mg/mL (N=283) n (%) [E]	Escape (N=35) n (%) [E]	0.3 mg/mL Total (N=307) n (%) [E]	
Eye Disorders	**105 (37.2) [192]**	**118 (41.8) [211]**	**149 (52.7) [296]**	**4 (11.4) [9]**	**153 (49.8) [305]**	**374 (44.2) [708]**
Conjunctival Papillae	2 (0.7) [2]	8 (2.8) [8]	3 (1.1) [4]	0	3 (1.0) [4]	13 (1.5) [14]
Conjunctivitis Allergic	2 (0.7) [2]	2 (0.7) [2]	4 (1.4) [4]	1 (2.9) [2]	5 (1.6) [6]	9 (1.1) [10]
Dry eye	2 (0.7) [2]	3 (1.1) [3]	4 (1.4) [4]	0	4 (1.3) [4]	9 (1.1) [9]
Eye Irritation	12 (4.3) [14]	9 (3.2) [9]	6 (2.1) [6]	0	6 (2.0) [6]	27 (3.2) [29]
Eye Pain	14 (5.0) [17]	9 (3.2) [11]	11 (3.9) [11]	0	11 (3.6) [11]	34 (4.0) [39]
Foreign Body Sensation in Eyes	19 (6.7) [22]	20 (7.1) [21]	17 (6.0) [19]	0	17 (5.5) [19]	56 (6.6) [62]
Mydriasis	4 (1.4) [4]	5 (1.8) [6]	21 (7.4) [24]	1 (2.9) [2]	22 (7.2) [26]	31 (3.7) [36]
Photophobia	53 (18.8) [61]	72 (25.5) [80]	89 (31.4) [107]	3 (8.6) [3]	92 (30.0) [110]	217 (25.6) [251]
Punctate Keratitis	1 (0.4) [1]	5 (1.8) [5]	3 (1.1) [3]	0	3 (1.0) [3]	9 (1.1) [9]
Vision Blurred	26 (9.2) [29]	30 (10.6) [33]	54 (19.1) [67]	1 (2.9) [1]	55 (17.9) [68]	111 (13.1) [130]
General Disorders and Administration Site Conditions	**30 (10.6) [34]**	**27 (9.6) [29]**	**30 (10.6) [35]**	**2 (5.7) [2]**	**32 (10.4) [37]**	**89 (10.5) [100]**
Instillation Site Irritation	29 (10.3) [33]	24 (8.5) [26]	27 (9.5) [31]	1 (2.9) [1]	28 (9.1) [32]	81 (9.6) [91]
Infections and Infestations	**12 (4.3) [12]**	**10 (3.5) [11]**	**7 (2.5) [7]**	**1 (2.9) [1]**	**8 (2.6) [8]**	**30 (3.5) [31]**
Conjunctivitis	5 (1.8) [5]	4 (1.4) [5]	1 (0.4) [1]	0	1 (0.3) [1]	10 (1.2) [11]

Ocular adverse reactions were often reported with a very long duration and the observed pattern for the most reported ocular AE are coherent with the reported AE: majorly continuous for mydriasis (range duration all arms included 2 to 1091 days, mean duration 130 days) and majorly intermittent

for the other events which are photophobia (range duration all arms included 1 to 1444 days, mean duration 173 days), vision blurred (range duration all arms included 1 to 734 days, mean duration 149 days), eye irritation (range duration all arms included 1 to 795 days), Instillation site irritation (range duration all arms included 1 to 1278 days), foreign body sensation (range duration all arms included 1 to 693 days) and eye pain (range duration all arms included 1 to 1150 days). Events were longer or comparable to the vehicle in SYD except for eye irritation (151.6 days in SYD and 216.9 days for vehicle). Two non-serious events of Mydriasis and photophobia assessed as related to study drug (0.01% atropine sulfate for both) were recovered with sequelae with no further details. Upon request, the applicant added information on the duration of certain TEAEs (photophobia, vision blurred, eye irritation) in section 4.8 of the SmPC.

Ocular TEAEs were for the majority mild (27.7% control; 28.4% in atropine 0.01%; 33.9% in atropine 0.03%) and moderate (11.7% control; 14.2% in atropine 0.01%; 20.1% in atropine 0.03%) in severity. Severe TEAEs were reported in low proportions (0.7% control; 0.4% in atropine 0.01%; 1.1% in atropine 0.03%) and consisted of blindness transient (serious, intermittent, recovered, duration of event of one day, not related, control arm), ulcerative keratitis (continuous, recovered with sequelae, duration of event of 7 days, not related, control arm)**,** papilledema (serious, continuous, not recovered, drug withdrawn, not related, atropine 0.01% arm), photophobia (intermittent, not recovered, dose not changed, related to study drug, atropine 0.03% arm), vision blurred (intermittent, duration of event of 258 days, recovered, drug not changed, related to study drug, atropine 0.03% arm), instillation site irritation (intermittent, not recovered, drug not changed, related to study drug, atropine 0.03% arm), optic neuritis (serious, continuous, duration of event of 52 days, recovered, drug withdrawn, not related, atropine 0.03% arm) in one patient each and foreign body sensation in eye (intermittent, duration of event of 12 days, recovered, not related, drug not changed, atropine 0.03% arm) in two patients each.

In the atropine 0.03% arm, three events of severe intensity were assessed as related to study drug in one participant (3 years old patient): intermittent photophobia (time to onset 2 days, bilateral, not recovered), intermittent vision blurred (time to onset 2 days, bilateral, severe from day 535 to day 793, not recovered) and intermittent instillation site irritation (time to onset 62 days, bilateral, severe from day 535, not recovered). No ocular TEAEs of severe intensity occurred between Month 24 and Month 36. The data above are summarised in Table 36 as follows.

Table 36: Summary of ocular TEAEs related to study drug, by system organ class and preferred term through month 24 - safety set, study SYD-101--011

System Organ Class Preferred Term	Vehicle (N=282) n (%) [E]	STN1012701 0.1 mg/mL (N=282) n (%) [E]	STN1012701 0.3 mg/mL (N=283) n (%) [E]	Total (N=847) n (%) [E]
Number Of Participants With At Least One Ocular Drug-Related TEAE	**87 (30.9) [133]**	**98 (34.8) [157]**	**127 (44.9) [234]**	**312 (36.8) [524]**
Eye Disorders	**68 (24.1) [99]**	**85 (30.1) [128]**	**115 (40.6) [202]**	**268 (31.6) [429]**
Accommodation Disorder	0	1 (0.4) [1]	6 (2.1) [6]	7 (0.8) [7]
Anisocoria	0	0	2 (0.7) [2]	2 (0.2) [2]
Asthenopia	1 (0.4) [1]	0	0	1 (0.1) [1]
Blepharitis	0	0	1 (0.4) [1]	1 (0.1) [1]
Chalazion	0	0	1 (0.4) [1]	1 (0.1) [1]
Conjunctival Hyperaemia	1 (0.4) [1]	0	1 (0.4) [1]	2 (0.2) [2]
Conjunctival Papillae	1 (0.4) [1]	2 (0.7) [2]	1 (0.4) [1]	4 (0.5) [4]
Conjunctivitis Allergic	0	0	1 (0.4) [1]	1 (0.1) [1]
Diplopia	0	0	1 (0.4) [1]	1 (0.1) [1]
Dry Eye	0	0	1 (0.4) [1]	1 (0.1) [1]
Eye Allergy	1 (0.4) [1]	0	0	1 (0.1) [1]
Eye Discharge	0	1 (0.4) [1]	0	1 (0.1) [1]
Eye Irritation	9 (3.2) [10]	4 (1.4) [4]	3 (1.1) [3]	16 (1.9) [17]
Eye Pain	8 (2.8) [10]	6 (2.1) [8]	9 (3.2) [9]	23 (2.7) [27]
Eye Pruritus	1 (0.4) [1]	1 (0.4) [1]	0	2 (0.2) [2]
Foreign Body Sensation in Eyes	11 (3.9) [11]	13 (4.6) [14]	10 (3.5) [11]	34 (4.0) [36]
Lacrimation Increased	1 (0.4) [1]	0	0	1 (0.1) [1]
Mydriasis	0	5 (1.8) [6]	19 (6.7) [21]	24 (2.8) [27]
Myopia	1 (0.4) [1]	0	0	1 (0.1) [1]
Ocular Hyperaemia	0	1 (0.4) [1]	0	1 (0.1) [1]
Photophobia	38 (13.5) [42]	62 (22.0) [66]	80 (28.3) [95]	180 (21.3) [203]
Pupil Fixed	0	0	1 (0.4) [1]	1 (0.1) [1]
Vision Blurred	18 (6.4) [19]	22 (7.8) [24]	41 (14.5) [46]	81 (9.6) [89]
Visual Acuity Reduced	0	0	1 (0.4) [1]	1 (0.1) [1]
General Disorders and Administration Site Conditions	**28 (9.9) [32]**	**26 (9.2) [27]**	**28 (9.9) [32]**	**82 (9.7) [91]**
Instillation Site Discomfort	0	0	1 (0.4) [1]	1 (0.1) [1]
Instillation Site Irritation	16 (5.7) [19]	19 (6.7) [20]	18 (6.4) [21]	53 (6.3) [60]
Instillation Site Pain	12 (4.3) [13]	7 (2.5) [7]	10 (3.5) [10]	29 (3.4) [30]
Investigations	**1 (0.4) [1]**	**1 (0.4) [1]**	**0**	**2 (0.2) [2]**
Intraocular Pressure Increased	1 (0.4) [1]	0	0	1 (0.1) [1]
Vital Dye Staining Cornea Present	0	1 (0.4) [1]	0	1 (0.1) [1]
Infections and Infestations	**1 (0.4) [1]**	**0**	**0**	**1 (0.1) [1]**
Conjunctivitis Bacterial	1 (0.4) [1]	0	0	1 (0.1) [1]
Skin and Subcutaneous Tissue Disorders	**0**	**1 (0.4) [1]**	**0**	**1 (0.1) [1]**
Madarosis	0	1 (0.4) [1]	0	1 (0.1) [1]

TEAE: treatment-emergent adverse event

Note: The total number of AEs counts all treatment-emergent AEs for participants. At each level of participant summarisation, a participant was counted once for the most related event if the participant reported one or more events. Related events include those reported as 'Possibly Related' or 'Related' or with missing relationship. Events are summarised based on treatment received at the time of event.

n represents the number of participants at each level of summarisation.

[E] represents the number of events at each level of summarisation.

Adverse Events were coded using MedDRA, V26.0

Up to Month 24, a higher incidence of ocular TEAEs assessed as study drug related were reported in the atropine 0.03% (44.9%) compared to atropine 0.01% (34.8%) and control (30.9%). The most reported PT in all treatment arms were photophobia (28.3% in atropine 0.03%; 22,0% in atropine 0.01% and 13.5% in control), vision blurred (14.5% in atropine 0.03%; 22.0% in atropine 0.01% and

13.5% in control), Mydriasis (6.7% in atropine 0.03%; 1.8% in atropine 0.01% and 0% in control) and Instillation site disorders (6.4% in atropine 0.03%; 6.7% in atropine 0.01% and 5.7% in control). Photophobia, Mydriasis and Vision blurred were more reported in the atropine groups with a higher frequency in the 0.03% which is consistent with the known safety profile of atropine. Accommodation disorder was more reported in the atropine 0.03% (2.1%) compared to atropine 0.01% (0.4%) and control (0%).

Other ocular TEAEs related to the study drug reported in more than 1 participant were instillation site irritation, foreign body sensation in eyes, instillation site pain (more reported in control), eye pain, eye irritation (more reported in control), conjunctival papillae, anisocoria, eye pruritus and conjunctival hyperaemia without marked difference between treatment groups (less than 1% difference).

Up to Month 36, similar findings were observed. A total of 589 ocular TEAEs in 329 participants were considered as related to the study treatment, with a higher frequency in the STN1012701 0.3 mg/mL group: 92 (32.6%) participants in Vehicle group (152 events), 102 (36.2%) participants in STN1012701 0.1 mg/mL group (172 events), 132 (46.6%) participants in STN1012701 0.3 mg/mL randomised group (256 events) and 4 (11.4%) participants in STN1012701 0.3 mg/mL escape group (9 events). In escape STN1012701 0.3 mg/mL group, the only ocular TEAE considered related to the study drug reported in more than 1 participant was photophobia (8.6%). The data above are summarized in Table 37 as follows.

Table 37: Summary of ocular TEAEs related to study drug, by system organ class and preferred term through month 36 – safety set, study SYD-101-001

System Organ Class Preferred Term	Vehicle (N=282) n (%) [E]	STN1012701 0.1 mg/mL (N=282) n (%) [E]	STN1012701 0.3 mg/mL			Total (N=847) n (%) [E]
			STN1012701 0.3 mg/mL (N=283) n (%) [E]	Escape (N=35) n (%) [E]	0.3 mg/mL Total (N=307) n (%) [E]	
Number Of Participants With At Least One Ocular Drug-Related TEAE	**92 (32.6) [152]**	**102 (36.2) [172]**	**132 (46.6) [256]**	**4 (11.4) [9]**	**136 (44.3) [265]**	**329 (38.8) [589]**
Eye Disorders	**74 (26.2) [115]**	**87 (30.9) [139]**	**120 (42.4) [221]**	**3 (8.6) [7]**	**123 (40.1) [228]**	**283 (33.4) [482]**
Accommodation Disorder	0	1 (0.4) [1]	6 (2.1) [6]	0	6 (2.0) [6]	7 (0.8) [7]
Anisocoria	0	0	3 (1.1) [3]	0	3 (1.0) [3]	3 (0.4) [3]
Asthenopia	1 (0.4) [1]	0	0	0	0	1 (0.1) [1]
Blepharitis	0	0	1 (0.4) [1]	0	1 (0.3) [1]	1 (0.1) [1]
Chalazion	0	0	1 (0.4) [1]	0	1 (0.3) [1]	1 (0.1) [1]
Conjunctival Hyperaemia	2 (0.7) [2]	0	1 (0.4) [1]	0	1 (0.3) [1]	3 (0.4) [3]
Conjunctival Papillae	1 (0.4) [1]	2 (0.7) [2]	1 (0.4) [1]	0	1 (0.3) [1]	4 (0.5) [4]
Conjunctivitis Allergic	0	0	1 (0.4) [1]	0	1 (0.3) [1]	1 (0.1) [1]
Diplopia	0	0	1 (0.4) [1]	0	1 (0.3) [1]	1 (0.1) [1]
Dry Eye	0	0	1 (0.4) [1]	0	1 (0.3) [1]	1 (0.1) [1]
Eye Allergy	1 (0.4) [1]	0	0	1 (2.9) [1]	1 (0.3) [1]	2 (0.2) [2]
Eye Discharge	0	1 (0.4) [1]	0	0	0	1 (0.1) [1]
Eye Inflammation	0	0	1 (0.4) [1]	0	1 (0.3) [1]	1 (0.1) [1]
Eye Irritation	10 (3.5) [11]	4 (1.4) [4]	3 (1.1) [3]	0	3 (1.0) [3]	17 (2.0) [18]
Eye Pain	8 (2.8) [10]	6 (2.1) [8]	9 (3.2) [9]	0	9 (2.9) [9]	23 (2.7) [27]
Eye Pruritus	1 (0.4) [1]	0	0	0	0	1 (0.1) [1]
Foreign Body Sensation in Eyes	11 (3.9) [11]	14 (5.0) [15]	11 (3.9) [12]	0	11 (3.6) [12]	36 (4.3) [38]
Lacrimation Increased	1 (0.4) [1]	0	0	0	0	1 (0.1) [1]
Mydriasis	3 (1.1) [3]	5 (1.8) [6]	20 (7.1) [23]	1 (2.9) [1]	21 (6.8) [25]	29 (3.4) [34]
Myopia	1 (0.4) [1]	0	0	0	0	1 (0.1) [1]
Ocular Discomfort	0	0	1 (0.4) [1]	0	1 (0.3) [1]	1 (0.1) [1]
Ocular Hyperaemia	0	1 (0.4) [1]	0	0	0	1 (0.1) [1]
Photophobia	43 (15.2) [50]	66 (23.4) [74]	83 (29.3) [101]	3 (8.6) [3]	86 (28.0) [104]	195 (23.0) [228]
Punctate Keratitis	0	2 (0.7) [2]	0	0	0	2 (0.2) [2]
Pupil Fixed	0	0	1 (0.4) [1]	0	1 (0.3) [1]	1 (0.1) [1]
Vision Blurred	20 (7.1) [22]	22 (7.8) [25]	43 (15.2) [53]	1 (2.9) [1]	44 (14.3) [54]	86 (10.2) [101]
Visual Acuity Reduced	0	0	1 (0.4) [1]	0	1 (0.3) [1]	1 (0.1) [1]
General Disorders and Administration Site Conditions	**30 (10.6) [34]**	**27 (9.6) [29]**	**30 (10.6) [35]**	**2 (5.7) [2]**	**32 (10.4) [37]**	**89 (10.5) [100]**
Instillation Site Discomfort	0	0	1 (0.4) [1]	0	1 (0.3) [1]	1 (0.1) [1]
Instillation Site Irritation	29 (10.3) [33]	24 (8.5) [26]	27 (9.5) [31]	1 (2.9) [1]	28 (9.1) [32]	81 (9.6) [91]
Instillation Site Pain	1 (0.4) [1]	2 (0.7) [2]	3 (1.1) [3]	1 (2.9) [1]	4 (1.3) [4]	7 (0.8) [7]
Instillation Site Pruritus	0	1 (0.4) [1]	0	0	0	1 (0.1) [1]
Infections and Infestations	**2 (0.7) [2]**	**2 (0.7) [2]**	**0**	**0**	**0**	**4 (0.5) [4]**
Conjunctivitis	0	2 (0.7) [2]	0	0	0	2 (0.2) [2]
Conjunctivitis Bacterial	2 (0.7) [2]	0	0	0	0	2 (0.2) [2]
Skin and Subcutaneous Tissue Disorders	**1 (0.4) [1]**	**1 (0.4) [1]**	**0**	**0**	**0**	**2 (0.2) [2]**
Madarosis	0	1 (0.4) [1]	0	0	0	1 (0.1) [1]
Yellow Skin	1 (0.4) [1]	0	0	0	0	1 (0.1) [1]
Investigations	**0**	**1 (0.4) [1]**	**0**	**0**	**0**	**1 (0.1) [1]**
Vital Dye Staining Cornea Present	0	1 (0.4) [1]	0	0	0	1 (0.1) [1]

The event of yellow skin reported up to Month 24 was initially considered as a non-ocular related TEAE. When reprocessing the data for the Month 36 results, yellow skin was categorised as an ocular related TEAE as it was described as "yellow skin around the eye".

In the SmPC section 4.8, the applicant included the most reported TEAEs assessed as study related which consisted of photophobia, mydriasis and vision blurred. The applicant also included the TEAEs Accommodation disorder, eye irritation, foreign body sensation in eyes and anisocoria. This is endorsed. The applicant provided justification for not including in section 4.8 of the SmPC, the following terms: Instillation site irritation, Instillation site pain (as the term Eye pain and Eye irritation are already included under the SOC Eye disorders), Eye pruritus (pooled with other similar PT as Eye irritation), Conjunctival hyperaemia (reported only once up to Month 36) and Conjunctivitis (since the aetiology is not clear, the two conjunctivitis cases do not have to be included in the SmPC, but the applicant committed to analyse allergic and BAK-induced toxicity conjunctivitis as part of the PSUR, see information further below). The applicant included two other terms based on data up to 36 month since a causal relationship cannot be excluded: Conjunctival papillae (vehicle: 2 subjects; 0.1 mg/mL: 8 subjects; 0.3 mg/mL: 3 subjects) with some assessed as related by the investigator (vehicle: 1 subject; 0.1 mg/mL: 2 subjects; 0.3 mg/mL: 1 subjects) and Punctate keratitis with two events assessed as related by the investigators being reported in STN1012701 0.1 mg/mL group between months 24 and 36.

In the phase 3 Study SYD-101-001, one event of allergic conjunctivitis was considered related by the Investigator. The grade 1 event occurred on day 23 and resolved 13 days afterwards. The study drug was not withdrawn, which questions whether the conjunctivitis was related to allergy against atropine (or the excipient BAK). Until the new safety data cut-off, no additional events of allergic conjunctivitis were reported. Requesting inclusion of allergic conjunctivitis as ADR in section 4.8 based on this one particular report may indeed not be justified. However, based on the known allergenic potential and reports of allergic conjunctivitis after treatment with atropine ocular solutions in children with myopia in the literature. The applicant agreed to analyse allergic and BAK-induced toxicity conjunctivitis as part of the upcoming first three PSURs with a once-yearly PSUR frequency, and longer if deemed necessary based on the gathered information.

Between Year 1 and Year 2 of treatment exposure, a decrease could be observed regarding the proportions of reported Ocular TEAEs assessed as related to study drug (38.5% vs 15.5% in atropine 0.03%; 32.3% vs 9.2% for atropine 0.01% and 27.3% vs 7.8% for control group for Year 1 and 2 respectively). Thus, the number of participants with at least one ocular TEAE in the 2nd year decreased by ~60-70% compared to the number of participants with TEAEs in the 1st year (converting to a relative reduction by -71.4, -71.5, -59.7%). Between Year 1 and Year 2, the incidences of photophobia (11.7% vs 3.9%, 20.6% vs 5.3%, and 25.4% vs 6.7% for control, atropine 0.01% and atropine 0.03% respectively) and vision blurred (5.7% vs 1,8%, 6.7% vs 1.8%, and 11.7% vs 4.9% for control, atropine 0.01% and atropine 0.03% respectively) assessed as related to study drug decreased. Similar findings were found when looking at other possibly related/related TEAEs. The data above are summarised in Table 38 as follows.

Table 38: TEAEs related to study treatment reported during the first and second study years – safety set, study SYD-101-001

	Vehicle		STN1012701 0.1 mg/mL		STN1012701 0.3 mg/mL	
	Year 1	Year 2	Year 1	Year 2	Year 1	Year 2
At least 1 related TEAE (%)	27.3	7.8	32.3	9.2	38.5	15.5
Photophobia	11.7	3.9	20.6	5.3	25.4	6.7
Vision blurred	5.7	1.8	6.7	1.8	11.7	4.9
Instillation site irritation	5.3	0.7	6.7	0.7	6.0	1.8
Instillation site pain	3.9	0.4	2.5	0	3.2	0.4
Foreign body sensation in eyes	3.5	1.4	4.6	0.4	3.5	0.4
Eye pain	2.5	0.4	1.4	1.4	1.8	1.4
Eye irritation	2.1	1.8	1.1	0.7	1.1	0.4
Asthenopia	0.4	0	0	0	0	0
Conjunctival hyperaemia	0.4	0.4	0	0	0.4	0
Conjunctival papillae	0.4	0	0.7	0	0	0.4
Eye allergy	0.4	0	0	0	0	0
Eye pruritus	0.4	0	0.4	0	0	0
Lacrimation increased	0.4	0	0	0	0	0
Myopia	0.4	0	0	0	0	0
Conjunctivitis bacterial	0.4	0	0	0	0	0
Accommodation disorder	0	0	0.4	0.4	1.8	0.4
Conjunctivitis allergic	0	0	0	0	0.4	0
Diplopia	0	0	0	0	0.4	0
Eye discharge	0	0	0.4	0	0	0
Mydriasis	0	0	1.8	0	6.4	1.4
Ocular hyperaemia	0	0	0.4	0	0	0
Pupil fixed	0	0	0	0	0.4	0
Instillation site discomfort	0	0	0	0	0.4	0
Madarosis	0	0	0.4	0	0	0
Aniscoria	0	0	0	0	0	0.7
Blepharatis	0	0	0	0	0	0.4
Chalazion	0	0	0	0	0	0.4
Dry eye	0	0	0	0	0	0.4
Visual acuity reduced	0	0	0	0	0	0.4
Intraocular pressure increased	0	0.4	0	0	0	0
Vital dye staining cornea present	0	0	0	0.4	0	0

Ocular TEAEs decreased through the years with 593 in year 1, 157 in year 2 and 111 in year 3 and similar tendency was seen for ocular treatment related TEAE. Regarding severity, the majority of the TEAEs were mild to moderate through the years up to 36 months. Four ocular TEAEs were severe (Table 29) and of those three occurred during year 1 (optic neuritis, blindness transient and papilledema) and one during year 3 (ulcerative keratitis, vehicle group). Up to 36 months, 10 ocular TEAEs lead to study drug discontinuation with the majority (0.9%; n=8) occurring during the first year and the other two during the second year. No serious ocular TEAEs occurred between Month 12 to Month 36. The data above are summarised in Table 39 as follows.

