CLINICAL STUDY PROTOCOL
IND 128,081

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

PROTOCOL NO. SYD-101-001
NCT03918915

Sponsor Sydnexis, Inc.
445 Marine View Avenue, Suite 295
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CONFIDENTIAL

All financial and nonfinancial support for this study will be provided by Sydnexis, Inc. The concepts and information contained in this document or generated during the study are considered proprietary and may not be disclosed in whole or in part without the expressed, written consent of Sydnexis.

The study will be conducted according to the International Council for Harmonisation harmonised tripartite guideline E6(R2): Good Clinical Practice.

PROTOCOL APPROVAL – SPONSOR SIGNATORY

Study Title	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
Protocol Number	SYD-101-001
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Protocol accepted and approved by:

President
Patrick Johnson, PhD
Sydnexis, Inc.
445 Marine View Avenue, Suite 295
Del Mar, CA 92014 USA

Signature _____ Date _____

DECLARATION OF INVESTIGATOR

I have read and understood all sections of the protocol entitled "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" and the accompanying investigator's brochure.
I agree to supervise all aspects of the protocol and to conduct the clinical investigation in accordance with the current protocol, the International Council for Harmonisation harmonised tripartite guideline E6(R2): Good Clinical Practice, and all applicable government regulations. I will not make changes to the protocol before consulting with Sydnexis, Inc. or implement protocol changes without independent ethics committee/institutional review board approval except to eliminate an immediate risk to participants. I agree to administer study treatment only to participants under my personal supervision or the supervision of a subinvestigator.
I will not supply the investigational drug to any person not authorized to receive it. Confidentiality will be protected. Participant identity will not be disclosed to third parties or appear in any study reports or publications.
I will not disclose information regarding this clinical investigation or publish results of the investigation without authorization from Sydnexis, Inc.

Signature of Principal Investigator	Date

Printed Name of Principal Investigator

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1.1 SYNOPSIS

Title:

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

Study Description:

This multinational Phase 3 study has been designed to evaluate the following clinical hypotheses:

- SYD-101 is safe as assessed by the incidence and severity of adverse events (AEs) compared with Vehicle
- SYD-101 is superior to Vehicle in slowing the progression of myopia

Objectives:

Efficacy

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

Safety

- To evaluate the safety and tolerability of SYD-101

Endpoints and Scheduled Analyses:

Analysis of safety and efficacy data will be performed at Month 24, Month 36, and Month 48. For regulatory submission in the European Union (EU) and United States (US), endpoints will be analyzed as requested by the respective regulatory authorities. Refer to Sections 3 and 9 of this protocol for details.

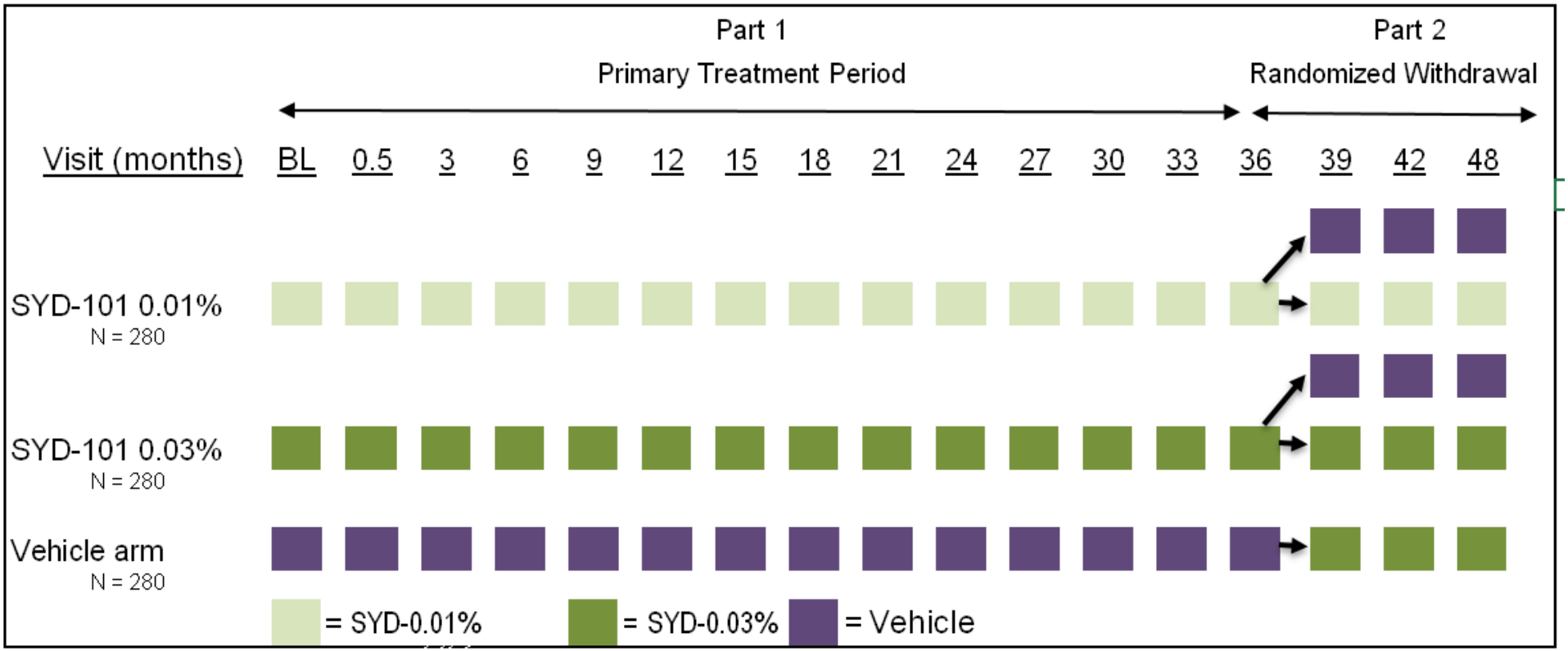
Efficacy

- Proportion of participants with confirmed myopic progression >0.75 diopters (D)
- Mean annual progression rate of myopia
- Proportion of participants with annual myopia progression rate ≤0.50 D/year
- Proportion of participants with annual myopia progression rate ≤0.25 D/year
- Proportion of participants with an increase of myopia >0.50 D
- Time to progression of myopia >0.75 D
- 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 sites with the requisite equipment; at least 50% of study participants)

Endpoints and Scheduled Analyses (continued):	*Safety* • Evaluation of AEs and serious AEs • Changes from baseline in vital sign measurements • Mean change from baseline in pupil diameter • Changes from baseline in eye examination findings (including best-corrected visual acuity (BCVA), biomicroscopy, intraocular pressure, and ophthalmoscopy) • Changes from baseline in corneal endothelial cell count (selected sites only; approximately 25% of study participants) • Tolerability questionnaire responses In addition, pregnancy tests will be administered to female participants of childbearing potential. Pregnancy outcomes will be assessed.
Study Population:	A total of approximately 840 male and female pediatric participants with myopia, who are in good general health, and between 3 and 14 years of age (inclusive) will be enrolled in this study.
Phase:	3
Description of Sites Enrolling Participants:	Up to 41 study sites located in the United States (US) and up to 6 study sites located in Europe.
Description of Study Intervention:	There are 3 study drugs in this study, SYD-101 0.01%, SYD-101 0.03%, and Vehicle. Study drug will be administered as eyedrops. Each night at bedtime, 1 drop of assigned study drug will be instilled in each eye. SYD-101 0.01% is a sterile topical ophthalmic solution of atropine sulfate. SYD-101 0.03% is a sterile topical ophthalmic solution of atropine sulfate. Vehicle (control) is identical to SYD-101, except that it does not contain active drug and uses H_2O instead of deuterium oxide (D_2O). *Escape Medication*: If a participant has measured myopia progression ≥2.00 D from baseline in spherical equivalent (SE) at a visit occurring between Month 18 and Month 36 (inclusive), and myopia progression is confirmed 6 months later at the next scheduled visit (ie, visit between Month 24 and Month 42 [inclusive]), then treatment with escape medication (active SYD-101 0.03%) may be initiated at the confirmatory visit and continued until Month 48.
Study Duration:	The anticipated duration of clinical study conduct is 70 months, including recruitment/enrollment and 48 months of treatment with study drug.

Participant Duration: The duration of participation for each study participant will be up to 48 months, plus a Screening visit (screening procedures will be performed up to 21 days prior to study enrollment on Day 1).

1.2 STUDY SCHEMA



Abbreviation: BL, baseline.

1.3 SCHEDULE OF ACTIVITIES (SOA)

Study Period	Screening	Part 1: Primary Treatment Period													Part 2: Randomized Withdrawal			
Visit	SCR	BL	Week 2	Mo 3	Mo 6	Mo 9	Mo 12	Mo 15	Mo 18	Mo 21	Mo 24	Mo 27	Mo 30	Mo 33	Mo 36	Mo 39	Mo 42	Mo 48/EOS
Visit Window	Within 21 days prior to Day 1 [a]	Day 1 [a]	Day 14 ± 3	Week 13 ± 1	Week 26 ± 2	Week 40 ± 2	Week 52 ± 2	Week 65 ± 2	Week 78 ± 2	Week 91 ± 2	Week 104 ± 2	Week 117 ± 2	Week 130 ± 2	Week 143 ± 2	Week 156 ± 2	Week 169 ± 2	Week 182 ± 2	Week 208 ± 2 (or ET)
Informed Consent/Assent [b]	X						X				X				X			
Inclusion/Exclusion Review	X	X																
Demographics/Med Hx [c]	X																	
Con Meds/Procedures [d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events [d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs [e]	X						X				X				X			X
Urine Pregnancy Test [f]		X					X				X				X			X
Tolerability Questionnaire [g]				X	X		X		X		X		X		X		X	X
QOL Questionnaire [h]					X		X				X				X			X
BCVA by ETDRS [i]	X	X		X	X		X		X		X		X		X		X	X
Binocular Near-BCVA		X			X		X		X		X		X		X		X	X
Pupil Diameter		X			X		X		X		X		X		X		X	X
Accommodative Amplitude		X			X		X		X		X		X		X			X
Specular Microscopy [j]		X					X				X							X
Biomicroscopy	X	X		X	X		X		X		X		X		X		X	X
IOP [k]		X					X				X				X			X
Cycloplegic Autorefraction [l]	X	X			X		X		X		X		X		X		X	X
Cycloplegic Biometry [m]	X						X				X				X			X
Dilated Ophthalmoscopy	X	X			X		X		X		X		X		X		X	X
Randomization		X													X			
Supply Study Drug		X			X		X		X		X		X		X		X	
Study Coordinator Call [n]			X			X		X		X		X		X		X		
Activities/Compliance Questionnaire [o]	X																	
eCRF Completion	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: AE, adverse event; BCVA, best-corrected visual acuity; BL, baseline; Con Meds/Procedures, concomitant medications and concurrent procedures; eCRF, electronic case report form; EOS, end of study; ET, early termination; ETDRS, Early Treatment of Diabetic Retinopathy Study; IOP, intraocular pressure; Med Hx, medical history; Mo, month; QOL, Quality of Life; SCR, Screening.

Note: Eye assessments will be performed in both eyes at all timepoints.

a. Screening and Day 1 procedures may be performed on the same calendar day. Ophthalmic exams performed during the screening period (within 21 days of Baseline/Day 1) do not need to be repeated on Day 1.

b. Informed consent is an ongoing process. Participant capacity to assent will be evaluated annually; confirmation of continued affirmative assent will be sought and documented as appropriate.
c. Demographic data will include age, sex, ethnicity/race, and eye color. Participant medical history will include parental myopia history.
d. AEs, concomitant medications, and concurrent procedures will be monitored throughout the study, with scheduled inquiries at visits. If any issues are reported by a participant or parent/guardian, an unscheduled visit will be performed promptly to assess for AEs.
e. Vital sign measurements will include blood pressure, heart rate, height, and body weight.
f. Females of childbearing potential only; additional pregnancy tests may be performed at any time/day during the study. Females will be queried annually regarding childbearing potential status.
g. The investigator's designee will administer a tolerability questionnaire to participant (or parents/guardians) to assess potential side effects of study drug (blurred vision, burning/stinging, eye pain, grittiness in eye, sensitivity to light, headache).
h. The investigator's designee will administer a QOL questionnaire to participant (or parents/guardians)
i. BCVA will be measured in each eye prior to cycloplegia with the participant wearing current correction and will be qualified by study-certified visual acuity testing using the ETDRS charts. If the vision is more than 1 line (≥5 letters) worse than baseline, the testing will be redone using trial frames or phoropter. Standard manual refraction may also be performed, if needed, to confirm loss of BCVA using the standard refraction technique.
j. Corneal endothelial cell count data will be obtained using specular microscopy (selected sites only; approximately 25% of participants).
k. IOP measurements will be taken prior to pupil dilation.
l. For cycloplegic autorefraction, 1 drop of 1% cyclopentolate will be applied 2 times to each eye, with 5 minutes between drops. The autorefraction will occur at least 40 minutes (but no more than 60 minutes) after the second drop of 1% cyclopentolate has been instilled. If a participant has progression of myopia >0.75 D, the participant will need to return to the clinic within 3 to 28 days for an unscheduled visit to confirm the progression. Standard manual refraction should be performed at screening for initial BCVA and if Spherical Equivalent is ≥0.75 D (to verify components of inclusion #9) and may be performed as needed throughout the study.
m. Axial length will be measured by cycloplegic biometry (at sites with the requisite equipment; at least 50% of participants).
n. At Week 2, and between clinic visits, the study coordinator will phone the participant or parent/guardian to encourage compliance and ask about any complaints (potential AEs).
o. Time spent on various activities (near-vision activities, daylight outdoor leisure, exercise, wearing a wide-brimmed hat or dark glasses while outdoors) and adherence to the dosing regimen will be collected via a questionnaire on a phone or web-based application. The questionnaires will be completed weekly for the first 6 months and then monthly until Month 48/End of Study.

2 INTRODUCTION

2.1 BACKGROUND AND RATIONALE

2.1.1 EPIDEMIOLOGY OF MYOPIA

Myopia, or nearsightedness, is defined as having a refractive error of worse than 0.50 diopters (D). Myopia is the most common ocular disorder with an estimated prevalence of 13% to 49% in adult population-based studies (Pan 2012, Eye Diseases Prevalence Research Group 2004). In Europe, the prevalence of myopia is increasing (Williams 2015); in the United States, 41.6% of the population had a diagnosis of myopia as of 2004 – up from 25% in 1971 (Vitale 2009); and in Asia, myopia has been classified as an epidemic with estimates of greater that 50% of the population having myopia in 2020 (Holden 2016). Not only is the prevalence increasing across the globe, the severity of myopia is increasing as well (Matsumura 1999, Vitale 2009, Leo 2011, Morgan 2012).

