Sydnexis

SYD-101-001

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

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Statistical Analysis Plan Final 1.1

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Document History

Version	Date	Changes
1.0	16MAR2023	Original Version
1.1	10JUL2023	1) Section 4 -Clarifying language was added to data cut-off regarding 28-day window and potential extension for myopic progression confirmatory visits. 2) Section 8.1.1-If only 2 SE assessments are made for an eye at a given visit, the difference between 2 SE refractions was expanded from 0.25D to 0.45D to be considered valid. 3) Section 4.3.3-Now clarifies that subjects who receive incorrect treatment for only a small period of study (e.g., 1 incorrect kit) will be included in all analyses under their original randomized treatment. 4) Section 8.1.3- Explains how sub-group analyses will be performed when there is no variance among imputations due to no missing data or all imputations being the same. 5) Visit windows for Primary Analysis Endpoints added to Table 4-1

List of Abbreviations

AE	adverse event
ATC	Anatomical Therapeutic Chemical
BCVA	best‐corrected visual acuity
CI	Confidence interval
CRF	case report form
D	diopters
D_2O	deuterium oxide
ECG	electrocardiogram
eg	*exempli gratia* (for example)
EOS	End of Study
EMA	European Medicines Agency
ET	Early Termination
EU	European Union
FAS	full analysis set
FDA	Food and Drug Administration
H_2O	dihydrogen monoxide
ICH	International Conference on Harmonisation
ie	*id est* (in other words)
IOP	intraocular pressure
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
MHRA	Medicines and Healthcare Products Regulatory Agency
MMRM	mixed model repeated measures

MNAR	missing not at random
REML	restricted maximum likelihood
PPS	per protocol analysis set
PT	preferred term
QOL	quality of life
SAE	serious adverse event
SD	standard deviation
SE	spherical equivalent
SOC	system organ class
SYD-101	Sydnexis' formulation of atropine sulfate (0.01% or 0.03%) topical ophthalmic solution
TEAE	treatment-emergent adverse events
US	United States

1. Introduction

Myopia, or nearsightedness, is the pathological elongation of the eye defined by having a refractive error of worse than 0.50 D. Myopia is the most common ocular disorder with an estimated prevalence of 13–49% in adult population-based studies (Pan 2012, Eye Diseases Prevalence Research Group 2004). The prevalence of myopia is increasing globally; in the US, 41.6% of the population had a diagnosis of myopia as of 2004 – up from 25% in 1971 (Vitale 2009); in Europe, the prevalence of myopia is increasing (Williams 2015); 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 and Young 2011, Morgan 2012).

The onset of myopia typically occurs during childhood and usually stabilizes when the child reaches puberty. While the symptoms of myopia (nearsightedness) can be corrected for using prescription eyeglasses, the underlying condition of abnormal elongation of the eye, remains. High myopia (>6.00 D) is associated with significant risk of pathologic ocular disease including glaucoma, cataract, retinal detachment, choroidal degeneration, choroidal neovascularization, and retinoschisis, all of which can cause irreversible vision loss (Wong 2014). Therefore, catching the onset of myopia as early as possible and ultimately retarding progression of myopia has been the topic of recent research. 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 created the need for a treatment to decrease myopic progression in children with the hope for reducing the incidence of these blinding eye diseases later in life.

Atropine is a nonselective muscarinic antagonist approved in both the EU and the US 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. While the mechanism is not specifically known, many clinical trials have been conducted concluding that atropine 1% administered nightly effectively slows the abnormal elongation of the eye (myopia progression) in children. For example, studies of topical 1.0% atropine in children (Chua 2006) demonstrated a 77% reduction in myopia progression (as measured by spherical equivalent), however, the study reported side effects such as excessive cycloplegia and mydriasis (which persists for weeks after even a single administration) and 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. Recently,

numerous studies across the globe in 1000's of patients have shown that lower doses of atropine (0.01%-0.05%) can effectively minimize myopic progression while reducing both side effects and rebound.

Sydnexis is currently developing SYD-101 (atropine sulfate ophthalmic solution 0.01% and 0.03%), as a treatment for the progression of myopia in pediatric patients. Sydnexis has conducted stability studies of compounded atropine 0.01% in aqueous (water-based) solutions that have shown rapid atropine degradation after 2 months at 25°C, thus having an unacceptable shelf life for a commercial formulation. Sydnexis has discovered that by using D_2O rather than H_2O as an excipient, base-catalysed hydrolysis can be attenuated, significantly increasing the shelf life of atropine 0.01% at 25°C to that of a high-quality pharmaceutical product for use in children. Current stability projections show a greater than 2-year shelf life for the D_2O formulation.

This statistical analysis plan for protocol for the Phase 3 SYD-101-001 study will examine several safety and efficacy endpoints (described in Sections 8 and 9) at planned analysis time points (described in Section 3.1). The analyses presented in this document are based on Protocol Version 3.0.

2. Objectives

The objective of this study is to evaluate the safety, tolerability and efficacy of SYD-101 for slowing the progression of myopia in children.

3. Investigational Plan

3.1. Overall Study Design and Plan

This is a 48-month, 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). Clinical sites in the US and in Europe will participate in this study. A total enrollment of approximately 840 pediatric participants is planned for this study. The study will have 3 treatment groups: SYD-101 0.01%, SYD-101 0.03%, and the Vehicle of SYD-101.

Participants will be assessed according to the schedule of procedures and assessments.

Allocation to study treatment will occur in a double-masked manner on 2 occasions:

- initial randomization at Baseline (for Primary Treatment Period [Part 1]) will be in a 1:1:1 ratio of SYD-101 0.01%: SYD-101 0.03%: Vehicle and stratified by baseline spherical equivalent (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)
- re-randomization at Month 36 (for Randomized Withdrawal Period [Part 2]): 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; all participants initially assigned (at Baseline) to Vehicle will be re-assigned to receive masked SYD-101 0.03%. Re-randomization of SYD-101 participants will not be stratified. Participants who have escaped to open-label SYD-101 0.03% therapy at or prior to Month 36 will remain on escape medication

There are 3 planned database locks for this study. The first will occur after all participants have completed the Month 24 visit and any required confirmatory visits for the purpose of submitting data for EU regulatory submission to the EMA (ie, Month 24 analysis). The second database lock will occur after all participants have completed the Month 36 visit and any required confirmatory visits for US regulatory submission to the FDA (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).

3.2. Primary Estimands

The primary efficacy endpoint will differ for the European Medicines Agency (EMA) and US Food and Drug Administration (FDA) submissions based on guidance received from the different regulatory authorities.

Table 3-1 Summary of Primary 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 (i.e., 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 or escape medication and assuming no dosing interruptions/discontinuations due to logistical issues. For discontinuations due to tolerability reasons (i.e., 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 myopic progression >0.75 D at or before Month 36
Treatment Condition(s)	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 Summary	Difference in the mean annual progression rate of myopia through Month 24 between SYD-101 0.01% and Vehicle Difference in the mean annual progression rate of myopia through Month 24 between SYD-101 0.03% and Vehicle	Difference in proportion of participants with confirmed myopic progression >0.75D at or before Month 36 between SYD-101 0.01% and Vehicle Difference in proportion of participants with confirmed myopic progression >0.75D at or before Month 36 between SYD-101 0.03% and Vehicle

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

Table 3-2 Summary of Intercurrent Event Approaches 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 (e.g. have progressed)	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	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 (e.g. have progressed)	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 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 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.
Study 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 Treatment 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

3.3. Secondary and Exploratory Efficacy Endpoints

The table below lists the secondary (key and other) efficacy endpoints and exploratory efficacy endpoints for the EMA and FDA submissions. The endpoints are listed in order of testing.