Table 39: TEAEs related to study treatment by study year – safety set, study SYD-101-001

	Vehicle			STN1012701 0.1 mg/mL			STN1012701 0.3 mg/mL		
	Year 1	Year 2	Year 3	Year 1	Year 2	Year 3	Year 1	Year 2	Year 3*
At least 1 related TEAE (%)	27.3	7.8	5.7	32.3	9.2	8.5	38.5	15.5	10.4
Photophobia	11.7	3.9	2.8	20.6	5.3	4.6	25.4	6.7	4.6
Vision blurred	5.7	1.8	1.4	6.7	1.8	1.1	11.7	4.9	2.6
Instillation site irritation	5.3	0.7	0	6.7	0.7	0.7	6.0	1.8	2.0
Instillation site pain	3.9	0.4	0	2.5	0	0	3.2	0.4	0.7
Foreign body sensation in eyes	3.5	1.4	0	4.6	0.4	0.4	3.5	0.4	0.3
Eye pain	2.5	0.4	0	1.4	1.4	1.1	1.8	1.4	0
Eye irritation	2.1	1.8	0.7	1.1	0.7	0.4	1.1	0.4	0.3
Accommodation disorder	0	0	0	0.4	0.4	0	1.8	0.4	0.3

2.8.8.2.3. Non-ocular adverse events

Table 40: Summary of frequency non-ocular TEAEs with 1% of greater incidence through month 24 – safety set, study SYD-101-001

System Organ Class Preferred Term	Vehicle (N=282) n (%) [E]	STN1012701 0.1 mg/mL (N=282) n (%) [E]	STN1012701 0.3 mg/mL (N=283) n (%) [E]	Total (N=847) n (%) [E]
All non-ocular TEAE	**134 (47.5) [340]**	**111 (39.4) [218]**	**127 (44.9) [233]**	**372 (43.9) [791]**
Infections and infestations	**75 (26.6) [107]**	**49 (17.4) [68]**	**52 (18.4) [70]**	**176 (20.8) [245]**
COVID-19	34 (12.1) [36]	22 (7.8) [22]	24 (8.5) [26]	80 (9.4) [84]
Influenza	6 (2.1) [6]	4 (1.4) [4]	3 (1.1) [3]	13 (1.5) [13]
Nasopharyngitis	7 (2.5) [8]	11 (3.9) [13]	11 (3.9) [12]	29 (3.4) [33]
Pharyngitis Streptococcal	4 (1.4) [6]	3 (1.1) [5]	4 (1.4) [4]	11 (1.3) [15]
Upper respiratory tract infection	7 (2.5) [10]	7 (2.5) [7]	3 (1.1) [3]	17 (2.0) [20]
Nervous system disorders	**46 (16.3) [61]**	**34 (12.1) [38]**	**42 (14.8) [53]**	**122 (14.4) [152]**
Headache	42 (14.9) [53]	30 (10.6) [34]	41 (14.5) [46]	113 (13.3) [133]
Injury, Poisoning and Procedural Complications	**18 (6.4) [32]**	**20 (7.1) [27]**	**21 (7.4) [28]**	**59 (7.0) [87]**
Concussion	3 (1.1) [3]	3 (1.1) [3]	3 (1.1) [3]	9 (1.1) [9]
Ligament Sprain	4 (1.4) [4]	3 (1.1) [3]	2 (0.7) [2]	9 (1.1) [9]
Skin And Subcutaneous Tissue Disorders	**17 (6.0) [19]**	**16 (5.7) [17]**	**11 (3.9) [11]**	**44 (5.2) [47]**
Acne	7 (2.5) [7]	5 (1.8) [5]	3 (1.1) [3]	15 (1.8) [15]
Psychiatric Disorders	**20 (7.1) [26]**	**8 (2.8) [10]**	**9 (3.2) [11]**	**37 (4.4) [47]**
Anxiety	6 (2.1) [6]	4 (1.4) [4]	1 (0.4) [1]	11 (1.3) [11]
Attention Deficit Hyperactivity Disorder	7 (2.5) [7]	2 (0.7) [2]	0	9 (1.1) [9]
General Disorders and Administration Site Conditions	**7 (2.5) [9]**	**6 (2.1) [6]**	**8 (2.8) [8]**	**21 (2.5) [23]**
Pyrexia	3 (1.1) [4]	6 (2.1) [6]	4 (1.4) [4]	13 (1.5) [14]
Immune System Disorders	**6 (2.1) [7]**	**2 (0.7) [2]**	**8 (2.8) [8]**	**16 (1.9) [17]**
Seasonal Allergy	4 (1.4) [5]	2 (0.7) [2]	6 (2.1) [6]	12 (1.4) [13]

TEAE: treatment-emergent adverse event
Note: At each level of participant summarisation, a participant was counted once if the participant reported one or more events. Events are summarised based on treatment received at the time of event.
n represents the number of participants at each level of summarisation.
[E] represents the number of events at each level of summarisation.
Adverse Events were coded using MedDRA, V26.0

Up to Month 24, the most reported non-ocular TEAEs (≥10%) were Headache (14.9% in control [53 events], 10.6% in atropine 0.01% [34 events] and 14.5% in atropine 0.03% [46 events]) and COVID-19 (12.1% in control, 7,8% in atropine 0.01% and 8.5% in atropine 0.03%). Other frequent non-ocular TEAEs (incidence ≥1%) were nasopharyngitis (3.4%), upper respiratory tract infection (2.0%), acne (1.8%), influenza (1.5%), pyrexia (1.5%), seasonal allergy (1.4%), pharyngitis streptococcal

(1.3%), anxiety (1.3%), concussion (1.1%), ligament sprain (1.1%) and attention deficit hyperactivity disorder (1.1%). For most of these events such as respiratory infections and similar events described above, it seems unlikely that they were caused by low doses of locally administered atropine and were more consistent with the paediatric population. Of note, atropine inhibits sweat secretion and thus may influence temperature regulation. There was a trend for slightly higher incidences of pyrexia in the atropine treatment groups (vehicle: 1.1% with 3 events, 0.1 mg/mL: 2.1% with 6 events, 0.3 mg/mL: 1.4% with 4 events). Up to Month 36, there were 3 new events of pyrexia, 2 in the vehicle group and 1 in the 0.1 mg/mL atropine group. Overall, the rates of pyrexia until month 36 were relatively balanced between the groups (vehicle: 1.8% with 5 events, 0.1 mg/mL: 2.5% with 7 events, 0.3 mg/mL: 1.4% with 4 events) and no dose-related increase is detected. The low dose of atropine included in Ryjunea is acknowledged. Regarding anxiety and ADHD, most events were reported in the vehicle group.

Up to Month 36, among 1087 non-ocular TEAEs reported, the most frequent (≥10%) non-ocular TEAEs included Headache with 51 (18.1%) participants in the Vehicle group, 35 (12.4%) participants in the STN1012701 0.1 mg/mL group, and 46 (16.3%) participants in the STN1012701 0.3 mg/mL, and COVID-19 with 46 (16.3%) participants in the Vehicle group, 30 (10.6%) participants in the STN1012701 0.1 mg/mL group, and 33 (11.7%) participants in the STN1012701 0.3 mg/mL group.

In escape STN1012701 0.3 mg/mL group, the most frequently reported non-ocular TEAE was COVID-19 (2 [5.7%] participants). Other frequent (≥1%) non-ocular TEAEs included nasopharyngitis (4.4%), upper respiratory tract infection (3.0%), acne (2.4%), seasonal allergy (2.2%), influenza (2.1%), anxiety (2.0%), attention deficit hyperactivity disorder, pyrexia (1.9% each), pharyngitis streptococcal, ligament sprain, depression, SARS-Cov-2 Test Positive (1.5% each), oropharyngeal pain (1.3%), cough (1.2%), concussion and arthralgia (1.1% each).

Table 41: Summary of frequency non-ocular TEAEs with 1% or greater incidence though month 36 – safety set, study SYD-101-001

System Organ Class Preferred Term	Vehicle (N=282) n (%) [E]	STN1012701 0.1 mg/mL (N=282) n (%) [E]	STN1012701 0.3 mg/mL			Total (N=847) n (%) [E]
			STN1012701 0.3 mg/mL (N=283) n (%) [E]	STN1012701 0.1 mg/mL (N=282) n (%) [E]	STN1012701 0.3 mg/mL (N=283) n (%) [E]	
All non-ocular TEAE	**148 (52.5) [468]**	**132 (46.8) [300]**	**142 (50.2) [312]**	**6 (17.1) [7]**	**146 (47.6) [319]**	**424 (50.1) [1087]**
Infections and infestations	**88 (31.2) [149]**	**62 (22.0) [92]**	**72 (25.4) [103]**	**3 (8.6) [3]**	**75 (24.4) [106]**	**224 (26.4) [347]**
COVID-19	46 (16.3) [49]	30 (10.6) [31]	33 (11.7) [37]	2 (5.7) [2]	35 (11.4) [39]	111 (13.1) [119]
Influenza	7 (2.5) [7]	5 (1.8) [5]	6 (2.1) [6]	0	6 (2.0) [6]	18 (2.1) [18]
Nasopharyngitis	10 (3.5) [13]	13 (4.6) [16]	14 (4.9) [15]	0	14 (4.6) [15]	37 (4.4) [44]
Pharyngitis Streptococcal	5 (1.8) [10]	4 (1.4) [6]	4 (1.4) [4]	0	4 (1.3) [4]	13 (1.5) [20]
Upper respiratory tract infection	11 (3.9) [19]	9 (3.2) [10]	5 (1.8) [6]	0	5 (1.6) [6]	25 (3.0) [35]
Nervous system disorders	**56 (19.9) [78]**	**41 (14.5) [48]**	**47 (16.6) [62]**	**1 (2.9) [1]**	**48 (15.6) [63]**	**145 (17.1) [189]**
Headache	51 (18.1) [68]	35 (12.4) [40]	46 (16.3) [55]	1 (2.9) [1]	47 (15.3) [56]	133 (15.7) [164]
Injury, Poisoning and Procedural Complications	**21 (7.4) [38]**	**25 (8.9) [34]**	**25 (8.8) [34]**	**0**	**25 (8.1) [34]**	**71 (8.4) [106]**
Concussion	3 (1.1) [3]	3 (1.1) [3]	3 (1.1) [3]	0	3 (1.0) [3]	9 (1.1) [9]
Ligament Sprain	4 (1.4) [5]	5 (1.8) [5]	4 (1.4) [4]	0	4 (1.3) [4]	13 (1.5) [14]
Respiratory, Thoracic And Mediastinal Disorders	**24 (8.5) [27]**	**17 (6.0) [24]**	**16 (5.7) [16]**	**2 (5.7) [2]**	**18 (5.9) [18]**	**59 (7.0) [69]**
Cough	4 (1.4) [4]	3 (1.1) [3]	2 (0.7) [2]	1 (2.9) [1]	3 (1.0) [3]	10 (1.2) [10]
Oropharyngeal Pain	5 (1.8) [5]	4 (1.4) [6]	2 (0.7) [2]	0	2 (0.7) [2]	11 (1.3) [13]
Psychiatric Disorders	**27 (9.6) [44]**	**14 (5.0) [18]**	**16 (5.7) [19]**	**0**	**16 (5.2) [19]**	**57 (6.7) [81]**
Anxiety	11 (3.9) [12]	5 (1.8) [6]	1 (0.4) [1]	0	1 (0.3) [1]	17 (2.0) [19]
Attention Deficit Hyperactivity Disorder	10 (3.5) [10]	3 (1.1) [3]	3 (1.1) [3]	0	3 (1.0) [3]	16 (1.9) [16]
Depression	5 (1.8) [5]	4 (1.4) [4]	4 (1.4) [4]	0	4 (1.3) [4]	13 (1.5) [13]
Skin And Subcutaneous Tissue Disorders	**23 (8.2) [30]**	**20 (7.1) [23]**	**12 (4.2) [12]**	**0**	**12 (3.9) [12]**	**55 (6.5) [65]**
Acne	10 (3.5) [10]	6 (2.1) [6]	4 (1.4) [4]	0	4 (1.3) [4]	20 (2.4) [20]
Musculoskeletal And Connective Tissue Disorders	**13 (4.6) [14]**	**9 (3.2) [9]**	**9 (3.2) [10]**	**0**	**9 (2.9) [10]**	**31 (3.7) [33]**
Arthralgia	2 (0.7) [2]	4 (1.4) [4]	3 (1.1) [3]	0	3 (1.0) [3]	9 (1.1) [9]
General Disorders and Administration Site Conditions	**10 (3.5) [14]**	**8 (2.8) [9]**	**8 (2.8) [8]**	**0**	**8 (2.6) [8]**	**26 (3.1) [31]**
Pyrexia	5 (1.8) [6]	7 (2.5) [7]	4 (1.4) [4]	0	4 (1.3) [4]	16 (1.9) [17]
Immune System Disorders	**10 (3.5) [11]**	**5 (1.8) [5]**	**10 (3.5) [13]**	**0**	**10 (3.3) [13]**	**25 (3.0) [29]**
Seasonal Allergy	7 (2.5) [8]	4 (1.4) [4]	8 (2.8) [10]	0	8 (2.6) [10]	19 (2.2) [22]
Investigation	**7 (2.5) [8]**	**8 (2.8) [8]**	**5 (1.8) [5]**	**0**	**5 (1.6) [5]**	**20 (2.4) [21]**
SARS-Cov-2 Test Positive	5 (1.8) [6]	3 (1.1) [3]	5 (1.8) [5]	0	5 (1.6) [5]	13 (1.5) [14]

Abbreviations: MedDRA = Medical Dictionary For Regulatory Activities; SARS-Cov-2 = Severe acute respiratory syndrome coronavirus 2; TEAE = treatment-emergent adverse event

Note: At each level of participant summarisation, a participant was counted once if the participant reported one or more events. Events are summarised based on treatment received at the time of event.

Most non-ocular TEAEs were mainly mild (23.4% in control, 20.9% in atropine 0.01% and 23.3% in atropine 0.03%) to moderate (23.0% in control, 17.0% in atropine 0.01% and 17.7% in atropine 0.03%) in severity. Severe non-ocular TEAEs were low and higher in atropine 0.03% (3.9% vs 1.1% in control and 1.4% in atropine 0.01%). Severe non-ocular TEAEs consisted of dizziness postural (serious, control), fall (control), forearm fracture (control), intentional overdose (1 in each arm), craniocerebral injury (atropine 0.01%), colitis ulcerative (serious, atropine 0.01%), COVID-19 (serious, atropine 0.03%), headache (atropine 0.03%); seizure (serious, atropine 0.03%), radius fracture (atropine 0.03%), eating disorders (serious, atropine 0.03%), major depression (atropine 0.03%),

suicide attempt (atropine 0.03%), anaphylactic reaction (atropine 0.03%), supraventricular tachycardia (serious, atropine 0.03%) and pectus excavatum (serious, atropine 0.03%) in one patient each and appendicitis (atropine 0.03%) in two patient. None of these events were assessed as related to study drug and none of the overdose occurred with study drug.

Non-ocular TEAEs of severe intensity that occurred between Month 24 and Month 36 included: Vehicle group: 1 event of anxiety, 1 event of depression, 1 event of major depression, 1 event of suicidal ideation all in a single (0.4%) participant and STN1012701 0.1 mg/mL group: 1 event of cartilage injury in 1 (0.4%) participant. None were assessed as related to study treatment.

Table 42: Summary of non-ocular TEAEs related to study drug, by system organ class and preferred term through month 24 – safety set, study SYD-101-001

System Organ Class Preferred Term	Vehicle (N=282) n (%) [E]	STN1012701 0.1 mg/mL (N=282) n (%) [E]	STN1012701 0.3 mg/mL (N=283) n (%) [E]	Total (N=847) n (%) [E]
Number Of Participants With At Least One Non-Ocular Drug-Related TEAE	**13 (4.6) [13]**	**16 (5.7) [18]**	**32 (11.3) [33]**	**61 (7.2) [64]**
Nervous System Disorders	**11 (3.9) [11]**	**15 (5.3) [17]**	**32 (11.3) [32]**	**58 (6.8) [60]**
Headache	11 (3.9) [11]	15 (5.3) [17]	32 (11.3) [32]	58 (6.8) [60]
Cardiac Disorders	**0**	**1 (0.4) [1]**	**0**	**1 (0.1) [1]**
Sinus Tachycardia	0	1 (0.4) [1]	0	1 (0.1) [1]
Gastrointestinal Disorders	**0**	**0**	**1 (0.4) [1]**	**1 (0.1) [1]**
Nausea	0	0	1 (0.4) [1]	1 (0.1) [1]
Psychiatric Disorders	**1 (0.4) [1]**	**0**	**0**	**1 (0.1) [1]**
Insomnia	1 (0.4) [1]	0	0	1 (0.1) [1]
Skin And Subcutaneous Tissue Disorders	**1 (0.4) [1]**	**0**	**0**	**1 (0.1) [1]**
Yellow Skin	1 (0.4) [1]	0	0	1 (0.1) [1]

TEAE: treatment-emergent adverse event
Note: The total number of AEs counts all treatment-emergent AEs for participants. At each level of participant summarisation, a participant was counted once if the participant reported one or more events. Related events include those reported as 'Possibly Related' or 'Related' or with missing relationship. Events are summarised based on treatment received at the time of event.
n represents the number of participants at each level of summarisation.
[E] represents the number of events at each level of summarisation.
Adverse Events were coded using MedDRA, V26.0

Non-ocular TEAEs were assessed as related to study drug in more than 1 patient consisted of Headache (11.3% in atropine 0.03% vs 5.3% in atropine 0.01% and 3.9% in control). While the overall numbers of headache events (regardless of relatedness) were comparable or even slightly higher in the vehicle group, clearly more events of headache were considered related by the Investigator for the high dose group (vehicle: 3.9%, 0.1 mg/mL: 5.1%, 0.3 mg/mL: 11.3%). The applicant clarified that the exact hour/minute timing of the TEAEs was not recorded in the pivotal study. Therefore, it remains unknown whether the TEAEs occurred shortly after dose administration or later. The average duration of headache events was presented but no dose-related effect was observed (185.5 days in STN1012701 0.1 mg/mL group; 135.9 days in STN1012701 0.3 mg/mL group; 132.8 days in Vehicle group). Higher rates of continued headaches were reported for the vehicle group (incidence with continuous pattern: 7.5% in STN1012701 0.1 mg/mL group; 10.9% in STN1012701 0.3 mg/mL group; 28.2% in Vehicle group), while the rates of intermittent headaches were relatively higher in the atropine groups (incidence with intermittent pattern: 92.5% in STN1012701 0.1 mg/mL group; 89.1% in STN1012701 0.3 mg/mL group; 71.8% in Vehicle group). Up to Month 36, Headache was the only non-ocular TEAE considered related to the study drug by the Investigator that was reported in more than 1 participant overall. It was reported at a higher frequency in the STN1012701 0.3 mg/mL randomised group (11.7%) than the Vehicle (4.3%) and the STN1012701 0.1 mg/ml

(6.4%) groups. In the escape STN1012701 0.3 mg/mL group, only 1 non-ocular TEAE was considered related to the study drug: headache, reported in 1 (2.9%) participant.

Other non-ocular TEAE assessed as study drug relate were reported in one patient each: sinus tachycardia (continuous, mild, dose not changed, not recovered, atropine 0,01%), nausea (intermittent, duration of event 1 day, mild, dose not changed, recovered, atropine 0,03%), insomnia (control) and yellow skin (control). The one related event of nausea was considered mild/grade 1 and co-occurred with mild/grade 1 headache. Both events resolved on the same day. For the event of sinus tachycardia (grade 1, continuous), the onset was on Day 140 and the event was still ongoing at the time of the data cut-off (up to Month 24). The applicant provided the case narrative. The patient was treated with a betablocker (metoprolol, Vasocardin). Both treatment with SYD001 and the event continued. However, two weeks after first occurrence of the event, the participant withdrew from the study (reason: "withdrawal by subject"). The event was considered possibly related to the study drug. The only concomitant medication was Aerius (desloratadine). Of note, tachycardia is listed as very rare adverse reaction for desloratadine (Aerius). The applicant describes that the participant had no reported underlying medical condition that could explain the mild tachycardia and that it is unusual that tachycardia would last as long as in this patient when appropriate treatment is given. Two other events of tachycardia during the phase 3 trial, one in the STN1012701 0.3 mg/ml group and one in the vehicle group. The event in the STN1012701 0.3 mg/ml group (SAE, narratives provided in the initial submission) was considered not related to study drug (not reasonably temporally associated with administration) but instead attributed to the concomitant disease of Wolff-Parkinson-White syndrome. The occurrence in the vehicle group was an event of postural orthostatic tachycardia syndrome (ongoing). Due to the low dose included in Ryjunea, tachycardia may be more relevant for a scenario of overdosing. Section 4.9 of the SmPC already describes tachycardia as potential symptom of overdose. In addition, section 4.4 includes a warning stating that Ryjunea must be used with special caution in patients with tachycardia (and other cardiac disorders). These measures are considered sufficient at this point in time but as suggest by the applicant, another assessment for inclusion of this event in 4.8 should be made once the phase 3 study is complete.

Regarding non-ocular TEAEs reported between Year 1 and 2 of treatment exposure, the number of participants with at least one non-ocular TEAE were considerably more frequent in the 1st year (4.3, 5.3, 10.2%) than in the 2nd year (0.7, 1.1, 2.8%), converting to a relative reduction by approximately 72-84%. Between Year 1 and Year 2, the frequency of Headache decreased (3.5% vs 0,7%; 5.0% vs 1,1%; and 10.2% vs 2,8% for control, atropine 0,01% and atropine 0,03% respectively). During Year 2, the only non-ocular TEAEs reported as study drug related was headache. Similar results were observed at month 36 with 1.1% in vehicle, 0.7% in STN1012701 0.1 mg/mL and 1.0% in STN1012701 0.3 mg/mL. Regarding severity per year, while the number of reported events of Headache decreased through the years, the number of mild and severe events remained stable between Year 2 and Year 3. 19 non-ocular SAEs were reported up to month 36 of which the majority occurred during year 1 of treatment and none were assessed as related to study drug. Furthermore, 3 non-ocular TEAEs led to study drug discontinuation of 3 (0.4%) participants by end of month 36, all in the STN1012701 0.3 mg/mL randomised group and these events occurred all in the first year and were not considered as related to study drug.

2.8.8.3. Serious adverse event/deaths/other significant events

2.8.8.3.1. Serious ocular adverse events

Table 43: Summary of serious ocular treatment-emergency adverse events by system organ class and preferred term through month 24 – safety set, study SYD-101-001

System Organ Class Preferred Term	Vehicle (N=282) n (%) [E]	STN1012701 0.1 mg/mL (N=282) n (%) [E]	STN1012701 0.3 mg/mL (N=283) n (%) [E]	Total (N=847) n (%) [E]
All Treatment-Emergent Serious Adverse Events	**1 (0.4) [1]**	**1 (0.4) [1]**	**1 (0.4) [1]**	**3 (0.4) [3]**
Eye Disorders	**1 (0.4) [1]**	**1 (0.4) [1]**	**0**	**2 (0.2) [2]**
Blindness Transient	1 (0.4) [1]	0	0	1 (0.1) [1]
Papilloedema	0	1 (0.4) [1]	0	1 (0.1) [1]
Nervous System Disorders	**0**	**0**	**1 (0.4) [1]**	**1 (0.1) [1]**
Optic Neuritis	0	0	1 (0.4) [1]	1 (0.1) [1]

Note: At each level of participant summarisation, a participant was counted once if the participant reported one or more events. Events are summarised based on treatment received at the time of event.
n represents the number of participants at each level of summarisation.
[E] represents the number of events at each level of summarisation.
Adverse Events were coded using MedDRA

Up to Month 24, serious ocular-TEAEs occurred in one patient in each arm (0.4%) and consisted of blindness transient (severe, recovered) in control, papilledema (severe, not recovered, drug withdrawn) in atropine 0.01% and Optic neuritis (severe, recovered, study drug withdrawn) in atropine 0.03%. None were assessed as related to study drug. No serious ocular TEAEs occurred between Month 24 and Month 36.

Of note, the TEAE of papilloedema occurred twice. One event was reported as SAE in a participant with a history of idiopathic intracranial hypertension, and the other event was reported in the participant who experienced the SAE of optic neuritis. Both events were considered either unlikely related or not related by the Investigator. Ryjunea was withdrawn in both cases. The common PHV databases were checked: there were no entries of papilloedema for the substance atropine. Until the new data cut-off (up to 36 Month), there were no additional cases of papilloedema. Considering that papilloedema occurs by definition secondary to increased intracranial pressure, which seems to be unlikely caused by Ryjunea eyedrops, routine pharmacovigilance is considered acceptable for now. This issue was raised because papilloedema is a very rare event and the occurrence of two cases in this small trial seems unusual.

2.8.8.3.2. Serious non-ocular adverse events

Table 44: Summary of serious non-ocular treatment-emergency adverse events by system organ class and preferred term through month-24 - safety set, study SYD-101-001

System Organ Class Preferred Term	Vehicle (N=282) n (%) [E]	STN1012701 0.1 mg/mL (N=282) n (%) [E]	STN1012701 0.3 mg/mL (N=283) n (%) [E]	Total (N=847) n (%) [E]
All Treatment-Emergent Serious Adverse Events	**5 (1.8) [6]**	**3 (1.1) [3]**	**7 (2.5) [9]**	**15 (1.8) [18]**
Injury, Poisoning and Procedural Complications	**2 (0.7) [3]**	**2 (0.7) [2]**	**1 (0.4) [1]**	**5 (0.6) [6]**
Concussion	0	1 (0.4) [1]	0	1 (0.1) [1]
Fall	1 (0.4) [1]	0	0	1 (0.1) [1]
Forearm Fracture	1 (0.4) [1]	0	0	1 (0.1) [1]
Intentional Overdose	1 (0.4) [1]	1 (0.4) [1]	0	2 (0.2) [2]
Radius Fracture	0	0	1 (0.4) [1]	1 (0.1) [1]
Nervous System Disorders	**2 (0.7) [2]**	**0**	**1 (0.4) [1]**	**3 (0.4) [3]**
Ataxia	1 (0.4) [1]	0	0	1 (0.1) [1]
Dizziness Postural	1 (0.4) [1]	0	0	1 (0.1) [1]
Seizure	0	0	1 (0.4) [1]	1 (0.1) [1]
Psychiatric Disorders	**1 (0.4) [1]**	**0**	**1 (0.4) [2]**	**2 (0.2) [3]**
Eating Disorder	0	0	1 (0.4) [1]	1 (0.1) [1]
Suicidal Ideation	1 (0.4) [1]	0	0	1 (0.1) [1]
Suicide Attempt	0	0	1 (0.4) [1]	1 (0.1) [1]
Blood And Lymphatic System Disorders	**0**	**0**	**1 (0.4) [1]**	**1 (0.1) [1]**
Lymphadenitis	0	0	1 (0.4) [1]	1 (0.1) [1]
Cardiac Disorders	**0**	**0**	**1 (0.4) [1]**	**1 (0.1) [1]**
Supraventricular Tachycardia	0	0	1 (0.4) [1]	1 (0.1) [1]
Congenital, Familial and Genetic Disorders	**0**	**0**	**1 (0.4) [1]**	**1 (0.1) [1]**
Pectus Excavatum	0	0	1 (0.4) [1]	1 (0.1) [1]
Gastrointestinal Disorders	**0**	**1 (0.4) [1]**	**0**	**1 (0.1) [1]**
Colitis Ulcerative	0	1 (0.4) [1]	0	1 (0.1) [1]
General Disorders and Administration Site Conditions	**0**	**0**	**1 (0.4) [1]**	**1 (0.1) [1]**
Systemic Inflammatory Response Syndrome	0	0	1 (0.4) [1]	1 (0.1) [1]
Infections and Infestations	**0**	**0**	**1 (0.4) [1]**	**1 (0.1) [1]**
Covid-19	0	0	1 (0.4) [1]	1 (0.1) [1]

Note: At each level of participant summarisation, a participant was counted once if the participant reported one or more events. Events are summarised based on treatment received at the time of event.
n represents the number of participants at each level of summarisation.
[E] represents the number of events at each level of summarisation.
Adverse Events were coded using MedDRA.