Myopia progression in children is the result of elongation of the axial length of the eye. Retarding progression of myopia has been the topic of significant research since high myopia (>6.00 D) is associated with significant risk of pathologic changes including glaucoma, cataract, retinal detachment, choroidal degeneration, choroidal neovascularization, and retinoschisis, all of which can cause irreversible vision loss (Wong 2014). Myopia is among the 5 conditions that have been identified as immediate priorities by the World Health Organization in its Global Initiative for the Elimination of Avoidable Blindness (WHO 2015). The recent increase in the awareness of myopia has been fueled by research suggesting that an increase in near activities (such as electronic screen time; Huang 2015, Leo, 2017, Aldrich 2018) and lack of outdoor activity (Xiong 2017) may increase one's risk for developing myopia. In fact, schools in Taiwan have implemented new guidance referred to as ROC711, which requires mandatory outdoor time for children while at school, increased outdoor activity during school hours, and even homework outside of classroom recommendations to specifically reduce the incidence of myopia in their population (Wu 2018).

2.1.2 TREATMENT OF MYOPIA AND ATROPINE

The recent increase in the awareness of myopia has created the need for a treatment to decrease myopic progression. Historically, the majority of clinical trials have investigated nonpharmacologic interventions for treatment of the progression of myopia, including progressive lenses and rigid gas-permeable contact lenses, but these have yielded disappointing results.

Atropine is a nonselective muscarinic antagonist approved in both the European Union and the United States as a 1% ophthalmic solution for cycloplegia during refraction and for treatment of uveitis and iritis in both adults and children (>3 months of age). Topical atropine 1% has been used chronically in young children for many years for a number of approved therapeutic ophthalmic indications including amblyopia therapy, iritis treatment, and uveitis treatment, and off-label for arresting or slowing myopia progression.

The mechanism of atropine's reduction of myopia progression has been hypothesized to be a consequence of the elimination of the ability to accommodate, local retinal effects that slow progression, or potential biochemical changes from binding atropine with muscarinic acetylcholine receptors within the eye. Another mechanism may be via increased ultraviolet A exposure (Prepas 2008). While the mechanism is not specifically known, many clinical trials have been conducted concluding that atropine 1% administered nightly effectively slows myopia progression in children.

Early studies of topical 1.0% atropine were small, poorly designed, and lacked appropriate controls. Chua and colleagues launched the Atropine for the Treatment of Myopia (ATOM)1 study, which was the first randomized, double-masked, placebo-controlled trial designed primarily to test whether topically administered atropine 1.0% could slow the progression of mild and moderate myopia in children between 8 and 12 years of age (Chua 2006). This study was conducted in Singapore in 400 children who received atropine 1% drops or placebo daily over 2 years. Myopia progression was reduced 77% (progression of 0.28 D vs 1.20 D). However, despite the reduced myopic progression, the study reported cycloplegia and mydriasis, which in some cases led to discontinuation of its use in children receiving atropine. More importantly, there was a rebound effect after discontinuing the medication where myopia was noted to increase at a faster than normal pace. These data prompted additional studies to evaluate lower doses of atropine to try to minimize the side effects while maintaining efficacy. Lee and colleagues conducted a retrospective, case-controlled study enrolling myopic school-aged children from Taiwan, who received 0.05% atropine eye drops every evening, compared with a control group of 36 untreated children (Lee 2006). Mean myopia progression for the treated group was 0.28 ± 0.26 D annually, whereas that of the control group was significantly higher at 0.75 ± 0.35 D per year. In another study (Shih 1999), concentrations of 0.5%, 0.25%, and 0.1% atropine were evaluated and found that all 3 concentrations were effective in delaying myopia progression in a controlled study with 2 years of follow-up.

It wasn't until 2012 when another double-masked, randomized study (ATOM2) tested the safety and efficacy of lower dose atropine solutions in Singapore (Chia 2012). Four-hundred children aged 6 to 12 years with myopia of at least 2.00 D and astigmatism of 1.50 D or less were enrolled in the study with 0.5%, 0.1%, and 0.01% atropine administered once a day at bedtime to both eyes for 2 years. No control group was included in this study; instead, the control group from ATOM1 was used for comparison. Although the reduction of mean myopic progression and axial length was less in the 0.01% group than the higher doses, the differences between groups were clinically insignificant and, importantly, the rebound effect was negligible in the atropine 0.01% group as compared to the higher doses. Atropine 0.01% had minimal effects on accommodation and pupil size and no effect on visual acuity. The authors concluded atropine 0.01% had minimal side effects and similar efficacy in controlling myopia progression when compared with other dilutions.

In a recent follow-up of the ATOM2 study, 356 children (89%) were reviewed at 26, 32, and 36 months after drug administration was discontinued, and spherical equivalent (SE), axial length, visual acuity, pupil size, and accommodation were measured (Chia 2014). Those findings indicated that there was a myopic rebound in patients who had received either atropine 0.5% or atropine

0.1%. In the patients who had received atropine 0.01%, the atropine effect on progression was sustained, with no rebound effect.

A clinical study of 200 children between 9 and 12 years of age with baseline bilateral myopia of 0.50 D to 2.00 D and less than 1.50 D astigmatism were included in a prospective study conducted in multiple centers in Spain (Diaz-Llopis 2018). Subjects received either atropine 0.01% solution (applied nightly to both eyes) or no treatment and were followed for 5 years. The annual progression rate was 0.14 ± 0.35 D in the atropine group compared to 0.65 ± 0.54 D in the untreated control. The authors concluded that atropine 0.01% eye drops applied once daily before bedtime slowed down the progression of myopia, further recommending it as a therapeutic option. The 0.01% atropine solutions used for this study were prepared and renewed monthly.

A few well-controlled studies are now ongoing that have similar designs in that they are masked and vehicle-controlled. In the United States, the Myopia Treatment Study (MTS1), funded by the National Institutes of Health, will evaluate 186 children receiving 0.01% atropine or artificial tears for 2 years (National Clinical Trial [NCT] 0333425). In Ireland, the MOSAIC study will evaluate 250 children receiving 0.01% atropine or placebo for 2 years (ISRCTN36732601). Studies with similar designs are also ongoing in Australia and Japan. For further details, see the investigator's brochure (IB).

2.1.3 RATIONALE FOR STUDY

While clinical trial results with dilute atropine are a marked improvement over those seen with 1% atropine, there are no approved, commercially available formulations of atropine 0.01%. In some countries in Europe and in the United States, patients can obtain atropine 0.01% from a compounding pharmacy with a prescription. However, there are several issues with compounded 0.01% atropine that have created the need for the rapid approval of a pharmaceutical quality 0.01% atropine product. First and foremost, compounded topical atropine 0.01% products are currently prescribed to control myopia in young children and recent data demonstrate that once the concentration of atropine is reduced below 1.0% the formulation becomes unstable. An unstable product with very limited shelf-life (that goes untested by compounding pharmacies) may lack the efficacy that doctors rely upon when they prescribe such a product, especially to children, and may also contain untested degradation products with unknown safety concerns. Coupled with the lack of guaranteed sterility and frequent shut-downs of the compounding pharmacies, young patients are being subject to unnecessary risks when they use compounded low-dose atropine. This situation has been exacerbated because the World Society of Paediatric Ophthalmology and Strabismus (WSPOS 2017) and American Academy of Ophthalmology (Pineles 2017) have both endorsed use of 0.01% atropine drops as the preferred treatment for pediatric myopia; as a result, downsides associated with use of off-label compounded low-dose atropine will only be magnified in the years to come.

Sydnexis has developed low-dose formulations of atropine using deuterium oxide (D_2O) as an excipient; D_2O significantly extends the shelf life at 25°C at near physiologic pH, creating a room temperature stable formulation. This Phase 3 study is being conducted to establish the safety and efficacy of atropine 0.01% and 0.03% in a topical ophthalmic solution [SYD-101] in children to slow progression of myopia.

2.2 NONCLINICAL INFORMATION

To address the safety of SYD-101 and to support the safety of this SYD-101 clinical trial, a 26-week ocular toxicity study has been conducted in male pigmented (Dutch Belted) rabbits. Six animals in each of the following 5 groups were dosed 1 drop bilaterally for 26 weeks: negative control (three times daily [TID]); vehicle control (TID); SYD-101 0.01% (TID); SYD-101 0.01% (once daily [QD]); and atropine 1% (QD). Clinical observations were unremarkable and dosing was well tolerated. For further details on nonclinical studies, see the IB.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

There have been many long-term studies using atropine 1% chronically in children as young as 3 years old with no significant adverse events (AEs) (Paediatric Eye Disease Investigator Group 2002, Chua 2006, Li 2009, Scheiman 2008, Tong 2009). Common side effects with atropine 1% include photophobia and blurred vision due to cycloplegia (SmPC, Minims Atropine Sulfate 1% Eye Drops, solution, Pan 2012), dry eye, burning stinging, tearing, and increased heart rate and blood pressure. More dilute concentrations have been well tolerated (Shih 1999) with allergic conjunctivitis reported only in the 0.5% and 0.1% treatment groups (Chia 2012). Upon cessation of atropine 1% after 2 years of treatment in the ATOM1 study, there was a marked rebound on the myopia progression (Tong 2009), but even at 3 years of follow-up, the treated group had significantly less myopia than the control group.

More dilute concentrations have been well tolerated (Shih 1999) with allergic conjunctivitis reported only in the 0.5% and 0.1% treatment groups (Chia 2012). In the ATOM2 study, the low-dose atropine (0.01%) had a minimal loss of accommodation (2-3 D), minimal pupil dilation (0.8 mm), and no effect on near visual acuity (Chia 2012). Clark (2015) reported 2 cases of intermittent light sensitivity to bright sunlight and 1 case with a history of migraine headaches with intermittent blurred vision; no case was symptomatic enough to warrant discontinuation of atropine 0.01%. In a study conducted in Spain (Diaz-Llopis 2018), 2% of the atropine 0.01%-treated patients discontinued medication due to AEs, including photophobia, reading difficulty, mydriasis, and headaches; up to 5% of patients reported slight photophobia, difficulties in very near reading, and excessive mydriasis that did not require treatment withdrawal. Gong and colleagues conducted a meta-analysis of 19 peer-reviewed studies on the efficacy and AEs of atropine in childhood myopia; no corneal AEs were identified with any strength and there were no differences in the incidence of AEs between Asians and Caucasians (Gong 2017).

To demonstrate the safety of atropine on visual function, retinal sensitivity was measured over time in atropine-treated myopic children. Thirty-five of 50 children enrolled in the ATOM2 study consented to have full-field electroretinogram (ffERG) recordings at baseline, 24 months (end of treatment [EOT]), and 32 months (8 months after cessation of atropine). Twenty-nine children had good quality ffERG on all 3 visits; their mean age was 9.5 ± 0.8 years and mean SE was 5.0 ± 1.6 D. There was no significant correlation of axial length with any ffERG measures (saturated amplitude, scotopic and photopic ffERG amplitude, implicit time). Multivariate analysis showed that a change in 30 Hz flicker response amplitude was associated with increased axial length, but there was no evidence that changes in other responses were associated with age, axial length, or atropine doses. The conclusion was that the atropine treatment did not have an impact on scotopic or photopic visual responses (Fang 2013).

The Sydnexis topical ophthalmic formulations of atropine 0.01% and 0.03%, SYD-101 0.01% and SYD-101 0.03%, have not been tested in humans. See the IB for additional details.

2.3.2 KNOWN POTENTIAL BENEFITS

Recognition of the myopia rebound effect with atropine 1% led to testing lower solutions (0.5%, 0.1%, 0.05%, and 0.01%) (Wu 2011, Chia 2012, Chia 2014, Chia 2015, Clark 2015, Polling 2016). It was noted in all of these studies that there was significantly less rebound effect after cessation of the more dilute atropine and that patients using atropine 0.01% do not require bifocal wear as accommodation is preserved. A 5-year study conducted in Spain found that atropine 0.01% reduced the myopia progression from 0.65 D/year to 0.15 D/year or 77% (Diaz-Llopis 2018).

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

The risks associated with atropine 0.01% and anticipated with atropine 0.03% eyedrops are minimal and reversible upon treatment withdrawal (Chia 2012). Transient dilation and nominal changes in accommodative amplitude resulting from 0.01% and 0.03% atropine will be mitigated by the implementation of a once-nightly (QHS) dosing regimen, as the pharmacological effects of the formulation should be minimized within 8 to 12 hours.

The American Academy of Ophthalmology produced a technology assessment concluding that level 1 evidence supports the use of atropine to prevent myopic progression and that the 0.01% minimizes the myopic rebound (Pineles 2017). The World Society of Paediatric Ophthalmology and Strabismus produced a consensus statement on myopia (2017), “Atropine 0.01% dose appears to offer an appropriate risk-benefit ratio, with no clinically significant visual side effects balanced against a reasonable and clinically significant 50% reduction in myopia progression.”

3 OBJECTIVES AND ENDPOINTS

OBJECTIVE	ENDPOINT	JUSTIFICATION FOR ENDPOINT
Efficacy		
To evaluate the efficacy of SYD-101 for slowing the progression of myopia in children	• Proportion of participants with confirmed myopic progression >0.75 D at Month 36 (and Month 24 for EU), based on SE as measured by cycloplegic autorefraction	Measuring SE by cycloplegic autorefraction has become the standard in myopia trials. For each participant, the autorefraction will be done 3 times for the right eye and 3 times for the left eye. The SE for each measurement will be calculated for each eye and then averaged by eye; the participant's averaged right eye SE and averaged left eye SE will then be averaged (ie, a **single averaged SE value** for a given visit will be obtained for each participant by taking the "average of the averages"). A single averaged SE value will be used for analyses to reduce bias at the study site level as well as to reduce variability in the measure. To qualify for reaching the primary endpoint of progression of myopia of >0.75 D, the study participant will need to return to the clinic within 3 to 28 days for an unscheduled visit to confirm the progression. This confirmatory step will further reduce variability in the measure. A change of 0.75 D represents a meaningful change in visual performance (3 lines of vision) and warrants a new prescription. Analysis of data will be performed at Month 24, Month 36, and Month 48. The primary efficacy analysis for EU regulatory submission will be performed at Month 24; this is the most frequent duration published and is supported by major ophthalmology societies to demonstrate safety and efficacy of atropine in myopia. A duration of 24 months is also supported by European Medicines Agency/International Council for Harmonisation (ICH) Guidance, which states ethical and practical concerns are raised when using a placebo control for long-term outcome measures. As requested by the FDA, the primary efficacy analysis for US regulatory submission will be performed at Month 36.
	• Mean annual progression rate of myopia based on 36 months of follow-up for the US (24 months for EU)	The annual rate of myopic progression frequently appears in the literature as a key endpoint and therefore will serve as a reference to other clinical trials. Medical Products Agency (Sweden) requested a continuous variable as it provides for more information.