Table 3-3 Secondary Efficacy and Exploratory Endpoints

Endpoint	EMA	FDA
Key Secondary Efficacy Endpoint		
1.	Proportion of participants with myopic progression >0.75 D at or before Month 24	Mean annual progression rate of myopia through month 36
Other Secondary Efficacy Endpoints		
2.	Proportion of participants with annual myopia progression rate through Month 24 ≤0.50 D/year	Proportion of participants with annual myopia progression rate through Month 36 ≤0.50 D/year
3.	Proportion of participants with annual myopia progression rate through Month 24 ≤0.25 D/year	Proportion of participants with annual myopia progression rate through Month 36 ≤0.25 D/year
4.	Proportion of participants with increase of myopia of >0.50 D at or before Month 24	Proportion of participants with increase of myopia of >0.50 D at or before Month 36
5.	Time to progression of myopia of >0.75 D through Month 24	Time to progression of myopia of >0.75 D through Month 36
6.	Mean annual progression rate using Month 24 data on Subgroup of participants with refractive history of progression ≥ 0.5 D / year	Mean change from baseline in axial length at Month 36 (at sites with the requisite equipment; at least 50% of participants)
7.	Mean annual progression rate using Month 24 data on Subgroup of participants with refractive history of progression ≥ 0.75 D / year	
8.	Mean change from baseline in axial length at Month 24 (at sites with the requisite equipment; at least 50% of participants)	
Exploratory Efficacy Endpoints		
	Mean change from baseline in SE at Month 48 (ie, 12 months after randomized withdrawal	Mean change from baseline in SE at Month 48 (ie, 12 months after randomized withdrawal
	Mean time spent with selected activities	Mean time spent with selected activities
		Mean annual progression rate using Month 24 data on Subgroup of participants with refractive history of progression ≥ 0.5 D/year
		Mean annual progression rate using Month 24 data on Subgroup of participants with refractive history of progression ≥ 0.75 D/year

Key secondary and other secondary endpoints estimands will be based on the same target population and assessed under the same treatment conditions as the primary efficacy estimands.

The intercurrent events for key secondary endpoints will be handled in the following manner for the FDA and EMA key secondary estimands as presented in the table below.

Table 3-4 Intercurrent Event Approaches 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
Escape Medication	EMA Composite • Participants who receive escape medication 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	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.

Intercurrent Event	Strategy for Key Secondary Estimands	Justification
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.
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

Intercurrent events for the majority of secondary endpoints will be handled in the following manner for the FDA and EMA secondary estimands as presented in the table below.

Table 3-5 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	Prohibited treatments include therapies that have known efficacy for slowing myopia progression (eg, MiSight multifocal contact lenses, Ortho-K lenses, compounded atropine, etc.) and

	multiply imputed assuming MAR	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

Intercurrent event approaches for the three secondary efficacy endpoints which will not use the methods summarized in the above table are detailed below.

Data after receipt of prohibited treatment or escape therapy will be censored for the axial length and for the time to event estimands and multiple imputation will not be performed for these endpoints. The censoring and analysis methods utilize a hypothetical MAR approach for study discontinuation (regardless of reason), receipt of prohibited treatments or escape therapy.

Time to progression of myopia will be calculated in days as the date of first confirmed SE measurement that represents a reduction 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 medication prior to myopic progression will be censored as of the date they received the prohibited treatment or escape medication.

For the analysis of annual progression rate for the fast progression subset, data after receipt of prohibited treatment or escape medication will be censored and multiple imputation will not be performed for this endpoint. The censoring and MMRM analysis methods will be utilized for study discontinuation (regardless of reason) and receipt of prohibited treatment or escape medication.

3.4. Safety Endpoints

The following safety endpoints will be included in the analysis:

- Evaluation of adverse events (AEs) and serious adverse events (SAEs)
- Tolerability to the masked study drug will be solicited via questionnaire
- Changes from baseline in findings detected by best-corrected visual acuity (BCVA), biomicroscopy including corneal staining, intraocular pressure (IOP), and ophthalmoscopy
- Changes from baseline in corneal endothelial cell count (selected sites only; approximately 25% of study participants)
- Mean change from baseline in pupil diameter
- Changes from baseline in vital sign measurements
- Pregnancy test results (female participants of childbearing potential only)

3.5. 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 measurements obtained 6 months later at the next scheduled visit to 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%) will 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. 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 assigned site staff.

4. General Statistical Considerations

All statistical analyses will be conducted using SAS Version 9.4 or higher (SAS Institute, Cary, North Carolina).

All statistical tests will be two-sided and will be performed at the 5% level of significance leading to 95% (2-sided) confidence intervals (CIs), unless otherwise stated. P-values will be rounded to 3 decimal places. If a p-value is less than 0.001 it will be reported as "<0.001." If a p-value is greater than 0.999 it will be reported as ">0.999."

Continuous data will be summarized by treatment group using descriptive statistics (number, mean, median, standard deviation (SD), minimum, and maximum). Categorical data will be summarized by treatment group using frequency tables (frequencies and percentages). Mean will be presented to one decimal place beyond the precision with which the data was captured. SD and median will be presented to two decimal places beyond the precision with which the data was captured. Minimum and maximum will be presented to the precision with which the data was captured. When count data are presented, the percentage will be suppressed when the count is zero in order to draw attention to the non-zero counts. A row denoted "Missing" will be included in count tabulations where specified on the shells to account for dropouts and missing values if needed. 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.

For measurements such as SE and axial length which are collected multiple times per eye, the per eye averages will be calculated from the available values for each eye and then the average value of the right and left eyes will be calculated. The average values will be presented as rounded to two decimal places in data listings, however no rounding will be performed prior to the final calculation of the average value for both eyes.

All study-related raw data that support the corresponding tables and figures will be presented in data listings. Additional data listings may be generated as needed. All table, listing and figure shells will appear in landscape format employing Courier New 9-point font. Unless otherwise noted, all tables will summarize participant results by treatment group sorted in the following order: Vehicle, SYD-101 0.01% and SYD-101 0.03%. After receipt of escape therapy or re-randomization, participants will be summarized under current treatment with the treatment group divided to show initial and current treatment (e.g., Vehicle to Escape, SYD-101 0.01% re-randomized to Vehicle, etc.). Unless otherwise noted, all data listings will be sorted by treatment group and participant identification number defined as investigator identification number concatenated with the participant number. Due to family relocation or site closure, participants could be transferred from one site to a different site. In such cases, participant identification number will remain unchanged. Participants who changed study sites will be included in a data listing.

The baseline value for an assessment is defined as the last non-missing measurement including unscheduled assessments before or on the day of treatment with study drug (Day 1). Change from baseline is defined as the post-baseline value minus the baseline value for the given

assessment. Please also see Section 9 for details regarding baseline considerations for safety analyses when participants receive more than one treatment.

When study day is used for display or in comparisons, the following algorithm will be used:

- study day = date of assessment - date of first dose +1,
  if date of assessment ≥ first dose date.
- study day = date of assessment - date of first dose,
  if date of assessment < first dose date.