Up to Month 24, a total of in 15 (1.8%) participants. In the vehicle group, 5 participants (1.8%) experienced 6 events (fall, forearm fracture, intentional overdose, ataxia, dizziness postural, suicidal ideation), while 3 participants (1.1%) in the 0.1 mg/mL group reported 3 events (concussion, intentional overdose, colitis ulcerative), and 7 (2.5%) participants in the 0.3 mg/mL group reported 9 events (radius fracture, seizure, eating disorder, suicide attempt, lymphadenitis, supraventricular

tachycardia, pectus excavatum, systemic inflammatory response syndrome [due to COVID-19], COVID-19). All TEAEs occurred in one patient each. No case of overdose occurred with the study drug and none of the events were assessed as related to study drug. The applicant provided narratives for all SAEs and the provided background information do not reveal reasons to doubt the Investigator's assessments. It should be noted that the event of supraventricular tachycardia was causally attributed to a newly diagnosed Wolff-Parkinson-White syndrome and the event of seizure occurred after drug abuse.

Only one serious non-ocular TEAEs occurred between Month 24 and Month 36: suicidal ideation in the Vehicle group. It was considered as not related to the study drug.

2.8.8.3.3. Deaths

In study SYD-101-001, no deaths were reported from baseline through Month 36.

2.8.8.4. Laboratory findings

2.8.8.4.1. Vital signs

Through month 24 and 36, no significant changes were observed regarding median values for blood pressure and heart rate. Weight and height increased with age as expected across treatment arms.

2.8.8.4.2. BCVA

Table 45: Summary of best corrected visual acuity letter change from baseline through month 24 – safety set, study SYD-101-001

	Vehicle (N=282) n (%)	STN1012701 0.1 mg/mL (N=282) n (%)	STN1012701 0.3 mg/mL (N=283) n (%)	Total (N=847) n (%)
Participants with post-baseline assessments	**261**	**261**	**263**	**785**
Most recent assessment				
≥ 15 letters gained	0	0	0	0
≥ 10 letters but < 15 letters gained	1 (0.4)	7 (2.7)	3 (1.1)	11 (1.4)
≥ 5 letters but < 10 letters gained	39 (14.9)	41 (15.7)	39 (14.8)	119 (15.2)
No change (< 5 letter change)	206 (78.9)	200 (76.6)	207 (78.7)	613 (78.1)
≥ 5 letters but < 10 letters lost	13 (5.0)	10 (3.8)	13 (4.9)	36 (4.6)
≥ 10 letters but < 15 letters lost	2 (0.8)	2 (0.8)	1 (0.4)	5 (0.6)
≥ 15 letters lost	0	1 (0.4)	0	1 (0.1)
Worst assessment				
≥ 15 letters gained	0	0	0	0
≥ 10 letters but < 15 letters gained	0	2 (0.8)	0	2 (0.3)
≥ 5 letters but < 10 letters gained	3 (1.1)	10 (3.8)	9 (3.4)	22 (2.8)
No change (< 5 letter change)	209 (80.1)	204 (78.2)	217 (82.5)	630 (80.3)
≥ 5 letters but < 10 letters lost	35 (13.4)	35 (13.4)	31 (11.8)	101 (12.9)
≥ 10 letters but < 15 letters lost	12 (4.6)	6 (2.3)	2 (0.8)	20 (2.5)
≥ 15 letters lost	2 (0.8)	4 (1.5)	4 (1.5)	10 (1.3)

Note: Assessment is based on the average of both eyes. Baseline is defined as last non-missing measurement prior to dosing. Percentages are calculated on the number of participants assessed with a value at both baseline and at least one post-baseline assessment. The most recent assessment is the last assessment prior to the Month 24 analysis cut off. Percentages are based on total assessed.

n represents the number of participants at each level of summarisation.

For BCVA, comparable proportions of patients across treatment groups had no change (<5 letter change) with 78.9% in control, 76.6% in atropine 0.01% and 78.7% in atropine 0.03% at the most

recent assessment. Approximately 15% in each treatment group had a >= 5 letters but <10 letters gained with a slightly higher proportion in the atropine 0.01%. More participants had an improved BCVA than a decreased BCVA and similar trends were seen in subgroups analysis.

Overall, treatment with Ryjunea did not seem to have an effect on the BCVA, as shown by comparable results between the three treatment groups with respect to incidences of letters lost and letters gained through month 24.

Similar results were observed up to Month 36.

Table 46: Summary of best corrected visual acuity letter change from baseline through month 36 – safety set, study SYD-101-001

	Vehicle (N=282) n (%)	STN1012701 0.1 mg/mL (N=282) n (%) [E]	STN1012701 0.3 mg/mL			Total (N=847) n (%)
			STN1012701 0.3 mg/mL (N=283) n (%) [E]	Escape (N=35) n (%) [E]	0.3 mg/mL Total (N=307) n (%) [E]	
Participants with post-baseline assessments	261	261	263	17	277	789
Most recent assessment						
⩾ 15 letters gained	0	0	0	0	0	0
⩾10 letters but < 15 letters gained	5 (1.9)	6 (2.3)	9 (3.4)	2 (11.8)	11 (4.0)	22 (2.8)
⩾ 5 letters but < 10 letters gained	42 (16.1)	50 (19.2)	49 (18.6)	2 (11.8)	51 (18.4)	141 (17.9)
No change (< 5 letter change)	204 (78.2)	189 (72.4)	199 (75.7)	11 (64.7)	208 (75.1)	593 (75.2)
⩾ 5 letters but < 10 letters lost	9 (3.4)	16 (6.1)	6 (2.3)	2 (11.8)	7 (2.5)	32 (4.1)
⩾ 10 letters but < 15 letters lost	1 (0.4)	0	0	0	0	1 (0.1)
⩾ 15 letters lost	0	0	0	0	0	0
Worst assessment						
⩾ 15 letters gained	0	0	0	0	0	0
⩾ 10 letters but < 15 letters gained	0	1 (0.4)	0	1 (5.9)	1 (0.4)	2 (0.3)
⩾ 5 letters but < 10 letters gained	2 (0.8)	9 (3.4)	9 (3.4)	2 (11.8)	11 (4.0)	21 (2.7)
No change (< 5 letter change)	206 (78.9)	201 (77.0)	213 (81.0)	12 (70.6)	222 (80.1)	620 (78.6)
⩾ 5 letters but < 10 letters lost	38 (14.6)	40 (15.3)	32 (12.2)	2 (11.8)	34 (12.3)	112 (14.2)
⩾ 10 letters but < 15 letters lost	13 (5.0)	6 (2.3)	3 (1.1)	0	3 (1.1)	22 (2.8)
⩾ 15 letters lost	2 (0.8)	4 (1.5)	6 (2.3)	0	6 (2.2)	12 (1.5)

2.8.8.4.3. Binocular near-BCVA

Table 47: Summary of binocular near visual acuity letter change from baseline through month 24 – safety set, study SYD-101-001

	Vehicle (N=282) n (%)	STN1012701 0.1 mg/mL (N=282) n (%)	STN1012701 0.3 mg/mL (N=283) n (%)	Total (N=847) n (%)
Participants with post-baseline assessments	**259**	**260**	**264**	**783**
Most recent assessment				
≥ 3 lines gained	4 (1.5)	2 (0.8)	1 (0.4)	7 (0.9)
≥ 2 lines but < 3 lines gained	5 (1.9)	2 (0.8)	3 (1.1)	10 (1.3)
≥ 1 line but < 2 lines gained	38 (14.7)	30 (11.5)	26 (9.8)	94 (12.0)
No change (< 1-line change)	195 (75.3)	214 (82.3)	214 (81.1)	623 (79.6)
≥ 1 line but < 2 lines lost	15 (5.8)	12 (4.6)	17 (6.4)	44 (5.6)
≥ 2 lines but < 3 lines lost	2 (0.8)	0	3 (1.1)	5 (0.6)
≥ 3 lines lost	0	0	0	0
Worst assessment				
≥ 3 lines gained	1 (0.4)	0	0	1 (0.1)
≥ 2 lines but < 3 lines gained	2 (0.8)	1 (0.4)	1 (0.4)	4 (0.5)
≥ 1 line but < 2 lines gained	28 (10.8)	15 (5.8)	18 (6.8)	61 (7.8)
No change (< 1-line change)	197 (76.1)	208 (80.0)	187 (70.8)	592 (75.6)
≥ 1 line but < 2 lines lost	27 (10.4)	32 (12.3)	48 (18.2)	107 (13.7)
≥ 2 lines but < 3 lines lost	4 (1.5)	3 (1.2)	7 (2.7)	14 (1.8)
≥ 3 lines lost	0	1 (0.4)	3 (1.1)	4 (0.5)

Note: Assessment at each post-baseline visit is based on the average of both eyes.
Baseline is defined as last non-missing measurement prior to dosing. Percentages are calculated on the number of participants assessed with a value at both baseline and at least one post-baseline assessment. Worst assessment is defined as smallest increase in visual acuity (or largest decrease) from baseline.
Line change = 10 x [-log(20/dfollow-up) – (-log(20/dbaseline))], where dfollow-up is the denominator of the Snellen fraction at post-baseline visit and dbaseline is the denominator of the Snellen fraction at Baseline.
n represents the number of participants at each level of summarisation.

For binocular near BCVA, across treatment groups more than 75% of the patients had no changes (<1 line change), with a higher proportion in atropine groups (nearly 80%). Across treatment groups more than 10% had >= 1 line but <2 lines gained at the most recent assessment with a higher proportion in the control group. Across treatment groups, more patients had an improved near visual acuity than a decreased near visual acuity. In the atropine 0.03% group, at the worst assessment a higher proportion of patients had a >= 1 line but <2 lines (18.2%) lost compared to atropine 0.01% (12.3%) and control (10.4%).

Overall, there seemed to be a trend for a dose-dependent worsening (lower incidences for lines gained, higher incidences for lines lost of binocular near visual acuity) in the Ryjunea groups compared to vehicle. This may be explained by the mechanism of action of atropine. A potential worsening in this regard needs to be considered for evaluation of the overall benefit of Ryjunea. It is unclear whether these potential effects would persist after cessation of treatment. Data on binocular near visual acuity were further discussed and analysed using actual logMAR value compared to baseline. At month 24 and 36, no statistically significant difference was observed (p value>0.05) for accommodation amplitude and binocular near visual acuity.

Table 48: Accommodation and visual acuity values at 24 months – full analysis set

Visit	Vehicle Mean (SD)	STN1012701 0.1mg/mL Mean (SD)	STN1012701 0.3mg/mL Mean (SD)
Accommodation Amplitude (D)			
Baseline	19.08 (10.044)	20.42 (10.067)	19.04 (9.905)
P value (vs Vehicle)		0.1161	0.9610
24 Months	19.11 (8.371)	19.56 (9.539)	17.67 (01.332)
P value (vs Vehicle)		0.5892	0.1033
Binocular Near Visual Acuity (log Mar)			
Baseline	0.03 (0.072)	0.02 (0.055)	0.03 (0.057)
P value (vs Vehicle)		0.0691	0.1497
24 Months	0.01 (0.048)	0.01 (0.035)	0.02 (0.049)
P value (vs Vehicle)		0.2663	0.2970

Table 49: Accommodation and visual acuity values at 36 months – full analysis set

Visit	Vehicle Mean (SD)	STN1012701 0.1mg/mL Mean (SD)	STN1012701 0.3mg/mL Mean (SD)
Accommodation Amplitude (D)			
Baseline	19.08 (10.044)	20.42 (10.067)	19.04 (9.905)
P value (vs Vehicle)		0.1161	0.9610
24 Months	19.11 (8.371)	19.56 (9.539)	17.67 (10.332)
P value (vs Vehicle)		0.5892	0.1033
36 Months	19.30 (9.083)	20.28 (10.170)	17.32 (10.389)
P value (vs Vehicle)		0.3064	0.0401
Binocular Near Visual Acuity (log Mar)			
Baseline	0.03 (0.072)	0.02 (0.055)	0.03 0.057)
P value (vs Vehicle)		0.0691	0.1497
24 Months	0.01 (0.048)	0.01 (0035)	0.02 (0.049)
P value (vs Vehicle)		0.2663	0.2970
36 Months	0.02 (0.048)	0.01 (0.037)	0.01 (0.053)
P value (vs Vehicle)		0.1441	0.5306

2.8.8.4.4. Treatment-Emergent Clinically Significant Biomicroscopic Abnormalities

Table 50: Summary of treatment-emergent clinically significant biomicroscopic abnormalities through month 24 - safety set, study SYD-101-001

	Vehicle (N=282) n (%)	STN1012701 0.1 mg/mL (N=282) n (%)	STN1012701 0.3 mg/mL (N=283) n (%)	Total (N=847) n (%)
Number of participants with at least one clinically significant slit-lamp biomicroscopy finding	**7**	**9**	**13**	**29**
Lids	4 (1.4)	6 (2.1)	4 (1.4)	14 (1.7)
Conjunctiva	2 (0.7)	2 (0.7)	3 (1.1)	7 (0.8)
Iris	0	0	1 (0.4)	1 (0.1)
Cornea	3 (1.1)	2 (0.7)	6 (2.1)	11 (1.3)
Lens	0	0	0	0

Note: At each level of participant summarisation, a participant was counted once even if the participant experienced more than one treatment-emergent clinically significant abnormality. Data is summarised for worse eye, defined as the eye with the greater degree of abnormality. Findings were summarised based on treatment received at the time of finding. Percentages are calculated using the number of participants in the safety set.

n represents the number of participants at each level of summarisation.

Treatment emergent clinically significant biomicroscopic abnormalities were slightly more reported in atropine 0.03% (4.6% vs 2.4% in control and 3.1 % in atropine 0.01%) with the most reported abnormalities concerning the lid and the cornea. In the majority of the cases, the clinically significant abnormalities coincided and could be medically linked with TEAEs.

Table 51: Shift from baseline in corneal staining scored through month 24 – safety set, study SYD-101-001

	Vehicle (N=283) Baseline					STN1012701 0.1 mg/mL (N=282) Baseline					STN1012701 0.3 mg/mL (N=283) Baseline				
	0	0.5	1	2	3	0	0.5	1	2	3	0	0.5	1	2	3
Maximum post-baseline value															
0 - None	223	3	0	0	0	223	4	0	0	0	225	1	0	0	0
0.5 - Trace	30	5	0	0	0	27	4	0	0	0	28	5	0	0	0
1 - Mild	6	1	0	0	0	6	5	0	0	0	9	3	1	0	0
2 - Moderate	2	0	0	0	0	1	0	0	0	0	1	0	0	0	0
3 - Severe	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Total	261	9	0	0	0	257	13	0	0	0	263	9	1	0	0
Most recent post-baseline value															
0 - None	251	3	0	0	0	245	9	0	0	0	249	3	0	0	0
0.5 - Trace	8	5	0	0	0	10	1	0	0	0	10	4	1	0	0
1 - Mild	3	0	0	0	0	1	3	0	0	0	4	2	0	0	0
2 - Moderate	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0
3 - Severe	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Total	262	8	0	0	0	257	13	0	0	0	263	9	1	0	0

Note: Data is summarised for worse eye, defined as the eye with the higher grade at summarised visit. Counts represent participants with a baseline value in addition to having a value at any post-baseline visit.
Baseline is the last non-missing assessment prior to dosing.

As advised in the EMA SA, also due to the novel D_2O excipient, the applicant performed corneal staining with fluorescein. Only few shifts to higher staining scores were observed with no notable differences between the treatment groups. Majority of the patients had no trace of staining and the few patients who had staining shifted from mild to trace or none across treatment group. Proportions of patients presenting moderate staining were few (2 in control and one in each atropine group) and none had a severe staining.

Up to Month 36, treatment-emergent clinically significant biomicroscopic abnormalities were reported in 10 participants in the Vehicle group, 13 participants in the STN1012701 0.1 mg/mL group, and 15 participants in the STN1012701 0.3 mg/mL randomised group through Month 36. In addition, 2 participants receiving escape therapy had at least one clinically significant biomicroscopic abnormality. Most abnormalities were reported for lids (20/40 participants) and cornea (16/40 participants). No clinically significant abnormality of the lens was reported.

In all treatment groups, most participants who had no corneal staining at baseline still had no staining at the subsequent visits. Among those who had no corneal staining at baseline but had staining at a subsequent visit, most shifted to traces only and a few to mild staining.

2.8.8.4.5. Treatment-Emergent Clinically Significant Ophthalmoscopy Abnormalities

Regarding treatment-emergent clinically significant ophthalmoscopy, one patient had bilateral retinal vessel tortuosity (mild, resolved, no action required) in control arm and one patient had bilateral papilledema (moderate, resolved, no action required) in atropine 0.03%. Both events were not assessed as related to study drug.

At Month 36, 3 participants in the Vehicle group, 1 participant in the STN1012701 0.1 mg/mL group, and 2 participants in the STN1012701 0.3 mg/mL randomised group had at least one clinically significant ophthalmoscopy abnormality. Treatment-emergent clinically significant ophthalmoscopy abnormalities that occurred between Month 24 and Month 36 included: retinal periphery, reported as lattice degeneration of both eyes (TEAE not related, Vehicle), macula, reported as naevus pigmetosus of right eye (vehicle), optic nerve, reported as superior sloping of left eye (STN1012701 0.1 mg/mL group), retinal periphery, reported as inferior retinal hole of left eye (TEAE not related, STN1012701

0.3 mg/mL randomised group). No participants on escape therapy had a clinically significant ophthalmoscopy abnormality.

2.8.8.4.6. Pupil diameter

At baseline, mean pupil diameter (mm) were comparable between treatment groups (5.183 in control vs 5.122 in atropine 0.01% and 5.162 in atropine 0.03%). A clear dose-dependent increase in mean pupil diameter from baseline to month 24 was noted (mean [SD] change from baseline; vehicle: 0.036 [1.2801] mm, 0.1 mg/mL: 0.409 [1.2953] mm, 0.3 mg/mL: 0.815 [1.3801] mm), which can be expected based on the pharmacological effect of atropine. Furthermore, in the atropine groups, the lowest mean change in pupil dilatation was observed in the 0.01% atropine arm (0.409 in atropine 0.01%) compared to atropine 0.03% (0.815 in atropine 0.03%). Increased pupil diameter is likely related to the increase in photophobia. The summary of Clinical Pharmacology provides a literature overview on the effect of atropine on pupil size (for the lower dose, 0.01% = 0.1 mg/mL), which shows roughly comparable values.

Up to Month 36, the mean (SD) change from baseline in pupil diameter was -0.033 (1.2047) mm in Vehicle group, 0.364 (1.3007) mm in STN1012701 0.1 mg/mL group and 0.650 (1.3815) mm in STN1012701 0.3 mg/mL randomised group. In participants who were on escape medication, the mean (SD) change from baseline in pupil diameter was 0.736 (1.1064) mm.

2.8.8.4.7. Binocular accommodative amplitude

At baseline, mean binocular accommodative amplitude (D) was slightly higher in atropine 0.01% compared to the control and atropine 0.03% (19.085 D in control, 20.425 D in atropine 0.01% and 19.044 in atropine 0.03%). Through month 24, the mean change from baseline were -0.429 D in control, -1.028 D in atropine 0.01% and -1.280 in atropine 0.03%. As seen with binocular near visual acuity, the same trend was noted for binocular accommodative amplitude, with a dose-dependent worsening of the score at month 24 (mean [SD] change from baseline; vehicle: -0.429 [9.6504] D, 0.1 mg/mL: -1.028 [9.6744] D, 0.3 mg/mL: -1.280 [9.7991] D). The updated data on binocular accommodation amplitude at month 36 (Table 33) did not reveal changes compared to month 24. For both the vehicle and the low dose group, measured accommodation amplitudes at month 36 were similar to baseline, while this parameter was lower than baseline for the higher dose group, in line with month 24.

2.8.8.4.8. Central endothelial cell density (cells/mm2)

Regarding central endothelial cell density (which was measured in approximately 25% of study participants) baseline mean were comparable between treatment groups with 3081.69 in control, 3084.08 in atropine 0.01% and 3022.41 in atropine 0.03%. Through month 24, comparable change from Baseline in Central Endothelial Cell Density (cells/mm2) were observed in control (-27.04 cells/mm2) and atropine 0.03% (-25.83 cells/mm2) while being lower in atropine 0.01% (-4.26 cells/mm2). These results are to be taken with caution as only ¼ of the patients had measures.

Overall, no relevant changes were noted between the three treatment groups with respect to central endothelial cell density (cells/mm^2). These data with those on corneal staining suggest that there are no obvious safety concerns of D2O for the cornea. The change from baseline in corneal endothelial cell density was not measured through Month 36, in study SYD-101-001.

2.8.8.4.9. Intraocular pressure (mmHg)

Up to month 24, across treatment groups one patient in control and one patient in atropine 0.03% had an increase in IOP (mmHg) from baseline > 10 mmHg. In control group, the event was continuous, recovered (duration 127 days), mild, drug interrupted and assessed as related to study drug. In atropine group the event was intermittent, not recovered, mild, assessed as not related.

Intraocular pressure (IOP) was determined at certain study visits (prior to pupil dilation). The procedure for pressure evaluation used iCare or Goldmann tonometer with a major use of iCare tonometer by the site since it does not require local anaesthesia, does not indent the cornea, is quicker, and less invasive than Goldmann tonometer.

Table 52: Summary of change from baseline in intraocular pressure (mmHg) – safety population

Visit	Vehicle (N=282)		STN1012701 0.1mg/mL (N=282)		STN1012701 0.3mg/mL (N=283)	
	Actual	Change from Baseline	Actual	Change from Baseline	Actual	Change from Baseline
Baseline						
N	280		282		281	
Mean (SD)	15.396 (2.8023)		15.770 (2.4906)		15.699 (2.7166)	
Median	15.500		16.000		16.000	
Min Max	7.50, 21.00		7.00, 21.00		7.00, 21.00	
Month 12						
N	247	245	247	247	247	245
Mean (SD)	15.259 (2.9435)	-0.0.16 (2.9739)	15.638 (2.6860)	-0.030 (2.7996)	15.478 (3.0109)	-0.249 (3.1479)
Median	15.500	0.000	16.000	0.000	16.000	-0.500
Min Max	7.50, 23.50	-8.50, 9.50	7.50, 22.00	-9.50, 8.50	7.00, 23.50	-9.50, 12.50
p-value				0.9570		0.4008
Month 24						
N	226	224	227	227	227	225
Mean (SD)	15.522 (2.8882)	0.281 (3.2381)	15.520 (2.9069)	-0.225 (2.9938)	15.499 (2.7173)	-0.318 (3.2957)
Median	15.500	0.000	15.500	0.000	15.500	0.000

Except for STN1012701 0.3 mg/mL at Month 36 where a slight decrease was observed, the difference in mean IOP of both STN1012701 doses compared to vehicle up to Month 36 were not statistically significant (p>0.05).