OBJECTIVE	ENDPOINT	JUSTIFICATION FOR ENDPOINT
Efficacy (continued)		
To evaluate the efficacy of SYD-101 for slowing the progression of myopia in children	• Proportion of participants with annual myopia progression rate ≤0.50 D/year	A rate of progression of ≤0.50 D/year is considered very low and will add further characterization to the effects of SYD-101.
	• Proportion of participants with annual myopia progression rate ≤0.25 D/year	A change of ≤0.25 D is within testing error of autorefraction and is therefore considered to be negligible.
	• Proportion of participants with an increase of myopia of >0.50 D at Month 36 (Month 24 for EU)	Results of the ATOM2 study showed that 0.01% atropine reduced myopic progression by 0.49 D over 2 years (<0.25 D/year). As an endpoint, the proportion of patients with an increase of myopia of >0.50 D at Month 36 (Month 24 for EU) would enable comparison of this study's results with those of other clinical trials in addition to further characterizing the effects of SYD-101.
	• Time to progression of myopia >0.75 D	This measures the time to failure.
	• Mean annual progression rate on Subgroup of participants with refractive history of progression ≥ 0.5D (month 24 for EU)	Patients with previous myopia progression are more likely to have worse subsequent progression.
	• Mean annual progression rate on Subgroup of participants with refractive history of progression ≥ 0.75D (month 24 for EU)	Patients with previous myopia progression are more likely to have worse subsequent progression.
	• Mean change from baseline in axial length (at sites with the requisite equipment; at least 50% of study participants)	While myopia is primarily due to elongation of axial length, most pediatric clinics lack the biometry equipment to measure this. Therefore, axial length will be measured for participants enrolled at sites with the requisite equipment.
Exploratory		
	• Mean change from baseline in SE at Month 48 (ie, 12 months after randomized withdrawal)	This analysis will be conducted to evaluate the persistence of effect of SYD-101. High-dose atropine (eg, 1%) is associated with a significant rebound effect upon cessation of therapy.
	• Mean time spent on various activities will be solicited via questionnaire	Activities such as time spent outdoors during daylight and working on near-vision tasks are associated with decreases and increases in myopia progression, respectively.

OBJECTIVE	ENDPOINT	JUSTIFICATION FOR ENDPOINT
	• Proportion of agreement to QOL statements	Use of SYD-101 eyedrops may affect the QOL of the participant. Selected questions are taken from a questionnaire used in an amblyopia pediatric population (Holmes 2008).
Safety		
To evaluate the safety and tolerability of SYD-101	• Evaluation of AEs and SAEs	Severity and causality of AEs are standard endpoints.
To evaluate the safety and tolerability of SYD-101	• Changes from baseline in vital sign measurements	Vital signs are standard non-invasive investigations of systemic health suitable for a pediatric population.
	• Mean change from baseline in pupil diameter	Atropine has mydriatic properties. This analysis will be conducted to investigate the extent of dilation to determine if it is significant with SYD-101.
	• Mean change from baseline in binocular accommodative amplitude	Atropine has cycloplegic properties. This analysis will be conducted to investigate the extent of change in near-accommodation to determine if it is significant with SYD-101.
	• Changes from baseline in findings detected by best-corrected visual acuity (BCVA), biomicroscopy, intraocular pressure (IOP), and ophthalmoscopy	Clinically significant findings from the complete eye examination will be recorded as adverse events.
	• Changes from baseline in corneal endothelial cell count (selected sites only; approximately 25% of study participants)	Effect on endothelial cell counts will be assessed in a subset of participants enrolled at sites with the requisite specular microscopy equipment.
	• Tolerability to the masked study drug will be solicited via questionnaire	Symptoms such as blurred vision, burning/stinging, eye pain, grittiness in eye, sensitivity to light, and headache are potential side effects to the study drug.
	• Pregnancy test results (female participants of childbearing potential only)	This population is at risk for becoming pregnant and outcomes of pregnancy will be assessed.

4 STUDY DESIGN

4.1 OVERALL DESIGN

The clinical hypotheses for this study are as follows:

- SYD-101 is safe as assessed by the incidence and severity of AEs compared with Vehicle
- SYD-101 is superior to Vehicle in slowing the progression of myopia
    - For European Medicines Agency (EMA) submission, the primary assessment of myopia progression will be assessed by the mean annual progression rate of myopia
    - For US Food and Drug Administration (FDA) submission, the primary assessment of progression will be assessed by the proportion of participants with an increase in myopia >0.75 D

This is a Phase 3, multicentered, randomized, double-masked, vehicle-controlled study to assess the safety and efficacy of SYD-101 eyedrops in male and female children between 3 and 14 years of age (inclusive) with myopia of 0.50 D to 6.00 D (inclusive).

The study will have 3 treatment groups: SYD-101 0.01%, SYD-101 0.03%, and the Vehicle of SYD-101. Each night at bedtime, 1 drop of masked study drug will be instilled in each eye. See Section 1.2 for the figure describing the treatment assignments.

- **Baseline Randomization.** At Baseline, participants will be randomly assigned into 1 of 3 treatment arms, with participants allocated in a 1:1:1 ratio to receive either SYD-101 0.01%, SYD-101 0.03%, or Vehicle during Part 1 (Primary Treatment Period). Allocation to the treatment groups will be stratified according to the following 2 factors: baseline SE and age (see Section 6.3 for stratification details). Enrollment thresholds may be utilized to limit the number of participants in each level of demographic characteristic such as age group, baseline SE group, race, etc. These thresholds will be defined within the interactive voice response system (IVRS)/interactive web response system (IWRS) and may be modified during the course of the study.
- **Re-randomization.** At Month 36, participants will be randomly assigned to receive study treatment during Part 2 (Randomized Withdrawal Period) as follows:
    - Those initially assigned to the SYD-101 0.01% arm will be re-randomized in a 1:1 ratio to receive either masked SYD-101 0.01% or Vehicle
    - Those initially assigned to the SYD-101 0.03% arm will be re-randomized in a 1:1 ratio to receive either masked SYD-101 0.03% or Vehicle

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

For participants with measured myopia progression ≥2.00 D from baseline in SE at a visit occurring between Month 18 and Month 36 (inclusive), and measurements obtained 6 months later at the next scheduled visit confirm myopia progression (ie, confirmation at a visit between Month 24 and Month 42 [inclusive]), then treatment with **escape medication** (active SYD-101 0.03%) may be initiated at the confirmatory visit and continued until Month 48. Participants on escape medication will adhere to the same visit schedule. No medications will be dispensed during or after the Month 48/End of Study (EOS) visit.

Clinic visits (with an investigator) will be 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 will occur at Week 2 and between clinic visits, from Months 9 through 39.

Specular microscopy will be done so that approximately 25% of participants will have an assessment for endothelial cell counts at sites with the requisite equipment. Axial length will be measured at sites with the requisite equipment (at least 50% of study participants).

There are 3 planned database locks for this study. The first will occur after all participants have completed the Month 24 visit for the purpose of submitting data for regulatory submission to the EU (ie, Month 24 analysis). The second database lock will occur after all participants have complete the Month 36 visit for regulatory submission to the US (ie, Month 36 analysis). The final database lock will occur after all participants have completed the last study visit (Month 48 or ET) to allow assessment of the persistence of effect of SYD-101 after 12 months of randomized withdrawal (ie, Month 48/Final analysis). Details regarding efficacy analyses are provided in Section 9.4.2.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

A placebo control is the gold standard clinical trial design appropriate for conditions without any approved treatments so that superiority of the treatment can be established. In the case of pediatric myopia, low-dose atropine has been investigated in many trials, many of which used a placebo control and found atropine to be effective. Parents/guardians of the participants may not understand the scientific and regulatory need for a placebo control or a randomized withdrawal. Therefore, this study utilizes the following strategies to encourage recruitment and adherence to the study procedures: uneven randomization (allocation to treatment with active SYD-101: Vehicle in a 2:1 ratio at Baseline), re-randomization to treatment with active SYD-101 0.03% at Month 36 for all participants initially assigned to receive Vehicle, and allowance for treatment with active SYD-101 0.03% as escape medication (per Section 6.5.2) for participants with measured myopia progression once confirmed.

4.3 JUSTIFICATION FOR SELECTED DOSES

The 0.01% dose of atropine was selected for this study based on published dose-response data concluding this dose provided the optimal benefit with the least amount of adverse effects.

Although several studies have demonstrated the beneficial effects of 0.01% atropine, the literature has also reported that patient responses to 0.01% atropine can vary. Investigators have noted the potential for factors such as dark iris color and rapid progression of myopia to lessen a child's response to low-dose atropine. Therefore, the slightly stronger dose of 0.03% atropine has also been selected for this study as it may mitigate inter-patient variability reported in the literature (ie, offer additional benefit to participants with dark irises and/or those who may experience more rapid myopia progression).

Both selected doses, 0.01% and 0.03% atropine, offer potential benefit while remaining below the dose threshold of 0.05% atropine, as results reported in literature have shown doses at or above 0.05% to be associated with increased risk of AEs.

4.4 END OF STUDY DEFINITION

A participant is considered to have completed the study if s/he has completed all phases of the study including the last visit or the last scheduled procedure shown in the Schedule of Activities (SOA), Section 1.3.

5 STUDY POPULATION

Participants will be assigned to study drug only if they meet all of the inclusion criteria and none of the exclusion criteria.

Deviations from the inclusion and exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability, or participant safety. Therefore, adherence to the criteria as specified in the protocol is essential.

5.1 INCLUSION CRITERIA

Participants must meet all of the inclusion criteria to be included in the study:

1. Parent/guardian has the ability to understand the study informed consent form (ICF) and agrees to sign the ICF prior to initiation of any protocol-related procedures; participant has the ability to give assent, as applicable, at the time of parental/guardian consent
2. Participant is male or female between 3 and 14 years of age (inclusive) at the time of Screening
3. Participant and parent/guardian are willing and able to comply with study instructions, study visits, and procedures
4. Participant (or parent/guardian) has demonstrated ability to administer artificial eyedrops at the Screening or Baseline visit
5. 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
6. Postmenarchal female participants must have negative urine pregnancy test results

The following inclusion criteria (#7 through #11) are required of **both eyes:**

7. 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
8. If the baseline myopia (SE) is <0.75 D, participant must have a history of myopia progression of 0.50 D in the previous 6 to 12 months
9. If baseline myopia (SE) is ≥0.75 D, 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

10. BCVA of 75 letters (Snellen equivalent 20/32) or better

11. Normal IOP <21 mmHg

5.2 EXCLUSION CRITERIA

Participants who meet any of the exclusion criteria will be excluded from the study:

1. Participant is a female who is 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 (eg, Marfan syndrome, Stickler syndrome) or a condition that may affect visual function or development (eg, diabetes mellitus, chromosome anomaly)

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

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 (eg, 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 (eg, required conversion from extended wear lenses to daily wear lenses, full-time use of contact lenses or spectacles)

5.3 LIFESTYLE CONSIDERATIONS

During this study, participants are asked to continue with usual indoor and outdoor activities.

Study participants will be required to remove contact lenses at night throughout the duration of study treatment. Participants are required to wear corrective lenses (contact lenses or spectacles) on a full-time basis.

Use of continuous extended-wear contact lenses is not permitted during the study. Participants who have been using extended-wear contact lenses will be required to change to daily wear lenses at least 14 days prior to Baseline.

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently randomly assigned to the study intervention or entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials publishing requirements, and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals with concurrent infection or inadequate corrective lenses may be rescreened. Rescreened participants should be assigned the same participant number as for the initial screening. A given participant may only be rescreened once.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

Sites will recruit participants from their database as well as locally. Group enrollment shortly after the study opens will be encouraged. Any advertisement must be approved by the institutional review board (IRB)/ethics committee (EC). Participants will be encouraged to remain in the study by offering escape medication and eye examinations at no cost, as well as required glasses or contacts necessary to adhere to the spectacle correction requirement.

Refer to the Manual of Procedures (MOP) for additional information.

6 STUDY INTERVENTION

6.1 STUDY DRUG ADMINISTRATION

6.1.1 DESCRIPTION OF STUDY DRUG

The active study treatment, SYD-101, is a sterile topical ophthalmic solution of atropine sulfate. The Vehicle (control) treatment formulation is identical to SYD-101, except that it does not contain active drug (atropine sulfate) and H_2O is used instead of D_2O. Components of each study drug are listed in Table 6-1.

Table 6-1: 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; H_2O, water; NaOH, sodium hydroxide.

6.1.2 DOSING AND ADMINISTRATION

Prior to randomization, the participant or parent/guardian will administer 1 drop of an artificial tear to each eye to demonstrate cooperation and performance with eyedrop instillation. Once study entry procedures have been completed, the investigator's designee will obtain the randomization assignment and drug kit number from the IVRS/IWRS and provide training to the participant or parent/guardian in the correct administration. One drop will be administered to each eye nightly. Detailed instructions are described in the MOP including resupply procedures.

6.2 STUDY DRUG PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 ACQUISITION AND ACCOUNTABILITY

The investigator designee must keep an accurate accounting of the number of investigational units received from Sydnexis and the number of units returned to Sydnexis or the sponsor's designee during and at the completion of the study. A detailed inventory must be completed for the study drug.

All clinical study drug and/or supplies will be returned to Sydnexis or its designee for destruction.

6.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

SYD-101 and Vehicle are clear ophthalmic solutions packaged in identical white, 5-mL low-density polyethylene (LDPE) ophthalmic bottles and supplied by Sydnexis or its designee. All study drugs will

be labeled with the protocol number and medication kit numbers. The label will also specify the storage conditions (room temperature) and state that the study drug is limited to investigational use.

6.2.3 PRODUCT STORAGE AND STABILITY

The study drug must be stored between 5°C (41°F) and 25°C (77°F) and protected from excessive heat. Do not freeze. Temperature will be monitored while stored at sites. Refer to the Pharmacy Manual for further information.

6.2.4 PREPARATION

Not applicable.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND MASKING

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

For Part 1, prior to initiation of study treatment, randomization will occur by site staff via the IVRS/IWRS once it is confirmed that the participant meets the final study entry criteria (see Sections 5.1 and 5.2). The IVRS/IWRS will provide the participant identification number used on all study documents and will be used to manage the randomization and treatment assignment based on a stratified randomization scheme prepared by Sydnexis' designee. Initial randomization will be 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 >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).

