EU Risk Management Plan for Atropine sulfate

RMP version to be assessed as part of this application:

RMP Version number: 1.0

Data lock point for this RMP: 15 Sep 2024

Date of final sign-off: 26 Mar 2025

Rationale for submitting an updated RMP: This EU Risk Management Plan (RMP) has been updated in response to the Pharmacovigilance Risk Assessment Committee (PRAC) and Committee for Medicinal Products for Human Use (CHMP) preliminary list of questions (Day 218) for the initial Marketing Authorization Application (MAA) for Atropine sulfate 0.1 mg/mL.
Summary of significant changes in this RMP:

Removed of a specific follow up form as a routine pharmacovigilance activity for missing information Long-term safety.
Removed 0.3 mg/mL strength.Editorial changes related to above.

QPPV name: Tapio Kerttula

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorisation applicant´s QPPV. The electronic signature is available on file.

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Abbreviations

BAK	Benzalkonium chloride
D	Diopter
DLP	Data Lock Point
D_2O	Deuterium oxide
EPAR	European Public Assessment Report
GLP	Good Laboratory Practice
MAA	Marketing Authorisation Application
MD	Multi-Dose
PK	Pharmacokinetics
RefMP	Reference medicinal product
RMM	Risk Minimisation Measure
RMP	Risk Management Plan
TID	three times a day (ter in die)
QD	once a day (quaque die)

Part I: Product(s) Overview

Active substance(s) **(INN or common name)**	Atropine sulfate
Pharmacotherapeutic group(s) (ATC Code)	Mydriatics and cycloplegics (S01FA01)
Marketing Authorisation Applicant	Santen Oy
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Ryjunea
Marketing authorisation procedure	Centralised Procedure
Brief description of the product	*Chemical class:* non-selective muscarinic antagonist
	Summary of the mode of action The active substance atropine sulfate acts as a competitive and reversible antagonist at all muscarinic acetylcholine receptors. The exact mechanism through which atropine slows myopia progression is not known. Published literature provides evidence that the mechanism of action of atropine in myopia and in mydriatic/cycloplegic indications, are not identical.
	Important information about its composition: The eye drops contain deuterium oxide (D_2O) as a solvent and Benzalkonium chloride as a preservative.
Hyperlink to the Product Information	
Indication(s) in the EEA	*Current*: 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.
	Proposed (if applicable): N/A
Dosage in the EEA	*Current:* one drop into each eye once daily
	Proposed (if applicable): N/A
Pharmaceutical form(s) and strengths	*Current (if applicable):* 0.1 mg/mL eye drops, solution, MD
	Proposed (if applicable): N/A

Is / will the product be subject to additional monitoring in the EU?	No

Part II: Safety specification

Part II: Module S1 - Epidemiology of the indication(s) and target population(s)

This RMP is submitted within a hybrid marketing authorisation application (Article 10(3) of Directive 2001/83/EC) with the marketed product Atropin-POS® 0.5% eyedrops, solution as the Reference medicinal product (RefMP). The indication for Atropine sulfate 0.1 mg/mL differs (slowing the progression of myopia in paediatric patients) from the RefMP (elimination of accommodation for diagnostic purposes). Therefore, the epidemiology of the indication is presented here.

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.

Myopia, or near sightedness, is defined as having a refractive error of worse than −0.50 D. Progressive myopia in children is the result of excessive elongation of the anterior/posterior axis of the eye (axial length).

Prevalence: Myopia is the most common ocular disorder with an estimated prevalence of 13% to 49% in adult population-based studies[1,2].

Demographics of the population in the proposed indication and risk factors for the disease: The suggested population consists of children aged 3 to 14 years (age at the initiation of treatment).

Research suggests that an increase in near activities, such as electronic screen time, and lack of outdoor activity, may increase one's risk for developing myopia[3,4,5].

The main existing treatment options: Historically, most clinical trials have investigated non-pharmacologic interventions for the treatment of progressive myopia, including progressive lenses and rigid gas permeable contact lenses, but these have yielded disappointing results. There is no authorised pharmaceutical treatment option available in the EU.