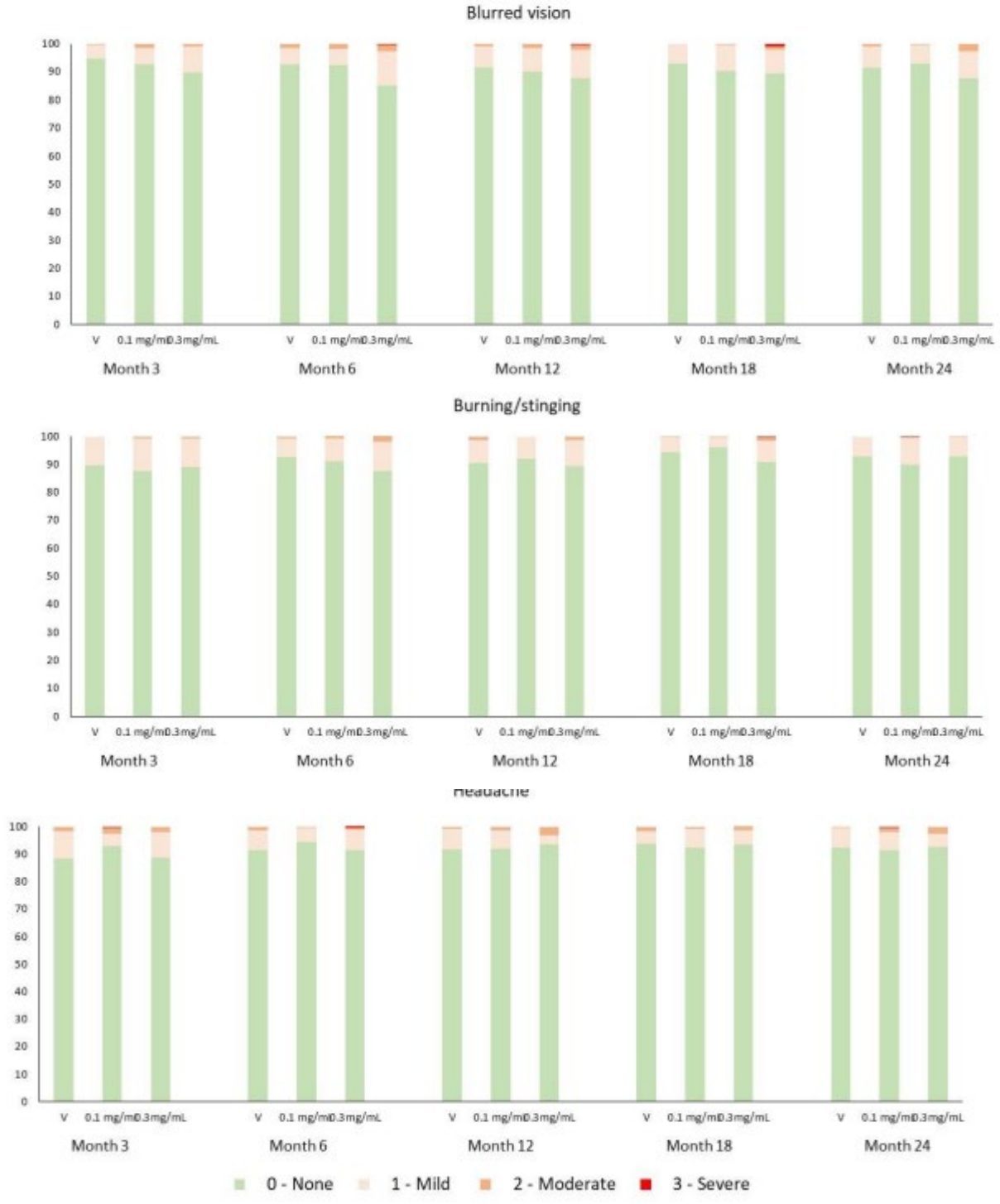
2.8.8.4.10. Tolerability assessment

A questionnaire was used to assess tolerability (blurred vision, burning/stinging, eye pain, grittiness in eye, sensitivity to light and headache). Results were obtained for more than 95% of the patients at month 3 with a decrease observed at month 24 with the results being assessed for more than 80% of the patients.

The tolerability questionnaire was completed at Months 3 and 6 and every 6 months thereafter until Month 24. It is critically noted that it was recommended to increase the frequency for providing the tolerability questionnaire (i.e., also including questionnaires on Week 2 and Months 2, 4, and 5) in the scientific advice (EMEA/H/SA/4009/1/2018/PED/III). This was not followed by the applicant. Also, no recall period had been specified and the occurrence of AEs was apparently not questioned regularly via a questionnaire on a phone or web-based application, as recommended (i.e., weekly for the first 6 months and then monthly until Month 48/EoS). Thus, tolerability and AEs were reported less frequently than recommended, especially during the first 6 months. Lack of these data is unfortunate, since some ocular TEAEs were more frequent earlier during treatment. The chosen frequency for the tolerability questionnaires was justified as being different from the proposal made in the scientific advice (after baseline a 2-week phone call was performed followed by followed by a 3-month clinic visit which was decreased to every 6 months while adverse events continued to be collected every 3 months), as due to wanting to reduce the patient's burden and in context of the COVID-19 situation. Furthermore, a

self-report tool such as a generic patient-reported adverse event questionnaires was suggested as the basis of a specific instrument.

Moreover, it was also pointed out that it remained unclear whether the proposed scoring (severity of the adverse events were scored on a 4-point scale none, mild, moderate or severe) had content validity, i.e. whether it captures all potential adverse effects of low dose atropine. The clinical site was delegated their own discretion to assess severity of the symptoms and the seriousness was not assessed with the tolerability questionnaires.



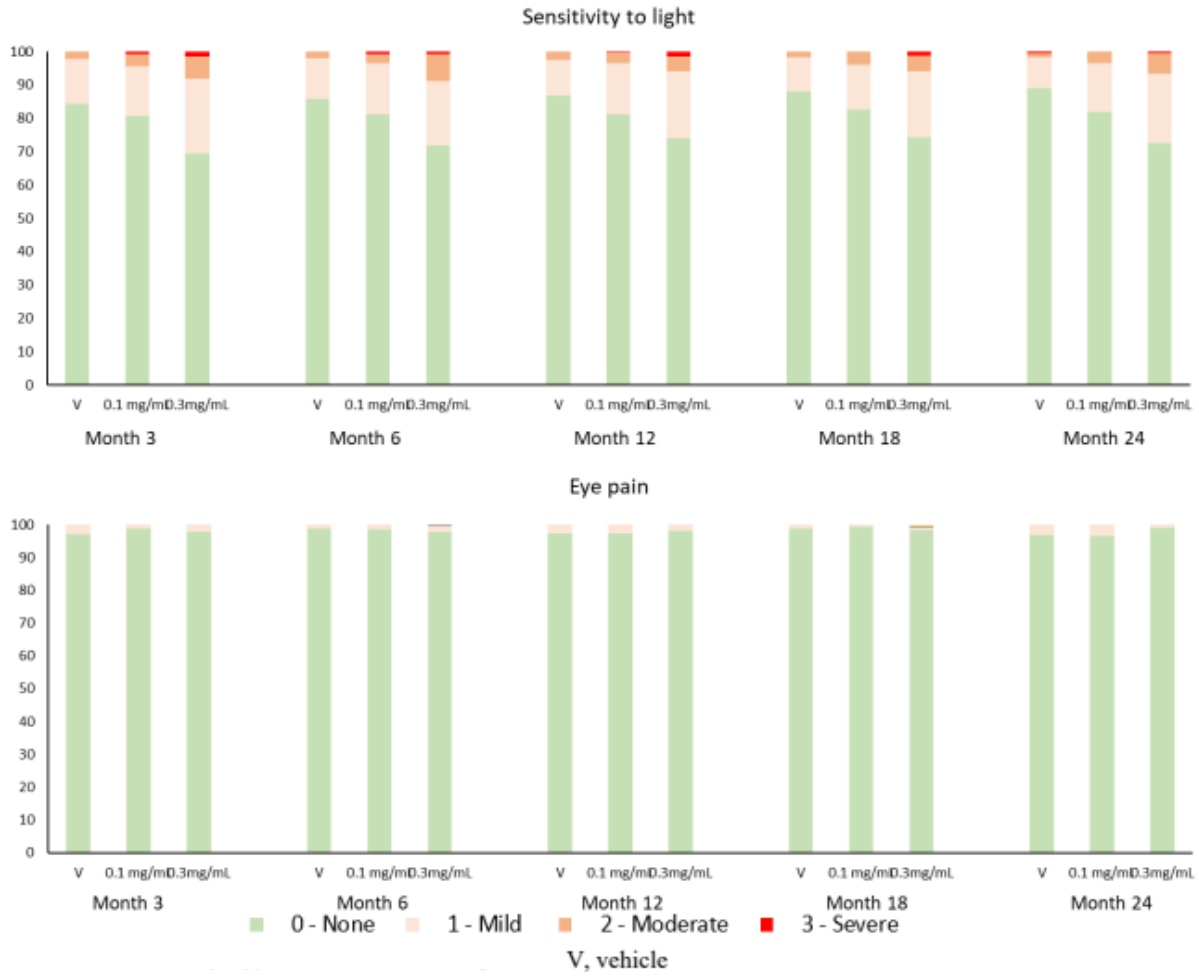


Figure 9: Results from the tolerability questionnaire over 24 month of treatment – SYD-101-001

Approximately 90% of the patients in each treatment arms did not present adverse event of blurred vision through month 24 (91.6% in control, 93% in atropine 0.01% and 87.8% in atropine 0.03%). Severe events of blurred vision were reported in one patient at month 6 and month 12 (both intermittent) and in two patients at month 18 (intermittent and continuous) in atropine 0.03% vs none in both atropine 0.01% and control. Mild or moderate events of blurred vision were in majority intermittent through month 24.

Approximately 90% of the patients did not present burning/stinging through month 24 (93.0% in control, 89.9% in atropine 0.01% and 93.0% in atropine 0.03%). Severe events were reported in one patient in atropine 0.03% at month 18 (intermittent) and in one patient in atropine 0.01% at month 24 (intermittent). Mild or moderate events of burning/stinging were in majority intermittent through month 24.

Approximately 98% of the patients did not present eye pain through month 24 (96.9% in control; 96.5% in atropine 0.01% and 99.1% in atropine 0.03%). Severe events were reported in atropine 0.03% at month 18 (intermittent). Mild or moderate events of eye pain were in majority intermittent through month 24.

Around 95% of the patients did not present grittiness in the eye through month 24 (94.7% in control, 96% in atropine 0.01% and 95.2% in atropine 0.03%). Severe events were reported in one patient in atropine 0,03% et month 12 (intermittent) and in one patient in atropine 0.03% at month 18 (continuous).

Around 92% of the patients did not present headache through month 24 (92.5% in control; 91.6% in atropine 0.01% and 92.2% in atropine 0.03%). Severe events occurred in one patient in atropine 0.01% at month 3 (intermittent), in atropine 0.03% at month 6 (intermittent) and at month 24 in atropine 0.01% (continuous).

Table 53: Summary of sensitivity to light per tolerability assessment through month 24 – safety set

	Vehicle	STN1012701 0.1 mg/mL	STN1012701 0.3 mg/mL
Month 3 – N assessed	270	273	274
No sensitivity to light – n (%)	228 (84.4)	220 (80.6)	190 (69.3)
Severe intermittent sensitivity to light – n (%)	0	2 (0.7)	3 (1.1)
Severe continuous sensitivity to light – n (%)	0	0	1 (0.4)
Month 6 – N assessed	260	261	266
No sensitivity to light – n (%)	223 (85.8)	212 (81.2)	191 (71.8)
Severe intermittent sensitivity to light – n (%)	0	2 (0.8)	1 (0.4)
Severe continuous sensitivity to light – n (%)	0	0	1 (0.4)
Month 12 – N assessed	249	254	254
No sensitivity to light – n (%)	216 (86.7)	206 (81.1)	188 (74.0)
Severe intermittent sensitivity to light – n (%)	0	0	3 (1.2)
Severe continuous sensitivity to light – n (%)	0	1 (0.4)	1 (0.4)
Month 18 – N assessed	233	236	237
No sensitivity to light – n (%)	205 (88.0)	195 (82.6)	176 (74.3)
Severe intermittent sensitivity to light – n (%)	0	0	1 (0.4)
Severe continuous sensitivity to light – n (%)	0	0	2 (0.8)
Month 24 – N assessed	227	227	229
No sensitivity to light – n (%)	202 (89.0)	186 (81.9)	166 (72.5)
Severe intermittent sensitivity to light – n (%)	1 (0.4)	0	0
Severe continuous sensitivity to light – n (%)	0	0	1 (0.4)

Note: percentages do not add up to 100% as only 3 categories are displayed from the 7 categories reported in Table 14.3-12.1a; mild and moderate sensitivity to light is not reported in this table.

At month 24, 72.5%; 81.9% and 89% of the patients did not present sensitivity to lightness in respectively atropine 0.03%; atropine 0.1% and control. Comparable results were observed through month 24. Severe events were observed mostly in atropine groups: in 4 patients in atropine 0.03% (including one continuous) and two patients in atropine 0.01% (intermittent) at month 3; 2 patients in atropine 0.01% (intermittent) and two patients in atropine 0.03% (including one continuous) at month 6; 4 patients in atropine 0.03% (including one continuous) and 1 patient in atropine 0.01% (continuous) at month 12; 3 patients (including one continuous) in atropine 0.03% at month 18 and 1 patient in atropine 0.03%. Overall severe events of sensibility to light were mostly reported in atropine 0.03% up to month 24.

Overall, the results from a tolerability questionnaire showed comparable results between the three treatment groups for the queried potential side effects of burning/stinging, eye pain, grittiness in eye and headache. A clear dose-related effect was only seen for sensitivity to light and to a lesser extent for blurred vision, in line with the above presented AE profile. Sensitivity to light did only slightly decrease over time, e.g., from Month 3 (15.6%, 19.4%, 30.7% of subjects in the vehicle, 0.1 mg/mL and 0.3 mg/mL groups) to Month 24 (11.0%, 18.1%, 27.5%). Furthermore, severe-grade sensitivity of light occurred mainly in the atropine groups, including 6 cases of continuous severe symptoms in the 0.03% atropine group.

Similar results were found up to Month 36.

2.8.8.5. In vitro biomarker test for patient selection for safety

Not applicable.

2.8.8.6. Safety in special populations

In study SYD-101-001, several intrinsic parameters were analysed with regards to the safety of STN1012701. The study was not powered for subgroup analyses; these analyses are considered descriptive only.

2.8.8.6.1. Age

Only a small number of children between 3 and <6 years of age were recruited (vehicle: n=9, 0.1 mg/mL: n=8, 0.3 mg/mL: n=8). Of this age subgroup, 9 children reported 23 TEAEs and all events were either eye disorders (mainly photophobia and vision blurred) or administration site conditions (such as instillation site pain).

Table 54: Overall summary of treatment-emergent adverse events through month 24 by subgroup – safety set, study-101-001

	Vehicle n (%) [E]	STN1012701 0.1 mg/mL n (%) [E]	STN1012701 0.3 mg/mL n (%) [E]
Age 3–<6 years	**N=9**	**N=8**	**N=9**
Any TEAE	6 (66.7) [17]	4 (50.0) [12]	5 (55.6) [15]
Ocular TEAE	3 (33.3) [4]	2 (25.0) [7]	4 (44.4) [12]
Non-ocular TEAE	4 (44.4) [13]	3 (37.5) [5]	2 (22.2) [3]
Any serious TEAE	0	0	0
Ocular TEAE	0	0	0
Non-ocular TEAE	0	0	0
Any study drug-related TEAE	3 (33.3) [4]	2 (25.0) [6]	3 (33.3) [11]
Ocular TEAE	3 (33.3) [4]	2 (25.0) [6]	3 (33.3) [11]
Non-ocular TEAE	0	0	0
Any study drug-related SAE	0	0	0
Any TEAE leading to study drug discontinuation	0	0	0
Any TEAE leading to death	0	0	0
Age 6–<9 years	**N=61**	**N=62**	**N=62**
Any TEAE	39 (63.9) [118]	36 (58.1) [93]	35 (56.5) [81]
Ocular TEAE	24 (39.3) [51]	19 (30.6) [41]	25 (40.3) [46]
Non-ocular TEAE	27 (44.3) [67]	24 (38.7) [52]	20 (32.3) [35]
Any serious TEAE	0	0	1 (1.6) [1]
Ocular TEAE	0	0	1 (1.6) [1]
Non-ocular TEAE	0	0	0
Any study drug-related TEAE	18 (29.5) [30]	17 (27.4) [34]	19 (30.6) [30]
Ocular TEAE	18 (29.5) [29]	16 (25.8) [30]	19 (30.6) [27]
Non-ocular TEAE	1 (1.6) [1]	3 (4.8) [4]	3 (4.8) [3]
Any study drug-related SAE	0	0	0
Any TEAE leading to study drug discontinuation	1 (1.6) [1]	1 (1.6) [1]	2 (3.2) [2]
Ocular TEAE	1 (1.6) [1]	1 (1.6) [1]	2 (3.2) [2]
Non-ocular TEAE	0	0	0
Any TEAE leading to death	0	0	0
Age 9–<12 years	**N=110**	**N=110**	**N=111**
Any TEAE	69 (62.7) [182]	70 (63.6) [175]	83 (74.8) [213]
Ocular TEAE	44 (40.0) [79]	54 (49.1) [96]	66 (59.5) [121]
Non-ocular TEAE	49 (44.5) [103]	41 (37.3) [79]	57 (51.4) [92]
Any serious TEAE	2 (1.8) [3]	2 (1.8) [2]	1 (0.9) [1]
Ocular TEAE	0	1 (0.9) [1]	0
Non-ocular TEAE	2 (1.8) [3]	1 (0.9) [1]	1 (0.9) [1]
Any study drug-related TEAE	36 (32.7) [54]	44 (40.0) [68]	54 (48.6) [105]
Ocular TEAE	33 (30.0) [50]	43 (39.1) [62]	52 (46.8) [91]
Non-ocular TEAE	4 (3.6) [4]	6 (5.5) [6]	13 (11.7) [14]

Any study drug-related SAE	0	0	0
Any TEAE leading to study drug discontinuation	0	1 (0.9) [1]	2 (1.8) [2]
Ocular TEAE	0	1 (0.9) [1]	1 (0.9) [1]
Non-ocular TEAE	0	0	1 (0.9) [1]
Any TEAE leading to death	0	0	0
Age 12–14 years	**N=102**	**N=102**	**N=101**
Any TEAE	69 (67.6) [238]	63 (61.8) [163]	75 (74.3) [238]
Ocular TEAE	42 (41.2) [81]	46 (45.1) [81]	62 (61.4) [135]
Non-ocular TEAE	54 (52.9) [157]	43 (42.2) [82]	48 (47.5) [103]
Any serious TEAE	3 (2.9) [4]	2 (2.0) [2]	6 (5.9) [8]
Ocular TEAE	1 (1.0) [1]	0	0
Non-ocular TEAE	3 (2.9) [3]	2 (2.0) [2]	6 (5.9) [8]
Any study drug-related TEAE	36 (35.3) [58]	38 (37.3) [67]	57 (56.4) [121]
Ocular TEAE	33 (32.4) [50]	37 (36.3) [59]	53 (52.5) [105]
Non-ocular TEAE	8 (7.8) [8]	7 (6.9) [8]	16 (15.8) [16]
Any study drug-related SAE	0	0	0
Any TEAE leading to study drug discontinuation	1 (1.0) [1]	0	3 (3.0) [4]
Ocular TEAE	0	0	1 (1.0) [2]
Non-ocular TEAE	1 (1.0) [1]	0	2 (2.0) [2]
Any TEAE leading to death	0	0	0

N, number of participants; [E], the number of events

Table 55: Overall summary of treatment-emergent adverse events through month 24 by subgroup – safety set, study SYD-101-001

	Vehicle n (%) [E]	STN1012701 0.1 mg/mL n (%) [E]	STN1012701 0.3 mg/mL n (%) [E]
Age 6–14 years	**N=273**	**N=274**	**N=274**
Any TEAE	177 (64.8) [538]	169 (61.7) [431]	193 (70.4) [532]
Ocular TEAE	110 (40.3) [211]	119 (43.4) [218]	153 (55.8) [302]
Non-ocular TEAE	130 (47.6) [327]	108 (39.4) [213]	125 (45.6) [230]
Any serious TEAE	5 (1.8) [7]	4 (1.5) [4]	8 (2.9) [10]
Ocular TEAE	1 (0.4) [1]	1 (0.4) [1]	1 (0.4) [1]
Non-ocular TEAE	5 (1.8) [6]	3 (1.1) [3]	7 (2.6) [9]
Any study drug-related TEAE	90 (33.0) [142]	99 (36.1) [169]	130 (47.4) [256]
Ocular TEAE	84 (30.8) [129]	96 (35.0) [151]	124 (45.3) [223]
Non-ocular TEAE	13 (4.8) [13]	16 (5.8) [18]	32 (11.7) [33]
Any study drug-related SAE	0	0	0
Any TEAE leading to study drug discontinuation	2 (0.7) [2]	2 (0.7) [2]	7 (2.6) [8]
Ocular TEAE	1 (0.4) [1]	2 (0.7) [2]	4 (1.5) [5]
Non-ocular TEAE	1 (0.4) [1]	0	3 (1.1) [3]
Any TEAE leading to death	0	0	0

Age 3–<12 years	N=180	N=180	N=182
Any TEAE	114 (63.3) [317]	110 (61.1) [280]	123 (67.6) [309]
Ocular TEAE	71 (39.4) [134]	75 (41.7) [144]	95 (52.2) [179]
Non-ocular TEAE	80 (44.4) [183]	68 (37.8) [136]	79 (43.4) [130]
Any serious TEAE	2 (1.1) [3]	2 (1.1) [2]	2 (1.1) [2]
Ocular TEAE	0	1 (0.6) [1]	1 (0.5) [1]
Non-ocular TEAE	2 (1.1) [3]	1 (0.6) [1]	1 (0.5) [1]
Any study drug-related TEAE	57 (31.7) [88]	63 (35.0) [108]	76 (41.8) [146]
Ocular TEAE	54 (30.0) [83]	61 (33.9) [98]	74 (40.7) [129]
Non-ocular TEAE	5 (2.8) [5]	9 (5.0) [10]	16 (8.8) [17]
Any study drug-related SAE	0	0	0
Any TEAE leading to study drug discontinuation	1 (0.6) [1]	2 (1.1) [2]	4 (2.2) [4]
Ocular TEAE	1 (0.6) [1]	2 (1.1) [2]	3 (1.6) [3]
Non-ocular TEAE	0	0	1 (0.5) [1]
Any TEAE leading to death	0	0	0

N, number of participants; [E], the number of events

The applicant provided a comparative analysis of the ocular TEAEs of photophobia and vision blurred between paediatric age subgroups. Overall, the incidences of these TEAEs tended to be higher in the two older paediatric age groups (9 to <12 and 12 to 14 years of age) compared to the younger children (3 to <6 years of age, 6 to <9 years of age). Also, headache tended to be reported more frequently in older age groups. Nevertheless, it is likely that reporting may have been influenced by different communication skills between the age subgroups.

Table 56: Summary of ocular treatment-emergent adverse events with different frequency across age subgroup through month 24 – safety set

Preferred term	Vehicle	STN1012701 0.1 mg/mL	STN1012701 0.3 mg/mL
3 to <6 years - N	9	8	9
Photophobia – n (%)	1 (11.1)	2 (25.0)	2 (22.2)
Vision blurred – n (%)	1 (11.1)	1 (12.5)	2 (22.2)
6 to <9 years - N	61	62	62
Photophobia – n (%)	10 (16.4)	11 (17.7)	6 (9.7)
Vision blurred – n (%)	4 (6.6)	4 (6.5)	6 (9.7)
9 to <12 years - N	110	110	111
Photophobia – n (%)	19 (17.3)	32 (29.1)	34 (30.6)
Vision blurred – n (%)	10 (9.1)	8 (7.3)	21 (18.9)
12 to 14 years - N	102	102	101
Photophobia – n (%)	17 (16.7)	23 (22.5)	44 (43.6)
Vision blurred – n (%)	8 (7.8)	16 (15.7)	22 (21.8)
6 to 14 years – N	273	274	274
Photophobia – n (%)	46 (16.8)	66 (24.1)	84 (30.7)
Vision blurred – n (%)	22 (8.1)	28 (10.2)	49 (17.9)
3 to <12 years – N	180	180	182
Photophobia – n (%)	30 (16.7)	45 (25.0)	42 (23.1)
Vision blurred – n (%)	15 (8.3)	13 (7.2)	29 (15.9)

Note: At each level of participant summarisation, a participant was counted once if the participant reported one or more events. Events are summarised based on treatment received at the time of event.
n represents the number of participants at each level of summarisation.
Adverse Events were coded using MedDRA, V26.0

Concerning BCVA (Best Corrected Visual Acuity) Letter Change from Baseline Through Month 24 in subgroup category age, the majority of the patients by age category (≥75%) did not present a change (<5 letter change). Across the different age category, there were more participants who had an improved BCVA (>= 5 letters but <10 letters gained) than a decreased BCVA (>= 5 letters but <10 letters lost) at the most recent assessment.

No unexpected events occurred in children between 3 and <6 years of age, but the interpretability is extremely limited due to the small number of participants of this age range. In particular, patients under 6 years old are considered at risk of ocular pathology such as amblyopia, cataract, strabismus and other conditions with irreversible consequences on the vision in children below 6 years old and it is unknown how long-term exposure with atropine, including low dosage, could impact on that risk. It is the applicant's position that the increased risk of developing irreversible visual loss due to blurred vision associated with atropine treatment is considered unlikely. It can be agreed with the applicant, that monitoring as per standard clinical practice may increase the likelihood of detecting any emergent ophthalmic conditions that may be worsened by blurred vision. Moreover, although blurred vision accounted for 12% of all TEAEs, it was mostly of mild intensity and was intermittent in 5-10% of participants. Furthermore, it is acknowledged that patients will be treated bilaterally and given corrected visual prescription thus reducing the risk of developing irreversible visual loss. Moreover, based on the provided information and additional M36 data, observed results in this very young population can be considered to support the treatment of the age group 3 to <6 years with both treatment regimens.