To maintain treatment masking for Part 2, sites will 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% will be re-randomized in a 1:1 ratio to masked SYD-101 0.01% or Vehicle; participants initially assigned (at Baseline) to SYD-101 0.03% will be re-randomized in a 1:1 ratio to masked SYD-101 0.03% or Vehicle. The Re-randomization of SYD-101 participants will not be stratified. All participants who were initially assigned (at Baseline) to Vehicle will be re-randomized to masked SYD-101 0.03% at Month 36.

Sites will also contact the IVRS/IWRS at the time a participant qualifies to initiate treatment with escape medication (ie, at confirmatory visit when measurements confirm progression of myopia ≥2.00 D in SE from baseline) for ANY participant who has qualified for and desires to use escape medication.

Study drug will be labeled with medication kit numbers, and the IVRS/IWRS will provide each site with the specific medication kit number(s) for each randomized participant at the time of

randomization and any required drug resupply visit. Additionally, to maintain study masking, the IVRS/IWRS will assign a new medication kit for all participants at any timepoints study treatments might switch based on study design (ie, the re-randomization at Month 36, at escape for confirmed ≥2.00 D progression), even if the new medication kit will be of the same treatment type of the medication kit currently assigned. Sites will dispense study drug according to the IVRS/IWRS instructions. Sites will receive the IVRS/IWRS confirmation notifications for each transaction. All notifications are to be maintained with the study source documents.

Masking of individual participant treatment assignments will be maintained throughout the study for all participants and required site staff until the database is locked for the 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 should be notified prior to the unmasking, and the reason for breaking the mask will be documented in the source documentation. The investigator should inform the medical monitor of the unmasking if there is no notification prior to the unmasking. The treatment assignment for the participant can be determined by designated site staff calling into the IVRS/IWRS via password-protected access. The reason for breaking the code must be recorded in the participant's source documents and electronic case report form (eCRF).

To minimize bias, results of the Month 24 analyses for EU submission will neither be made public, nor shared with study sites nor study monitors until after completion of the Month 36 analysis.

6.4 STUDY INTERVENTION COMPLIANCE

Participants will be queried on adherence to the dosing regimen on the Activities/Compliance Questionnaire. Refer to the MOP for further information.

6.5 CONCOMITANT THERAPY

The decision to administer a prohibited medication/treatment is done with the safety of the study participant as the primary consideration. Whenever possible, the medical monitor should be notified before the prohibited medication/treatment is administered.

Medication considered necessary for the participant's welfare may be given at the discretion of the investigator. Participants should be 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 will be recorded on the appropriate eCRF page.

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

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

6.5.1 PROHIBITED THERAPY

Due to the potential for drug-drug interactions, monoamine oxidase inhibitors are prohibited. Refer to the MOP for further information.

During the study, participants must not use the following:

- Any lenses to reduce myopia progression is prohibited, 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

6.5.2 ESCAPE MEDICATION

For participants with measured myopia progression ≥2.00 D from baseline in SE at a visit occurring between Month 18 and Month 36 (inclusive), and myopia progression is confirmed 6 months later at the next scheduled visit (ie, visit between Month 24 and Month 42 [inclusive]), treatment with **escape medication** (active SYD-101 0.03% on an open-labeled basis) may be initiated at the confirmatory visit and continued until Month 48.

As with masked study treatment, open-label SYD-101 0.03% (escape medication) will be provided by the sponsor, managed and tracked using IVRS/IWRS, and dispensed to participants by the study coordinator.

7 STUDY DRUG DISCONTINUATION AND PARTICIPANT DISCONTINUATION OR WITHDRAWAL FROM STUDY

7.1 DISCONTINUATION OF STUDY DRUG

Discontinuation from study drug does not mean discontinuation from the study, and remaining study procedures should be completed as indicated by the study protocol. If a clinically significant finding is identified (including, but not limited to changes from baseline) after enrollment, the investigator or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an AE.

The data to be collected at the time of study intervention discontinuation will include the procedures as listed in the schedule of activities.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to discontinue the study at any time, for any reason, and without prejudice to further treatment. The investigator may remove a participant if, in the investigator's judgment, continued participation would pose unacceptable risk to the participant or to the integrity of the study data. Reasons for removal or withdrawal might include the following:

- Withdrawal of consent
- Administrative decision by the investigator or sponsor
- Significant protocol deviation
- Participant noncompliance or other significant protocol deviation
- Pregnancy
- Safety concern by the investigator or sponsor
- Lost to follow-up

With the exception of withdrawal of consent, participant withdrawal should be discussed with the sponsor, when possible, prior to withdrawing. Notification of early participant discontinuation from the study and the reason for discontinuation will be made to Sydnexis and will be clearly documented on the appropriate eCRF. If a participant discontinues prior to completing the study, the procedures outlined for the Month 48 visit should be performed at the ET visit (ie, last visit the participant attends).

Participants who sign the ICF and are randomized but do not receive study drug may be replaced by randomization of an additional participant (ie, the replacement participant will not necessarily receive the same treatment assignment as the original participant being replaced). Participants who sign the ICF, are randomized and receive the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study, will not be replaced.

7.3 LOST TO FOLLOW-UP

At any point during the trial, if a participant fails to return for a scheduled visit and is unable to be contacted by the site staff, he or she will be considered lost to follow-up. This does not include a single missed visit of which the site was notified or a missed visit with subsequent contact from the participants indicating an intention to continue on the study. The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit within the visit window and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study. If this make-up visit is outside the allowable window, a protocol deviation will be recorded.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up, and a protocol deviation will be recorded.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 EFFICACY ASSESSMENTS

Refer to the MOP for details on the efficacy measures and procedures.

- **Spherical Equivalent (SE)** as measured by cycloplegic autorefraction; 3 SE readings will be obtained for each eye and the average calculated for both eyes (average of averages). One drop of 1% cyclopentolate will be applied 2 times to each eye, with 5 minutes between drops. The cycloplegic autorefraction will occur within the window of maximum cycloplegic effects, ie, at least 40 minutes (but no more than 60 minutes) after the second drop of 1% cyclopentolate has been instilled. A third drop of 1% cyclopentolate may be applied to each eye if there is a delay before performing refraction. The cycloplegic autorefraction will occur at least 40 minutes (but no more than 60 minutes) after the last drop. Refer to the MOP for further details. If a participant has progression of myopia >0.75 D, the participant will need to return to the clinic within 3 to 28 days for an unscheduled visit to confirm the progression.
- **Axial Length** will be measured by cycloplegic biometry at sites with the requisite equipment, either IOLMaster, LENSTAR, or Pentacam (at least 50% of participants). Axial length measurements will be obtained 3 times in each eye.

8.2 SAFETY AND OTHER ASSESSMENTS

Findings that are of clinical significance will be recorded as AEs on the eCRF. Refer to the MOP for details on the assessments.

- **Demographics and Medical History**, including the following information, will be recorded at Baseline: age, sex, ethnicity/race, eye color, participant medical history, and parental myopia history.
- **Concomitant Medications and Concurrent Procedures** will be recorded on the eCRF.
- **Vital Sign Measurements** will include heart rate, blood pressure, height, and body weight.
- **Pregnancy Testing** will be 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.
- **Standard Manual Refraction** will be performed for initial BCVA and to verify inclusion #9. Manual refraction may be performed, if needed, to ensure proper corrective lenses during the course of the study. The refraction correction being worn for each eye will be assessed to determine if adjustment is needed to meet the following:

- Myopia (by SE) in both eyes must be corrected to ±0.50 D of the investigator's cycloplegic measurement of refractive error
- Cylinder power in both eyes must be within ±0.50 D of the investigator's standard refraction technique, which can be based on cycloplegic or non-cycloplegic refraction
- Cylinder axis for both eyes must be within ±5 degrees of the axis found on the investigator's refraction when cylinder power is ≥1.00 D or within ±15 degrees when the cylinder power is <1.00 D

Measurement of refractive error may be performed as an over-refraction or without refractive correction.

- **Best-Corrected Visual Acuity** (BCVA) will be measured in each eye prior to cycloplegia with the participant wearing current correction. Best-corrected visual acuity will be qualified by study-certified visual acuity testing using the Early Treatment of Diabetic Retinopathy Study (ETDRS) charts. If the vision is more than 1 line (≥5 letters) worse than baseline, the testing will be redone using trial frames or phoropter. Standard manual refraction may also be performed, if needed, to confirm loss of BCVA using the standard refraction technique.

- **Binocular Near-BCVA** will be measured using the ATS4 Near Acuity Test with participant wearing current refractive correction prior to administration of cycloplegia.

- **Pupil Diameter** will be measured prior to any cycloplegia using a hand-held pupil card provided to the sites.

- **Binocular Accommodative Amplitude** will be measured with the participant wearing current refractive correction prior to cycloplegia with a study-specified accommodation near-point rule.

- **Corneal Endothelial Cell Count** data will be obtained using specular microscopy at selected sites with the required equipment (approximately 25% of study participants).

- **Biomicroscopy (with fluorescein)** will be performed by slit-lamp examination of lids, conjunctiva, cornea, iris and lens with findings reported as normal, abnormal clinically significant, or abnormal not clinically significant. Corneal staining will be graded on the following scale: 0 = none, 0.5 = trace, 1 = mild, 2 = moderate, and 3 = severe.

- **Intraocular Pressure** will be measured with a tonometer per study site's standard operating procedures.

- **Ophthalmoscopy.** A dilated fundus examination will be performed to evaluate any posterior segment abnormalities.

- **Tolerability Questionnaire.** The investigator's designee will administer a questionnaire to participants (or parents/guardians) to assess potential side effects of study drug (blurred

vision, burning/stinging, eye pain, grittiness in eye, sensitivity to light, headache); severity (scored on a 0 to 3 scale [none, mild, moderate, severe]) and frequency will be recorded.

- **QOL Questionnaire.** The investigator's designee will administer a questionnaire to participants (or parents/guardians) to assess potential impact of treatment on the participant's quality of life. Responses will be marked as strongly agree, agree, neither agree or disagree, disagree, strongly disagree. See the MOP for further details.
- **Activities/Compliance Questionnaire:** Time spent on various activities (near-vision activities, daylight outdoor leisure, exercise, wearing a wide-brimmed hat or dark glasses while outdoors) and adherence to the dosing regimen will be collected via a questionnaire.

Unscheduled visits can be included if safety concerns arise. Additional examinations may be performed as necessary to ensure the safety and wellbeing of participants during the study. An eCRF must be completed for each unscheduled visit.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS (AE)

The investigator is responsible for reporting all AEs that are observed or reported during the study, regardless of their relationship to study drug.

An **AE** is defined as any untoward medical occurrence in a participant enrolled into this study regardless of its causal relationship to study drug. Participants will be instructed to contact the investigator at any time after randomization if any symptoms develop.

A treatment-emergent AE (**TEAE**) is defined as any event not present before exposure to study drug or any event already present that worsens in either intensity or frequency after exposure to study drug.

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

An SAE is defined as any event that, in the view of either the investigator or sponsor:

- Results in death
- Is immediately life-threatening
- Results in inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Is a congenital anomaly/birth defect

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

8.3.3.1 SEVERITY OF EVENT

For AEs not included in the protocol-defined grading system, the following guidelines will be used to describe severity.

- **Mild**: Event requires minimal or no treatment and does not interfere with the participant's daily activities.
- **Moderate**: Event results in a low level of inconvenience or concern with the therapeutic measure(s). Moderate events may cause some interference with functioning.
- **Severe**: Event interrupts a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious."

8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION

A determination will be made of the relationship (if any) between an AE and the study drug. A causal relationship is present if a determination is made that there is a reasonable possibility that the AE may have been caused by the drug.

- **Not Related:** A causal relationship can be excluded, and another documented cause of the AE is most plausible
- **Unlikely Related:** A causal relationship is improbable, and another documented cause of the AE is most plausible
- **Possibly Related:** A causal relationship is clinically/biologically plausible and there is a plausible time sequence between onset of the AE and administration of the study drug
- **Related:** A causal relationship is clinically/biologically highly plausible, there is a plausible time sequence between onset of the AE and administration of the study drug, and there is a reasonable response on withdrawal

8.3.3.3 EXPECTEDNESS

The investigator will be responsible for determining whether an AE is expected or unexpected based on the information provided in the IB. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

8.3.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

Any medical condition that is present at the time that the participant is screened will be considered as medical history and not reported as an AE. However, if the study participant's condition deteriorates at any time after the time of informed consent, it will be recorded as an AE.

Changes in the severity of an AE will be documented in the source and eCRF to allow an assessment of the duration of the event at each level of severity to be performed. Adverse events characterized as intermittent require documentation of onset and duration of each episode.

The collection of AEs and SAEs will commence from the time the ICF is signed and continue until the last day of study participation. Events will be followed for outcome information until resolution or stabilization during the study or continue until 7 days (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation.

Adverse events will be monitored throughout the study beginning at the time of informed consent. At each post-Screening visit, the investigator will begin by querying for AEs by asking each participant a general, non-directed question, such as "How have you been feeling since the last visit?" Directed questioning and examination will then be done as appropriate. If the participant presents a potential AE during a telephone visit, the participant will come to the clinic for an unscheduled visit to assess the potential AE. All reported AEs will be documented on the appropriate page of the eCRF, including seriousness, severity, relationship to study drug, action taken, and outcome (including date of resolution or stabilization, if AE is not ongoing). If AEs occur, the first concern will be the safety of the study participants.

8.3.5 ADVERSE EVENT REPORTING

All AEs reported or observed during the study will be recorded on the AE page in the eCRF. Information to be collected includes the following:

- Drug treatment
- Dose
- Event term
- Time of onset
- Investigator-specified assessment of severity and relationship to study drug
- Time of resolution of the event
- Seriousness
- Any required treatment or evaluations
- Outcome

Adverse events resulting from concurrent illnesses, reactions to concurrent illnesses, reactions to concurrent medications, or progression of disease states must also be reported. All AEs will be followed to adequate resolution. The Medical Dictionary for Regulatory Activities (MedDRA) will be used to code all AEs.

Any medical condition that is present at the time that the participant is screened but does not deteriorate should not be reported as an AE. However, if it deteriorates at any time during the study, it should be recorded as an AE.