Note that the date of first dose is Day 1 and the day before the date of first dose is Day -1 (for analysis, there is no Day 0 for study day). First dose refers to first dose of any study treatment unless otherwise specified.

For all efficacy and safety analyses, analysis visit windows will be used for assigning assessments to an analysis visit, as per Table *4-1* below.

Table 4-1 Visit Windows

Scheduled Visit	**Target Day**	**Analysis Visit Window (Days)**
Screening	-21 to 1	Not applicable
Day 1	1	Not applicable
Week 2	14	2 to 52
Month 3	91	53 to 136
Month 6	182	137 to 231
Month 9	280	232 to 322
Month 12	364	323 to 409
Month 15	455	410 to 500
Month 18	546	501 to 591
Month 21	637	592 to 682
Month 24	728	683 to 773
Month 27	819	774 to 864
Month 30	910	865 to 955
Month 33	1001	956 to 1046
Month 36	1092	1047 to 1137
Month 39	1183	1138 to 1228
Month 42	1274	1229 to 1319
Month 48	1456	1320 to 1516

Visit Windows for Primary Analysis Endpoints

Scheduled Visit	**Target Day**	**Analysis Visit Window (Days)**
Screening	-21 to 1	Not applicable
Day 1	1	Not applicable
Month 6	182	2 to 273
Month 12	364	274 to 455
Month 18	546	456 to 637
Month 24	728	638 to 773 *Upper Limit M24 Cut Off
Month 30	910	774 to 1001
Month 36	1092	1002 to 1137 *Upper Limit M36 Cut Off
Month 42	1274	1138 to 1365
Month 48	1456	1365 to 1516

Only those assessments which are assigned to an analysis visit will be included in the summary tables and figures which are presented by visit. In the event, that there are multiple visits which fall into the same analysis visit window with non-missing data for an assessment and the visits include a scheduled and unscheduled visit(s), the assessment from the scheduled visit will be selected for analysis with one exception for BCVA. For BCVA, if there is a scheduled visit BCVA assessment and an unscheduled visit BCVA assessment in window performed on the same date, then the unscheduled visit BCVA assessment for that date will be used for analysis as it would be a re-test performed after refraction. If there are only unscheduled visit assessments performed within a window the visit closest to the target day of the study visit will be used for analysis. If there are two equal closest unscheduled visits occurring within the analysis visit

window (one before and one after the target day), then the earlier assessment will be used for analysis.

For summaries of an event at or before a given time point, such as progression at or before Month 24, all assessments (including unscheduled visits) on or before the Month 24 Visit or the upper limit of the corresponding visit window if no visit occurs in the Month 24 window, will be considered. All assessments will be presented in the data listings.

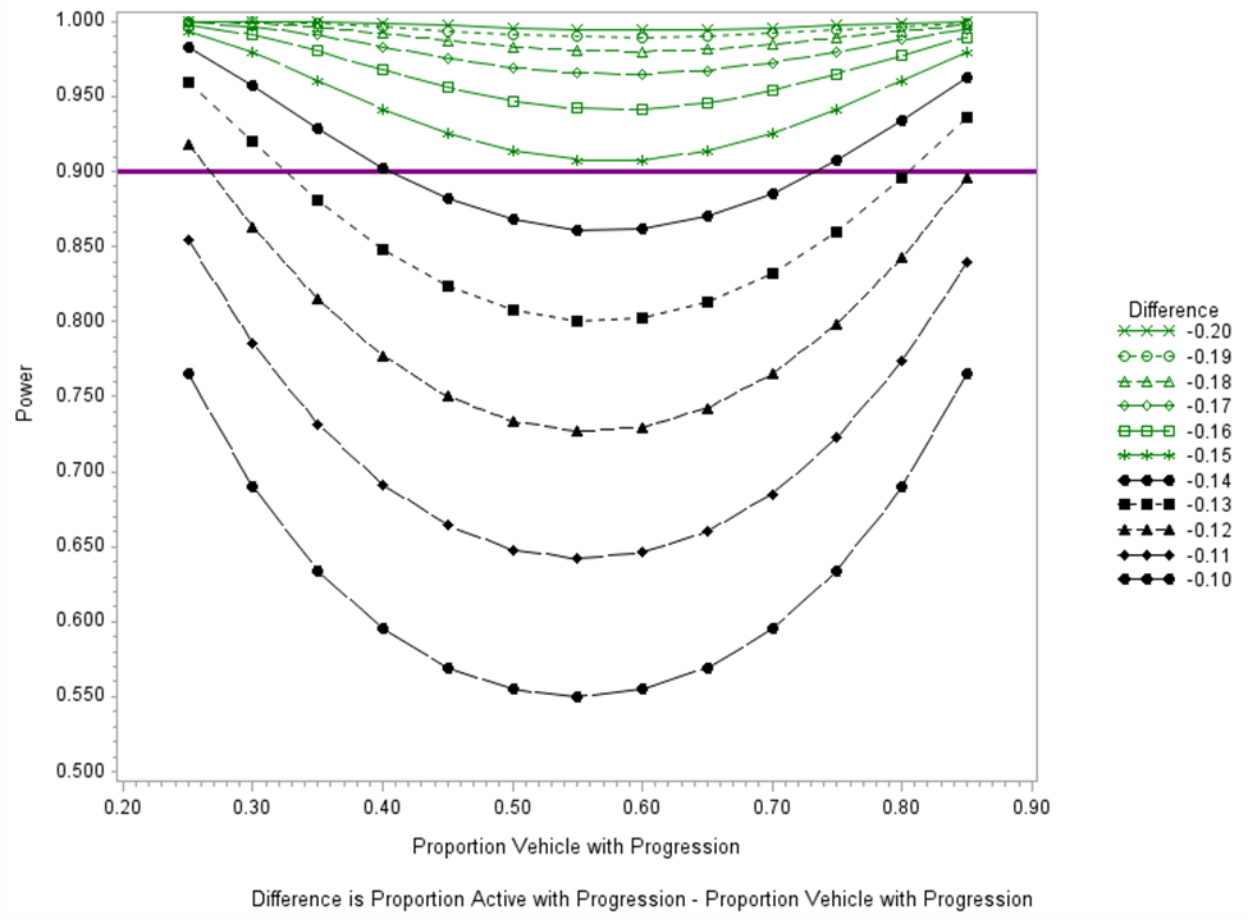
For a given participant, the Month 24 analysis will include all assessments (events, medications, etc.) with a start day on or before Month 24 Visit + 28 days (to allow for potential myopic progression confirmatory visit) for that participant or the upper limit of the Month 24 visit window (study day 773) + 28 days if no visit occurs in the Month 24 window. Participants who switch to escape therapy at the Month 24 visit will have all data included through the Month 24 visit. For participants whose first observed myopic progression >0.75 D is at the Month 24 visit and whose confirmatory visit cannot be scheduled within 28 days, the participants Month 24 data cut off will be extended to the date of their confirmatory visit.

For a given participant, the Month 36 analysis will include all assessments (events, medications, etc.) with a start day on or before the Month 36 Visit + 28 days (to allow for potential myopic progression confirmatory visit) for that participant or the upper limit of the Month 36 visit window (study day 1137) + 28 days if no visit occurs in the Month 36 window for that participant. The analysis at Month 48 will include all data in the database. (Observations after the upper limit of the Month 48 visit window for will be listed but excluded from analysis unless the participant was still receiving study medication.)