The applicant was asked to further justify the proposed contraindication for patients with amblyopia, strabismus and cataracts. It is noted that these contraindications are not included in the reference medicinal product. Reference is made to the EMA *Guideline on Summary of product characteristics (Sep2009_rev2),* which states that lack of data alone should not lead to a contraindication. If, however, patients have been excluded from studies due to a contraindication on grounds of safety, they should be mentioned in this section. In case the contraindication cannot sufficiently be justified on grounds for safety, a more appropriate alternative would be to add a warning in SmPC section 4.4, if appropriately justified and describing the population in section 5.1. The applicant was asked to further elaborate on whether this potential contraindication/warning would apply to all age groups. In the response, the applicant removed cataract from the contraindications and explained that patients with this condition were excluded from the Phase 3 trial, because the presence of cataract may confound assessment of visual acuity and refraction. Instead, section 4.4 includes a warning stating that "Depending on the type and opacity of the cataract, visual acuity and refraction may not be accurately assessed.". This was acceptable. The applicant preferred to keep amblyopia and strabismus as contraindications in section 4.3 and argued that blurred vision may not only exacerbate these conditions, but potentially also make monitoring more difficult. Of note, the RefMP Atropin POS does not include amblyopia and strabismus. The applicant's argumentation with respect to the suggested contraindications of amblyopia and strabismus is not fully understood. It is agreed that intermittent blurred vision may temporarily further impact the condition of these patients. However, administration of 1% atropine is described as a treatment option for (unilateral) amblyopia in the literature (reviewed by Yeritsyan et al 2024, DOI: 10.7759/cureus.56705). In this case higher dosed atropine is only administered in the better eye. Still, it seems counterintuitive to contraindicate Ryjunea in these patient populations. The applicant removed the contraindication in the SmPC and added instead a warning in section 4.4 which is endorsed.

2.8.8.6.2. Iris colour

Table 57: Summary of ocular treatment-emergent adverse events with different frequency in iris colour subgroups through month 24 – safety set

Preferred term	Vehicle	STN1012701 0.1 mg/mL	STN1012701 0.3 mg/mL
Iris colour: light – N	78	98	84
Mydriasis – n (%)	0	2 (2.0)	13 (15.5)
Vision blurred – n (%)	6 (7.7)	11 (11.2)	20 (23.8)
Iris colour: dark – N	204	184	199
Mydriasis – n (%)	1 (0.5)	3 (1.6)	7 (3.5)
Vision blurred – n (%)	17 (8.3)	18 (9.8)	31 (15.6)

Note: At each level of participant summarisation, a participant was counted once if the participant reported one or more events. Events are summarised based on treatment received at the time of event.
n represents the number of participants at each level of summarisation.
Adverse Events were coded using MedDRA, V26.0
Iris colour was summarised at the participant level. Blue, green, grey and hazel eyes were categorised as light. Eyes that are black, brown, or other were categorised as dark. If a participant had different coloured eyes, the participant was classified as having dark eyes if either eye was dark.

Lighter irises are expected to have greater pupil size and accommodation change than darker irises following use of the same atropine dosage (Loughman et al, 2023). In study SYD-101-001, nearly two-third of the included patients had dark coloured iris. In atropine 0.03%, vision blurred and mydriasis were more frequent in participants with light iris (23.8% and 15.5%) than dark iris (15.6% and 3.5%) while comparable proportions were observed for atropine 0.01% and control. Regarding BCVA, through month 24, for the majority of the patients across both subgroup, no change (< 5 letter change) were observed in the most recent assessment.

Similar results were observed up to Month 36. Differences in frequency of vision blurred and mydriasis between participants with light or dark iris were observed only in the STN1012701 0.3 mg/mL randomised group: they were more frequent in participants with light iris (25.0% and 15.5%) than dark iris (16.6% and 4.0%).

2.8.8.6.3. Fast progressor status

The fast progressor subgroup 1 (n=291) consisted of participants with progression of -0.50 D/year or worse based on historical refraction for any of the 3 history time intervals. Similar tendencies could be observed compared to the safety set. A slightly lower frequency of TEAEs was reported in atropine 0.01% (65.3%) compared to control (68.8%). Non ocular TEAEs were more reported in the control group. Comparable proportions of ocular and non-ocular TEAEs were reported in atropine 0.01%. TEAEs assessed as related to study drug were mainly ocular TEAEs (44.7% vs 29.5% in atropine 0.01% and control). Serious TEAEs were low and comparable between treatment arms. None were assessed as study drug related. TEAEs leading to study drug were low and reported in atropine group solely (1.1% in atropine 0.01%).

Table 58: Overall summary of TEAEs through month 24 – fast progressors subgroup 1, SUD-101-001

Number Of Participants With	Vehicle (N=93) n (%) [E]	STN1012701 0.1 mg/mL (N=95) n (%) [E]
Any TEAE	**64 (68.8) [169]**	**62 (65.3) [159]**
Ocular TEAE	37 (39.8) [59]	38 (40.0) [80]
Non-ocular TEAE	50 (53.8) [110]	39 (41.1) [79]
Any Serious TEAE	**2 (2.2) [3]**	**2 (2.1) [2]**
Ocular TEAE	0	0
Non-ocular TEAE	2 (2.2) [3]	2 (2.1) [2]
Any Study Drug-Related TEAE	**26 (28.0) [34]**	**28 (29.5) [49]**
Ocular TEAE	23 (24.7) [28]	28 (29.5) [49]
Non-ocular TEAE	6 (6.5) [6]	0
Any Study Drug-Related Serious TEAE	**0**	**0**
Ocular TEAE	0	0
Non-ocular TEAE	0	0
Any TEAE Leading to Study Drug Discontinuation	**0**	**1 (1.1) [1]**
Ocular TEAE	0	1 (1.1) [1]
Non-ocular TEAE	0	0
Any TEAE Leading to Death	**0**	**0**
Ocular TEAE	0	0
Non-ocular TEAE	0	0

TEAE: treatment-emergent adverse event
n represents the number of participants at each level of summarisation.
[E] represents the number of events at each level of summarisation.
Adverse Events were coded using MedDRA v22.0.

The fast progress subgroup 2 (n=225) consisted of participants with progression of -0.75 D/year or worse based on historical refraction for any of the 3 history time intervals. TEAEs were slightly more reported in the control group (70.4%) compared to atropine 0.01% (61.8%). Ocular TEAEs were more reported in atropine group while non-ocular TEAEs were more reported in control group. TEAEs assessed as study drug related were mainly ocular TEAEs (28.9% in atropine 0.01% and 22.5% in control). Serious TEAEs were reported in comparable proportions between treatment arms. TEAEs leading to study discontinuation were low and reported in atropine group solely (1.1% in atropine 0.01%).

Table 59: Overall summary of TEAEs through month 24 – fast progressors subgroup 2, study SYD-101-001

Number Of Participants With	Vehicle (N=71) n (%) [E]	STN1012701 0.1 mg/mL (N=76) n (%) [E]
Any TEAE	**50 (70.4) [140]**	**47 (61.8) [116]**
Ocular TEAE	26 (36.6) [42]	32 (42.1) [60]
Non-ocular TEAE	40 (56.3) [98]	28 (36.8) [56]
Any Serious TEAE	**2 (2.8) [3]**	**2 (2.6) [2]**
Ocular TEAE	0	0
Non-ocular TEAE	2 (2.8) [3]	2 (2.6) [2]
Any Study Drug-Related TEAE	**18 (25.4) [23]**	**22 (28.9) [34]**
Ocular TEAE	16 (22.5) [19]	22 (28.9) [34]
Non-ocular TEAE	4 (5.6) [4]	0
Any Study Drug-Related Serious TEAE	**0**	**0**
Ocular TEAE	0	0
Non-ocular TEAE	0	0
Any TEAE Leading to Study Drug Discontinuation	**0**	**1 (1.1) [1]**
Ocular TEAE	0	1 (1.1) [1]
Non-ocular TEAE	0	0
Any TEAE Leading to Death	**0**	**0**
Ocular TEAE	0	0
Non-ocular TEAE	0	0

TEAE: treatment-emergent adverse event
n represents the number of participants at each level of summarisation.
[E] represents the number of events at each level of summarisation.
Adverse Events were coded using MedDRA v22.1.

Overall, between both fast progressor subgroups, no significant differences were seen with the safety analysis and between subgroups.

2.8.8.6.4. Race

Analyses by subgroup for TEAEs and BCVA change letter did not show significant differences between races (Asian [Non-Indian], Non-Asian, Indian, Caucasian [White]). A comparison of TEAEs by race suffers from only few recruited non-Caucasian participants. Based on the available information, no clear trends were noted.

2.8.8.6.5. Gender

Table 60: Summary of ocular treatment-emergent adverse events with different frequency in gender subgroups through month 24 – safety set

Preferred term	Vehicle	STN1012701 0.1 mg/mL	STN1012701 0.3 mg/mL
Male – N	133	115	127
Photophobia – n (%)	20 (15.0)	26 (22.6)	34 (26.8)
Vision blurred – n (%)	9 (6.8)	9 (7.8)	16 (12.6)
Female – N	149	167	156
Photophobia – n (%)	27 (18.1)	42 (25.1)	52 (33.3)
Vision blurred – n (%)	14 (9.4)	20 (12.0)	35 (22.4)

Note: At each level of participant summarisation, a participant was counted once if the participant reported one or more events. Events are summarised based on treatment received at the time of event.
n represents the number of participants at each level of summarisation.
Adverse Events were coded using MedDRA, V26.0

Higher incidences of any TEAEs were reported in females (vehicle: 66.4%, 0.1 mg/mL: 65.3%, 0.3 mg/mL: 75.6%) compared to males (vehicle: 63.2%, 0.1 mg/mL: 55.7%, 0.3 mg/mL: 63.0%). This trend of higher incidences in females is also clearly visible for ocular TEAEs, especially in the Ryjunea groups with roughly 10-11% higher incidences of ocular TEAEs, compared to a ~3% higher incidence in the vehicle group. Overall, subgroup analysis by gender showed similar trends to the safety analysis set and a higher incidence of photophobia, vision blurred and headache in females compared to males.

Up to Month 36, differences between male and female participants were observed only in the STN1012701 0.3 mg/mL group: photophobia and vision blurred were more frequent in females (34.0% and 23.1%) than males (28.3% and 14.2%).

2.8.8.6.6. Patient with renal or hepatic impairment

There is limited data from study SYD-101-001 regarding patients with medical history of renal of hepatic disease with atropine low dose. No adjustment of the dose is necessary for atropine 1% in patients with renal or hepatic impairment.

2.8.8.6.7. Use in pregnancy and Lactation

In SYD-101-001, pregnancy testing were performed using a human chorionic gonadotropin pregnancy urine dipstick test (female participants of childbearing potential only). Female participants will be queried annually regarding childbearing potential status. No pregnancy were reported in SYD-101-001.

In SYD-101-001 study, in the STN1012701 0.3 mg/mL randomised group, a 13-year-old female had a spontaneous vaginal delivery at Day 1090. The last dose of the study drug was received on Day 1098, Month 36 was completed; The participant pregnancy test results were negative at Day 1, Day 352, Day 737 and Day 1099.

2.8.8.7. Immunological events

Not applicable.

2.8.8.8. Safety related to drug-drug interactions and other interactions

Systemic drug interaction is considered low with atropine. The possibility for systemic drug-drug interaction is considered low with STN1012701 0.1 mg/mL and/or 0.3 mg/mL. Animal data show low and short-term plasma exposure in rabbit after dosing of 0.1 mg/mL atropine sulfate eye drops. The applicant harmonised the section 4.5 of the SmPC with the reference product.

2.8.8.9. Discontinuation due to adverse events

A total of 8 ocular TEAEs lead to study drug discontinuation with the highest frequency being reported in atropine 0.03% (4 patients; 1.4%) followed by atropine 0.01% (2 patients; 0.7%) and control (1 patient, 0.4%). Events which lead to study discontinuation and were assessed as study drug related consisted of instillation site irritation (intermittent, duration of event 36 days, moderate, resolved) in one patient (control); eye irritation (intermittent, moderate, duration of event 115 days, resolved) in one patient (atropine 0.01%), photophobia (continuous, moderate, drug interrupted, duration of event 15 days, recovered) and mydriasis (continuous, moderate, drug interrupted, duration of event 15 days, recovered) in one patient (atropine 0.03%), mydriasis (intermittent, mild, duration of event 25 days, drug interrupted, recovered) in one patient (atropine 0.03%) and mydriasis (continuous, moderate, duration of event 19 days, drug interrupted, recovered) in one patient (atropine 0.03%).A total of 4 non-ocular TEAEs lead to study discontinuation: 1 patient in control and 3 patients in atropine 0.03%. The events consisted of yellow skin around the eyes in control (assessed as related, mild, duration of 74 days, recovered), lymphadenitis (serious, moderate, duration of event 7 days, recovered), depression (moderate, not recovered) and gastroenteritis bacterial (moderate, not recovered) in atropine 0.03%. All events occurred in one patient each and none of the events in atropine 0.03% arm were assessed as related to study drug.

Up to Month 36, overall, a total of 10 ocular TEAEs led to study drug discontinuation of 8 (0.9%) participants: 2 (0.7%) participants in the Vehicle group (2 events), 1 (0.4%) participant in the STN1012701 0.1 mg/mL group (1 event), and 4 (1.4%) participants in the STN1012701 0.3 mg/mL randomised group (5 events). In addition, 2 ocular TEAEs leading to study drug discontinuation were reported in 1 (2.9%) participant who was on escape medication. Most reported events consisted of mydriasis (3 events in 3 [1.1%] participants in the STN1012701 0.3 mg/mL randomised group, 1 event in 1 [2.9%] participant in the escape STN1012701 0.3 mg/mL group) and photophobia (1 event in 1 [0.4%] participant in the STN1012701 0.3 mg/mL randomised group, 1 event in 1 [2.9%] participant in the escape STN1012701 0.3 mg/mL group). Other events occurred once and included instillation site irritation (0.4%) and yellow skin* around the eye (0.4%) in the Vehicle group; papilledema (0.4%) in the STN1012701 0.1 mg/mL group; and optic neuritis (0.4%) in the STN1012701 0.3 mg/mL randomised group. All events but optic neuritis and papilledema were considered related to the study drug.

2.8.8.10. Overdose

No cases of overdose with atropine were reported in study SYD-101-001. In overdose, atropine can cause tachycardia, agitation, delirium, dilated pupils, dry mucous membranes, dry skin, and hypoactive bowel sounds. Atropine will be distributed in 2.5 ml bottle, considering that 1 mL contains 0.1 mg for atropine 0.01%, in case of overdose by ingestion the expected dose would be 0.25 mg. Thus, the risk is considered to be low compared to 0.5% and 1% dosage. Additionally, due to the ocular systemic route, an overdose after ocular administration (multiple instillation) is unlikely with 0.01% considering the eye's limited capacity to hold eye drop volume. If overdose occurs treatment should be symptomatic and supportive.

2.8.8.1. Drug abuse

Not applicable.

2.8.8.2. Withdrawal and rebound

The potential for myopic rebound after 36 months is being evaluated in part 2 of study SYD-101-001 (see Clinical Efficacy section for further discussion). Data up to Month 48 are not yet available at this stage.

2.8.8.3. Effects on Ability to Drive or Operate Machinery or Impairment of Mental Ability

As photophobia and blurred vision are known effect of atropine, Ryjunea can impact visual acuity. Thus the product is not recommended in some situations, since atropine may have moderate influence on the ability to drive and use machines, which can last up to 14 days. This is mentioned in section 4.7 of the SmPC.

2.8.8.4. Product information

The reference medicinal product (RefMP) includes Rhinitis sicca as contraindication in section 4.3 of the SmPC, which is currently not the case for the SmPC of Ryjunea. However, dryness is a known effect of atropine although the lower dose of atropine included in Ryjunea as compared to the RefMP is acknowledged. No event associated with a potential drying effect to the nasal cavity related to the use of Ryjunea was reported in the phase 3 trial up until the latest data cut-off. According to the submitted AE Listings, there were also no noticeable increased rates of epistaxis. No patients with rhinitis sicca were included in the trial. However, based on the SmPC guideline, lack of data alone should not lead to a contraindication. Routine pharmacovigilance is considered sufficient to further investigate a potential increased risk with respect to adverse events associated with a potential drying effect to the nasal cavity.

2.8.8.5. Post marketing experience

Ryjunea is the first marketing authorisation currently applied in the EU, thus no post-marketing data are available which is endorsed. Two AMM are available for atropine EIKANCE 0.01%® (Australia) and Xingqi Meioupin® 0.01%. Two cases were found for EIKANCE 0.01%® in the Database of Adverse Event Notifications (DAEN) until sept 2024 but no narrative were available. Some of the reported events (photophobia, eye irritation, eye pain, dry mouth) are in line with the safety profile of atropine but limited information does not allow to conclude on the cases. Regarding Xingqi Meioupin® 0.01% eye drops, no information were found by the applicant.

Risk of off-label use in patient below 3 years old is considered to be low as myopia is usually not diagnosed in such young children. Risk of off label use with more frequent dosage or in other approved indications for higher dosage (uveitis and iritis where 5 mg/mL and 10 mg/mL ophthalmic solutions) are a possibility. Cases of off label use with Atropine sulphate will be monitored by the applicant and reported in PSURs and in signal management as part of routine pharmacovigilance activities.

2.8.8.1. Safety data issued from the literature

The applicant provided an analysis of the literature (up to Feb 2023) with 36 articles describing 32 studies conducted with low-dose atropine used alone for the treatment of myopia in children. The

eligibility criteria in terms of age deviated between the studies. Among the included studies, treatment duration ranged from 6 months (3 studies), 1 year (8 studies), 2 years (7 studies), 3 years (3 studies), 5 years (1 study) to up to 8 years (1 study). The submission also includes a recent Cochrane review (2023) and 6 meta-analyses. It should be mentioned that the majority of studies were conducted in Asian countries. As described further above, iris colour seemed to affect the tolerability of Ryjunea, at least for the higher dose (0.03%), with higher incidences of mydriasis and vision blurred. Overall, these data are considered supportive as they do not reflect the safety profile of the proposed formulation, but of low dose of atropine in general in the treatment of myopia in children, regardless of the formulation, which is not necessarily mentioned in the studies. Furthermore, no proper discussion was provided by the applicant regarding the retrieved articles.

In general, as also described by the applicant, the safety reporting was either incomplete or only cursory in most studies. A comparison of exact incidences of adverse events between studies in the literature (and study SYD-101-001) does not seem meaningful due to expected differences in reporting. The safety findings of study SYD-101-001 seem to be in accordance with the known safety profile of atropine 0,01% and 0,03% with mild and dose dependant adverse effects which are reversible after withdrawal: photophobia, vision blurred, mydriasis, headache. Other adverse effects were reported such as allergic conjunctivitis, eye irritation, dermatitis eyelids, difficulty reading, pruritus, eye swelling, dry eye, ocular hyperaemia.

Overall, considering information provided by the literature research, the meta-analyses and the Cochrane review, the risk for adverse effects seems to be clearly dose dependent. A dose level of 0.01% atropine was well-tolerated and incidences of adverse events were often comparable to placebo. The safety profile was mainly characterised by photophobia/glare and (near) blurred vision, in line with Study SYD-101-001.

In several articles (Cui et al.; Fu et al. 2020), it is mentioned that photophobia was resolved by wearing sunglasses or sun hats during outdoor activities and with no other discomfort in normal indoor or daily outdoor light. Although different proportions of photophobia could be found in the literature, in general there is a higher proportion of photophobia in the early stage after treatment. Additionally, for vision blurred, the use of progressive lens spectacles can be recommended. In LAMP2 study (Yam Jc et al. 2020), photochromic glasses were needed in approximately 30% of participants in atropine 0,01% and progressive lens spectacles were not required in general (less than 2% of the patients treated by atropine 0,01%). The applicant clarified that progressive lens spectacles were not allowed in study SYD-101-001 and that the use of photochromic glasses although allowed was not recorded. This does not have an impact on the interpretation of safety results.

Fu et al, 2020 showed that atropine 0.01% and 0.02% had similar impact on pupil diameter and accommodative amplitude after 12 months of treatment. Moon and Shin reported that 0.01% atropine had less change on accommodative amplitude and pupil diameter compared with 0.025% and 0.05% atropine, but there was no difference in the vision-related quality of life among all groups. Accommodative amplitude decreased and pupil diameter increased more in older children than in younger children after the administration of low concentrations of atropine. Furthermore, lighter irises would expect a greater pupil size and accommodation change than darker irises following use of the same atropine dosage. (Loughman et al, 2023). Pupil dilation was roughly comparable or in the same range as reported for Ryjunea. No literature data seem to be available for a concentration of 0.03% atropine. However, in the LAMP study (Yam et al 2019), dose levels of 0.025% and 0.05% already showed significantly increased rates of photophobia compared to 0.01%. This is confirmed by Study SYD-101-001 (0.03% concentration).

In two studies, it was mentioned that the tested formulation of 0.01% atropine contained 0.01% of benzalkonium chloride (Lee et al. 2022 and Chia et al. 2012). The study of Chia et al. was conducted

on 400 patients aged from 6-12 years old and compared 0.5%; 0.1% and 0.01%. The safety of 0.01% was shown to be better than 0.1% and 0.5%. The study Lee et al. was conducted on 150 patients aged from 6-16 years old and compared atropine 0.01% vs placebo. Adverse events (treatment: 8.7% vs. placebo: 2.1%; group difference p = 0.17). In both studies, atropine was consistent with the known safety profile.

Adverse events of allergic reaction or allergic conjunctivitis were reported in some studies in the literature, but based on the available information, this seemed to be an issue at doses higher than those included in Ryjunea. Some events of allergic conjunctivitis with 0.01% atropine were reported in the LAMP study (Yam et al 2019), but on the same level as the placebo group. In the phase 3 Study SYD-101-001, one event of allergic conjunctivitis was considered related by the Investigator.

Furthermore, the applicant provided a manuscript of an investigator-sponsored open-label, prospective, observational cohort study from a single US centre which included 148 children (≤17 years of age) with myopia, who started treatment with 0.01% or 0.03% atropine. Doses could be escalated/titrated up to 0.05% as needed for myopia progression control. Mean age at atropine treatment initiation was 8.0 years, and mean duration of follow-up was 2.9 years. Data on AEs were unfrequently collected from participants at each study visit using a brief questionnaire. AEs were not judged to be related to intervention. The AE profile was overall roughly consistent with results from study SYD-101-001 and the literature. Notably, more participants reported ≥1 AE in the group who started on 0.01% atropine but whose dose was up titrated to 0.03% (69%), compared to participants remaining on the 0.01% (50%). Due to the open-label, uncontrolled and non-randomised study design, data are regarded only supplementary. The study did not report efficacy data.

The applicant provided an update of the literature reference from January 2024 until August 2024. Overall, the findings are in line with the previous search performed. The provided literature (https://doi.org/*10.3389/fphar.2024.1343698*) is in favour of a dose-dependent rebound effect when treatment is stopped in particular individuals with shorter treatment durations, younger age, and higher baseline SE tend to experience more significant rebound effects. Similarly, the article *https://doi.org/10.1111/ceo.14368* showed evidence of rapid myopia progression following cessation of 0.01% atropine. Another article was in favour of minimal rebound https://jptcp.com/index.php/jptcp/article/view/3911. A potential rebound effect that could negate the effect of 0.01% atropine after cessation of treatment is obviously an important factor for the benefit/risk assessment of Ryjunea. For Study SYD-101-001, no data are available from the randomised withdrawal phase.

2.8.9. Discussion on clinical safety

The safety of STN1012701 0.1 mg/mL compared to vehicle was evaluated in a single phase III pivotal randomised, double-masked vehicle-controlled study (SYD-101-001). The proposed safety evaluation is considered appropriate to assess the safety profile of atropine low-dose including patient burden. The study arms consist of atropine 0.01%, atropine 0.03% and vehicle-control (H20). However, literature suggests that atropine 0.02% is the highest concentration that does not produce significant clinical symptoms from accommodation paresis or pupillary dilation.

Atropine ophthalmic solutions at higher strengths (0.5%, 1%) are approved in the European Union for a number of indications (use as a mydriatic agent prior to determination or the refractive index, chronic use in acute and chronic intraocular inflammation of the iris). From a safety perspective, it is of relevance to note that the label of the significantly higher dosed reference product recommends use of up to 3 times per day, while the SmPC of Ryjunea recommends once daily administration before bedtime.

The study duration of 48 months (36 months of exposure and 12 months of withdrawal) is endorsed regarding a safety aspect as long-term implications for vision, ocular health and accommodation are unknown. It is not clear whether long-term use could cause premature presbyopia, predispose to cataracts, or even cause retinal light harm in case of a small long-term dilation of the pupil. At this stage, data up to month 48 which will comprise data from the randomised withdrawal phase (between months 36 and 48) are not yet available. Month 48 data will provide further long-term treatment safety information.

The formulation contains a novel excipient D20 which D2O is not a component of any approved topical ophthalmic drug products in Europe and thus is a novel excipient for eye drops. Non-clinical data showed that D2O was not considered to be related to any kind of toxicity when dosed for 26 weeks once a day or three times per day in STN1012701 0.1 mg/mL formulation or three times per day in placebo control article. The use of the excipient D2O to replace H2O in the product Ryjunea (atropine sulphate, 0.1 mg/mL eye drops, solution) is not considered to present a risk and long-term safety of D2O will be monitored through routine pharmacovigilance. Additionally, the proposed formulation is not preservative-free as it contains BAK at 0.01%, which is a crucial issue, known to provoke irritation and burns, thus impacting compliance, management in daily-life practice and safety. No safety issue arose from pre-clinical data based on the 26-week ocular toxicity study with STN1012701 0.1 mg/mL in pigmented rabbit. In study SYD-101-001, all arms contained BAK as preservative in their formulation thus, the methodology does not allow to assess the risk associated with BAK in comparison with atropine or D20, in particular risk of ocular surface toxicity, as BAK is known to cause eye irritation, symptoms of dry eyes and may affect the tear film and corneal surface. Use of BAK is at risk in patients with concurrent disorders of the cornea. The long-term safety will be assessed through routine pharmacovigilance in the PSURs. Use of BAK is at risk in patients with concurrent disorders of the cornea. In the SmPC, there is a warning for BAK in section 4.4 Special warnings and precautions for use as BAK is considered as an excipient with known effect (Annex to the European Commission guideline on 'Excipients in the labelling and package leaflet of medicinal products for human use' SANTE-2017-11668). Furthermore, the CHMP has recommended to investigate the feasibility of optimising the formulation with regards to this preservative.