Natural history of the indicated condition in the untreated population: Worsening of myopia is associated with increased risk of pathologic changes including glaucoma, cataract, retinal detachment, choroidal degeneration, choroidal neovascularisation and retinoschisis, all of which can cause irreversible vision loss[3]. Myopia is among the 5 conditions that have been identified as immediate priorities by the World Health Organization (WHO) in its Global Initiative for the Elimination of Avoidable Blindness[7].

Important co-morbidities: No important co-morbidities are identified.

Part II: Module SII - Non-clinical part of the safety specification

As this is an Article 10(3) Marketing Authorisation Application (MAA), the Applicant has not conducted a full programme of toxicological and pharmacological studies for Atropine sulfate 0.1 mg/mL and is relying on the non-clinical findings from studies performed for the RefMP and published literature.

To support the use of Atropine sulfate 0.1mg/mL in myopia the Applicant has conducted a repeat-dose toxicology study to define a 26-week ocular toxicity and systemic exposure in rabbits after once a day (QD) and three times a day (TID) dosing. The study nor published data pertaining to the RefMP and atropine sulfate in general do not raise any new safety concerns.

Repeat dose toxicity

In the study conducted by the Applicant, male Dutch Belted rabbits (n=6/group) were administered one drop of a negative control agent (balanced salt solution), a placebo control agent (deuterated water containing 0.01% benzalkonium chloride) or Atropine sulfate 0.1 mg/mL in both eyes three times daily for 26 weeks. Two additional groups of male rabbits (n=6/group) were administered one drop of Atropine sulfate 0.1 mg/mL or atropine sulfate ophthalmic solution 10 mg/mL (1%) in both eyes, one time per day for 26 weeks.

Following once daily or three times daily dosing, atropine plasma concentrations were below the quantification limit (< 0.250 ng/mL) and in most of the timepoints AUC values could not be calculated. Following once a day dosing of atropine sulfate ophthalmic solution 10 mg/mL mean Cmax and AUC_{0-2h} 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.

Under the conditions of the study, Atropine sulfate 0.1 mg/mL was well tolerated when given once or three times daily for 6 months to male Dutch Belted 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 Atropine sulfate 0.1 mg/mL three times daily. This finding was considered of uncertain relationship to Atropine sulfate 0.1 mg/mL administration.

Part II: Module SIII - Clinical trial exposure

SIII.1 Brief overview of development

The applicant has performed a single pivotal trial SYD-101-001 (STAR-study). It is a single, multicenter Phase 3 study with a randomised, double-masked, vehicle-controlled design. The total study duration will be 48 months, comprising a Primary Treatment Period of 36 months and a randomised Withdrawal Period of 12 months. This RMP and the MAA contain data until 36 months observation.

Total of 852 subjects were enrolled and assigned in a 1:1:1 allocation to receive treatment with Atropine sulfate 0.1 mg/mL, 0.3 mg/mL or vehicle for 36 months (Primary Treatment Period). At Month 36, all subjects will be re-randomised to a further 12 months of treatment (Randomised Withdrawal Period). Subjects allocated at baseline to receive Atropine sulfate 0.1 mg/mL or 0.3 mg/mL will be allocated (1:1) to continue treatment on their current Atropine sulfate dose or switch to Vehicle. All subjects allocated at baseline to receive Vehicle were re-randomised to receive Atropine sulfate 0.3 mg/mL.

SIII.2 Clinical trial exposure

The dosage of Atropine sulfate was one drop into each eye once daily. Duration of the exposure is presented in **Table 1** and demographic characteristics of the subjects in **Table 2** and **Table 3**.