4.1. Sample Size

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 4-1 are based on the Chi-squared test at a 2-sided significance level of 0.025.

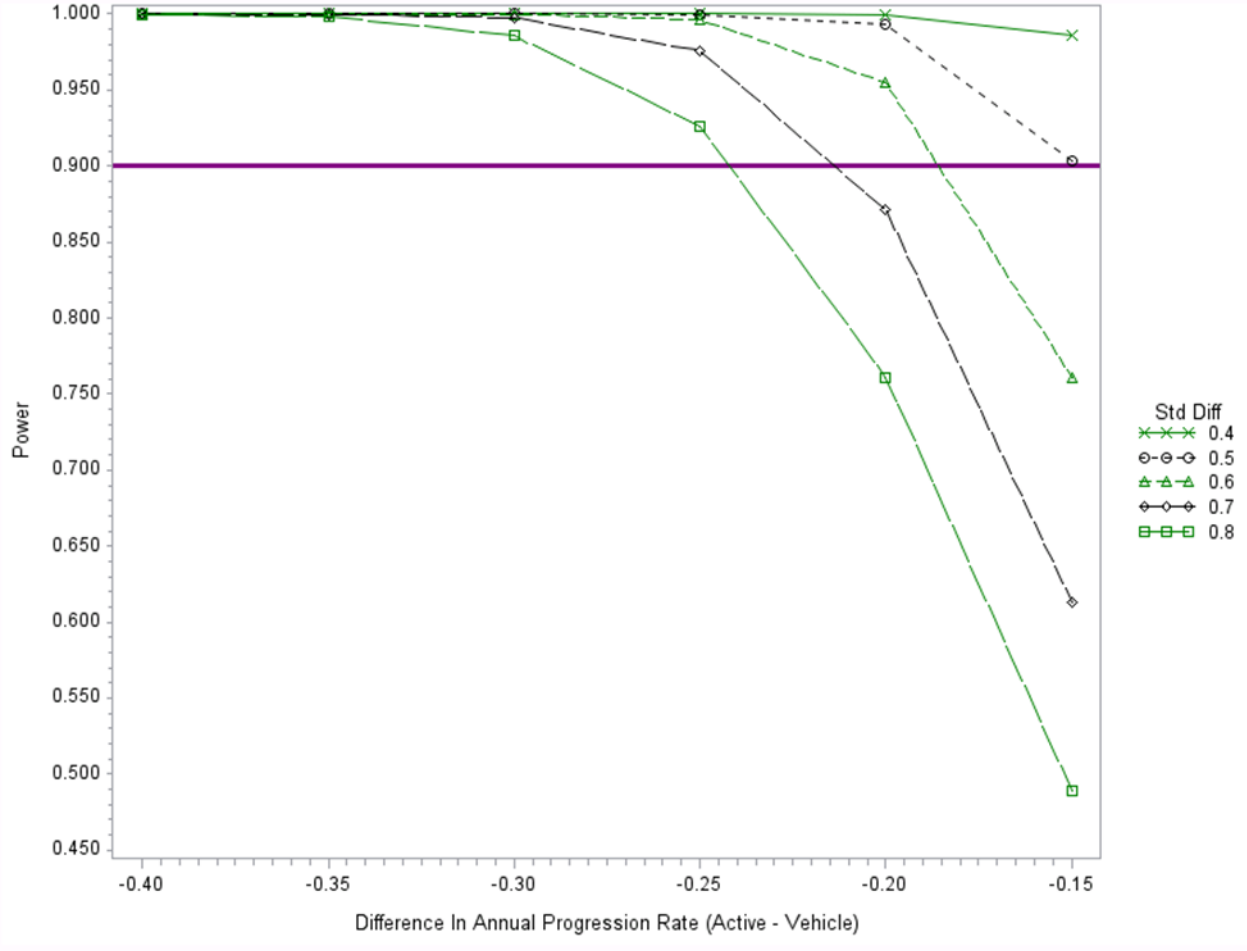
Figure 4-1 Power for 2-Sided Chi-Square Test Evaluated at Alpha=0.025 for Proportion Responders When 280 Participants Per Arm



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 *4-2* are based on a 2-sample t-test evaluated at the 0.025 significance level.

Figure 4-2 Power for 2-Sided T-Test Evaluated at Alpha=0.025 for Annual Progression Rate When 280 Participants Per Arm



Furthermore, to estimate the statistical power of the two region- specific primary endpoints, simulations based on various assumptions regarding the mean vehicle annual progression rate, the mean active annual progression rate based on % reduction from the vehicle annual progression rate, the SD for the APR as well as allowing for participant dropout/study treatment discontinuation and escape medication have been considered to investigate statistical power for a range of sample sizes. Simulations were run after the protocol was finalized to assess protocol sample size assumptions. For the most likely assumption of parameters examined, a mean placebo/control APR of 0.65 D and a mean active APR 0.325 D (a 50% reduction from the mean vehicle/control APR) both with a SD of 0.55 D and an annual dropout/study treatment discontinuation rate of 7%, a sample size of 217 participants per treatment arm provides an approximate 97% power for the FDA endpoint and an approximate 99.96% power for the EMA endpoint assuming a significant level of 0.025.

4.2. Randomization, Stratification, 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. 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). 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 escape medication.

For Part 2, to maintain masking, 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% (not on escape medication) 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% (not on escape medication) will be re-randomized in a 1:1 ratio to masked SYD-101 0.03% or Vehicle. Re-randomization of SYD-101 participants will not be stratified. All participants who were initially assigned (at Baseline) to Vehicle (not on escape medication) will be re randomized to masked SYD-101 0.03% at Month 36. Participants who have escaped to open label SYD-101 0.03% therapy at or prior to Month 36 will remain on escape therapy medication.

Masking of individual participant treatment assignments will be maintained throughout the study for all participants and site staff until the database is locked for the EOS analysis at Month 48.

Prior to the Month 24 database lock, all study team members at PPD, Santen, and Sydnexis will be masked to the treatment assignments, with the exception of the PPD randomization, IRT, and Clinical Supplies teams as their roles require access to the randomization and materials schedules.

Following the 24-Month database lock, PPD will send the study data and randomization code to Santen team members who will be responsible for running the statistical programs and producing the tables, listings, and graphs for the CSR. The data will be subset so that only observations through the Month 24 timepoint are included and only the initial randomization assignments will be provided. An independent medical writer will prepare the CSR and clinical modules of the MAA under Santen's supervision. Sydnexis will appoint a designee to review and approve the CSR who will not have day-to-day contact with any study sites. Santen team members will be unmasked and will not have any contact with study sites.

After the Month 36 database lock, the PPD Project Manager, PPD Oversight Director and the PPD Biostatistics and Programming team members as well as Sydnexis designees will become unmasked at the participant-level. Only the initial treatment assignments will be unmasked. The re-randomization of subjects at Month 36 will remain masked until the Month 48 database lock. The PPD Clinical team members responsible for monitoring participant data (Clinical Research Associates/Clinical Trial Managers), the PPD Medical Monitor, and Data Management team members, will remain masked to participant-level treatment assignments until after the Month 48 database lock. PPD will maintain separate access-controlled areas for the generation and distribution of the unmasked Month 36 analyses and will document team members who have access to these areas in the TMF.