Supportive data are available from a literature review describing the use of atropine in children with myopia when used in a range of doses between 0.01% and 1.0%. Of note, compounded atropine ophthalmic solutions at different strengths are used off-label for slowing myopia progression.

Exposure and Disposition

The double masked, randomised pivotal study has 2 active treatment groups (atropine 0.1 mg/mL and 0.3 mg/mL) and one vehicle group. One drop of assigned masked study drug is administered each night into each eye. In study SYD-101-001, 852 participants were randomised at baseline in study SYD-101-001 including 283, 284 and 285 in control group (H20), atropine 0.01% group and atropine 0.03% group respectively. The safety set includes a total of 847 participants (vehicle: N=282, 0.1 mg/mL: N=282, 0.3 mg/mL: N=283) which is not in line with a recommendation given during EMA SA. During the scientific advice the number of included participants by treatment arms was considered to be actually too low to detect even a common adverse event (appear in ≥1/100) with sufficient precision and it was recommended that the sample size is increased to have at least 300 evaluable subjects per treatment group at the end of the 2-year treatment period. Concern in particular was raised for the 0,03% atropine dosing regimen for which safety data from literature are sparse. The applicant justified that after re-randomisation at 48 months 400-to-500 subjects will have received 0.03% SYD-101 for at least one year and that pooling of the active arms will provide sufficient safety data for the vehicle in comparison to placebo provided that no unexpected adverse events will occur. The applicant provided safety data up to 36 months, patients who were receiving the vehicle up to this point will be re-randomised according to protocol to the SYD-101 0.03% while patient treated by SYD-

101 0.01% and 0.03% will either remain treated by SYD-101 0.01% or 0.03% respectively or be re-randomised to receive the vehicle. At month 36, 221 patients were treated with the vehicle, which means that up to 48 months 414 subjects are expected to complete at least 1 year of treatment under 0.3 mg/ml. Regarding the SYD-101 0.01% arm, a total of 230 patients completed Month 24 and 210 patients completed Month 36.

Of note, up to Month 24, there was a rather significant dropout until the data cut-off, as only a total of 232 (82.0%) participants in vehicle group, 228 (80.3%) participants in the 0.1 mg/mL group and 231 (81.1%) participants in the 0.3 mg/mL group completed Month 24. It is however reassuring that the dropouts were relatively balanced between the groups. Still, 5 (1.8%) participants discontinued the study due to AEs in the 0.03% atropine group (but none in the 0.01% or vehicle groups). Up to Month 24, the mean duration of exposure (SD) was 682.1 (158.95) days and comparable between the groups with more than 80% of the patients in each arm being treated ≥ 547 days. The reported compliance was overall high (97.91%) and only slightly lower in the 0.3 mg/mL group (97.55%), compared to the vehicle group (98.26%) and the 0.1 mg/mL group (97.92%). However, the compliance was calculated based on the number of reported missed doses and it cannot be excluded that there may have been some underreporting of missed doses in this paediatric population.

Up to the data lock point (05 June 2024), a total of 221 patients (78.1%) participants in vehicle group, 210 (73.9%) in STN1012701 0.1 mg/mL and 219 (76.8%) in in STN1012701 0.3 mg/mL completed Month 36. Up to Month 36, the overall mean (SD) duration of exposure was 973.4 (284.05) days, without marked differences between groups. Compliance was high and comparable between groups (above 97 % in all groups; 98.04% in Vehicle group, 97.80% in STN1012701 0.1 mg/mL group, and 97.50% in STN1012701 0.3 mg/mL randomised group) with only one patient in the STN1012701 0.3 mg/mL having a compliance below 50%.

Patient's disposition and demographic characteristics are further described and discussed in *Efficacy section*.

Ocular adverse events

In study SYD-101-001, among the 847 participants in the safety set, 554 reported a total of 1545 treatment emergent adverse events. Up to Month 24, a higher incidence of TEAEs was reported in the atropine 0.03% (70.0%) arm, compared to atropine 0.01% (64.9%) arm and control (61.3%) arm. This was driven by a clearly higher reported incidence of ocular TEAEs in the atropine 0.03% arm (55.5%), followed by atropine 0.01% (42.9%) and control (40.1%) arms, which is consistent with a dose-adverse effect correlation and suggesting that the safety profile of Ryjunea is mainly characterised by local adverse reactions.

Similar results were observed up to Month 36 with a higher proportion of patients presenting at least one TEAEs in the 0.3 mg/mL group (72.4%) compared to STN1012701 0.1 mg/mL group (64.9%) and vehicle group (68.8%) due to ocular TEAE (44.7% in vehicle, 44.7% % STN1012701 0.1 mg/mL group and 57.6% in STN1012701 0.3 mg/mL group and TEAE study related (34.4% in vehicle, 38.3% STN1012701 0.1 mg/mL group and 48.8% in STN1012701 0.3 mg/mL group) which were mainly ocular TEAEs (32.6% in vehicle, 36.2% STN1012701 0.1 mg/mL group and 46.6% in STN1012701 0.3 mg/mL group).

Up to month 24, in study SYD-101-001, the imbalances with respect to ocular TEAEs were driven by three particular events, namely photophobia (vehicle: 16.7%, 0.1 mg/mL: 24.1%, 0.3 mg/mL: 30.4%), vision blurred (vehicle: 8.2%, 0.1 mg/mL: 10.3%, 0.3 mg/mL: 18%), and mydriasis (vehicle: 0.4%, 0.1 mg/mL: 1.8%, 0.3 mg/mL: 7.1%). These adverse events are in line with the mechanism of action of atropine as well as the administration site and a high proportion of these events were also considered related by the Investigator. Other ocular events such as Eye irritation, Eye pain, Instillation

site pain, Instillation site Irritation, Foreign body sensation were either more reported in the control arm or observed in similar frequency between control and treatment groups, except for the AE of conjunctival papillae.

Similarly, through Month 36, the most frequently (≥10%) reported ocular TEAEs included photophobia (25.6%) and vision blurred (13.1%). Other frequent (≥1%) ocular TEAEs included instillation site irritation (9.6%), foreign body sensation in eyes (6.6%), eye pain (4.0%), mydriasis (3.7%), eye irritation (3.2%), conjunctival papillae (1.5%), conjunctivitis (1.2%), conjunctivitis allergic (1.1%), dry eye (1.1%), and punctate keratitis (1.1%). Photophobia, vision blurred and mydriasis were clearly more frequently reported in the STN1012701 0.3 mg/mL group.

Ocular adverse reactions were often reported with a very long duration and the observed pattern for the most reported ocular AE are coherent with the reported AE: majorly continuous for mydriasis (range duration all arms included 2 to 1091 days, mean duration 130 days) and majorly intermittent for the other events which are photophobia (range duration all arms included 1 to 1444 days, mean duration 173 days) and vision blurred (range duration all arms included 1 to 734 days, mean duration 149 days). Upon request, the applicant added information on the duration of certain TEAEs (photophobia, vision blurred, eye irritation) in section 4.8 of the SmPC.

Ocular TEAEs were for the majority mild (27.7% control; 28.4% in atropine 0.01%; 33.9% in atropine 0.03%) and moderate (11.7% control; 14.2% in atropine 0.01%; 20.1% in atropine 0.03%) in severity. Severe TEAEs were reported in low proportions (0.7% control; 0.4% in atropine 0.01%; 1.1% in atropine 0.03%). In the atropine 0.03% arm, three events of severe intensity were assessed as related to study drug in one participant (3 years old patient): intermittent photophobia, intermittent vision blurred and intermittent instillation site irritation. No ocular TEAEs of severe intensity occurred between Month 24 and Month 36.

TEAEs considered as study-drug related were reported in higher proportion in atropine 0.03% arm (47.0%) while being comparable between atropine 0.01% (35.8%) and control (33.0%) arms. TEAEs assessed as study drug-related were mainly ocular TEAEs and in higher incidence in the atropine 0.03% arm (44.9%) compared to atropine 0.01% (34.8%) and control arm (30,9%). A higher incidence of ocular TEAEs assessed as study drug related were reported in the atropine 0,03% (44,9%) compared to atropine 0.01% (34.8%) and control (30.9%). The most reported PT in all treatment arms were photophobia (28,3% in atropine 0.03%; 22,0% in atropine 0,01% and 13,5% in control), vision blurred (14,5% in atropine 0,03%; 22,0% in atropine 0.01% and 13.5% in control), Mydriasis (6.7% in atropine 0.03%; 1,8% in atropine 0.01% and 0% in control) and Instillation site disorders (6.4% in atropine 0.03%; 6.7% in atropine 0.01% and 5.7% in control). Photophobia, Mydriasis and Vision blurred were more reported in the atropine groups with a higher frequency in the 0.03% which is consistent with the known safety profile of atropine. Accommodation disorder was more reported in the atropine 0.03% (2.1%) compared to atropine 0.01% (0.4%) and control (0%). Other ocular TEAEs related to the study drug reported in more than 1 participant were instillation site irritation, foreign body sensation in eyes, instillation site pain (more reported in control), eye pain, eye irritation (more reported in control), conjunctival papillae, anisocoria, eye pruritus and conjunctival hyperaemia without marked difference between treatment groups (less than 1% difference).

Up to Month 36, similar findings were observed. A total of 589 ocular TEAEs in 329 participants were considered as related to the study treatment, with a higher frequency in the STN1012701 0.3 mg/mL group: 92 (32.6%) participants in Vehicle group (152 events), 102 (36.2%) participants in STN1012701 0.1 mg/mL group (172 events), 132 (46.6%) participants in STN1012701 0.3 mg/mL randomised group (256 events) and 4 (11.4%) participants in STN1012701 0.3 mg/mL escape group (9 events). In escape STN1012701 0.3 mg/mL group, the only ocular TEAE considered related to the study drug reported in more than 1 participant was photophobia (8.6%).

In the section 4.8 of the SmPC, the applicant included the most reported TEAEs assessed as study related which consisted of photophobia, mydriasis and vision blurred. The applicant also included the TEAEs Accommodation disorder, eye irritation, foreign body sensation in eyes and anisocoria. The applicant provided justification for not including in section 4.8 of the SmPC, the following terms: Instillation site irritation, Instillation site pain (as the term Eye pain and Eye irritation are already included under the SOC Eye disorders), Eye pruritus (pooled with other similar PT as Eye irritation), Conjunctival hyperaemia (reported only once up to Month 36) and Conjunctivitis (since the aetiology is not clear, the two conjunctivitis cases do not have to be included in the SmPC). The applicant included two other terms based on data up to 36 month since a causal relationship cannot be excluded: Conjunctival papillae (vehicle: 2 subjects; 0.1 mg/mL: 8 subjects; 0.3 mg/mL: 3 subjects) with some assessed as related by the investigator (vehicle: 1 subject; 0.1 mg/mL: 2 subjects; 0.3 mg/mL: 1 subjects) and Punctate keratitis with two events assessed as related by the investigators being reported in STN1012701 0.1 mg/mL group between months 24 and 36.

Furthermore, allergic conjunctivitis was detected as adverse reaction in the literature review, especially for higher doses. Requesting inclusion of allergic conjunctivitis as ADR in section 4.8 based on the one particular report may not be justified. Based on the known allergenic potential and reports of allergic conjunctivitis after treatment with atropine ocular solutions in children with myopia in the literature, the applicant agreed to analyse allergic and BAK-induced toxicity conjunctivitis as part of the upcoming first three PSURs (PSUR frequency: once yearly), and longer if deemed necessary based on the gathered information.

Between Year 1 to Year 2 of treatment exposure, a decrease could be observed regarding the proportions of reported Ocular TEAEs assessed as related to study drug (38.5% vs 15,5% in atropine 0.03%; 32.3% vs 9.2% for atropine 0.01% and 27.3% vs 7.8% for control group for Year 1 and 2 respectively). Thus, the number of participants with at least one ocular TEAE in the 2nd year decreased by ~60-70% compared to the number of participants with TEAEs in the 1st year (converting to a relative reduction by -71.4, -71.5, -59.7%). Between Year 1 and Year 2, the incidences of photophobia (11.7% vs 3,9%, 20.6% vs 5.3%, and 25.4% vs 6.7% for control, atropine 0.01% and atropine 0.03% respectively), and vision blurred (5.7% vs 1.8%, 6.7% vs 1.8%, and 11.7% vs 4.9% for control, atropine 0.01% and atropine 0.03% respectively) assessed as related to study drug decreased. Overall, ocular TEAEs decreased through the years with 593 in year 1, 157 in year 2 and 111 in year 3 and similar tendency was seen for ocular treatment related TEAE. Regarding severity, the majority of the TEAEs were mild to moderate through the years up to 36 months. Four ocular TEAEs were severe (table 29) and of those three occurred during year 1 (optic neuritis, blindness transient and papilledema) and one during year 3 (ulcerative keratitis, vehicle group).

Non-ocular TEAEs

Non-ocular TEAEs were more reported in the control arm (47.5%), compared to atropine 0.03% (44.9%) and atropine 0.01% (39.4%) arms. The most reported non-ocular TEAEs (≥10%) were Headache (14.9% in control [53 events], 10.6% in atropine 0.01% [34 events] and 14.5% in atropine 0.03% [46 events]) and COVID-19 (12.1% in control, 7.8% in atropine 0.01% and 8.5% in atropine 0.03%). Other frequent non-ocular TEAEs (incidence ≥1%) were nasopharyngitis (3.4%), upper respiratory tract infection (2.0%), acne (1.8%), influenza (1.5%), pyrexia (1.5%), seasonal allergy (1.4%), pharyngitis streptococcal (1.3%), anxiety (1.3%), concussion (1.1%), ligament sprain (1.1%) and attention deficit hyperactivity disorder (1.1%). For most of these events such as respiratory infections and similar events described above, it seems unlikely that they were caused by low doses of locally administered atropine and were more consistent with the paediatric population. Of note, atropine inhibits sweat secretion and thus may influence temperature regulation. There was a trend for slightly higher incidences of pyrexia in the atropine treatment groups (vehicle: 1.1% with 3 events, 0.1 mg/mL: 2.1% with 6 events, 0.3 mg/mL: 1.4% with 4 events). Up to Month 36, there were 3 new

events of pyrexia, 2 in the vehicle group and 1 in the 0.1 mg/mL atropine group. Overall, the rates of pyrexia until month 36 were relatively balanced between the groups (vehicle: 1.8% with 5 events, 0.1 mg/mL: 2.5% with 7 events, 0.3 mg/mL: 1.4% with 4 events) and no dose-related increase is detected. The low dose of atropine included in Ryjunea is acknowledged. Regarding anxiety and ADHD, most events were reported in the vehicle group.

Up to Month 36, among 1087 non-ocular TEAEs reported (52.5% vehicle, 46.8% STN1012701 0.1 mg/mL group and 47.6% STN1012701 0.3 mg/mL), the most frequent (≥10%) non-ocular TEAEs included Headache with 51 (18.1%) participants in the Vehicle group, 35 (12.4%) participants in the STN1012701 0.1 mg/mL group, and 46 (16.3%) participants in the STN1012701 0.3 mg/mL, and COVID-19 with 46 (16.3%) participants in the Vehicle group, 30 (10.6%) participants in the STN1012701 0.1 mg/mL group, and 33 (11.7%) participants in the STN1012701 0.3 mg/mL group.

Most non-ocular TEAEs were mainly mild (23.4% in control, 20.9% in atropine 0.01% and 23.3% in atropine 0.03%) to moderate (23.0% in control, 17.0% in atropine 0.01% and 17.7% in atropine 0.03%) in severity. Severe non-ocular TEAEs were low and higher in atropine 0.03% (3.9% vs 1.1% in control and 1.4% in atropine 0.01%). None of the severe non-ocular TEAEs were assessed as related to study drug and none of the reported overdose occurred with study drug. Non-ocular TEAEs of severe intensity that occurred between Month 24 and Month 36 included: Vehicle group: 1 event of anxiety, 1 event of depression, 1 event of major depression, 1 event of suicidal ideation* all in a single (0.4%) participant and STN1012701 0.1 mg/mL group: 1 event of cartilage injury in 1 (0.4%) participant. None were assessed as related to study treatment

Non-ocular TEAEs assessed as study drug related were low in proportions however a higher incidence was observed in the atropine 0.03% (11.3%) compared to atropine 0.01% (5.7%) and control (4.6%) arms. Non-ocular TEAEs were assessed as related to study drug in more than 1 patient consisted of Headache (11.3% in atropine 0.03% vs 5.3% in atropine 0.01% and 3.9% in control). While the overall numbers of headache events (regardless of relatedness) were comparable or even slightly higher in the vehicle group, clearly more events of headache were considered related by the Investigator for the high dose group (vehicle: 3.9%, 0.1 mg/mL: 5.1%, 0.3 mg/mL: 11.3%). The applicant clarified that the exact hour/minute timing of the TEAEs was not recorded in the pivotal study. Therefore, it remains unknown whether the TEAEs occurred shortly after dose administration or later. The average duration of headache events was presented but no dose-related effect was observed (185.5 days in STN1012701 0.1 mg/mL group; 135.9 days in STN1012701 0.3 mg/mL group; 132.8 days in Vehicle group). Higher rates of continued headaches were reported for the vehicle group (incidence with continuous pattern: 7.5% in STN1012701 0.1 mg/mL group; 10.9% in STN1012701 0.3 mg/mL group; 28.2% in Vehicle group), while the rates of intermittent headaches were relatively higher in the atropine groups (incidence with intermittent pattern: 92.5% in STN1012701 0.1 mg/mL group; 89.1% in STN1012701 0.3 mg/mL group; 71.8% in Vehicle group). Up to Month 36, Headache was the only non-ocular TEAE considered related to the study drug by the Investigator that was reported in more than 1 participant overall. It was reported at a higher frequency in the STN1012701 0.3 mg/mL randomised group (11.7%) than the Vehicle (4.3%) and the STN1012701 0.1 mg/ml (6.4%) groups. In the escape STN1012701 0.3 mg/mL group, only 1 non-ocular TEAE was considered related to the study drug: headache, reported in 1 (2.9%) participant.

Other non-ocular TEAE assessed as study drug relate were reported in one patient each: sinus tachycardia (atropine 0.01%), nausea (atropine 0.03%) and insomnia (control). The one related event of nausea was considered mild/grade 1 and co-occurred with mild/grade 1 headache. Both events resolved on the same day. Due to the low dose included in Ryjunea, tachycardia may be more relevant for a scenario of overdosing. Section 4.9 of the SmPC already describes tachycardia as potential symptom of overdose. In addition, section 4.4 includes a warning stating that Ryjunea must be used with special caution in patients with tachycardia (and other cardiac disorders). These measures are

considered sufficient at this point in time but as suggest by the applicant, another assessment for inclusion of this event in 4.8 should be made once the phase 3 study is complete.

Regarding non-ocular TEAEs reported between Year 1 and 2 of treatment exposure, the number of participants with at least one non-ocular TEAE were considerably more frequent in the 1st year (4.3, 5.3, 10.2%) than in the 2nd year (0.7, 1.1, 2.8%), converting to a relative reduction by approximately 72-84%. Between Year 1 and Year 2, the frequency of Headache decreased (3.5% vs 0.7%; 5.0% vs 1.1%; and 10.2% vs 2.8% for control, atropine 0.01% and atropine 0.03% respectively). During Year 2, the only non-ocular TEAEs reported as study drug related was headache. Similar results were observed at month 36 with 1,1% in vehicle, 0.7% in STN1012701 0.1 mg/mL and 0.7% in STN1012701 0.3 mg/mL. Regarding severity per year, while the number of reported events of Headache decreased through the years, the number of mild and severe events remained stable between Year 2 and Year 3. 19 non-ocular SAEs were reported up to month 36 of which the majority occurred during year 1 of treatment and none were assessed as related to study drug. Furthermore, 3 non-ocular TEAEs led to study drug discontinuation of 3 (0.4%) participants by end of month 36, all in the STN1012701 0.3 mg/mL randomised group and these events occurred all in the first year and were not considered as related to study drug

Serious TEAEs, Deaths and Discontinuation due to adverse events

Serious TEAEs were reported in low proportions and in slightly higher incidence in atropine 0.03% (2.8%), while being comparable between atropine 0.01% (1.4%) and control (1.8%). Serious TEAEs were for the majority non-ocular TEAEs, and in slightly higher incidence in the atropine 0.03% arm (2.5%), compared to atropine 0.01% arm (1.1%) and control (1.8%). Serious ocular-TEAEs occurred in one patient in each arm (0.4%) and consisted of blindness transient in control, papilledema in atropine 0.01% and Optic neuritis in atropine 0,03%. None were assessed as related to study drug. No serious ocular TEAEs occurred between Month 24 and Month 36.

Of note, the TEAE of papilloedema occurred twice. One event was reported as SAE in a participant with a history of idiopathic intracranial hypertension, and the other event was reported in the participant who experienced the SAE of optic neuritis. Both events were considered either unlikely related or not related by the Investigator. In the PHV database, there were no entries of papilloedema for the substance atropine. Until the new data cut-off (up to 36 Month), there were no additional cases of papilloedema. Considering that papilloedema occurs by definition secondary to increased intracranial pressure, which seems to be unlikely caused by Ryjunea eyedrops, routine pharmacovigilance is considered acceptable for now. This issue was raised because papilloedema is a very rare event and the occurrence of two cases in this small trial seems unusual.

A total of in 15 (1.8%) participants. In the vehicle group, 5 participants (1.8%) experienced 6 events (fall, forearm fracture, intentional overdose, ataxia, dizziness postural, suicidal ideation), while 3 participants (1.1%) in the 0.1 mg/mL group reported 3 events (concussion, intentional overdose, colitis ulcerative), and 7 (2.5%) participants in the 0.3 mg/mL group reported 9 events (radius fracture, seizure, eating disorder, suicide attempt, lymphadenitis, supraventricular tachycardia, pectus excavatum, systemic inflammatory response syndrome [due to COVID-19], COVID-19). All TEAEs occurred in one patient each. No case of overdose occurred with the study drug and none of the events were assessed as related to study drug. The event of supraventricular tachycardia was causally attributed to a newly diagnosed Wolff-Parkinson-White syndrome and the event of seizure occurred after drug abuse. In study SYD-101-001, no deaths were reported from baseline through Month 24. Only one serious non-ocular TEAEs occurred between Month 24 and Month 36: suicidal ideation in the Vehicle group. It was considered as not related to the study drug. TEAEs leading to study discontinuation were reported in similar proportions between atropine 0.01% and control (0.7%) arms, while reported in higher proportion in the atropine 0.03% (2.5%). In general, similar proportions of

ocular and non-ocular TEAEs lead to study discontinuation in treatment arms (1.4% vs 1.1% and 0.4% vs 0.4% for atropine 0.03% and control group respectively) except for atropine 0.01% where solely ocular TEAEs lead to study drug discontinuation (0.7%). A total of 8 ocular TEAEs lead to study drug discontinuation with the highest frequency being reported in atropine 0.03% (4 patients; 1.4%) followed by atropine 0.01% (2 patients; 0.7%) and control (1 patient, 0.4%). Events which lead to study discontinuation and were assessed as study drug related consisted of instillation site irritation in one patient (control); eye irritation in one patient (atropine 0.01%), photophobia and mydriasis in one patient (atropine 0.03%) and mydriasis in two patients (atropine 0.03%). A total of 4 non-ocular TEAEs lead to study discontinuation: 1 patient in control and 3 patients in atropine 0.03%. All events occurred in one patient each and none of the events in atropine 0.03% arm were assessed as related to study drug. Up to Month 36, overall, a total of 10 ocular TEAEs led to study drug discontinuation of 8 (0.9%) participants: 2 (0.7%) participants in the Vehicle group (2 events), 1 (0.4%) participant in the STN1012701 0.1 mg/mL group (1 event), and 4 (1.4%) participants in the STN1012701 0.3 mg/mL randomised group (5 events). Most reported events consisted of mydriasis (3 events in 3 [1.1%] participants in the STN1012701 0.3 mg/mL randomised group, 1 event in 1 [2.9%] participant in the escape STN1012701 0.3 mg/mL group) and photophobia (1 event in 1 [0.4%] participant in the STN1012701 0.3 mg/mL randomised group, 1 event in 1 [2.9%] participant in the escape STN1012701 0.3 mg/mL group). All events but optic neuritis and papilledema were considered related to the study drug.

Safety in special populations

Only a small number of children between 3 and <6 years of age were recruited (vehicle: n=9, 0.1 mg/mL: n=8, 0.3 mg/mL: n=8). Of this age subgroup, 9 children reported 23 TEAEs and all events were either eye disorders (mainly photophobia and vision blurred) or administration site conditions (such as instillation site pain). The applicant provided a comparative analysis of the ocular TEAEs of photophobia and vision blurred between paediatric age subgroups. Overall, the incidences of these TEAEs tended to be higher in the two older paediatric age groups (9 to <12 and 12 to 14 years of age) compared to the younger children (3 to <6 years of age, 6 to <9 years of age). Also, headache tended to be reported more frequently in older age groups. Nevertheless, it is likely that reporting may have been influenced by different communication skills between the age subgroups. Concerning BCVA (Best Corrected Visual Acuity) Letter Change from Baseline Through Month 24 in subgroup category age, the majority of the patients by age category (≥75%) did not present a change (<5 letter change). Across the different age category, there were more participants who had an improved BCVA (>= 5 letters but <10 letters gained) than a decreased BCVA (>= 5 letters but <10 letters lost) at the most recent assessment.