Table 1 Duration of exposure in the pivotal study SYD-101-001 at 36 months

			STN1012701 0.3 mg/mL			
	Vehicle	**STN1012701 0.1 mg/mL**	**STN1012701 0.3 mg/mL**	**Escape**	**0.3 mg/mL Total**	**Total**
	(N=282)	**(N=282)**	**(N=283)**	**(N=35)**	**(N=307)**	**(N=847)**
Duration of exposure (days)						
N	274	280	276	14	288	830
Mean (SD)	968.8 (284.56)	962.1 (285.09)	973.4 (283.48)	246.8 (130.72)	947.3 (315.84)	973.4 (284.05)
Median	1092.0	1093.0	1093.0	208.5	1093.5	1093.0
Min, max	2, 1159	50, 1161	12, 1146	62, 392	12, 1156	2, 1166
Duration category – n (%)						
⩽ 91	5 (1.8)	6 (2.1)	3 (1.1)	2 (5.7)	5 (1.6)	14 (1.7)
92 - 182	6 (2.1)	3 (1.1)	11 (3.9)	2 (5.7)	13 (4.2)	20 (2.4)
183 - 280	5 (1.8)	7 (2.5)	5 (1.8)	4 (11.4)	8 (2.6)	17 (2.0)
281 - 364	5 (1.8)	6 (2.1)	2 (0.7)	0	2 (0.7)	13 (1.5)
365 - 546	11 (3.9)	17 (6.0)	10 (3.5)	6 (17.1)	15 (4.9)	38 (4.5)
547 - 728	11 (3.9)	8 (2.8)	12 (4.2)	0	12 (3.9)	28 (3.3)
729 - 910	13 (4.6)	11 (3.9)	9 (3.2)	0	6 (2.0)	22 (2.6)
911 - 1092	85 (30.1)	79 (28.0)	77 (27.2)	0	73 (23.8)	237 (28.0)
1093 - 1274	133 (47.2)	143 (50.7)	147 (51.9)	0	154 (50.2)	441 (52.1)

Table 2 Age group and gender of the subjects in the pivotal study SYD-101-001

	Vehicle (N=282)	Atropine sulfate 0.1 mg/mL (N=282)	Atropine sulfate 0.3 mg/mL (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
Age category (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)

Table 3 Ethnicity of the subjects in the pivotal study SYD-101-001

Ethnicity	Vehicle (N=282)	Atropine sulfate 0.1 mg/mL (N=282)	Atropine sulfate 0.3 mg/mL (N=283)	Total (N=847)
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)

Part II: Module SIV - Populations not studied in clinical trials

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

The main exclusion criteria for Atropine sulfate 0.1 mg/mL eye drops, solution clinical trial development programme conducted by the MA Applicant are discussed below in **Table 4**.

Table 4 Exclusion criteria in the pivotal study SYD-101-001

Exclusion criteria which will remain as contraindications or otherwise restricted in the SmPC		
Criteria	**Implications for target population**	**Is it considered to be included as missing information (including rationale)?**
Known allergy or sensitivity to atropine or any of the components of study medication	This is a usual contraindication included in the SmPC.	No. It is not reasonable to try to gather more information on this condition since it will remain as a contraindication.
Participant is a female who was lactating	These patients are generally excluded from clinical trials.	No. It is not reasonable to try to gather more information on this condition. The SmPC states that Atropine sulfate 0.1mg/mL eye drops, solution, should not be used during breast-feeding.
Participant is a female who was pregnant, or intending to become pregnant within next 4 years	These patients are generally excluded from clinical trials.	No. It is not reasonable to try to gather more information on this condition. The SmPC states that Atropine sulfate 0.1 mg/mL eye drops, solution should only be used during pregnancy, especially in the last trimester, if strictly necessary and under medical supervision.
Current use of a monoamine oxidase inhibitor	The concomitant use of monoamine oxidase inhibitor with atropine sulfate could cause drug interactions which could affect the assessment of study drug.	No. It is not reasonable to try to gather more information on this interaction. The SmPC section 4.5 Interactions contains information on this interaction.
Exclusion criteria which are NOT proposed as contraindications		
Criteria	**Implications for target population**	**Is it considered to be included as missing information (including rationale)?**
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)	Such medical history or condition could confound the assessment of the study drug.	No. Categorising these conditions as missing information does not bring any additional value for the risk management of this product.
One or more biological parents with a history of myopia -≥9.00 D or worse	Such familial medical history of condition could confound the assessment of the study drug because children with myopic parent(s) are at higher risk of developing myopia.	No. Categorising these conditions as missing information does not bring any additional value for the risk management of this product.