The following are special considerations when determining and reporting AEs:

- Whenever possible, the investigator should group signs or symptoms that constitute a single diagnosis under a single AE term (eg, “cough, rhinitis, and sneezing” might be grouped together as “upper respiratory tract infection”)
- Any item from the Tolerability Questionnaire with a severity of moderate or severe is to be recorded as an AE
- Corneal staining with a severity of 2 or 3+ is to be recorded as an AE; if other signs or symptoms are present, a diagnosis, such as keratitis, should be recorded
- Progression of myopia, which is collected as a clinical efficacy variable and assessed as unequivocally associated with the disease progression and/or lack of efficacy, should not be reported as an AE unless progression is greater than anticipated in the natural course of the disease
- Any item from the Tolerability Questionnaire with a mild severity is not considered as an AE
- Corneal staining with a severity of 0.5 or 1+ is not considered as an AE
- Small changes in pupil diameter should not be reported as an AE, however, the pursuant symptoms such as photophobia may be an AE
- A pre-existing condition is not considered an AE unless the condition worsens (increases in frequency, severity, or specificity) during or following study drug administration. Fluctuations in a pre-existing condition should be assessed by the investigator, and those that fall within the limits of expected fluctuations for the disease state (and are not assessed as worsening of the disease) should not be considered AEs. Any change assessed as clinically significant worsening of the disease from baseline must be documented as an AE
- Elective surgery or routine diagnostic procedures are not considered AEs. However, an untoward medical event occurring during the prescheduled elective surgery or diagnostic procedure should be recorded as an AE
- Death itself is not considered an AE; it is instead the outcome of an AE

- A TEAE is an AE with an onset anytime from when the participant has received study drug through 30 days after the last dose of study drug, whether or not it is considered causally related to the study drug

8.3.6 SERIOUS ADVERSE EVENT REPORTING

Any AE that meets SAE criteria (Section 8.3.2) must be reported to the PPD Pharmacovigilance (PVG) Department immediately (ie, within 24 hours) after the time site staff first learn about the event. The study site will record all SAE information on the appropriate eCRF page and submit an SAE report via the electronic data capture (EDC) system.

If, for any reason, reporting an SAE in the EDC system is not possible (eg, the EDC system is unavailable), the study site will record the SAE on the paper SAE Reporting Form and fax it to PPD PVG (Table 8-1). Any SAE reported via fax must be entered into the EDC system as soon as possible. The safety hotline should only be used if the EDC system is unavailable and the paper SAE Reporting Form cannot be sent via fax (ie, the safety hotline will not be used routinely for SAE reporting).

Table 8-1: PPD Pharmacovigilance Contact Information

Region	Contact Information
Europe	Safety fax line: **+44 1223 374 102**
	Safety hotline: **+44 1223 374 240**
United States	Safety fax line: **+1 888 529 3580**
	Safety hotline: **+1 888 483 7729**

All SAEs will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the participant is stable. Other supporting documentation of the event may be requested by the study sponsor and should be provided as soon as possible.

The study sponsor will be responsible for notifying the FDA and other regulatory authorities of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible, but in no case later than 7 calendar days after the sponsor's initial receipt of the information. In addition, the sponsor must notify FDA and all participating investigators in an Investigational New Drug safety report of potential serious risks, from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the sponsor determines that the information qualifies for reporting.

8.3.7 REPORTING EVENTS TO PARTICIPANTS

Not applicable.

8.3.8 EVENTS OF SPECIAL INTEREST

Not applicable.

8.4 REPORTING OF PREGNANCY

If a female participant becomes pregnant during the study, the investigator will notify the sponsor's designee and the medical monitor immediately after the pregnancy is confirmed, and the participant will be permanently discontinued from study drug but remain in the study for monitoring of safety and outcome of pregnancy. The investigator will (1) notify the participant's physician that the participant was being treated with the study drug, and (2) follow the progress of the pregnancy to term on the participant providing written informed consent for release of these data. The investigator should document the outcome of the pregnancy and provide a copy of the documentation to the sponsor's designee.

8.5 PROCEDURES DURING COVID-19 PANDEMIC

If a participant visit cannot be performed as a direct result of COVID-19 (eg, the site is closed, social distancing rules), the investigator's designee will complete a phone/video call in lieu of a clinic visit to:

- Query the parent for any healthy changes since the last visit for potential AEs. The investigator will speak directly with the parent/participant for additional details regarding any AEs; if medically warranted, the participant will return to the clinic as soon as is feasible
- Inquire about changes in concomitant medications
- Complete the Tolerability Questionnaire and the Quality of Life Questionnaire
- IP will be dispensed from IRT and shipped to the participant via courier as per local regulation or parent/participant may collect from the site when a phone visit is complete

These will be considered as non-substantial protocol deviations. The Investigator will attempt to have participants return to the clinic for safety exams as operation permit at the study site for out-of-window visits.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

9.1.1 PRIMARY EFFICACY ESTIMANDS

The primary efficacy endpoint will differ for the EMA and US FDA submissions based on guidance received from the different regulatory authorities (endpoints are defined and justified in Section 3). The primary estimand for each regulatory agency is summarized in the table below.

Table 9-1: Summary of Estimands for EMA and FDA

Objective:	**To evaluate the efficacy of SYD-101 for slowing the progression of myopia in children**	
Estimand Label	EMA Primary	FDA 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	Difference in the proportion of participants with confirmed myopic progression >0.75 D at or before Month 36 allowing for use of prohibited treatment or escape medication and assuming no dosing interruptions/discontinuations due to logistical issues. For discontinuations due to tolerability reasons (ie, due to a related AE), participants will be considered to have progressed
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	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	Proportion of participants with confirmed myopic progression >0.75 D at or before Month 36
Treatment Condition	Test: SYD-101 0.01% Test: SYD-101 0.03% Reference: Vehicle All without use of escape therapy for myopia control	Test: SYD-101 0.01% Test: SYD-101 0.03% Reference: Vehicle Escape medication for myopia control allowed
Population-Level Summaries	Difference in mean annual progression rate of myopia through Month 24 between SYD-101 0.01% and Vehicle	Difference in proportion of participants with confirmed myopic progression >0.75 D at or before

	Difference in mean annual progression rate of myopia through Month 24 between SYD-101 0.03% and Vehicle	Month 36 between SYD-101 0.01% and Vehicle Difference in proportion of participants with confirmed myopic progression >0.75 D at or before Month 36 between SYD-101 0.03% and Vehicle

Intercurrent events will be handled in the same manner for both the FDA and EMA primary estimands as presented in the table below.

Table 9-2: Summary of Intercurrent Event Handling for Primary Estimands

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.

Due to technical issues or non-compliant participants (eg, wiggly child), not all SE assessments performed may be valid. For sensitivity analysis based on valid SE values, the final average SE (over both eyes) will be calculated only if there is a valid per eye average SE for each eye. A per eye average SE value will be considered valid if there are three non-missing assessments performed for that eye. However, if there are three non-missing SE assessments for a given eye, but one of the SE values differs from the other two SE values for that eye by at least 1 D, only the two SE values that

are within 1 D of each other will be considered valid and used to calculate the valid average SE for that eye. Otherwise, all three SE values will be used to calculate the per aye average SE. If there are only two non-missing assessments available for a given eye and the two SE values for that eye are within 0.25 D of each other (i.e., -0.25 D ≤ SE Measurement 1 – SE Measurement 2 ≤ 0.25 D) then the per eye average SE of those two assessments will be considered valid. Otherwise, the per eye SE value will be considered invalid for that eye at that visit.

Additional sensitivity analyses utilizing different approaches for missing data an intercurrent events will be performed. These analyses are summarized in the following table and full details will be provided in the statistical analysis plan.

Table 9-3: Summary of Additional Sensitivity Analyses

Analysis	Intercurrent Events					
	Intermittent Missing Data	Receipt of Prohibited Treatment	Receipt of Escape Therapy	Treatment Discontinuation	Study Discontinuation	Invalid SE Values
Sensitivity Analysis 1 PPS MAR Multiple Imputation	Hypothetical Multiple imputation assuming MAR	EMA Endpoint: While on Treatment MMRM using observed data until receipt of prohibited treatment (no multiple imputation) FDA Endpoint: Composite Observations after receipt of prohibited treatment will be considered non-responders (e.g., have progressed)	EMA Endpoint: While on Treatment MMRM using observed data until receipt of escape medication (no multiple imputation) FDA Endpoint: Composite Observations after receipt of escape medication will be considered non-responders (e.g., have progressed)	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 EMA Endpoint: Hypothetical Observations after discontinuation (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 discontinuation (DC) due to a related AE are non-responders Observations after DC for other reasons will be multiply imputed assuming MAR EMA Endpoint: Hypothetical Observations after discontinuation (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	Hypothetical Multiple imputation assuming MAR

Analysis	Intercurrent Events					
	Intermittent Missing Data	Receipt of Prohibited Treatment	Receipt of Escape Therapy	Treatment Discontinuation	Study Discontinuation	Invalid SE Values
Sensitivity Analysis 2 FAS Treatment Policy for Prohibited and Rescue Treatments	Hypothetical Multiple imputation assuming MAR	Treatment Policy Use observed data	Treatment Policy Use observed data	Treatment Policy Use observed data	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 EMA Endpoint: Hypothetical Observations after discontinuation (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	Treatment Policy Use observed data

Analysis	Intercurrent Events					
	Intermittent Missing Data	Receipt of Prohibited Treatment	Receipt of Escape Therapy	Treatment Discontinuation	Study Discontinuation	Invalid SE Values
Sensitivity Analysis 3 FAS MAR Tipping Point Add fixed values of c to SYD imputed values	Hypothetical Multiple imputation assuming MAR	Hypothetical Observations after receipt of prohibited medication will be multiply imputed assuming MAR	Hypothetical Observations after receipt of escape medication will be multiply imputed assuming MAR	Treatment Policy Use observed data	Hypothetical Multiple imputation assuming MAR	Treatment Policy Use observed data
Sensitivity Analysis 4 FAS MNAR – exclude prohibited and escape observations before MNAR	Hypothetical Multiple imputation assuming MAR	Hypothetical Observations after receipt of prohibited medication will be multiply imputed assuming MNAR using a sequential vehicle-based pattern regression	Hypothetical Observations after receipt of escape medication will be multiply imputed assuming MNAR using a sequential vehicle-based pattern regression	Treatment Policy Use observed data	Hypothetical Observations after receipt study discontinuation will be multiply imputed assuming MNAR using a sequential vehicle-based pattern regression	Treatment Policy Use observed data
Sensitivity Analysis 5 FAS MNAR – include vehicle post prohibited and escape observations	Hypothetical Multiple imputation assuming MAR	Treatment policy for vehicle Use observed data Hypothetical for SYD Observations after receipt of prohibited medication will be multiply imputed assuming MNAR using a sequential vehicle-based pattern regression	Treatment policy for vehicle Use observed data Hypothetical for SYD Observations after receipt of prohibited medication will be multiply imputed assuming MNAR using a sequential vehicle-based pattern regression	Treatment Policy Use observed data	Hypothetical Observations after study discontinuation will be multiply imputed assuming MNAR using a sequential vehicle-based pattern regression	Treatment Policy Use observed data

Analysis	Intercurrent Events					
	Intermittent Missing Data	Receipt of Prohibited Treatment	Receipt of Escape Therapy	Treatment Discontinuation	Study Discontinuation	Invalid SE Values
Sensitivity Analysis 6 FAS for FDA only – missing = progression	Hypothetical Multiple imputation assuming MAR	Hypothetical Observations after receipt of prohibited medication will be multiply imputed assuming MAR	Hypothetical Observations after receipt of prohibited medication will be multiply imputed assuming MAR	Treatment Policy Use observed data	Composite If participant has missing assessment at Month X and participant discontinued study prior to Month x, a progression will be imputed for Month X	Treatment Policy Use observed data
Sensitivity Analysis 7 FAS for EMA only – MMRM no imputation	Hypothetical MMRM assumes MAR	Hypothetical Observations after receipt of prohibited medication will be censored. MMRM assumes MAR	Hypothetical Observations after receipt of escape medications will be censored. MMRM assumes MAR	Treatment Policy Use observed data	Hypothetical MMRM assumes MAR	Treatment Policy Use observed data

EMA Submission:

The primary efficacy analysis for the EMA submission will test the following hypothesis:

- H_0: 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.

US FDA Submission:

The primary efficacy analysis for the FDA submission will test the following hypothesis:

- H_0: The proportion of participants with myopic progression > 0.75 D at or before Month 36 is equal between Vehicle and SYD-101.
- H_1: The proportion of participants with myopic progression > 0.75 D at or before Month 36 is different between Vehicle and SYD-101.

For submission to both the EMA and FDA, the primary efficacy analysis (EMA and FDA) will be tested at alpha=0.05 (2-sided) level of significance. Each dose of SYD-101, 0.01% and 0.03%, will be independently compared to Vehicle. A truncated Hochberg adjustment (γ=0.80) will be performed to establish significance for comparisons of each of the active doses to Vehicle whilst controlling the overall type I error. With truncation parameter γ=0.80, if both comparisons result in a *P*-value <0.045, then both comparisons will be statistically significant. If one comparison results in a *P*-value ≥0.045, then the second comparison will be statistically significant if the resulting *P*-value is <0.025.

Note there is no correction for multiplicity for the primary efficacy analysis for EMA and for FDA. This is in accordance with ICH Guidance E17-General Principles for Planning & Design of MRCT where it is stated “because regulatory approvals are based on different primary endpoints by different authorities, no multiplicity adjustment is needed for regulatory decision-making.”

9.1.2 SECONDARY EFFICACY ENDPOINTS

Refer to Section 3 for definition and justification of endpoints.

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 utilized 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 favor of SYD-101 for that dose, ie, 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.)

Again, no correction for multiplicity for the different efficacy analysis for EMA and for FDA is required.

Table 9-4 summarizes all efficacy endpoints in order of testing for the EMA and FDA analyses.

Table 9-4: Order of Testing Efficacy Endpoint for EMA and FDA Analyses

Endpoint	EMA	FDA
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	Proportion of participants with myopic progression >0.75 D at or before Month 36 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	Mean annual progression rate of myopia through month 36 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	Proportion of participants with annual myopia progression rate through Month 36 ≤0.50 D/year Truncated Hochberg to control alpha for the two pairwise SYD to Vehicle comparisons

Endpoint	EMA	FDA
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	Proportion of participants with annual myopia progression rate through Month 36 ≤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	Proportion of participants with increase of myopia of >0.50 D at or before Month 36 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	Time to progression of myopia of >0.75 D through Month 36 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	Mean change from baseline in axial length at Month 36 (at sites with the requisite equipment; at least 50% of participants) Truncated Hochberg to control alpha for the two pairwise SYD to Vehicle comparisons
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)	

Endpoint	EMA	FDA
	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.

Intercurrent events will be handled in the for the FDA and EMA key secondary estimands as presented in the table below.