No unexpected events occurred in children between 3 and <6 years of age, but the interpretability is extremely limited due to the small number of participants of this age range. In particular, patients under 6 years old are considered at risk of ocular pathology such as amblyopia, cataract, strabismus and other conditions with irreversible consequences on the vision in children below 6 years old and it is unknown how long-term exposure with atropine, including low dosage, could impact on that risk. It is the applicants position that the increased risk of developing irreversible visual loss due to blurred vision associated with atropine treatment is considered unlikely. It can be agreed with the applicant, that monitoring as per standard clinical practice may increase the likelihood of detecting any emergent ophthalmic conditions that may be worsened by blurred vision. Moreover, although blurred vision accounted for 12% of all TEAEs, it was mostly of mild intensity and was intermittent in 5-10% of participants. Furthermore, it is acknowledged that patients will be treated bilaterally and given corrected visual prescription thus reducing the risk of developing irreversible visual loss. Based on the provided information and additional M36 data, observed results in this very young population can be considered to support the treatment of the age group 3 to <6 years with both treatment regimens.

In study SYD-101-001, nearly two-third of the included patients had dark coloured iris. In atropine 0,03%, vision blurred and mydriasis were more frequent in participants with light iris (23.8% and 15.5%) than dark iris (15.6% and 3.5%) while comparable proportions were observed for atropine 0,01% and control. Regarding BCVA, through month 24, for the majority of the patients across both subgroup, no change (< 5 letter change) were observed in the most recent assessment.

Analyses by subgroup for TEAEs and BCVA change letter did not show significant differences between races. A comparison of TEAEs by race suffers from only few recruited non-Caucasian participants. Based on the available information, no clear trends were noted. Subgroup analysis by gender showed similar trends to the safety analysis set and a higher incidence of photophobia, vision blurred and headache in females (vehicle: 66.4%, 0.1 mg/mL: 65.3%, 0.3 mg/mL: 75.6%) compared to males (vehicle: 63.2%, 0.1 mg/mL: 55.7%, 0.3 mg/mL: 63.0%). This trend of higher incidences in females is also clearly visible for ocular TEAEs, especially in the Ryjunea groups with roughly 10-11% higher incidences of ocular TEAEs, compared to a ~3% higher incidence in the vehicle group In atropine 0,03%, vision blurred and mydriasis were more frequent in participants with light iris (23.8% and 15.5%) than dark iris (15.6% and 3.5%) while comparable proportions were observed for atropine 0.01% and control. There is limited data from study SYD-101-001 regarding patients with medical history of renal of hepatic disease with atropine low dose. No adjustment of the dose is necessary for atropine 1% in patients with renal or hepatic impairment.

The fast progressor subgroup 1 (n=291) consisted of participants with progression of -0.50 D/year or worse based on historical refraction for any of the 3 history time intervals. Similar tendencies could be observed compared to the safety set. The fast progress subgroup 2 (n=225) consisted of participants with progression of -0.75 D/year or worse based on historical refraction for any of the 3 history time intervals. TEAEs were slightly more reported in the control group (70.4%) compared to atropine 0.01% (61.8%). Overall, between both fast progressor subgroups, no significant differences were seen with the safety analysis and between subgroups.

Data up to Month 36 were consistent with the findings observed at Month 24.

Laboratory and other findings

Through month 24 and 36, no significant changes were observed regarding median values for blood pressure and heart rate. Weight and height increased with age as expected across treatment arms.

Treatment with Ryjunea did not seem to have an effect on the BCVA, as shown by comparable results between the three treatment groups with respect to incidences of letters lost and letters gained through month 24.

For binocular near BCVA, across treatment group more than 75% of the patients had no changes (< 1 line change), with a higher proportions in atropine groups (nearly 80%). Across treatment groups more than 10% had >= 1 line but < 2 lines gained at the most recent assessment with a higher proportion in the control group. There seemed to be a trend for a dose-dependent worsening (lower incidences for lines gained, higher incidences for lines lost of binocular near visual acuity in the Ryjunea groups compared to vehicle. This may be explained by the mechanism of action of atropine. A potential worsening in this regard needs to be considered for evaluation of the overall benefit of Ryjunea. At baseline, mean binocular accommodative amplitude (D) was slightly higher in atropine 0.01% compared to the control (19.085 D in control, 20.425 D in atropine 0.01%). Through month 24, the mean change from baseline were -0.429 D in control and -1.028 D in atropine 0.01%. As seen with binocular near visual acuity, the same trend was noted for binocular accommodative amplitude, with a dose-dependent worsening of the score at month 24 (mean [SD] change from baseline; vehicle: -0.429 [9.6504] D, 0.1 mg/mL: -1.028 [9.6744] D, 0.3 mg/mL: -1.280 [9.7991] D). Data on binocular near visual acuity were further discussed and analysed using actual logMAR value compared to

baseline. At month 24 and 36, no statistically significant difference were observed (p value>0.05) for accommodation amplitude and binocular near visual acuity.

Treatment emergent clinically significant biomicroscopic abnormalities were slightly more reported in atropine 0.03% (4.6% vs 2.4% in control and 3.1 % in atropine 0.01%) with the most reported abnormalities concerning the lid and the cornea. In the majority of the cases, the clinically significant abnormalities coincided and could be medically linked with TEAEs. As advised in the EMA-SA, also due to the novel D_2O excipient, the applicant performed corneal staining with fluorescein. Only few shifts to higher staining scores were observed with no notable differences between the treatment groups. Majority of the patients had no trace of staining and the few patients who had staining shifted from mild to trace or none across treatment group. Proportions of patients presenting moderate staining were few (2 in control and one in each atropine group) and none had a severe staining. Regarding treatment-emergent clinically significant ophthalmoscopy, one patient had bilateral retinal vessel tortuosity in control arm and one patient had bilateral papilledema in atropine 0.03%. Both events were not assessed as related to study drug. New findings up to Month 36 does not raise concern regarding safety and are consistent with Month 24.

Regarding central endothelial cell density (which was measured in approximately 25% of study participants) baseline mean were comparable between treatment groups with 3081.69 in control, 3084.08 in atropine 0.01% and 3022.41 in atropine 0.03%. Through month 24, comparable change from Baseline in Central Endothelial Cell Density (cells/mm2) were observed in control (-27.04 cells/mm2) and atropine 0.03% (-25.83 cells/mm2) while being lower in atropine 0.01% (-4.26 cells/mm2). These results are to be taken with caution as only ¼ of the patients had measures.

Overall, no relevant changes were noted between the three treatment groups with respect to central endothelial cell density (cells/mm^2). These data with those on corneal staining suggest that there are no obvious safety concerns of D2O for the cornea.

At baseline, mean pupil diameter (mm) were comparable between treatment groups (5.183 in control vs 5.122 in atropine 0.01% and 5.162 in atropine 0.03%). A clear dose-dependent increase in mean pupil diameter from baseline to month 24 was noted (mean [SD] change from baseline; vehicle: 0.036 [1.2801] mm, 0.1 mg/mL: 0.409 [1.2953] mm, 0.3 mg/mL: 0.815 [1.3801] mm), which can be expected based on the pharmacological effect of atropine. Furthermore, in the atropine groups, the lowest mean change in pupil dilatation was observed in the 0.01% atropine arm (0.409 in atropine 0.01%) compared to atropine 0,03% (0.815 in atropine 0.03%). Increased pupil diameter is likely related to the increase in photophobia. The summary of Clinical Pharmacology provides a literature overview on the effect of atropine on pupil size (for the lower dose, 0.01% = 0.1 mg/mL), which shows roughly comparable values. Up to Month 36, the mean (SD) change from baseline in pupil diameter was -0.033 (1.2047) mm in Vehicle group, 0.364 (1.3007) mm in STN1012701 0.1 mg/mL group and 0.650 (1.3815) mm in STN1012701 0.3 mg/mL randomised group. In participants who were on escape medication, the mean (SD) change from baseline in pupil diameter was 0.736 (1.1064) mm. Up to month 24, across treatment groups one patient in control and one patient in atropine 0.03% had an increase in IOP (mmHg) from baseline >10 mmHg. Intraocular pressure (IOP) was determined at certain study visits (prior to pupil dilation) and the procedure used for pressure evaluation was iCare or Goldmann tonometer with a major use of iCare tonometer by the site since it does not require local anaesthesia, does not indent the cornea, is quicker, and less invasive than Goldmann tonometer.

Except for STN1012701 0.3 mg/mL at Month 36 where a slight decrease was observed, the difference in mean IOP of both STN1012701 doses compared to vehicle up to Month 36 were not statistically significant (p>0.05).

Tolerability assessment

A questionnaire was used to assess tolerability (blurred vision, burning/stinging, eye pain, grittiness in eye, sensitivity to light and headache). Results were obtained for more than 95% of the patients at month 3 with a decrease observed at month 24 with the results being assessed for more than 80% of the patients. A question was raised in clinical efficacy section to ask the applicant to provide the questionnaires as they were not found in the submission.

The tolerability questionnaire was completed at Months 3 and 6 and every 6 months thereafter until Month 24. It is critically noted that it was recommended to increase the frequency for providing the tolerability questionnaire (i.e., also including questionnaires on Week 2 and Months 2, 4, and 5) in the scientific advice (EMEA/H/SA/4009/1/2018/PED/III). This was not followed by the applicant. Also, no recall period had been specified and the occurrence of AEs was apparently not questioned regularly via a questionnaire on a phone or web-based application, as recommended (i.e., weekly for the first 6 months and then monthly until Month 48/EoS). Thus, tolerability and AEs were reported less frequently than recommended, especially during the first 6 months. Lack of these data is unfortunate, since some ocular TEAEs were more frequent earlier during treatment. The chosen frequency was due to wanting to reduce the patient's burden and in context of the COVID-19 situation. Furthermore, a self-report tool such as a generic patient-reported adverse event questionnaires was suggested as the basis of a specific instrument. The clinical site was delegated their own discretion to assess severity of the symptoms and the seriousness was not assessed with the tolerability questionnaires.

More than 90% of the patients in each treatment arms did not present adverse events of blurred vision, eye pain, burning/stinging and headache through Month 24. Events were in the majority mild and intermittent through month 24. Severe events occurred in low proportions at different time up to month 24. At month 24, 72.5%; 81.9% and 89% of the patients did not present sensitivity to lightness in respectively atropine 0.03%; atropine 0.1% and control. Comparable results were observed through month 24. Severe events of sensibility to light were mostly reported in atropine 0,03% up to month 24.

Overall, the results from a tolerability questionnaire showed comparable results between the three treatment groups for the queried potential side effects of burning/stinging, eye pain, grittiness in eye and headache. A clear dose-related effect was only seen for sensitivity to light and to a lesser extent for blurred vision, in line with the above presented AE profile. Sensitivity to light did only slightly decrease over time, e.g., from Month 3 (15.6%, 19.4%, 30.7% of subjects in the vehicle, and 0.1 mg/mL 0.3 mg/mL groups) to Month 24 (11.0%, 18.1%, 27.5%). Furthermore, severe-grade sensitivity of light occurred mainly in the atropine groups, including 6 cases of continuous severe symptoms in the 0.03% atropine group.

Similar results were found up to Month 36.

Use in pregnancy and Lactation

In SYD-101-001, pregnancy testing were performed using a human chorionic gonadotropin pregnancy urine dipstick test (female participants of childbearing potential only). Female participants will be queried annually regarding childbearing potential status.

Overdose

No cases of overdose with atropine were reported in study SYD-101-001. Atropine will be distributed in 2.5 ml bottle, considering that 1 mL contains 0.1 mg for atropine 0.01%, in case of overdose by ingestion the expected dose would be 0.25 mg. Thus, the risk is considered to be low compared to 0.5% and 1% dosage. Additionally, due to the ocular systemic route, an overdose after ocular

administration (multiple instillation) is unlikely with 0.01% considering the eye's limited capacity to hold eye drop volume.

Withdrawal and rebound

The potential for myopic rebound after 36 months is being evaluated in part 2 of study SYD-101-001 (see *Clinical Efficacy* section for further discussion). Data up to Month 48 are not available at the time of the opinion however these will be provided post-approval as a PAES.

Effects on Ability to Drive or Operate Machinery or Impairment of Mental Ability

As photophobia and blurred vision are known effect of atropine, Ryjunea can impact visual acuity and thus the product is not recommended in some situations, since atropine may have moderate influence on the ability to drive and use machines which can last up to 14 days. This is mentioned in section 4.7 of the SmPC.

Product information

The reference medicinal product (RefMP) includes Rhinitis sicca as contraindication in section 4.3 of the SmPC, which is currently not the case for the SmPC of Ryjunea. However, dryness is a known effect of atropine. Although the lower dose of atropine included in Ryjunea as compared to the RefMP is acknowledged. No event associated with a potential drying effect to the nasal cavity related to the use of Ryjunea was reported in the phase 3 trial up until the latest data cut-off. According to the submitted AE Listings, there were also no noticeable increased rates of epistaxis. Based on the SmPC guideline, lack of data alone should not lead to a contraindication. Routine pharmacovigilance is considered sufficient to further investigate a potential increased risk with respect to adverse events associated with a potential drying effect to the nasal cavity.

Post-marketing experience

Ryjunea is the first marketing authorisation currently applied in the EU for the claimed indication, thus no post-marketing data are available. From any worldwide marketing authorisation for low dose of atropine with/out benzalkonium chloride as an excipient, some of the reported events (photophobia, eye irritation, eye pain, dry mouth) are in line with the safety profile of atropine but limited information does not allow to conclude on the cases.

Risk of off-label use in patient below 3 years old is considered to be low as myopia is usually not diagnosed in such young children. Risk of off label use with more frequent dosage or in other approved indications for higher dosage (uveitis and iritis where 5 mg/mL and 10 mg/mL ophthalmic solutions) are a possibility. Cases of off label use with Atropine sulphate will be monitored by the applicant and reported in PSURs and in signal management as part of routine pharmacovigilance activities.

Literature review

The applicant provided an analysis of the literature (up to Feb 2023) with 36 articles describing 32 studies conducted with low-dose atropine used alone for the treatment of myopia in children. The eligibility criteria in terms of age deviated between the studies. Among the included studies, treatment duration ranged from 6 months (3 studies), 1 year (8 studies), 2 years (7 studies), 3 years (3 studies), 5 years (1 study) to up to 8 years (1 study). The submission also includes a recent Cochrane review (2023) and 6 meta-analyses. It should be mentioned that the majority of studies were conducted in Asian countries. As described further above, iris colour seemed to affect the tolerability of Ryjunea, at least for the higher dose (0.03%), with higher incidences of mydriasis and vision blurred. Overall, these data are considered supportive as they do not reflect the safety profile of the proposed formulation, but of low dose of atropine in general in the treatment of myopia in children, regardless of

the formulation, which is not necessarily mentioned in the studies. Furthermore, no proper discussion was provided by the applicant regarding the retrieved articles.

In general, as also described by the applicant, the safety reporting was either incomplete or only cursory in most studies. A comparison of exact incidences of adverse events between studies in the literature (and study SYD-101-001) does not seem meaningful due to expected differences in reporting. The safety findings of study SYD-101-001 seems to be in accordance with the known safety profile of atropine 0,01% and 0,03% with mild and dose dependant adverse effects which are reversible after withdrawal: photophobia, vision blurred, mydriasis, headache. Other adverse effects were reported such as allergic conjunctivitis, eye irritation, dermatitis eyelids, difficulty reading, pruritus, eye swelling, dry eye, ocular hyperaemia.

Overall, considering information provided by the literature research, the meta-analyses and the Cochrane review, the risk for adverse effects seems to be clearly dose dependent. A dose level of 0.01% atropine was well-tolerated and incidences of adverse events were often comparable to placebo. The safety profile was mainly characterised by photophobia/glare and (near) blurred vision, in line with Study SYD-101-001.In several articles (Cui et al.; Fu et al. 2020), it is mentioned that photophobia was resolved by wearing sunglasses or sun hats during outdoor activities and with no other discomfort in normal indoor or daily outdoor light. Although different proportions of photophobia could be found in the literature, in general there is a higher proportion of photophobia in the early stage after treatment. Additionally, for vision blurred, the use of progressive lens spectacles can be recommended. In LAMP2 study (Yam Jc et al. 2020), photochromic glasses were needed in approximately 30% of participants in atropine 0.01% and progressive lens spectacles were not required in general (less than 2% of the patients treated by atropine 0.01%). Progressive lens spectacles were not allowed in study SYD-101-001 and that the use of photochromic glasses although allowed was not recorded. This does not have an impact on the interpretation of safety results.

Fu et al, 2020 showed that atropine 0.01% and 0.02% had similar impact on pupil diameter and accommodative amplitude after 12 months of treatment. Moon and Shin reported that 0.01% atropine had less change on accommodative amplitude and pupil diameter compared with 0.025% and 0.05% atropine, but there was no difference in the vision-related quality of life among all groups. Accommodative amplitude decreased and pupil diameter increased more in older children than in younger children after the administration of low concentrations of atropine. Furthermore, lighter irises would expect a greater pupil size and accommodation change than darker irises following use of the same atropine dosage. (Loughman et al, 2023). Pupil dilation was roughly comparable or in the same range as reported for Ryjunea. No literature data seem to be available for a concentration of 0.03% atropine. However, in the LAMP study (Yam et al 2019), dose levels of 0.025% and 0.05% already showed significantly increased rates of photophobia compared to 0.01%. This is confirmed by Study SYD-101-001 (0.03% concentration).

In two studies, it was mentioned that the tested formulation of 0.01% atropine contained 0.01% of benzalkonium chloride (Lee et al. 2022 and Chia et al. 2012). The study of Chia et al. was conducted on 400 patients aged from 6-12 years old and compared 0.5%; 0,1% and 0.01%. The safety of 0.01% was shown to be better than 0.1% and 0.5%. The study Lee et al. was conducted on 150 patients aged from 6-16 years old and compared atropine 0.01% vs placebo. Adverse events (treatment: 8.7% vs. placebo: 2.1%; group difference p = 0.17). In both studies, atropine was consistent with the known safety profile.

Adverse events of allergic reaction or allergic conjunctivitis were reported in some studies in the literature, but based on the available information, this seemed to be an issue at doses higher than those included in Ryjunea. Some events of allergic conjunctivitis with 0.01% atropine were reported in

the LAMP study (Yam et al 2019), but on the same level as the placebo group. In the phase 3 Study SYD-101-001, one event of allergic conjunctivitis was considered related by the Investigator

The applicant provided an update of the literature reference from January 2024 until August 2024. Overall, the findings are in line with the previous search performed. The provided literature (https://doi.org/*10.3389/fphar.2024.1343698*) is in favour of a dose-dependent rebound effect when treatment is stopped in particular individuals with shorter treatment durations, younger age, and higher baseline SE tend to experience more significant rebound effects. Similarly, the article *https://doi.org/10.1111/ceo.14368* showed evidence of rapid myopia progression following cessation of 0.01% atropine. Another article was in favour of minimal rebound https://jptcp.com/index.php/jptcp/article/view/3911. A potential rebound effect that could negate the effect of 0.01% atropine after cessation of treatment is obviously an important factor for the benefit/risk assessment of Ryjunea. For Study SYD-101-001, no data are available from the randomised withdrawal phase.

2.8.10. Conclusions on clinical safety

The safety profile of atropine 0.01% are in line with the known safety profile of atropine which consists commonly of ocular AEs such as blurred vision, photophobia, mydriasis and non-ocular AEs such as headache which in long-term use may have an impact on the patient's daily life. The 0.01% dosage has shown a tolerable safety profile with only slightly higher incidences of ocular adverse events compared to vehicle, mainly due to the TEAE of photophobia.

2.8.11. Discussion on clinical aspects

This application concerns Ryjunea 0.01%, a hybrid version of atropine eye drops solution, for slowing the progression of myopia in paediatric patients. The reference product Atropine-POS 0.5% atropine eye drops is indicated as a mydriatic agent prior to determination of the refractive index and for example for chronic use in acute and chronic intraocular inflammation of the iris. Nonclinical toxicity study has been provided for this application and considered sufficient. From a clinical perspective, this application does not contain new data on the pharmacokinetics and pharmacodynamics of the active substance; the applicant's clinical overview on these clinical aspects based on information from published literature was considered sufficient.

The proposed indication is supported by efficacy and safety results from conducted multicentre, randomised, double-masked, vehicle-controlled pivotal study in paediatric patients with myopia (Study SYD-101-001). The applicant did not conduct any clinical studies against the reference product, which is acceptable because of the differences in the strength, indication and composition (D20 instead of H2O). The annual progression rate of myopia in children treated with Ryjunea 0.01% compared to vehicle was significantly lower at month 24 and month 36. Additionally, bibliographic data are submitted.

A positive benefit/risk ratio can therefore be concluded. However, long term clinical effects are considered an important uncertainty given the limited study duration in relation to the 'at-risk period' for myopia (i.e., full duration of eye growth) and the lack of data on rebound effects from SYD-101-001. Therefore, in order to further characterise the efficacy and safety of Ryjunea and the rebound effects and progression of myopia after treatment cessation, the MAH should submit the 48 months follow-up results from the study SYD-101-001 (Annex II.D condition).

The CHMP, having considered the data submitted in the application and available on the chosen reference medicinal product, is of the opinion that no additional risk minimisation activities are

required beyond those included in the product information.

2.8.12. Conclusions on clinical aspects

Based on the presented studies, the overall benefit/risk balance of Ryjunea is positive regarding the 0.01% atropine strength 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"*.

The CHMP considers the following measures necessary to address the clinical issues:

Post-authorisation efficacy study (PAES): In order to further characterise the efficacy and safety of Ryjunea and the rebound effects and progression of myopia after treatment cessation, the MAH should submit the 48 months follow-up results from the study SYD-101-001 with due date 30.06.2026. (Annex II.D condition).

2.9. Risk Management Plan

2.9.1. Safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	Long-term safety

2.9.2. Pharmacovigilance plan

No additional pharmacovigilance activities.

Long-term safety will be evaluated in the PAES study.

2.9.3. Risk minimisation measures

Table 61: Summary of risk minimisation measures

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Long-term safety	Routine risk minimisation measures: • Proposed text in SmPC sections 4.2 and 4.4 with corresponding information in PIL. Additional risk minimisation measures: N/A	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: N/A Additional pharmacovigilance activities: N/A

2.9.4. Conclusion

The CHMP and PRAC considered that the risk management plan version 1.0 is acceptable.

2.10. Pharmacovigilance

2.10.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.10.2. Periodic safety update reports submission requirements

Based on different indication and different treatment duration, the PRAC is of the opinion that a separate entry in the EURD list for Ryjunea is needed, as it cannot follow the already existing entry for atropine. The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request the alignment of the new PSUR cycle with the international birth date (IBD). The IBD is 31.08.1945. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.11. Product information

2.11.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets 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

Myopia, or near-sightedness, appears during childhood and progress with age. Myopia, is clinically defined as a refractive error of –0.50 dioptres (D) or worse (WHO, 2015). High myopia, defined as a refractive error of -6.00 D or worse, is associated with a significant risk of pathologic changes including glaucoma, cataract, retinal detachment, choroidal degeneration, choroidal neovascularisation, and retinoschisis, all of which can cause irreversible loss of vision (Wong et al., 2014). Depending on the degree of ocular elongation of the axial length (AL), and the existence of other anomalies, diverse type of myopia are to be distinguished. Among them and particularly in children the most common observed myopia is axile, which presents an increase of AL, and refractive or accommodative myopia. Axile myopia is often associated with ocular complications such as cataract, retinal detachment, macular hole, retinal atrophy. Furthermore, it is understood that myopia appears to be a multifactorial disease with an incidence of ethnicity, iris colour and even lifestyle (indoor/outdoor activities). The diagnosis is made through patient history combined with standard comprehensive eye and vision examination including assessments for visual acuity, refraction, accommodation, strabismus/amblyopia, binocularity and ocular health (American Optometric Association, 2016). The main symptom is constant blurred distance vision, however, younger children will mainly complain of other symptoms such as headaches or tired eyes, sitting close to the TV or classroom blackboard and problems with hand eye coordination.

3.1.2. Available therapies and unmet medical need

There is no current treatment to prevent myopia, however it is of importance to early detect myopia in children with routine eye examination in order to focus on treatment aimed to slow/control its progression. Correcting vision and maintaining good ocular health are also desired and spending outdoor times highly recommended. There are currently several treatment options available such as:

Optical Correction

Vision in myopic children may be corrected using ordinary adapted spectacles or contact lenses. Spectacles are often the first line of treatment, especially in young children as they provide clear distance vision, with little to no side effects. Contact lenses are usually reserved for older children since they are more difficult to use, require a greater level of care and are associated with an increased potential for side effects such as eye redness, pain or vision loss due to ulcers (Walline et al., 2011). However, optical correction does not provide myopia control unlike multifocal spectacles/lenses.

Orthokeratology

Orthokeratology involves patients wearing reverse geometry contact lenses overnight, which results in temporary flattening of the cornea and provides clear vision during the day without any glasses or contact lenses. Reduction in myopia is achieved by central corneal epithelial thinning, midperipheral epithelial, and stromal thickening. However, orthokeratology is associated with an increased risk of ocular side effects.