Additionally, 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-Month 36 database lock; participant treatment assignments will remain masked until after the Month 48-lock. A masking plan will detail the names and roles of persons who will have access to the Month 24 and Month 36 aggregate data and participant treatment assignments.

4.3. Analysis Set

4.3.1. Informed Consent (ICF)

The ICF will include all patients who provide informed consent, including screen failures.

4.3.2. Full-analysis set (FAS)

The 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. All analyses using the FAS will group participants according to initial randomized treatment.

4.3.3. Safety set

The Safety set will include all participants who receive any amount of study drug (SYD-101 0.01%, SYD-101 0.03%, or Vehicle). The Safety set will be the primary population used for safety analyses. Treatment assignment will be based on the treatment actually received. Participants who receive one incorrect treatment kit but whose treatment is corrected to their randomized treatment at the next treatment dispensation will be included in all analyses as receiving the correct treatment.

4.3.4. Per-protocol analysis set (PPS)

The PPS will include all participants in the FAS who do not have any major protocol deviations and have at least 1 post baseline measurement for SE. The PPS will be defined separately for the Month 24, Month 36 and Month 48 analyses. Major protocol deviations will be identified prior to database lock and breaking the study mask at Month 24. Additional visits and/or participants may be excluded from the PPS at Months 36 and Month 48 based on review of accumulating

deviations. Efficacy endpoints analyzed for the PPS are to be treated as a sensitivity analysis. Treatment assignment will be based on the treatment actually received.

4.3.5. Special Subsets

The SYD-101 Efficacy Subset will include all participants in the FAS who were randomized to one of the two active treatment arms and stay on active treatment for the entire 48-month study.

The Vehicle to Escape Efficacy Subset will include all participants in the FAS who were randomized to one of the two active treatment arms, were re-randomized to vehicle at Month 36, and initiated escape medication before Month 48.

For the EMA Submission, additional special subsets are defined based on refractive histories of participants prior to enrollment. Refractive history was required for participants presenting with myopia (SE) of < 0.75 D and requested of all other participants, if available. The refractive history will be used to calculate annual progression rate for three intervals.

- First Refraction History Date (RH1) to Screening
- Second Refraction History Date (RH2) to Screening (if two historical refractions are available)
- RH1 to RH2 (if two historical refractions are available, the earlier history will be considered RH1)

For each interval, the annual progression rate will be calculated as the change in SE divided by the number of days (later date – earlier date + 1) and multiplied by 365.25 to obtain an annual progression rate for that interval. Using the annual progression rates calculated for the intervals above, the following 2 subsets below are defined and the study annual progression rate will be analyzed for these subgroups as secondary endpoints for EMA only.

- Fast Progressor Subgroup 1: This subgroup will include all randomized participants in the FAS. With refractive history of ≥ 0.50 D progression/year for any of the three history time intervals. Intervals of less than 28 days will not be included as they can overestimate a progression rate. It is expected to have approximately 250 randomized participants meeting this criterion.
- Fast Progressor Subgroup 2: This subgroup will include all randomized participants in the FAS with refractive history of ≥ 0.75 D progression/year for any of the three history time intervals. Intervals of less than 28 days will not be included as they can overestimate a progression rate. It is expected to have approximately 200 randomized participants meeting this criterion.

5. Participant Disposition

5.1. Disposition

Two separate disposition summaries will be provided:

A disposition of participants includes the number and percentage of participants for the following categories: participants who signed informed consent/assent, participants randomized, participants randomized by region and country, participants in the Safety analysis set, participants in the FAS, participants in PPS, participants who completed Month 24 and Month 36 visits, participants who completed the study, participants who discontinued from the study, participants who discontinued from the study treatment, and participants who received escape medication. Additional disposition summaries will be provided for subgroups such as Age, Sex, Race and Iris Color.

A separate summary will be provided for randomized withdrawal period and will contain counts and percentages of participants in the following categories:

- Those initially assigned to the SYD-101 0.01% arm (not on escape medication) 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 (not on escape medication) 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-assigned to receive masked SYD-101 0.03%

All percentages will be based on the number of FAS participants. Disposition data will be listed as well.

5.2. Protocol Deviations

Protocol deviations will be tracked by the clinical team on an ongoing basis based on the Protocol Deviations Rules document. The Protocol Deviation Rules document includes a description of identified potential deviations and assigns a rule number, deviation type (ICH/GCP Deviation vs. Protocol Deviation), deviation subtype (inclusion/exclusion criteria, visit scheduling, missing doses, treatment compliance, etc.), deviation type (efficacy vs. safety), significance (Significant vs. Non-Significant), deviation source (Medical Monitor Review, Site Monitoring, Automated Data Checks, etc.) and severity (Include Participant in All Analyses, Exclude Participant from PPS, Exclude efficacy assessments after date of deviation, Exclude efficacy assessment on the date of deviation, etc.) for each deviation. The Study Deviations Rules document may be updated as the study is ongoing and new deviations are identified. Each approved version of the Study Deviations Rules document will be maintained in the clinical project files.

Major protocol deviations are defined as the subset of deviations which are considered to have potential significant impact on analysis and results in the exclusion of a participant's data from analysis. Major protocol deviations that may be considered include, but are not limited to the following:

- Failure to fulfill any of the important inclusion/exclusion criteria
- Significant deviations in dosing adherence
- Taking prohibited medication or treatment listed in protocol Section 6.5.1
- Significant deviations in autorefraction process (e.g., only one autorefraction measurement taken per eye)

Participants with major protocol deviations will be tabulated by deviation sub-type for each treatment group. All percentages will be based on the number of FAS participants. Additionally, all major and minor deviations will be listed for all FAS participants.

6. Demographics and Baseline Characteristics

6.1. Demographics and Baseline Disease Characteristics

Demographic and baseline characteristics variables, including age (years), age category (3 years to <6 years, 6 years to <9 years, 9 years to <12 years, and 12 years to 14 years), sex, height, weight, ethnicity, race, region (Europe and US), degree of parental myopia (Mild, Moderate, High, Unknown), degree of parental myopia (presented separately for mother and father), baseline SE (average of right and left eyes), baseline SE category (0.50 D to 3.0 D and >3.0 D to 6.0 D), participants with myopia (SE) < 0.75 D, participants with myopia (SE) ⩾ 1.0 D, annual progression rate prior to baseline, participants with history of myopia progression of at least 0.5 D and at least 1.0 D in the past 12 months, axial length (average of right and left eyes), best-corrected visual acuity (BCVA) using ETDRS letters (average of right and left eyes), Binocular Near-BCVA (logMAR), pupil diameter (average of right and left eyes), intraocular pressure (IOP) (average of right and left eyes), corneal endothelial cell count (average of right and left eyes), iris color category by patient, average time outdoors category (<= Median or > Median) and average time near work category (<= Median or > Median) will be summarized by treatment group, as well as demographic groups such as Age, Sex, Race and Iris Color, and over all participants combined for the Safety set, FAS, and PPS, and optionally for Special Subgroups (Section 4.3.5). Age, height, weight, baseline SE, annual progression rate prior to baseline, axial length, BCVA, near binocular BCVA, pupil diameter, IOP, and corneal endothelial cell count will be summarized using descriptive statistics. Age categories, sex, ethnicity, region, race, and degree of parental myopia, baseline SE category, participants with myopia history, iris color category and activities categories (time near work and time outdoors) will be summarized with the number and percentage of participants in each parameter category.