Table 9-5: Summary of Intercurrent Event Handling for Key Secondary Estimands

Intercurrent Event	Strategy for Key Secondary 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 Composite • Participants who receive prohibited treatment will be considered non-responders FDA Hypothetical • Observations after receipt of prohibited treatment will be multiple imputed assuming MNAR using a sequential vehicle-based pattern regression. Observations after receipt of prohibited treatment will be removed for all treatment arms prior to imputation	Prohibited treatment includes therapies that have known efficacy for slowing myopia progression (eg, 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-101 to Vehicle

Intercurrent Event	Strategy for Key Secondary Estimands	Justification
Escape Medication	EMA Composite • Participants who receive escape medication will be considered non-responders FDA Hypothetical • Observations after receipt of escape medication will be multiple imputed assuming MNAR using a sequential vehicle-based pattern regression. Observations after receipt of escape medications will be removed for all treatment arms prior to imputation	The American Academy of Ophthalmology, among others, currently recommends low dose atropine for treatment of myopia progression. As escape medication use may be uneven between the groups, this could distort the medication effect of SYD-101 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	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	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

Intercurrent Event	Strategy for Key Secondary Estimands	Justification
Study Discontinuation	Hypothetical • Observations after DC due to a related AE will be multiply imputed assuming MNAR using a sequential vehicle-based pattern regression • 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 as participants, in clinical practice it would be expected to have non-ideal auto-refraction assessments

For all other secondary endpoints secondary endpoints excepting axial length, time to progression, and the Fast Progression subgroups, intercurrent events will be handled as specified in the table below.

Table 9-6: Intercurrent Event Approaches for Secondary Estimands

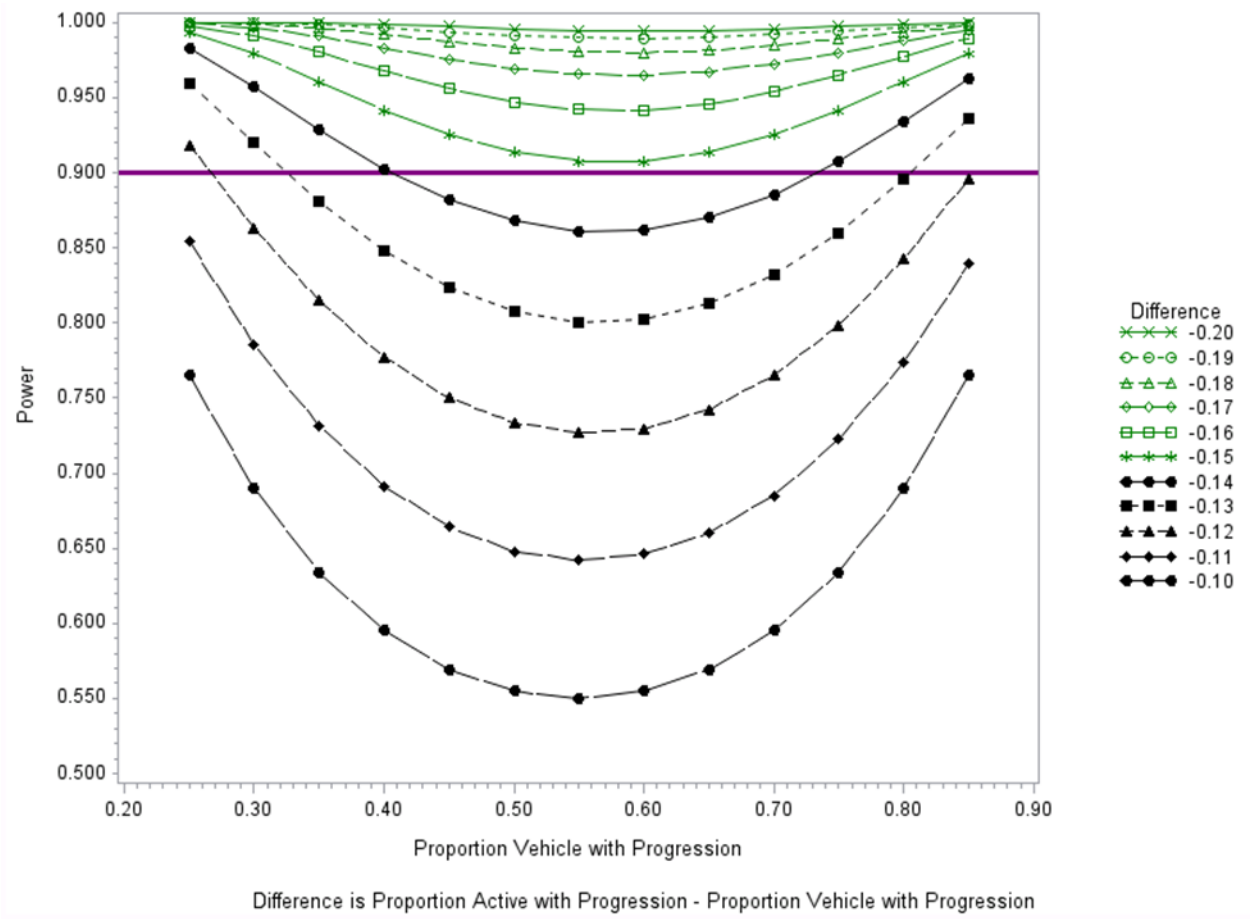
Intercurrent Event	Strategy for Secondary Estimands	Justification
Intermittent Missing Data	Hypothetical • Intermittent missing data will be multiply imputed assuming data is missing at random (MAR)	Intermittent missing data are expected to be missing at random/due to logistical issues
Prohibited Treatment	Hypothetical • Observations after receipt of prohibited treatment will be multiply imputed assuming MAR	Prohibited treatments include therapies that have known efficacy for slowing myopia progression (eg, 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-101 to Vehicle
Escape Medication	Hypothetical • Observations after receipt of escape medication will be multiply imputed assuming MAR	The American Academy of Ophthalmology, among others, currently recommends low dose atropine for treatment of myopia progression. As escape medication use may be uneven between the groups, this could distort

		the treatment effect of SYD-101 to Vehicle
Treatment Discontinuation	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 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	Hypothetical • Observations after DC due to a related AE will be multiply imputed assuming MNAR using a sequential vehicle-based pattern regression • 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 as participants, in clinical practice it would be expected to have non-ideal auto-refraction assessments

9.2 SAMPLE SIZE DETERMINATION

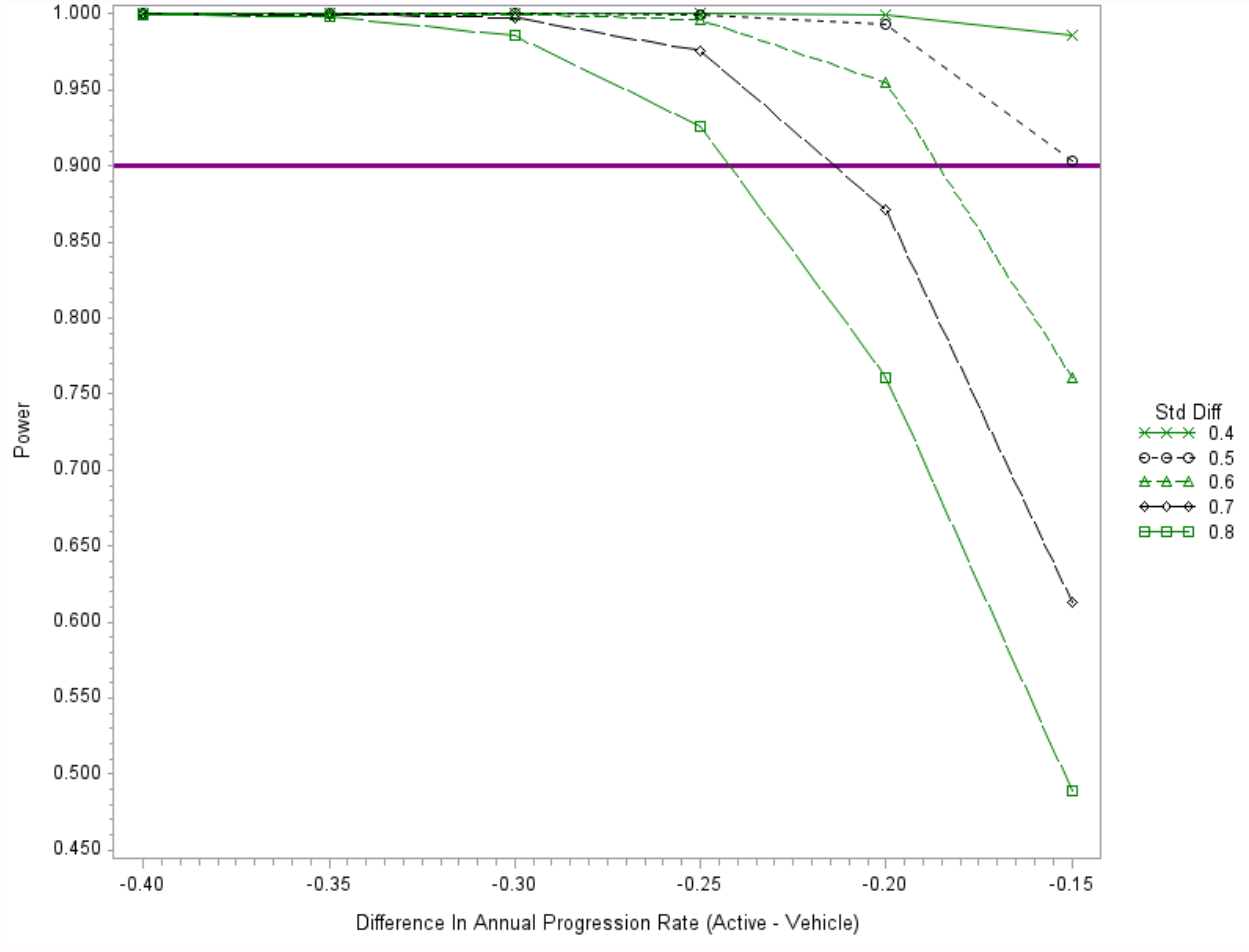
Group sample sizes of 280 in each treatment arm will achieve at least 90% power to detect a difference in the percentage of participants with myopic progression (>0.75 D) of at least 15% between a SYD-101 arm and Vehicle. Power calculations presented in Figure 9-1 are based on the Chi-squared test at a 2-sided significance level of 0.025.

Figure 9-1: 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 9-2 are based on a 2-sample t-test evaluated at the 0.025 significance level.

Figure 9-2: 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, enrollment of additional participants beyond 280 participants per treatment arm has not been planned.

9.3 POPULATIONS FOR ANALYSES

The Full Analysis Set (FAS) will include all randomized participants who receive at least 1 drop of study drug. The FAS will be the primary population used for the efficacy analyses. Treatment assignment will be based on the randomized treatment.

The Safety Analysis Set will include all participants who receive any amount of study drug (SYD-101 0.01%, SYD-101 0.03%, or Vehicle). The Safety Analysis Set will be the primary population used for safety analyses. Treatment assignment will be based on the treatment actually received.

The Per-Protocol Analysis Set will include all participants in the FAS who do not have any important protocol deviations and have at least 1 post-baseline measurement for SE. Important protocol deviations are to be defined and assigned prior to database lock and breaking the study mask. Efficacy endpoints analyzed for the Per-Protocol Analysis Set are to be treated as a sensitivity analysis. Treatment assignment will be based on the treatment actually received.

Additionally, for the EMA Submission special subsets are defined to identify participants with a history of fast progression based historical refraction data.

Subgroup 1: FAS Participants with progression ≥ 0.50 D/year based on historical refraction

Subgroup 2: FAS Participants with progression ≥ 0.75 D/year based on historical refraction

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

Statistical analyses will be reported with tables, figures, and listings. Tables and figures will be summarized by treatment group. Tables summarizing demographics and other baseline characteristics will also include a column for all participants combined.

In general, continuous variables will be summarized to indicate the population sample size (N), number of participants with available data (n), mean, SD, median, minimum, and maximum values. Categorical variables will be summarized by the N, n, number of participants in each category, and the percentage of participants in each category. Unless otherwise noted, the denominator to determine the percentage of participants in each category will be based on the number of participants with available data. Select ordinal data may be summarized using both descriptive statistics and counts and percentages of participants in each category, as appropriate.

Statistical significance testing will be 2-sided and performed using alpha=0.05.

9.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT

SE values will be calculated as per Section 3. Per protocol, the autorefraction procedure is to be performed 3 times in each eye. SE values will be calculated for each autorefraction for each eye as the sum of the sphere power with half of the cylinder power (SE = sphere + ½ cylinder). If there are less than three measurements for a given eye, the available SE values will be averaged for that eye prior to averaging the right and left per eye SE averages for the average SE value for analysis. The final average SE (over both eyes) will be missing if the per eye SE average SE is missing for either eye.

A combination of hypothetical, composite, and treatment policy strategies for intercurrent events will be used for the primary estimands. For FDA and EMA, intermittent missing data or observations post study or treatment discontinuation not due to a related AE will be multiply imputed using via Markov Chain Monte Carlo (MCMC) methods assuming the missing data is MAR (Missing at Random).

For the EMA, observations after specified prohibited or escape treatment will be observed until day of prohibited or escape treatment; observations following prohibited or escape treatment will be censored and not imputed. For the FDA primary estimand, observations post prohibited or escape treatment will be considered non-responders.

For the EMA primary estimand, observations post study or treatment discontinuation due to a related AE will be multiply imputed assuming missing data is MNAR (Missing Not at Random). For the FDA primary estimand, observations post study or treatment discontinuation due to a related AE will be considered non-responders.

For the EMA and FDA, observations with invalid SE values will be analyzed as observed.

For any imputations, the value to be imputed is the average SE value (average of both eyes). This same set of imputed SE values will be used to calculate the primary efficacy endpoints for EMA and FDA, as well as the key secondary and applicable secondary efficacy endpoints derived from SE. All imputations will be based on set SEEDS. It is planned to perform k=50 imputations, however the number of imputations may be increased depending on the amount of missing data.

MAR imputations will be performed separately for each treatment arm and the imputation model will include terms for age at baseline, baseline SE (average of both eyes), and SE values (average of both eyes) for each post baseline scheduled visit through the specified analysis timepoint, Month 24 or Month 36 as applicable.

Imputations for data assumed to be MNAR will be first imputed via MCMC multichain methods to obtain monotone data as above for MAR imputations. The remaining missing SE values will be imputed via a sequential vehicle-based pattern imputation using regression methods (Ratitch, 2011) for the scheduled SE visits through the analysis timepoint, Month 24 or Month 36, using a model including age at baseline and baseline SE (average of both eyes) followed by sequential visits through M24 or M36, imputed values for those on SYD-101 treatment will be based on the Vehicle group.

EMA Submission:

The annual progression rate of myopia for a given timepoint will be calculated as the negative change in SE (average of both eyes) from baseline, divided by the number of days to the timepoint (visit date − date of first dose of study drug + 1), and multiplied by 365.25 days/year. The average of SE for the right and left eyes will be used for analysis.