Atropine

Currently there is a marketing authorisation (MA) in Australia under the name of Eikance 0.01% Eye Drops in order to slow the progression of myopia in children aged from 4 to 14 years. Atropine treatment may be initiated in children when myopia progresses ≥-1.0 D per year.

As well, in France there is current use of atropine in children with myopia without defined criteria (prior to treatment range of progression) and without a marketing authorisation.

3.1.3. Main clinical studies

The applicant has conducted a single pivotal clinical Phase 3 (study SYD-101-001; STAR-trial) trial in 847 children with myopia of –0.50 D to –6.00 D to support the intended indication in EU and US. This is an ongoing, randomised, double-masked, vehicle-controlled study of 48 months, comprising a primary treatment period of 36 months and a re-randomised withdrawal period of 12 months.

Additionally, the applicant provided an extensive review of the relevant published literature describing the use of atropine in paediatric patients when used for the treatment of progression of myopia in children in a range of doses between 0.01% and <1.0%.

3.2. Favourable effects

The primary endpoint at 24 months was the difference in mean annual myopic progression rate compared to vehicle and was statistically significant in treatment group with a difference compared to Vehicle of: 0.132 D (95% CI: 0.061, 0.204; p-value of 0.0003) for SYD-101 0.01%. This difference is inferior to the one pre-specified in the sample size (0.18 D or more). At M36, the difference in APR of myopia compared to vehicle in the full analysis set, was 0.079 D/YR (95% CI 0.038, 0.120; p=0.0002) with the lower dose of SYD-101 0.01%. Supplementary analyses on the PPS and on the FAS using different imputation approaches (observed data after Prohibited Treatment, Escape Therapy and

Treatment Discontinuation; Tipping Point analysis; vehicle based imputation after Study Discontinuation, Prohibited and Escape Therapy; vehicle based imputation after Study Discontinuation and for the atropine arms after Prohibited and Escape Therapy; MMRM no imputations) were roughly consistent with the primary analysis.

The key secondary endpoint was the proportion of participants with myopic progression >0.75 D at or before Month 24 and was statistically met in treatment group, with a difference compared to Vehicle of: 10% (95% CI: 2.46, 17.49; p-value of 0.0181) for SYD-101 0.01%. At M36, the difference in confirmed myopia progression (>0.75D) compared to vehicle in the FAS, was -9.6% (95% CI -17.91, -1.26; p=0.0459) with the lower dose 0.1 mg/ml. In addition of supplementary analysis, subgroup analyses were performed and it appears that better efficacy in lighter myopia (in both groups) and younger patients (SYD-101 0.01) was observed. Similar results were obtained with the requested sensitivity analysis at M36, the difference in confirmed myopia progression (>0.75D) compared to vehicle in the full analysis set, was -9.1% (95% CI -17.11, -1.01; p=0.0533) with the lower dose 0.1 mg/ml.

It is acknowledged that efficacy appears to be maintained up to M36, however, in general lower efficacy is estimated at M36 as compared to M24 for both dosing groups. For the annual progression rate, results are still statistically significant at M36 for both dosing groups, though, for the subgroup of confirmed myopia progression (>0.75D) results for the higher dose group lost nominal statistical significance at M36. This was also true for the sensitivity analysis. However, overall it is concluded that efficacy is maintained for the lower dose.

Regarding data from additional analyses in the subgroup of participants with myopia progression of -0.5 D/year or worse, these results demonstrate an increase in magnitude of treatment effect in terms of efficacy for fast progressors (FP1) compared to the FAS, at 24 and 36 months, for both APR and SE.

In the FP1 group, Ryjunea 0.1 mg/ml demonstrated a difference to vehicle of 0.204 D/year (38%, p<0.0001) at 24 month and 0.154 D/year (33%, p=0.0002) at 36 month in APR, and of 0.388D (43%, p=0.0001) and 0.425D (38%, p=0.0012) in SE, respectively.

In the FAS, Ryjunea 0.1 mg/mL demonstrated a difference to vehicle of 0.132 D/year (30%, p=0.0003) at 24 month and 0.079 D/year (21%, p=0.0002) at 36 month in APR, and of 0.238 D (33%, p<0.0001) and 0.215 D (23%, p=0.0022) in SE, respectively.

For SE, these results show a reduction in myopia progression of 43% at 24 months and 38% at 36 months in the FP1 group compared to 33% and 23%, respectively, in the FAS.

Regarding data from additional analyses in participants with myopia progression of -0.5 D/year or worse, the analyses illustrate that in participants who had baseline myopia between -3.0 D and -6.0 D, the magnitude of the effect of atropine is lower than in the group with less severe myopia (baseline SE -0.5 D to -3.0 D).

3.3. Uncertainties and limitations about favourable effects

The applicant has withdrawn the 0.3 mg/ml strength. In addition, long term clinical effects are an important uncertainty given the limited study duration in relation to the 'at-risk period' for myopia (i.e., full duration of eye growth) and the lack of data on rebound effects from SYD-101-001. Therefore, in order to further characterise the efficacy and safety of Ryjunea and the rebound effects and progression of myopia after treatment cessation, the MAH should submit the 48 months follow-up results from the study SYD-101-001.

3.4. Unfavourable effects

Up to Month 24 and 36, the observed safety profile of atropine 0.01% and 0.03% were in line with the known safety profile of atropine. A higher incidence of ocular TEAEs was seen in atropine arms compared to vehicle (40.1% up month 24 and 68.8% up to Month 36), with a dose-adverse effect correlation being observed as a higher frequency was observed in the atropine 0.03% (55.5% up month 24 and 72.4% up to Month 36) than atropine 0.01% (42.9% up month 24 and 64.9% up to Month 36). The most reported Ocular TEAEs, photophobia (30.4% up to Month 24 and 30% up to Month 36 in atropine 0.03%; 24.1% up to Month 24 and 25.5% up to Month 36 in atropine 0.01% and 16.7% up to Month 24 and 18.8% up to Month 36 in control), vision blurred (18.0% up to Month 24 and 17.9% up to Month 36 in atropine 0.03%; 10.3% up to Month 24 and 10.6% up to Month 36 in atropine 0.01% and 8.2% up to Month 24 and 9.2% up to Month 36 in control) and mydriasis (7.1% up to month 24 and 7.2% up to Month 36 in atropine 0.03%; 1,8% up to Month 24 and 1.8% up to Month 36 in atropine 0,01% and 0,4% up to Month 24 and 1.4% up to Month 36 in control) were consistent with the mechanism of action of atropine. Ocular TEAEs were for the majority mild and moderate in intensity. Severe TEAEs were reported in low proportions (0.7% control; 0.4% in atropine 0.01%; 1.1% in atropine 0.03%) up to Month 24. No ocular TEAEs of severe intensity occurred between Month 24 and Month 36.

TEAEs assessed as study drug-related up to Month 24 and 36 were mainly ocular TEAEs and in higher incidence in the atropine 0,03% arm (44.9% up to Month 24 and 44.3% up to Month 36), compared to atropine 0.01% (34.8% up to Month 24 and 36.2% up to Month 36) and control arm (30.9% up to Month 24 and 32.6% up to Month 36). The most reported PT were photophobia and blurred vision as awaited with a higher frequency in the 0,03% than 0.01%. Furthermore, other TEAEs reported as related to atropine in more than one patient were also consistent with the know safety profile (instillation site pain, Instillation site irritation, foreign body sensation in eyes, eye pain, conjunctival papillae, anisocoria, eye pruritus and conjunctival hyperaemia). From Year 1 to Year 2, a decrease could be observed regarding the proportions of Ocular TEAEs assessed as related to study drug (38.5% vs 15.5% in atropine 0.03%; 32.3% vs 9.2% for atropine 0.01% and 27.3% vs 7.8% for control group for Year 1 and 2 respectively). Similar tendencies were observed between Year 2 and Year 3 in particular with a decrease in the incidence of the most reported ocular TEAEs (photophobia, vision blurred and mydriasis) through the years.

Non-ocular TEAEs were more reported in the control arm (47.5%), compared to atropine 0.03% (44.9%) and atropine 0.01% (39.4%) arms up to Month 24. Similar tendencies were observed up to Month 36 (52.5% vehicle, 46.8% STN1012701 0.1 mg/mL group and 47.6% STN1012701 0.3 mg/mL). The most reported non-ocular TEAEs (≥10%) up to Month 24 and 36 were Headache (14.9% vs 18.1% in control, 10,6%vs 12.4% in atropine 0.01% and 14.5% vs 16.3% in atropine 0,03%) and COVID-19 (12.1% vs 16.3% in control, 7.8% vs 10.6% in atropine 0.01% and 8.5% vs 11.7% in atropine 0,03%). Regarding non-ocular events considered related by the Investigator, headache was the only event reported more than once and was the only non-ocular related TEAE reported in Year 2 and 3. While the overall numbers of headache events (regardless of relatedness) were comparable between the treatment groups or even slightly higher in the vehicle group, clearly more events of headache were considered related by the Investigator for the high dose group (vehicle: 3.9%, 0.1 mg/mL: 5.1%, 0.3 mg/mL: 11.3%). While headache is a known non-ocular adverse effects with atropine, other reported non-ocular TEAEs were consistent with the paediatric population. Non-ocular TEAEs were mainly mild to moderate in intensity up to Month 36. Severe non-ocular TEAEs were low and higher in atropine 0.03% (3,9% vs 1.1% in control and 1.4% in atropine 0.01%) up to Month 24 and four additional events occurred in the vehicle and one in STN1012701 0.1 mg/mL. Up to Month 36, none of the severe non-ocular TEAEs were assessed as related to study drug and none of the reported overdose occurred with study drug. Between Year 1 and Year 2, the frequency of Headache decreased

(3.5% vs 0.7%; 5.0% vs 1.1%; and 10.2% vs 2,8% for control, atropine 0,01% and atropine 0,03% respectively). During the third year, the incidence continued to decrease or was comparable to Year 2 (3 (1.1%) participants in Vehicle group, 2 (0.7%) participants in STN1012701 0.1 mg/mL group and 2 (0.7%) participants in STN1012701 0.3 mg/mL randomised group).

Serious TEAEs were reported in low proportions and in slightly higher incidence in atropine 0.03% (2.8%), while being comparable between atropine 0.01% (1.4%) and control (1.8%). None were assessed as related to study drug. Only one serious non-ocular TEAEs occurred between Month 24 and Month 36: suicidal ideation in the Vehicle group and no serious ocular TEAE occurred between Month 24 and Month 36. It was considered as not related to the study drug. In study SYD-101-001, no deaths were reported from baseline through Month 36. TEAEs leading to study discontinuation were reported in similar proportions between atropine 0.01% and control (0.7%) arms, while reported in higher proportion in the atropine 0.03% (2.5%) up to Month 24. Ocular TEAEs leading to study discontinuation were low and higher in the atropine 0.03%. Ocular TEAEs assessed as study drug related and leading to study discontinuation were eye irritation (in one patient), photophobia (in one patient) and mydriasis (in three patients). Up to 36 months, 10 ocular TEAEs lead to study drug discontinuation with the majority (0.9%; n=8) occurring during the first year and the other two during the second year.

Subgroup analyses by gender showed a higher incidence for photophobia and vision blurred in female patients and in patients with light iris (for atropine 0.03%). No differences were seen by races and fast progressor status. Up to Month 36, no significant differences were seen for vital signs, BCVA, biomicroscopic abnormalities, corneal staining, endothelial cell density and IOP.

No case of overdose was reported with atropine 0.01% and 0.03% up to Month 36.

3.5. Uncertainties and limitations about unfavourable effects

No clinical pharmacology data are available for the relevant dose levels of Ryjunea in the target population. The systemic exposure of atropine in children after ocular administration of Ryjunea is unknown and can only be roughly estimated based on two older trials in adults which investigated a markedly higher dose of 1% atropine (Kaila et al., 1999; Lahdes et al., 1988).

Ryjunea includes benzalkonium chloride (BAK) as preservative. The incidence of AEs is relatively high in the vehicle group, but since the vehicle group also included BAK, it is not possible to elucidate the impact of this preservative on the safety profile of Ryjunea. BAK (benzalkonium chloride) is known to cause eye irritation, symptoms of dry eyes and may affect the tear film and corneal surface. The proposed formulation for atropine also contains D20 (deuterium oxide) a novel excipient for eye drops. Non-clinical and clinical data were reassuring for these two components and long-term safety of atropine will be monitored through the PSURs. The applicant agreed to monitor the AEs of allergic and toxic conjunctivitis with the upcoming first three PSURs (PSUR frequency: once yearly), and longer if deemed necessary based on the gathered information. Furthermore, the CHMP has recommended to investigate the feasibility of optimising the formulation with regards to this preservative.

In study SYD-101-001, the safety profile of atropine was assessed on 283, 284 and 285 participants in control group (H20), atropine 0.01% group and atropine 0.03% group respectively which was considered to be too low in particular regarding the highest dose 0.3 mg/mL. The applicant provided safety data up to 36 months, patients who were receiving the vehicle up to this point will be re-randomised according to protocol to the SYD-101 0.03% while patient treated by SYD-101 0.01% and 0.03% will either remain treated by SYD-101 0.01% or 0.03% respectively or be re-randomised to receive the vehicle. At month 36, 221 patients were treated with the vehicle, which means that up to 48 months 414 subjects are expected to complete at least 1 year of treatment under 0.3 mg/ml.

Regarding the SYD-101 0.01% arm, a total of 230 patients completed Month 24 and 210 patients completed Month 36. While the 0.01% dosage has shown a tolerable safety profile, the safety profile of 0.03% was shown to be worse as ocular adverse events (photophobia, mydriasis, vision blurred, accommodation disorders) are dose dependent. Although these events were majorly mild or moderate in intensity and intermittent, however ocular adverse reactions were often reported with a very long duration (overall mean duration in all treatment groups combined for photophobia: 173 days, vision blurred: 149 days, mydriasis: 130 days).

The TEAE of papilloedema occurred twice. One event was reported as SAE in a participant with a history of idiopathic intracranial hypertension (no more details provided), and the other event was reported in the participant who experienced the SAE of optic neuritis. Both events were considered either unlikely related or not related by the Investigator. However, the occurrence of two events of papilloedema in this small study appears very unusual, considering the low background rate of this event (~1:40,000 in a study without age selection; doi:10.1001/jamanetworkopen.2020.6625), and a relationship to Ryjunea should not be completely excluded at this stage. Until the new data cut-off (up to 36 Month), there were no additional cases of papilloedema. Considering that papilloedema occurs by definition secondary to increased intracranial pressure, which seems to be unlikely caused by Ryjunea eyedrops, routine pharmacovigilance is considered acceptable for now. This issue was raised because papilloedema is a very rare event and the occurrence of two cases in this small trial seems unusual.

Up to Month 24, one ocular TEAE of tachycardia was assessed as related to study treatment in atropine 0.01%. Due to the low dose included in Ryjunea, tachycardia may be more relevant for a scenario of overdosing. Section 4.9 of the SmPC already describes tachycardia as potential symptom of overdose. In addition, section 4.4 includes a warning stating that Ryjunea must be used with special caution in patients with tachycardia (and other cardiac disorders). These measures are considered sufficient at this point in time but as suggest by the applicant, another assessment for inclusion of this event in 4.8 should be made once the phase 3 study is complete.

The literature describes that atropine can reduce accommodation amplitude and near visual acuity, albeit to a smaller extent with lower atropine concentrations (ATOM 2 study, Chia et al 2012). Such a trend was also noted in Study SYD-101-001, as there seemed to be a slight dose-dependent worsening of binocular near visual acuity (lower incidences for lines gained, higher incidences for lines lost) and binocular accommodative amplitude in the Ryjunea groups compared to vehicle. This may be explained by the mechanism of action of atropine. It is unclear whether these potential effects would persist after cessation of treatment. Data on binocular near visual acuity were further discussed and analysed using actual logMAR value compared to baseline. At month 24 and 36, no statistically significant difference were observed (p value>0.05) for accommodation amplitude and binocular near visual acuity.

There is very limited data are available in patients under 6 years old (less than 3.1% of the included study population) and it is to be considered that this population is at risk of ocular pathology such as amblyopia, cataract, strabismus and other conditions with irreversible consequences on the vision and it is also unknown how long-term exposure with atropine, including low dosage, could impact on that risk. However, monitoring as per standard clinical practice may increase the likelihood of detecting any emergent ophthalmic conditions that may be worsened by blurred vision and although blurred vision accounted for 12% of all TEAEs, it was mostly of mild intensity and was intermittent in 5-10% of participants. It is acknowledged that patients will be treated bilaterally and given corrected visual prescription thus reducing the risk of developing irreversible visual loss. Moreover, based on the provided information and additional M36 data, observed results in this very young population can be considered to support the treatment of the age group 3 to <6 years with both treatment regimens. In the SmPC section 4.3, Ryjunea is contraindicated in patients with primary glaucoma and angle-closure glaucoma.

The applicant submitted safety data up to 36 months as requested, however, further long-term data (up to 48 months at least) will be submitted in a separate procedure. Currently no data on treatment rebound effects are available, as the study is still ongoing. As rebound effects might differ between used doses and age groups, data gained in this study might be too limited to fully characterise this potential risk.

3.6. Effects Table

Table 62: Effects table for Ryjunea in treatment of progression of myopia in children aged 3 to 18 years (data cut-off: 36 months)

At M36, the difference in confirmed myopia progression (>0.75D) compared to vehicle in the FAS, was -9.6% (95% CI -17.91, -1.26; p=0.0459) with the dose 0.1 mg/ml.

Effect	Short Description	Unit	Treatment (SYD-101 0.01%)	Control (Vehicle)	Uncertainties/ Strength of evidence	References
Favourable Effects						
The annual progression rate of myopia at Month 24	Mean change from baseline in SE	Diopt re	SYD-101 0.01% : -0.31D	- 0.44 D	Difference between vehicle and: - SYD-101 **0.01%:** 0.132 D (95% CI: 0.061, 0.204) Difference at 36 months between vehicle and: - SYD-101 0.01%: 0.079 D/YR (95% CI 0.038, 0.120; p=0.0002)	SYD-101-001 primary endpoint
The annual progression rate of myopia in FP1 at Month 24 and Month 36	Mean change from baseline in SE	Diopt re (% differ ence)			Difference between vehicle and SYD-101 **0.01%**: At 24 months: 0.388D (p=0.0001) (43%) At 36 months: 0.425D (p=0.0012) (38%)	Responses ; Additional analyses
Proportion of participants with myopic progression >0.75 D at or before Month 24	Mean change from baseline	Propo rtion of patie nts	SYD-101 0.01%: 25.55%	35.72%	Difference between vehicle and: - SYD-101 0.01%: 10% (95% CI: 2.46, 17.49) Difference at 36 months between vehicle and: - SYD-101 0.01%: -9.6% (95% CI -17.91, -1.26; p=0.0459)	SYD-101-001 key secondary endpoint
Unfavourable Effects						
Ocular TEAEs	Photophobia	%	Atropine 0.01%: 24.1% and 25.5%	Vehicle: 16.7% vs 18.8%	Consistent with the known safety profile of atropine.	(1) vs (2)
	Treatment related Photophobia	%	Atropine 0.01%: 22.0% and 23.4%	Vehicle: 13.5% vs 15.2%	Consistent with the known safety profile of atropine.	(1) vs (2)

Effect	Short Description	Unit	Treatment (SYD-101 0.01%)	Control (Vehicle)	Uncertainties/ Strength of evidence	References
	Blurred vision	%	Atropine 0.01%: 10.3% vs 10.6%	Vehicle: 8.2% vs 9.2%	Consistent with the known safety profile of atropine.	(1) vs (2))
	Treatment related blurred vision	%	Atropine 0.01%: 7.8% vs 7.8%	Vehicle: 6.4% vs 7.1%	Consistent with the known safety profile of atropine.	(1) vs (2))
	Mydriasis	%	Atropine 0.01%: 1.8% vs 1.8%	Vehicle: 0.4% vs 1.4%	Consistent with the known safety profile of atropine.	(1) vs (2)
	Treatment related mydriasis	%	Atropine 0.01%: 1.8% vs 1.8%	Vehicle: 0% vs 1.1%	Consistent with the known safety profile of atropine.	(1) vs (2)
	Accommodation disorders	%	Atropine 0.01%: 0.4% vs 0.4%	Vehicle: 0.4% vs 0.4%	Consistent with the known safety profile of atropine.	(1) vs (2)
Non-ocular TEAEs	Headache	%	Atropine 0.01%: 10,6% vs 12.4%	Vehicle: 14,9% vs 18,1%	Consistent with the known safety profile of atropine.	(1) vs (2)
	Treatment related Headache	%	Atropine 0.01%: 5.1% vs 6.4%	Vehicle: 3.9% vs 4.3%	Consistent with the known safety profile of atropine.	(1) vs (2)
Serious TEAEs		%	Atropine 0.01%: 1.4% vs 1.4%	Vehicle: 1.8% vs 2.1%	Slightly more reported in atropine 0.03%.	(1) vs (2)
TEAEs leading to study discontinuation		%	Atropine 0.01%: 0.7%vs 0.4%	Vehicle: 0.7% vs 0.7%	More reported in atropine 0.03%.	(1) vs (2)

Abbreviations: SE (Spherical equivalent); Dioptre (D), TEAE (Treatment emergent adverse events), FP1 (fast progressor subgroup 1 i.e. patients with a myopia progression rate of 0.5 D or more per year)
Notes:
1/Data up to Month 24 from study SYD101-001
2/Data up to Month 36 from study SYD101-001

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The applicant provided a single pivotal study (SYD-101-001) to support the MAA of atropine sulfate for the treatment of progression of myopia in children aged 3 to 18 years. To further support this data, the applicant provided an extensive review of the relevant published literature describing the use of atropine in paediatric patients when used for the treatment of progression of myopia in children in a range of doses between 0.01% and <1.0%.

The effect of Ryjunea 0.01% vs placebo in the overall patient population is of borderline clinical relevance, but statistically persuasive and supports a positive B/R. Ryjunea 0.01% met the primary and key secondary endpoints, and the effect for Ryjunea 0.01% was also statistically significant vs

placebo in the pre-defined fast progressor subgroup >0.5 D/year, to which the label has been restricted.

Long term clinical benefit is uncertain for 0.01% dosage given the limited study duration in relation to the 'at-risk period' for myopia (i.e., full duration of eye growth) and given the lack of data on rebound effects from SYD-101-001. Additionally, literature data with atropine show a loss of efficacy after treatment cessation, which is of major concern. This adds to the concern why assessment of Month 48 data remains needed. The applicant committed to submit the Month 48 data in a PAES. This approach is acceptable for Ryjunea 0.01%, as B/R is favourable for this strength and as literature indicates that rebound risk decreases with decreasing atropine concentrations, and results for Ryjunea 0.01% up to Month 36 support the proposed label (i.e., *slowing of myopia progression* in patients 3-14 years with a progression rate of >0.5D).

While the safety profile of atropine 0.01% is consistent with the known safety profile, with typical ocular reactions (expected based on the mechanism of action) of photophobia, blurred vision, mydriasis, accommodation disorders, and non-ocular TEAEs of headache, which mainly occurred with the higher dose of Ryjunea (0.03% atropine), all of these events may have an impact, in particular, on reading, concentration and learning. Moreover, patients may need to wear photochromic glasses or progressive lens spectacles as a measure. These events were mainly mild or moderate in severity and transient, although these events had long duration mydriasis (mean duration 130 days), photophobia (mean duration 173 days) and vision blurred (mean duration 149 days). The impact on the quality of life appears negligible with the lower dose, but more notable with the higher dose. However, only few participants who received the high dose discontinued the study due to AEs.

No unexpected events occurred in children between 3 and <6 years of age, but the interpretability is extremely limited due to the small number of participants of this age range. Based on the provided information and additional M36 data, observed results in the young population can be considered to support the treatment of the age group 3 to <6 years.

Even though results for Ryjunea 0.01% were statistically significant vs placebo in the primary analysis, there was no consistent dose-dependent treatment effect in the overall study population, or the fast-progressor subgroups. The 0.01% strength showed an acceptable safety profile. Literature demonstrated that the dosage 0.02% was the highest concentration that does not produce significant clinical symptoms from accommodation paresis or pupillary dilation. Since the treatment effect seems to also be of mild amplitude, a potentially slightly decreased accommodative amplitude should be discussed as soon as the Month 48 data are available.

Although the bioavailability of atropine is high, the lack of clinical data on systemic exposure after ocular administration of atropine to children is acceptable, considering the lower concentrations of atropine included in Ryjunea compared to the RefMP.

3.7.2. Balance of benefits and risks

While of only borderline clinical relevance, the effects for Ryjunea 0.01% are statistically persuasive in the pre-defined fast progressor subgroup >0.5 D/year, to which the label has been restricted. These effects are weighed against its relatively benign risk profile. Hence, for Ryjunea (0.01%), the benefit/risk balance is considered positive 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"*.

Regarding the remaining uncertainties on long-term clinical effects for tapering and rebound effect, the applicant committed to provide 48-months results as a PAES.

The safety profile of atropine 0.01% is in line with the known safety profile with reported events of photophobia, blurred vision, mydriasis, accommodation disorders, headache, which were dose dependent effects. The lower dose of Ryjunea (0.01% atropine) was well tolerated.

3.8. Conclusions

The overall benefit/risk balance of Ryjunea 0.01% atropine is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Ryjunea is favourable in the following indication:

Ryjunea is indicated 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.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

- ***Periodic Safety Update Reports***

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
Post-authorisation efficacy study (PAES): In order to further characterise the efficacy and safety of Ryjunea and the rebound effects and progression of myopia after treatment cessation, the MAH should submit the 48 months follow-up results from the study SYD-101-001.	30.06.2026.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.