History of, or currently receiving treatment for, any systemic infection or autoimmune disease considered serious by the investigator	These patients are generally excluded from clinical trials.	No. Categorising these conditions as missing information does not bring any additional value for the risk management of this product.
Participation in an investigational drug or device study within 30 days prior to Screening	These patients are generally excluded from clinical trials.	No. Not relevant for postmarketing phase.
Evidence of any ocular inflammation or infection in either eye, including blepharitis, conjunctivitis, keratitis, and scleritis	These patients are generally excluded from clinical trials with ophthalmic study drugs to maximise the reliability of study results.	No. Categorising these conditions as missing information does not bring any additional value for the risk management of this product.
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	Such medical history or condition could confound the assessment of the study drug.	No. Categorising these conditions as missing information does not bring any additional value for the risk management of this product.
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	The use of such treatments or medications could have impacted the assessment of the study drug.	No. Categorising these conditions as missing information does not bring any additional value for the risk management of this product.
History or evidence of any ocular surgery or planned future ocular surgery in either eye	The surgery could impact the assessment of the study drug.	No. Categorising these conditions as missing information does not bring any additional value for the risk management of this product.
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	Such abnormalities could confound the assessment of the study drug.	No. Categorising these conditions as missing information does not bring any additional value for the risk management of this product.
Unwillingness or inability to comply with study requirements and restrictions, including but not limited to those specified in Section 5.3 of the protocol (eg, required conversion from extended wear lenses to daily wear lenses, full time use of contact lenses or spectacles)	These patients are generally excluded from clinical trials to maximise the reliability of study results.	No. Categorising these conditions as missing information does not bring any additional value for the risk management of this product.
Removal of Participants from Therapy or Assessment	These patients are generally excluded from clinical trials to maximise the reliability of study results and to ensure safety of the subjects.	No. Categorising these conditions as missing information does not bring any additional value for the risk management of this product.

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged exposure.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programme

Table *5* below presents exposure of Atropine sulfate 0.1 mg/mL eye drops, solution in special populations in the clinical trial development programme conducted by the MA Applicant.

Table 5 Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Patients with relevant comorbidities: • Patients with hepatic impairment • Patients with renal impairment • Patients with cardiovascular impairment • Immunocompromised patients • Patients with a disease severity different from inclusion criteria in clinical trials	Patients with these comorbidities were not included in the clinical development conducted by the MA Applicant. Atropine has been used for decades and no specific risks have been observed in patients with these comorbidities. Patients with more severe myopia may require additional treatment. No special considerations are needed in these populations.

Part II: Module SV - Post-authorisation experience

This module is not applicable as this RMP is submitted within an initial marketing authorisation application and no post-marketing data is available.

SV.1 Post-authorisation exposure

Not applicable.

Part II: Module SVI - Additional EU requirements for the safety specification

Potential for misuse for illegal purposes

Atropine sulfate 0.1mg/mL eye drops, solution does not have any particular effect or characteristics that might increase the potential for misuse for illegal purposes. Therefore, no specific risk minimisation measures (RMM) are proposed.

Part II: Module SVII - Identified and potential risks

SVII.1 Identification of safety concerns in the initial RMP submission

Table 6 Safety concerns in the initial RMP of Atropine sulfate 0.1mg/mL eye drops, solution

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	Long-term safety

SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

The risks that are not considered important for inclusion in the list of safety concerns in the RMP are presented below. The risks and missing information are grouped based on the reasons for exclusion.

Known risks that require no further characterisation and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered by prescribers (e.g., actions being part of standard clinical practice in each EU Member state where the product is authorised):

Photophobia

Photophobia is a very common known non-serious side effect (likely affecting more than 1 in every 10 patients) and may have an impact on the quality of life of the patient. Experience in clinical trials with Atropine sulfate 0.1mg/mL eye drops, solution and with other Atropine sulfate preparations with higher concentration (≥ 1 mg/ml) show that photophobia is often not permanent. It is not classified as an important risk as the clinical impact to the patient is considered to be low in relation to the indication being treated. Photophobia is not preventable. However, the product label warns about the risk of photophobia associated with the Atropine sulfate treatment and therefore, doctors are able to counsel patients appropriately. Additionally, photochromatic glasses may be used to alleviate the impact of photophobia on the patient's quality of life.

Blurred vision

Blurred vision is a common known non-serious side effect, likely to affect more than 1 in every 100 patients. Blurred vision is known to occur with administration of most eye drop preparations and is usually transient. There are no specific measures to prevent it. The product label warns about this side effect, including the impact it may have on the patient's ability to drive and use machines. Therefore, prescribers are able to counsel patients appropriately regarding this risk.