SYD-101 0.01% and SYD-101 0.03% will be compared to Vehicle for the annual progression rate of myopia after 24 months of treatment using a REML-based MMRM model including fixed effects for treatment group, baseline age category, categorical visit, and the treatment group by visit interaction, with baseline SE value (average of both eyes) as a covariate. An appropriate covariance structure will be selected, and the Kenward-Roger Method will be used to calculate the denominator degrees of freedom for the test of fixed effects. All visits through Month 24 will be included in the model, with the primary comparison at the Month 24 visit.

The MMRM model will be repeated for each imputation and the results combined via SAS PROC MIANALYZE for final treatment estimates. The mean annual progression rate of myopia for each treatment and the estimated mean difference between each SYD-101 treatment group and Vehicle will be presented along with their corresponding 95% CIs.

The analysis of the primary endpoint will be based on the FAS. As a sensitivity analysis, an analysis will be repeated for the Per-Protocol Analysis Set and using other imputation approaches for the FAS.

US FDA Submission:

Progression is defined as an increased negative change where change is calculated as visit SE value − baseline SE value. As described in Section 3, a single averaged SE value (average of both eyes) will be used for analysis. Progression must be confirmed at the next assessment.

The proportion of participants with confirmed myopia progression (>0.75 D) at Month 36 (see Section 3) in the 3 treatment groups will be compared between each dose of SYD-101 and Vehicle using pairwise CMH tests to account for randomization factors (ie, baseline SE and age categories). The CMH tests will be repeated for each imputation and the results combined via SAS PROC MIANALYZE for final treatment estimates.

Rubin's pooling methodology utilized in SAS PROC MIANALYZE is based on assumption that the estimates are asymptotically normally distributed. The CMH test follows a Chi-Square distribution which is highly skewed for smaller degrees of freedom and can violate Rubin's assumptions. Prior to combination of data in the MIANALYZE procedure, the individual CMH test statistics will be transformed to an approximate Normal (0,1) variables using the Wilson-Hilferty transformation (Wilson & Hilferty, 1931; Goria, 1992).

The number and percentage of participants in each treatment group who meet the definition of myopic progression will be presented, as will estimates of the differences between each SYD-101 treatment group and Vehicle with 95% confidence intervals (CI) for the treatment differences.

The analysis of the primary endpoint will be based on the FAS. As a sensitivity analysis, analysis of the primary endpoint will be repeated for the Per-Protocol Analysis Set and using other imputation approaches for the FAS.

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINTS

All secondary endpoints will be primarily analyzed for the FAS and repeated for the Per-Protocol Analysis Set as sensitivity analyses. Additional sensitivity analyses using other imputation/tipping point approaches for the FAS will be performed for the key secondary endpoints only. For the EMA submission, the key secondary endpoint will be the proportion of participants with myopic progression >0.75 D at or before Month 24. The analysis will use the same methodology as stated in Section 9.4.2 as for the FDA primary efficacy endpoint.

For the US FDA submission, the key secondary endpoint will be the mean annual progression rate of myopia using data through Month 36. The analysis will use the same methodology as specified for this endpoint in Section 9.4.2 as for the EMA primary efficacy endpoint.

Proportionate progression rate endpoints using different cutoffs to define myopic progression at Month 36 (eg, ≤0.25 D/year, ≤0.50 D/year, and an increase of myopia of 0.50 D) will be analyzed similar to the primary FDA endpoint using pairwise CMH tests.

Time to progression of myopia will be calculated in days as the date of first confirmed SE measurement that represents a progression of >0.75 D or greater minus the date of first dose of study drug, plus one. Participants who do not experience myopic progression through 24 months (EMA) or 36 months (FDA) or who have an early discontinuation without a progression will be censored at the date of their last SE assessment at or before Month 24 (EMA) or Month 36 (FDA). Participants who receive a prohibited treatment or escape therapy prior to myopic progression will be censored as of the date they received the prohibited or escape therapy. 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. Kaplan-Meier estimates of the distribution of time-to-event will be tabulated and plotted by treatment group. The tabulation will include the Kaplan-Meier estimate of the medians, 25th and 75th quartiles, and 95% CIs (if estimable). The number and percent of participants censored and with events will be presented.

For the EMA submission, the fast progressors subset analyses of the mean annual progression rate of myopia using data through Month 24. The analysis will use the same methodology as specified for this endpoint in Section 9.4.2 as for the EMA primary efficacy endpoint, however data after receipt of prohibited treatment or escape medication will be censored and multiple imputation will not be performed for this endpoint.

The mean change from baseline in axial length will be analyzed similarly to the annual progression rate of myopia as detailed in Section 9.4.2 for the primary EMA analysis, however multiple imputation will not be performed and analysis of axial length will be performed on observed data only.

The testing procedure for multiple secondary endpoints is described in Section 9.1.

9.4.4 SAFETY ANALYSES

Safety will be assessed through summaries of AEs and changes in vital signs, BCVA, biomicroscopy, IOP, and ophthalmoscopy abnormalities. Safety data will be summarized by treatment group using the Safety Analysis Set.

Treatment-emergent AEs are defined as those AEs or SAEs that occur after the start of study drug dosing. All TEAEs will be summarized by treatment group (SYD-101 0.01%, SYD-101 0.03%, or Vehicle). In addition, all SAEs, including deaths, will be listed and summarized separately. Adverse events with onset date that is more than 30 days after study treatment discontinuation will be summarized separately.

Summaries that are displayed by system organ class (SOC) and preferred terms will be ordered by descending incidence of SOC and preferred term within each SOC. Summaries displayed by preferred term only will be ordered by descending incidence of preferred term. Summaries of the following types will be presented:

- Overall summary of number of unique TEAEs and treatment-emergent SAEs and participant incidence of TEAEs meeting various criteria
- Participant incidence of TEAEs by MedDRA SOC and preferred term
- Participant incidence of TEAEs by severity grade, MedDRA SOC, and preferred term
- Participant incidence of TEAEs by relationship to study drug, MedDRA SOC, and preferred term
- Participant incidence of severe TEAEs related to study drug by MedDRA SOC and preferred term
- Participant incidence of SAEs by MedDRA SOC and preferred term

At each level of summarization (eg, any AE, SOC, and preferred term), participants experiencing more than one TEAE will be counted only once. In the summary of TEAEs by severity grade, participants will be counted once at the highest severity reported at each level of summarization; in the summary of TEAEs by relationship, participants will be counted once at the closest relationship to study drug. Related events include those reported as “Possibly Related” or “Related” to study drug; events considered not related are those reported as “Unlikely” or “Not Related” to study drug.

Adverse event data will be presented in data listings by participant, treatment group, and event. Serious AEs and AEs leading to discontinuation of the study drug will be presented in separate data listings.

Descriptive statistics of the quantitative vital sign, BCVA, and IOP results will be presented by treatment group and study visit, as well as for the change from baseline at each visit. The baseline value is defined as the last non-missing value prior to the first dose of study drug. Categorical variables for biomicroscopy collection, ophthalmoscopy abnormalities, and responses to the tolerability questionnaire will be summarized by treatment group with counts and percentages of

participants in each category. Percentages will be based on the number of participants with relevant non-missing data at the visit of interest.

9.4.5 BASELINE DESCRIPTIVE STATISTICS

Demographic variables, including age, sex, ethnicity, and race, will be summarized by treatment group and over all participants combined for the Safety, FAS, and Per-Protocol Analysis Sets. Age will be summarized using descriptive statistics. Sex, ethnicity, and race will be summarized with the number and percentage of participants in each parameter category.

Baseline characteristics include medical history, eye color, height, weight, and body mass index (BMI). Body mass index will be calculated as: weight (kg) / [height (cm) / 100]^2. Baseline characteristics will be summarized for the Safety Analysis Set by treatment group and over all participants combined. Height, weight, and BMI at baseline will be summarized using descriptive statistics. Frequency counts and percentages to summarize participants reporting abnormal medical history by body system will be presented.

9.4.6 PLANNED INTERIM ANALYSES

There are no interim analyses planned for this study.

9.4.7 SUBGROUP ANALYSES

Subgroups will be defined based on the following:

- Baseline Age category (same as randomization stratification)
- Baseline Age category (ages 6 to 14 only)
- Baseline SE (same as randomization stratification)
- Baseline SE (≥ 1.0 D only)
- Ocular medical history (progression of SE vs. no progression of SE)
- Iris Color (dark vs light)
- Region (Europe vs United States)
- Race (Caucasian vs Indian vs Asian (Non-Indian) vs Non-Asian)
- Sex (Male vs Female)
- Average Time Outdoors (<= Median Average Time Outdoors, >Median Average Time Outdoors)
- Average Time Near Work (<= Median Average Time Near Work, >Median Average Time New Work)

The primary and key secondary efficacy endpoints will be analyzed separately for these subgroups using the FAS. The above subgroup analyses will be descriptive only. Additional subgroup analyses may be considered and will be documented in the statistical analysis plan.

9.4.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA

In general, all data collected and any derived data will be presented in participant data listings for all enrolled participants. Listings will be ordered by site, participant number, treatment group, and assessment or event date. The treatment group presented in listings will be based on the planned assignment, unless otherwise noted.

9.4.9 EXPLORATORY ANALYSES

Data collected after Month 36 will be considered exploratory analysis and summarized separately using descriptive statistics. Participants will be grouped by treatment pathway from the start of study through the re-randomization (original SYD-101 0.01% and SYD-101 0.03% participants) and transition to active treatment (original Vehicle participants) at Month 36:

- Participants initially randomized to SYD-101 0.01% at Baseline and re-randomized to SYD-101 0.01% at Month 36
- Participants initially randomized to SYD-101 0.01% at Baseline and re-randomized to Vehicle at Month 36
- Participants initially randomized to SYD-101 0.03% at Baseline and re-randomized to SYD-101 0.03% at Month 36

- Participants initially randomized to SYD-101 0.03% at Baseline and re-randomized to Vehicle at Month 36
- Participants initially randomized to Vehicle at Baseline and re-randomized to SYD-101 0.03% at Month 36

In general, data collected after Month 36 will be summarized according to the above groupings. As applicable, the groupings above may be further refined based on receipt of escape medication between Month 24 and Month 42 (inclusive). Changes in continuous measures will be relative to the data collection at the Month 36 visit, unless otherwise specified. Adverse events will be summarized separately for those events with onset after Month 36.

To evaluate the potential rebound effect once participants discontinue SYD-101 therapy, exploratory analyses will be conducted on the set of participants initially randomized to SYD-101 (0.01% or 0.03%) at Baseline who are re-randomized to Vehicle at Month 36. The mean annual progression rate from baseline to Month 36 will be numerically compared to the mean annual progression rate from Month 36 to Month 48 within this set of participants.

Select summaries will be provided for the group of participants initially randomized to SYD-101 (0.01% or 0.03%) at Day 1 (Baseline) and re-randomized to SYD-101 at Month 36 and who remain on SYD-101 for the entire duration of the study. This will be done to characterize the safety and efficacy profile of those participants receiving up to 48 months of SYD-101 treatment.

To evaluate the impact of a second course of SYD-101 therapy, participants initially randomized to SYD-101 (0.01% or 0.03%), who are re-randomized to Vehicle at Month 36 and who then initiate active escape therapy after receipt of Vehicle therapy will have their mean annual progression rate while on Vehicle therapy numerically compared to their mean annual progression rate from the date participants switch from Vehicle to SYD-101 therapy until Month 48.

Additional exploratory analyses may be performed.

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11 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

11.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

11.1.1 ETHICAL CONDUCT OF THE STUDY

This protocol was designed and will be conducted, recorded, and reported in compliance with the principles of Good Clinical Practice (GCP) as defined in the ICH E6(R2) Guideline for GCP. The principal investigator (PI) and the site staff are responsible for conducting this study in accordance with US Code of Federal Regulations (CFR), GCP, ethical principles that have their origin in the Declaration of Helsinki, and all other applicable laws and regulations.

11.1.1.1 PARTICIPANT INFORMATION, INFORMED CONSENT, AND CHILD ASSENT

An initial informed consent (for parent/guardian) and assent form (for participants, as applicable) will be provided to the investigator to prepare the ICF and assent documents to be used at the investigator's site. Updates to the informed consent template must be communicated to the sponsor or designee prior to IRB/EC approval. Written informed consent and assent, in accordance with local clinical investigation regulations and approved by the IRB/EC, must be obtained prior to participation in the study. The investigator will not undertake any measures specifically required for the clinical study unless and until valid consent and assent have been obtained.

Information must be given both in oral and written form. Written informed consent and assent documents that provide information about the study will be prepared and given to the parent/guardian and each applicable participant, respectively. Informed consent documents will contain all the elements required by the ICH E6(R2) Guideline for GCP and any additional elements required by local regulations. The information provided in the informed consent will be in a language understandable to the parent/guardian and may not include any language that appears to waive any of the parent/guardian's or participant's legal rights or appears to release the investigator, the sponsor, or the institution from liability or negligence.

The investigator will provide the parent/guardian and prospective participant sufficient time to consider whether to participate. The investigator will explain to the parent/guardian and participant that withdrawal from the study is possible at any time without detriment to care. The ICF and assent must include acknowledgement that medical records and medical data derived from the study may be forwarded to the sponsor or to the responsible authorities or federal authorities. At the first visit, and prior to initiation of any study-related procedures, the parent/guardian (or the participant's legally authorized representative) and the participant will be asked to give written informed consent and assent, respectively, after having been informed about the nature and purpose of the study, participation/discontinuation conditions, and risks and benefits. If the parent/guardian is unable to provide written informed consent, the participant's legally authorized representative may provide written consent as allowed by institution-specific guidelines. The informed consent and assent documents must be signed and dated by the parent/guardian (or the participant's legally authorized representative) and the participant, respectively, prior to study

participation. Copies of the signed informed consent and assent documents must be provided to the parent/guardian (or the participant's legally authorized representative) and the participant.

If the parent/guardian and/or the participant is unable to read, oral presentation and explanation of the ICF and/or assent must be provided to the parent/guardian and/or participant in the presence of an impartial witness or legally authorized representative. After the parent/guardian and participant provide oral and if capable written/dated informed consent and assent, respectively, the witness should sign and date the ICF and/or assent in accordance with the instructions of the relevant IRB/EC. By signing the ICF (assent), the witness attests that the written information was accurately explained to, and apparently understood by, the parent/guardian (participant), and that informed consent (assent) was freely given by the parent/guardian (participant).

Original signed/dated consent and assent forms must remain in the participant's study file and be available for verification by the sponsor or their designees at any time.

Informed consent is an ongoing process. Participant capacity to assent will be evaluated annually, and confirmation of continued affirmative assent will be sought and documented as appropriate.

11.1.1.2 CHILD ASSENT CONSIDERATIONS

The IRB/EC approval letter must clearly document the IRB/EC's assessment of risk in accordance with 21 CFR 50.51–50.54, Subpart D. The ICF should reflect the correct number of signature lines for the parent(s)/guardian(s) in accordance with the IRB/EC's risk assessment of the proposed research (see 21 CFR 50.55).