Age will be calculated as (date of informed consent – date of birth)/365.25.

The annual progression rate prior to baseline will be calculated is noted in Section 4.3.5 for the interval between RH1 and Screening.

A participant will be considered to have a history of progression of at least 0.5 D in the past 12 months if the difference between the SE at the earliest historical refraction performed within 365 days prior and the SE at the screening/baseline refraction is at least a 0.5 D progression. Similarly, a participant is considered to have a history of progression of at least 1.0 D in the past 12 months if the difference between the SE at the earliest historical refraction performed within 365 days prior and the SE at the screening/baseline refraction is at least a 1.0 D progression.

Iris color will be summarized at the participant level. Blue, green, grey, and hazel eyes will be categorized as light. Eyes that are black, brown, or other will be categorized as dark. If a

participant has different colored eyes, the participant will be classified as having dark eyes if either eye is dark.

Participant demographic and baseline characteristics will be presented in a listing.

6.2. Medical History

Medical histories are captured on the eCRF and the investigator will record verbatim term, location (ocular or non-ocular, OD/OS/OU for ocular), start date, and stop date or indication of ongoing. Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA, Version 21.1 or higher). The number and percentage of participants with any history will be reported by treatment group. Additionally, medical history will be summarized by the number and percentage of participants with medical history by MedDRA System Organ Class and Preferred Term (PT) by treatment group.

Medical histories will be summarized separately for ocular and non-ocular histories. For ocular summaries, participants will be counted at a given level (any medical history, by System Organ Class, and by PT) if the participant has a history reported in at least one eye.

Percentages will be calculated based on number of participants in the Safety set. Also, by-participant listings of medical histories will be presented.

6.3. Inclusion and Exclusion Criteria

Prior to randomization, the investigator will assess whether the participant fulfills all of the inclusion and exclusion criteria outlined in the protocol. If a participant does not fulfill all of the requirements, the specific inclusion criterion not met or exclusion criterion which was met will be recorded on the eCRF and presented in a data listing.

7. Treatments and Medications

All concurrent medications (prescription, over-the-counter, and supplements), adjunct therapies, and concurrent procedures will be recorded on the appropriate eCRF page. Collection of medications and procedures will begin at Screening and include any medications used within 30 days will be recorded in the eCRF. Any changes in concomitant medications also will be recorded in the participant's eCRF. Medications will be coded with the World Health Organization Drug (WHODrug) Dictionary, which will be updated throughout the life of the study.

7.1. Prior and Concomitant Medications

Prior medications are defined as those which are taken prior to the initiation of study treatment. This includes medications which start prior to Day 1 but continue while the participant is on study treatment.

Concomitant medications are defined as those medications which are taken on or after the initiation of study treatment (Day 1). This includes medications which start prior to Day 1 but continue while the participant is on study treatment.

Prior and concomitant medications will be summarized separately by presenting the total number of medications and the number and percentages of participant with at least one medication will be summarized by treatment group. The number and percentages of medications will also be summarized by treatment group and by ATC level 1 term, ATC level 2 term, and preferred term for the Safety set.

Prior and concomitant medications will be summarized separately for ocular and non-ocular medications. For ocular summaries, participants will be counted at a given level (any medication, by ATC level, and by PT) if the participant has a medication reported in at least one eye.

All medications will be presented in data listings with an indicator to identify whether their use is prior and /or concomitant.

7.2. Concurrent Procedures

Details regarding concurrent procedures will be listed.

7.3. Study Treatments

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. SYD-101 and Vehicle are clear ophthalmic solutions packaged in identical white, 5-mL low-density polyethylene (LDPE) ophthalmic bottles. Each night at bedtime, 1 drop of assigned study drug is to be instilled in each eye.

7.3.1. Extent of Exposure

Overall duration of exposure to any study treatment is defined as the total number of days a participant is exposed to any study drug (active SYP-101 or Vehicle) during the 48 month treatment period and will be presented as the total number of days from the first dose (Day 1) to the last dose date as recorded on the EOS/ET page: (last dose date – date of first dose + 1). If the last dose date on the EOS/ET page is missing, or if a participant is lost to follow-up, the latest available visit date will be used.

Overall duration of exposure to any study treatment will be calculated at Month 24 and Month 36 as follows: (date of Month 24 [or Month 36] visit – date of Day 1 visit +1).

Additionally, participants may change study treatment due to receipt of escape medication or re-randomization at Month 36. See Table *7-1* below for potential patterns of changes to study drug doses over time (not including early discontinuations of study therapy.) Duration of exposure for

each specific treatment for each participant will be calculated as Date of Last Dose for given treatment arm – Date of First Dose for given treatment arm + 1. The start date of escape medication will be the date of the first visit where the participant's end of visit status is marked as Continuing on Rescue Medication". The date of re-randomization at Month 36 will be used as the last dose date for SYD-101 treatment for SYD-101 0.01% and SYD-101 0.03% arm participants who are re-randomized to vehicle as well as the first dose for vehicle treatment for these participants. For the SYD-101 0.03% treatment arm, participants who are re-randomized to vehicle at Month 36 can receive SYD-101 0.03% in two non-consecutive time courses (from Baseline to Month 36 and from escape after re-randomization to Vehicle at Month 36 to Month 48), the duration of exposure for the two treatment courses will be summed to calculate the total exposure to SYD-101 0.03%.

Table 7-1 Potential Patterns of Dose Changes

Randomized Treatment	Treatment Period		Randomized Withdrawal	
	Baseline to Month 24	Month 24 to Month 36	Month 36 to 42	Month 42 to 48
SYD-101 0.01%	SYD-101 0.01%	SYD-101 0.01%	SYD-101 0.01%	SYD-101 0.01%
	SYD-101 0.01%	SYD-101 0.01%	SYD-101 0.01%	SYD-101 0.03% escape
	SYD-101 0.01%	SYD-101 0.01%	Vehicle	Vehicle
	SYD-101 0.01%	SYD-101 0.01%	Vehicle	SYD-101 0.03% escape
	SYD-101 0.01%	SYD-101 0.03% escape	SYD-101 0.03% escape	SYD-101 0.03% escape
SYD-101 0.03%	SYD-101 0.03%	SYD-101 0.03%	SYD-101 0.03%	SYD-101 0.03%
	SYD-101 0.03%	SYD-101 0.03%	SYD-101 0.03%	SYD-101 0.03% escape
	SYD-101 0.03%	SYD-101 0.03%	Vehicle	SYD-101 0.03% escape
	SYD-101 0.03%	SYD-101 0.03%	Vehicle	Vehicle
	SYD-101 0.03%	SYD-101 0.03% escape	SYD-101 0.03% escape	SYD-101 0.03% escape
Vehicle	Vehicle	Vehicle	SYD-101 0.03%	SYD-101 0.03%
	Vehicle	SYD-101 0.03% escape	SYD-101 0.03% escape	SYD-101 0.03% escape

Descriptive statistics including the number of participants, mean, SD, median, minimum, and maximum for the study treatment exposure will be summarized for overall exposure to any study drug, exposure for each treatment regardless of initial randomized treatment, and exposure to each treatment by initial randomized treatment group using the Safety analysis set. The durations of exposure and study participation will then be classified into one of the following categories: <= 91 days, 92 to 182 days, 183 to 280 days, 281 to 364 days, 365 to 546 days, 547 to 728 days, 729 to 910 days, 911 to 1092 days, 1093 to 1274 days, 1275 to 1456 days, and >=

1456 days and will be presented as the number and percentage of participants in each duration category. Summary tables for subgroups (Age, Sex, Race and Iris Color) will be created as well.