Use in patients with angle closure glaucoma and risk factor for intraocular pressure elevation such as narrow anterior chamber angle and flat anterior chamber (may cause acute angle closure glaucoma attack)

It is known that atropine may trigger acute angle closure glaucoma or increase intraocular pressure. If it is left untreated, serious visual impairment or even blindness may occur. However, the product label warns about the risk. Therefore, prescribers are able to counsel and treat patients appropriately regarding this possible side effect.

Use in pregnancy

No studies have been conducted in pregnant women. In the clinical trial SYD-101-001, pregnant subjects and subjects intending to become pregnant within next 4 years were excluded. However, one subject in the trial experienced pregnancy. No adverse effects were reported for the mother of the baby. A moderate amount of data on pregnant women indicate no malformative or feto/neonatal toxicity for other atropine sulfate preparations. Atropine sulfate may be systemically absorbed after ocular administration and is known to rapidly cross the placenta. Categorizing this risk as an important safety concern does not bring additional value on managing the risk because it can be manged by routine PV activities and risk minimisation measures. The product information contains warnings for use during pregnancy.

Labelled potential risk for Benzalkonium chloride containing eye drops, which is monitored as a part of routine myopia treatment on patient level:

Benzalkonium chloride related corneal toxicity

Atropine sulfate 0.1mg/mL eye drops, solution contains 0.1 mg/ml benzalkonium chloride (BAK) which has been reported to cause eye irritation, symptoms of dry eyes and may affect the tear film and corneal surface. Children and patients with dry eyes or compromised cornea may be more sensitive to the effects of BAK. The related adverse events are usually non-serious. The likelihood of the associated events are unknown as it is difficult to differentiate which component of the eye drops (BAK, Atropine sulfate, or other excipients) causes these effects. The product label contains BAK warnings. Additionally, the product label recommends regular monitoring for patients using Atropine sulfate 0.1mg/mL eye drops. Therefore, prescribers are able to guide and treat patients appropriately regarding this possible risk.

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

Missing information: Long-term safety

The long- term safety of Atropine sulfate 0.1 mg/mL eye drops, solution has not been established in controlled clinical studies. The safety profile after long-term administration is not expected to be different based on the currently available data.

Rebound has been observed after stopping treatment with Atropine sulfate with different strengths. Rebound with Atropine sulfate 0.1 mg/mL is currently unknown.

Risk-benefit impact: The safety beyond 36 months treatment including after cessation of treatment has not been established in controlled clinical studies. Existing non-clinical and clinical data does not suggest a specific safety concern with long-term use of Atropine sulfate 0.1 mg/mL eye drops, solution at this time.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

Not applicable.

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1. Presentation of important identified risks and important potential risks

Not applicable.

SVII.3.2. Presentation of the missing information

Missing information: Long-term safety

Evidence source: Knowledge of the long-term safety effects of prolonged exposure to Atropine sulfate 0.1 mg/mL eye drops, solution in clinical trials is currently limited.

Anticipated risk/consequence of the missing information: Treatment of myopia is expected to last several years. Existing non-clinical and clinical data does not suggest a specific safety concern with long-term use of Atropine sulfate 0.1 mg/mL eye drops, solution. However, long-term safety data from clinical trials is limited to up to 3 years of exposure. In addition, rebound has been observed after stopping treatment with Atropine sulfate with different strengths. Rebound with Atropine sulfate 0.1 mg/mL is currently unknown and will be investigated in the PAES study.

Part II: Module SVIII - Summary of the safety concerns

Table 7 Summary of the safety concerns

Summary of the safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	Long-term safety

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

None

III.2 Additional pharmacovigilance activities

None.

III.3 Summary Table of additional Pharmacovigilance activities

N/A

Part IV: Plans for post-authorisation efficacy studies

Table 8 Planned and on-going post-authorisation efficacy studies that are conditions of the marketing authorisation or that are specific obligations.