The IRBs/ECs are required to determine if child assents are appropriate for all studies that include pediatric participants. The IRB/ECs may opt to waive assent if the participants are not capable of understanding (ie, based on level of intellectual development or maturity) or if the study is in the best interest of the participant (ie, strong possibility of benefit and no other alternatives are available). If an IRB/EC chooses to waive assent, this must be documented in the IRB/EC approval letter or be documented in the meeting minutes.

The contents of an assent are not mandated by the US FDA; however, assents must be factually correct, written at an age appropriate level, and not include any coercive language. The assent must have a date and signature line for the child. State laws differ in their requirements for participants who have not reached the legal age of majority and IRB/ECs are responsible for following their local regulations. Use of an assent is not a substitute for parental/guardian permission. Parents/guardians must receive a full informed consent to review and sign.

11.1.1.3 IRB/EC APPROVAL

This protocol, ICF, and assent documents, and all relevant supporting data, including any advertisement used to recruit study participants, must be submitted to the IRB/EC for approval, which must be obtained before the study may be initiated. At least once a year, the investigator is

responsible for informing the IRB/EC of the progress of the study and of any changes made to the protocol. The investigator is also responsible for notifying the IRB/EC of any significant AEs that occur during the study and of the completion of the study.

11.1.1.4 PARTICIPANT CONFIDENTIALITY

The investigator must ensure that each participant's anonymity will be maintained and that their identities are protected from unauthorized parties. In eCRFs or other documents that are submitted to the sponsor, each participant should be identified by an identification code and not by their names. Study findings stored on a computer will be stored in accordance with local data protection laws. Each participant will be informed that representatives of the sponsor, independent IRB/EC, or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

The investigator should keep a participant enrollment log showing codes, names, and addresses. All data obtained during the course of this study will be transferred, stored, managed, and analyzed in compliance with applicable privacy policy.

If the investigative site is located in the United States, the sponsor or designee will ensure that the use and disclosure of protected health information obtained during a research study complies with the Health Insurance Portability and Accountability Act Privacy Rule, if applicable. The Privacy Rule provides federal protection for the privacy of protected health information by implementing standards to protect and guard against the misuse of individually identifiable health information of participants participating in the clinical studies. Authorization is required from each research participant, ie, specific permission granted by an individual to a covered entity for the use or disclosure of an individual's protected health information. A valid authorization must meet the implementation specifications under the Health Insurance Portability and Accountability Act Privacy Rule. Authorization may be combined in the informed consent document (approved by the IRB/EC) or it may be a separate document (approved by the IRB/EC) or provided by the investigator or sponsor (without IRB/EC). It is the responsibility of the investigator and institution to obtain such waiver/authorization in writing from the appropriate individual.

11.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to investigators, the Investigational New Drug, and regulatory authorities. If the study is prematurely terminated or suspended, the PI will promptly inform study participants, the IRB, and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to the study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to the following:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

The study may resume once concerns about safety, protocol compliance, and data quality are addressed and satisfy the sponsor, IRB, and/or FDA.

11.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their interventions. This confidentiality is extended to cover testing of clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the IRB, regulatory agencies, or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's/parent's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, institutional policies, or sponsor requirements.

Study participant research data, which are for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the sponsor's designee. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by the sponsor's designee research staff will be secured and password protected. At the end of the study, all study databases will be deidentified and archived.

11.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

Not applicable.

11.1.5 SAFETY OVERSIGHT

No internal data review committee will be used during this study.

11.1.6 STUDY MONITORING AND AUDITING

Details of clinical site monitoring are documented in a clinical monitoring plan. The clinical monitoring plan describes in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of monitoring reports.

All aspects of the study will be carefully monitored by the sponsor or authorized representatives of the sponsor at regular intervals and with respect to current GCP and standard operating procedures for compliance with applicable government regulations. These individuals will have access, both during the study and after study completion, to review and audit all records necessary to ensure integrity of the data and verify the entries in the eCRF. They will periodically review progress of the study with the PI.

Training sessions, regular monitoring of PI and designee by designated personnel, data verification, cross-checking, and data audits will be performed, and instruction manuals provided to ensure quality of all study data.

The sponsor's monitor or designee is responsible for inspecting the eCRF as defined in the monitoring plan throughout the study to verify adherence to the protocol; completeness, accuracy, and consistency of data; and, adherence to local regulations on the conduct of clinical research. It will be the responsibility of the PI to ensure that participants' medical records and other study-related records needed to verify entries in the eCRF are available at the PI's site during monitoring visits. In addition to the monitoring visits, communications (email, letter, telephone, and fax), by the study monitor will also be utilized to monitor that the investigation is conducted according to protocol design and regulatory requirements.

The PI agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

In accordance with ICH guidelines and GCP, this study may be selected for audit by the sponsor or designees. Inspection of the site facilities (ie, participant areas, drug storage areas, record storage areas) and review of study-related records will occur to evaluate the study conduct and compliance with the protocol, ICH, GCP, and applicable regulatory requirements.

Study close-out visits will be performed by the study monitor upon closure of the study.

11.1.7 QUALITY ASSURANCE AND QUALITY CONTROL

Each clinical site will perform internal quality management of study conduct, data and biological specimen collection, documentation, and completion. An individualized quality management plan will be developed to describe a site's quality management.

Quality control procedures will be implemented beginning with the data entry system, and data quality control checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written standard operating procedures, the monitors will verify that the clinical trial is conducted and data are generated and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, ICH GCP, and applicable regulatory requirements (eg, Good Laboratory Practices, Good Manufacturing Practices).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

11.1.8 DATA HANDLING AND RECORD KEEPING

11.1.8.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

This study is to be conducted in compliance with the regulations on electronic records and electronic signature.

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring that data are properly recorded on each participant's eCRFs and related documents in a timely manner. An investigator who has signed the protocol signature page should electronically sign the eCRFs to ensure that the observations and findings are recorded on the eCRFs correctly and completely. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

- Clinical data will be entered into eCRFs. Data entered into the eCRF will correspond with and be supported by source documentation maintained at the site(s). A final report of all participant data will be provided to each site at the end of the study to serve as eCRF documentation
- IVRS/IWRS will be used for randomizing the participant population

Source documents may include a participant's medical records, diaries, hospital charts, clinic charts, the investigator's participant study files, as well as the results of diagnostic tests, such as x-rays, laboratory tests, and ECGs. The investigator's copy of the eCRFs serves as part of the investigator's record of a participant's study-related data.

The following information should be entered into the participant's medical record:

- Participant's name
- Participant's contact information
- Date that the participant entered the study, participant number, and participant medication kit number
- Study title and/or the protocol number of the study and the name of Sydnexis
- Statement that informed consent was obtained (including the date) prior to any study procedures being performed and that the participant was provided a copy of the signed informed consent. A statement that country and local participant privacy-required documentation for this study has been obtained (including the date)
- Dates of all participant visits
- All concurrent medications (List all prescription and non-prescription medications being taken at the time of enrollment. At each subsequent visit, changes to the list of medications should be recorded)
- Occurrence and status of any AEs (including any procedure-related AEs)
- Date the participant exited the study, and a notation as to whether the participant completed the study or reason for discontinuation
- Results of laboratory tests performed by the site (eg, urine pregnancy test)
- Results, if applicable, of any procedures performed to confirm eligibility criteria
- Concurrent procedures performed during the study
- Documentation of the participant's medical history
- Vital signs and physical characteristics (height and weight)
- Printout from autorefractor
- Results of biomicroscopy/ophthalmoscopy examinations
- Documentation of whether any procedure, including study drug administration, was performed according to the protocol, noting any deviations (if applicable)
- Study drug accountability (stored separately with the accountability logs in order to maintain masking status for site staff with direct contact with participant and/or data)

11.1.8.2 STUDY RECORDS RETENTION

Study documents should be retained for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the study intervention. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

11.1.9 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol, ICH GCP, or MOP requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

The following practices are consistent with ICH GCP:

- Quality Assurance and Quality Control, Section 11.1.7

It is the responsibility of the site investigator to use continuous vigilance to identify and promptly report deviations. All deviations must be addressed in study source documents, reported to the sponsor's designee. Protocol deviations must be sent to the reviewing IRB per their policies. The site investigator is responsible for knowing and adhering to the reviewing IRB requirements. Further details about the handling of protocol deviations will be included in the MOP.

11.1.10 PUBLICATION AND DATA SHARING POLICY

Sydnexis, as the sponsor, has proprietary interest in this study. Authorship and manuscript composition will reflect joint cooperation between multiple investigators and sites and Sydnexis personnel. Authorship will be established prior to the writing of the manuscript. As this study involves multiple centers, no individual publications will be allowed prior to completion of the final report of the multicenter study except as agreed with Sydnexis.

This study will be registered on the ClinicalTrials.gov registry.

11.1.11 CONFLICT OF INTEREST POLICY

Due to potential conflict of interest, participants or members of the participant's household who are employees of the investigative site are not eligible for enrollment in the study.

11.2 ADDITIONAL CONSIDERATIONS

Not applicable.

11.3 ABBREVIATIONS

Abbreviation	Definition
µL	microliter
AE	adverse event
ATOM	Atropine for the Treatment of Myopia
BCVA	best-corrected visual acuity
BMI	body mass index
CFR	Code of Federal Regulations
D	diopters
D_2O	deuterium oxide
EC	ethics committee
eCRF	electronic case report form
EDC	electronic data capture
eg	*exempli gratia* (for example)
EMA	European Medicines Agency
EOS	End of Study
ET	Early Termination
ETDRS	Early Treatment of Diabetic Retinopathy Study
EU	European Union
FAS	full analysis set
FDA	Food and Drug Administration
ffERG	full-field electroretinogram
GCP	Good Clinical Practice
IB	investigator's brochure
ICF	informed consent form
ICH	International Council for Harmonisation
ie	*id est* (in other words)
IOP	intraocular pressure
IRB	institutional review board
IVRS	interactive voice response system
IWRS	interactive web response system
MAR	missing at random
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed model repeated measures
MNAR	missing not at random
MOP	Manual of Procedures
N	number of participants *or* Sample size
n	number of participants with available data
NCT	National Clinical Trial
PI	principal investigator
PVG	pharmacovigilance
QA	quality assurance
QC	quality control

Abbreviation	Definition
QD	*quaque die* (once a day)
QHS	*quaque hora somni* (every bedtime)
QOL	Quality of Life
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SE	spherical equivalent
SOA	Schedule of Activities
SOC	system organ class
SYD-101	Sydnexis' formulation of atropine sulfate (0.01% or 0.03%) topical ophthalmic solution
TEAE	treatment-emergent adverse event
TID	*ter in die* (3 times a day)
WSPOS	World Society of Paediatric Ophthalmology and Strabismus

11.4 PROTOCOL AMENDMENT HISTORY

Version	Date	Section affected	Description of Change	Brief Rationale
1.2	20 Feb 2019		**Original Document**	
2.0	13 Nov 2020	Description of Sites (Synopsis)	Up to 41 US sites and 6 EU sites	Update of actual sites
		Study Duration (Synopsis)	Anticipated duration of the study is 70 months	Delayed recruitment due to COVID-19
		Specular microscopy	Will be completed at early exit visit	Correction
		Escape Medication	Replaced 'will be initiated" with "may be initiated"	For flexibility
		Study Procedures	Standard manual refraction should be performed at screening visit for initial BCVA and if SE is >0.75 D. Lens will be assessed with findings as normal, abnormal clinically significant or abnormal not clinically significant	To verify components of inclusion #9 Correction. AREDs scale was not implemented
		Entry Criteria	Criterion #10 BCVA of 75 letters (Snellen equivalent 20/32) or better	Correct typographical error of 85 letters
		Participant Withdrawal	Should be discussed with the sponsor	Correction
		Efficacy Assessments	3 SE readings will be obtained for each eye and	Clarification

			the average calculated for both eyes Axial length can also be measured by Pentacam	
		Activities and Compliance Questionnaire	Deleted on a phone or web-based application	Data were collected via paper diary for about 6 months until the phone/web-based application could be launched
		Adverse Event	Revised definition to require that corneal staining ≥ 2+ and Tolerability items ≥ moderate must be recorded as an AE. These items with less severity are not AEs, nor are small changes in pupil diameter. Deleted 'The AE will be recorded on the eCRF under the highest level of severity achieved"	Clarification of procedures for consistency Conflicted with previous sentence
		Study Assessments and Procedures	Follow-up visits may be done by phone or video call in lieu of a clinic visit in the event the site is closed or social distancing cannot be maintained. Questionnaires will be completed by phone. Investigational product will be dispensed via courier or curbside pick-up	Due to COVID-19 lockdown requirements, alternative measures were put into place to continue monitoring of participants and to maintain dosing compliance
3.0	17 Feb 2023	Secondary Endpoints (Synopsis, Section 3 and Section 9.1.2	Addition of two secondary endpoints for EMA submission for subgroup analysis of participants with a refractive history of myopia progression of ≥ 0.5D and ≥ 0.75D	Requested by Sponsor partner for EMA submission since EMA is interested in this population. Patients with previous myopia progression are more likely to have worse subsequent progression
		Primary Efficacy Estimands, Section 9.1.1	Replaced endpoint with estimands. Added a table to summarize the estimands for EMA and FDA. Added a table to describe the handling of intercurrent events and their justification. Added a table of sensitivity analyses. Added text for truncation parameter and multiplicity	To update and clarify statistical methods for EMA and FDA
		Secondary Efficacy	Added text for truncated Hochberg adjustment. Added a table to	To update and clarify statistical methods for EMA and FDA

		Endpoints, Section 9.1.2	summarize the order of testing for EMA and FDA analyses of secondary endpoints. Added a table to describe the handling of intercurrent events and their justification for key secondary estimands and also for secondary estimands	
		Populations for analysis, Section 9.3	Added text for the subgroups of fast progressors	To support new secondary endpoints for EMA
		Analysis of the primary endpoint, Section 9.4.2 and secondary endpoints, Section 9.4.3, subgroup analyses, Section 9.4.7	Added text for the calculation of SE, imputations, modeling, and sensitivity analyses Additional detail provided on subgroup analyses	Clarification
		Justification for endpoints, Section 3	Added text that the SE for each measurement will be calculated for each eye and then averaged by eye.	Clarification
		Product Storage (Section 6.2.3)	Reference to Pharmacy Manual instead of MOP	Correction
		Protocol Deviations (Section 11.1.9)	Updated cross reference to Quality Assurance and Quality Control	Correction
		Abbreviations, Section 11.3	Added MAR, MNAR, MCMC	Updated to include new statistical terms
		References, Section 11.4	Added new references	Updated to include new statistical references