In addition, a summary table showing the number of participants on each treatment per visit will be included, up to 48 months.

Participant treatment status (continuing on masked medication and continuing on escape medication) will be collected at each visit and data will be presented in a listing.

7.3.2. Treatment Compliance and Modifications

Responses to questions regarding study drug compliance will be collected via a phone questionnaire or web-based application, first weekly for the first 6 months, then monthly. At each assessment, the application collects the number of doses missed for the past week for weekly assessments and past month for monthly assessments. The number of reported missed doses for completed assessments will be used for calculating the compliance of each reporting period. The per participant treatment compliance will be the mean value of the compliance calculated for each reporting period. For each reporting period, compliance will be calculated as (Number of Days in the reporting period – Number of Reported Missed Doses During the reporting period) / Number of Days in the reporting period × 100 as the expected number of doses is once per day. The number of days per dosing period will be 7 for weekly reports, 30 for monthly reports. If the dosing regimen is altered to 3 times/Week dosing for a participant for safety reasons, the denominator will only include planned dosing dates (e.g., 3 doses per week period, 13 does per month period). The number and percentage of participants in each compliance category ($\geqslant$90 , $\geqslant$ 70 to <90, $\geqslant$50 to <70, $\geqslant$30 to <50, <30, NC) will also be summarized. Compliance will be summarized for overall exposure to any study drug, exposure for each treatment regardless of initial randomized treatment, and exposure to each treatment by initial randomized treatment group using the Safety analysis set. Compliance will be summarized separately for participants who submit a minimum number of questionnaires, with that number determined based on data availability as the study progresses.

8. Efficacy Analysis

The analysis of the primary endpoint will be based on the FAS. The analysis will group participants according to initial randomized treatment regardless of the status of escape medication. As a sensitivity analysis, an analysis will be repeated for the PPS and using other imputation approaches for the FAS.

All secondary endpoints will be primarily analyzed for the FAS and repeated for the Per-Protocol Analysis Set as sensitivity analyses. Sensitivity analyses using other imputation approaches will be performed for the key secondary efficacy endpoints for the FAS. For the EU submission special subgroups will analyzed for FAS participants.

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

All efficacy endpoints will be summarized by treatment group and visit per the reporting conventions described in Section 4. Individual participant listings for each efficacy endpoint will be provided to support the summary tables.

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

8.1. Primary Efficacy Estimands

The primary efficacy estimands will differ for the EMA and FDA submissions based on guidance received from the different regulatory authorities. The full estimand definitions are provided in Section 3.2.

EMA Submission:
The estimand for progression of myopia is the difference in the mean annual progression rate using data through Month 24.

The primary efficacy analysis 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.

FDA Submission:
The estimand for progression of myopia is the difference in the proportion of participants with confirmed myopia progression >0.75 D at or before Month 36.

The primary efficacy analysis will test the following hypothesis:

- H_0: The proportion of participants with myopic progression at or before Month 36 is equal between Vehicle and SYD-101.
- H1: The proportion of participants with myopic progression 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. Type 1 error for this study will be controlled using a Hochberg-based multiple-sequence gatekeeping procedure which will be implemented separately for EMA and FDA. The combination gatekeeping and a truncated Hochberg approach is accepted methodology for type I error control when there are multiple dose comparisons across multiple endpoints (Dmitrienko 2011).

Note there is no correction for multiplicity for the efficacy analysis between regulatory agencies as efficacy will be assessed independently by each regulatory agency, EMA or FDA, in their

respective submission. This is in accordance with ICH Guidance E17-General Principles for Planning and 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."

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

8.1.1. Primary Analysis

Calculation of SE:
The primary efficacy endpoints for EMA and FDA are based SE. 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). 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 (i.e., a single averaged SE value for a given visit will be obtained for each participant by taking the "average of the averages").

Per protocol, the autorefraction procedure is to be performed 3 times in each eye. 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 final average SE (over both eyes) value for analysis. This final per participant average of SE from the right and left eyes will be used for analysis.

The final average SE (over both eyes) will be considered missing if a non-missing SE measurement is not available for both eyes at a given visit. For a given eye, SE is considered non-missing if there is at least one measurement with a non-missing sphere and a non-missing cylinder value recorded for the same autorefraction measurement. If the baseline final average SE (over both eyes) is missing from the autorefraction, the SE assessment result from the manual refraction will be used.

Data imputations:
A combination of hypothetical, composite, and treatment policy strategies for intercurrent events will be used for the primary estimands as detailed in Section 3.2. For the EMA and FDA, 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). However, for by eye analysis data will be analyzed as observed.

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.

Data sets will be sorted by treatment and participant id prior to imputation.

Valid SE Values:
Due to technical issues or non-compliant participants (e.g., wiggly child), not all SE assessments performed may be valid. For PPS 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 eye 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 0.45 D of each other (i.e., -0.45 D $\leq$ SE Measurement 1 – SE Measurement 2 $\leq$ 0.45 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.

EMA Submission Analysis: Annual Progression Rate

The primary estimand of the primary objective is annual progression rate of myopia. 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 progression rate will be missing if the SE (average of both eyes) is missing. The multiply imputed average SE (over both eyes) will be used to derive the annual progression rate.

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 as a covariate. No explicit structure will be assumed for the covariance among the repeated measures. However, in case there is a convergence problem with the unstructured covariance, then a compound symmetry covariance structure will be assumed. The Kenward-Roger Method will be used to calculate the denominator degrees of freedom for the test of fixed effects. All visits for the Month 24 analysis will be included in the model, with the primary comparison at the Month 24 visit.

The above model will be performed for each imputation and the results combined via SAS PROC MIANALYZE for final treatment estimates. The estimated mean annual progression rate of myopia for each treatment at each visit and the estimated mean difference between each SYD-101 treatment group and Vehicle at Month 24 will be presented along with their corresponding 95% CIs.

The analysis described above will be performed for annual progression rate of myopia by eye at Month 24 and repeated for the annual progression rate of myopia at Month 36 with the MMRM model including data for visits through Month 36 as a secondary analysis.

FDA Submission: Confirmed Progression > 0.75 D

Progression is defined as an increased negative change where change is calculated as visit value − baseline value. Progression will be considered missing if a valid SE measurement is not available for both eyes at the given visit. The multiply imputed SE data will be used to determine confirmed progression. For analyses, progression will be considered confirmed if at the next consecutive visit, regardless of the number of days from the prior visit, progression >0.75 D continues to be demonstrated.

The proportion of participants with confirmed myopia progression (>0.75 D) at Month 36 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 pairwise CMH tests will be performed and the Mantel-Haenszel common risk difference 95% CIs will be calculated for each of the k imputed datasets and the results combined via SAS PROC MIANALYZE for final treatment estimates. Point estimates and CIs will be presented in summary tables as percentages (i.e., the estimated proportions * 100).

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. These values will be based on the averages from the k imputations.

The same analysis will also be performed at Month 24 looking at progression at or before Month 24 as a secondary analysis.