Study Status	Summary of objectives	Efficacy uncertainties addressed	Milestones	Due Date
Efficacy studies which are conditions of the marketing authorisation				
A Multicenter, Randomized, Double Masked, Vehicle Controlled Study to Assess the Safety and Efficacy of SYD-101 Ophthalmic Solution for the Treatment of Myopia in Children On-going	The MAA for atropine sulfate 0.1 mg/mL eye drops, solution was prepared with 36 months interim data from this SYD-101-001 study. The study is continuing further, until 48 months. The data from 48 months will be used to gather more information on efficacy, rebound and the missing information long-term safety of atropine.	Long term efficacy and safety, rebound effect	Final report and safety variation submission.	

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

Risk Minimisation Plan

The safety information in the proposed product information is aligned to RefMP.

V.1. Routine Risk Minimisation Measures

Table 9 Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Missing information: Long-term safety	**SmPC section 4.2 Posology and method of administration** Treatment should be assessed during regular clinical evaluation. Consider tapering and stopping treatment once myopia is stabilised (less than 0.5 D progression over 2 years). Continue monitoring for one year after cessation of treatment. Consider restarting treatment in case of rebound myopia progression (0.5 D or worse per year, see section 4.4). **SmPC section 4.4** <u>Rebound myopia progression upon discontinuation</u> Discontinuation of Atropine sulfate eye drops may lead to rebound myopia progression. Continue monitoring for one year after cessation of treatment. Consider restarting treatment in case of rebound myopia progression (0.5 D or worse per year, see section 4.2). **PIL section 2** **Warnings and precautions**

	Stopping treatment may cause your myopia to worsen again (see section 3). After you stop taking this medicine, you should continue your eye checks for one year. Talk to your doctor or the doctor treating your child in case your eye sight worsens (rebound). **PIL section 3** **If you stop using Ryjunea** Do not stop using Ryjunea without first speaking to your doctor or the doctor treating your child. Stopping of this medicine may lead to a worsening of your myopia (rebound). After you stop taking this medicine, you should continue your eye checks for one year. Talk to your doctor or the doctor treating your child in case your eye sight worsens (rebound). **Other routine risk minimisation measures beyond the Product Information:** Legal status: Prescription only medicine

V.2. Additional Risk Minimisation Measures

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

V.3 Summary of risk minimisation measures

Table 10 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

Part VI: Summary of risk management plan for Atropine sulfate 0.1mg/mL eye drops, solution

This is a summary of the risk management plan (RMP) for Ryjunea (atropine sulfate 0.1 mg/mL eye drops, solution). The RMP details important risks of Ryjunea, how these risks can be minimised, and how more information will be obtained about Ryjunea's risks and uncertainties (missing information).

Ryjunea's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Ryjunea should be used.

This summary of the RMP for Ryjunea should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Ryjunea's RMP.

I. The medicine and what it is used for

Ryjunea is authorised 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.

It contains atropine sulfate as the active substance and it is given by ocular route.

Further information about the evaluation of Ryjunea's benefits can be found in Ryjunea's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage https://www.ema.europa.eu/en/medicines/human/EPAR/ryjunea.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Ryjunea, together with measures to minimise such risks and the proposed studies for learning more about Ryjunea's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Ryjunea is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Ryjunea are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be

regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Ryjunea. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	None
Important potential risks	None
Missing information	Long-term safety

II.B Summary of important risks

Missing information	
Risk minimisation measures	Routine risk minimisation measures: • Proposed text in SmPC sections 4.2 and 4.4 with corresponding information in PIL. Additional risk minimisation measures: • None

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

A Multicenter, Randomized, Double Masked, Vehicle Controlled Study to Assess the Safety and Efficacy of SYD-101 Ophthalmic Solution for the Treatment of Myopia in Children (SYD-101-001)

Purpose of the study:

The MAA for atropine sulfate 0.1 mg/mL eye drops, solution was prepared with 36 months interim data from this SYD-101-001 study. The study is continuing further, until 48 months. The data from 48 months will be used to gather more information on the missing information long-term safety of Ryjunea.

The safety objective of the study is to evaluate the safety, tolerability and rebound effect of atropine sulfate 0.1 mg/mL eye drops up to 48 months.

II.C.2 Other studies in post-authorisation development plan

There are no studies required for Ryjunea.

Annexes

Annex 4 - Specific adverse drug reaction follow-up forms

Not applicable.

Annex 6 - Details of proposed additional risk minimisation activities (if applicable)

Not applicable.