8.1.2. Sensitivity Analysis

Sensitivity analysis conducted for primary and key secondary endpoints using a combination of intercurrent event policies. Sensitivity Analysis 6 will be conducted for the confirmed progression > 0.75 D endpoint only, while Sensitivity Analysis 7 will be conducted for the annual progression rate primary endpoint only. Details for each sensitivity analyses are presented below and summarized in Appendix **Error! Reference source not found.**.

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

   For the EMA primary analysis repeated for PPS, intermittent missing data will be considered MAR and multiply imputed. Observations after prohibited medication/treatment or escape therapy will be censored and not imputed. Observations after treatment or study discontinuation due to a related AE will be multiply imputed assuming MNAR. All other observations after treatment or study discontinuation will be multiply imputed assuming MAR. Invalid SE values will be multiply imputed and assumed to be MAR.

   For the FDA primary analysis repeated for PPS, intermittent missing data will be considered MAR and will be multiply imputed. Observations after prohibited medication/treatment or escape therapy will be considered non-responders. Observations after treatment or study discontinuation due to a related AE will be imputed as non-responders. All other observations after treatment or study discontinuation will be multiply imputed assuming MAR. Invalid SE values will be multiply imputed and assumed to be MAR.

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

For the EMA the FAS intermittent missing observation will undergo multiple imputation assuming MAR. Observations after receipt of prohibited treatment, escape therapy or treatment discontinuation will be analyzed as observed. Observations after study discontinuation due to a related AE will be multiply imputed assuming MNAR with a vehicle-based imputation model. All other observations after study discontinuation will be multiply imputed assuming MAR. Invalid SE values will be analyzed as observed.

For the FDA the FAS intermittent missing observation will undergo multiple imputation assuming MAR. Observations after receipt of prohibited treatment, escape therapy or treatment discontinuation will be analyzed as observed. Observations after study discontinuation due to a related AE will be imputed as non-responders. All other observations after study discontinuation will be multiply imputed assuming MAR. Invalid SE values will be analyzed as observed.

3. Sensitivity Analysis 3 (FAS MAR Tipping Point)
   Data will first be multiply imputed for the FAS. Intermittent missing observations, observations after receipt of prohibited treatment or escape therapy, and observations after study discontinuation will undergo multiple imputation assuming MAR. For participants that discontinue treatment their observations will be analyzed as observed. Invalid SE values will be analyzed as observed. After imputations are performed, the tipping point method will be performed where a fixed value C is added to each SYD treatment imputed value. A range of values for C will be considered to identify the point at which statistical significance can no longer be claimed for either treatment arm.

4. Sensitivity Analysis 4 (FAS MNAR exclude Prohibited and Escape Observations)
   For the FAS intermittent missing observations will undergo multiple imputation assuming MAR. All observations after receipt of prohibited treatment or escape therapy will undergo multiple imputation assuming not at random (MNAR) with a vehicle-based imputation model. For participants that discontinue treatment, their observations will be analyzed as observed. Observations after study discontinuation will undergo multiple imputation assuming MNAR with a vehicle-based imputation model. Invalid SE values will be analyzed as observed.

5. Sensitivity Analysis 5 (FAS MNAR include Vehicle post Prohibited and Escape Observations)
   For the FAS intermittent missing observation will undergo multiple imputation assuming MAR. SYD observations after receipt of prohibited treatment or escape therapy will undergo multiple imputation assuming MNAR with a vehicle-based imputation model. For the vehicle group, observations after receipt of prohibited treatment or escape therapy will have observed data included in the MNAR imputation model and used for analysis. For participants that discontinue treatment their observations will be analyzed as observed. Observations after study discontinuation will undergo multiple imputation

assuming MNAR with a vehicle-based imputation model. Invalid SE values will be analyzed as observed.

6. Sensitivity Analysis 6 (confirmed progression endpoint only – all missing considered progression)
   For the FAS and confirmed progression endpoint only, intermittent missing observations will be multiply assuming MAR. Observations after receipt of prohibited medication or escape therapy will be considered MAR and undergo multiple imputation. For participants that discontinue treatment, their observations will be analyzed as observed. If a participant discontinues the study prior to Month 24 or 36 (depending on analysis timepoint) and has not achieved a confirmed progression prior to their study discontinuation, then the participant will be considered a non-responder, regardless of reason for discontinuation. Observations of participants that discontinue treatment or have invalid SE values will be analyzed as observed.

7. Sensitivity Analysis 7 (annual progression rate endpoint only - MMRM no imputations)
   For the FAS and annual progression rate analysis only, multiple imputations will not be performed for missing data. Observations after receipt of prohibited medication or escape therapy will be censored (e.g., set to missing.) Observations of participants that discontinue treatment or have invalid SE values will be analyzed as observed. The MMRM approach treats missing data as MAR.

The same analyses as detailed in section 8.1.1 above will be repeated for each sensitivity approach above.

All imputations will utilize prespecified SET SEEDS that will be identified prior to unmasking at for the Month 24 analysis and documented in a programming appendix.

Data assumed to be missing at random will be imputed via MCMC multichain methods with imputation 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) at each visit through the specified analysis timepoint, Month 24 or Month 36 as applicable. For the multiple imputation, it is planned to perform k=50 imputations, however the number of imputations may be increased depending on the amount of missing data.

All imputations for data assumed to be missing not at random 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 for the schedule SE visits through the analysis timepoint, Month 24 or Month 35, 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.

Data sets will be sorted by treatment and participant id prior to imputation.

8.1.3. Other Analysis

Subgroups will be defined based on the following:

- Baseline Age category (3 years to <6 years, 6 years to <9 years, 9 years to <12 years, and 12 years to 14 years)
- Baseline Age category (ages 6 to 14 only)
- Baseline Age category (ages 3 to <12 years)
- Baseline SE (0.50 D to 3.0 D and >3.0 D to 6.0 D)
- Baseline SE ($\geq$ 1.0 D only)
- Parental History of Myopia
    - No Parental History of Myopia (including unknown)
    - At least one parent with Myopia
- Ocular medical history (progression of SE vs. no progression of SE) within past 12 months
    - Participants with history of at least 0.5 D
    - Participants with history of progression of at least 1.0 D
- Iris Color (dark vs light)
- Region (Europe vs United States)
- Race (Caucasian (white) 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 efficacy endpoints will be analyzed separately for these subgroups using the FAS. The study is not powered for subgroup analysis; these analyses will be considered descriptive only. Forest type plots will be presented for the EMA and FDA primary efficacy endpoints and key secondary endpoints. The subgroup analyses will be performed using the same multiply imputed data as for the primary efficacy analyses.

For the annual progression rate efficacy endpoint, the mean and standard errors of annual progression rate will be calculated by imputation for each treatment arm by subgroup and the values combined via MIANALYZE to present the pooled estimate and corresponding 95% CI for each subgroup by treatment

For the confirmed progression efficacy endpoint, the proportion of participants with > 0.75 D progression and ASE [sqrt (p(1-p)/n)] will be calculated by imputation for each treatment arm by subgroup and the values combined via MIANALYZE to present the pooled estimate and corresponding 95% CI for each subgroup by treatment. Point estimates and CIs will be converted to percentages in the summary outputs (i.e., proportion * 100). For small subgroups, where there is no missing data or the imputed results are the same for all imputations (no variance between imputed sets), analysis will be performed on one dataset.

Additionally, an analysis on annual progression rate of myopia by eye at Month 24 with the same MMRM model as the primary analysis will be performed. For this analysis, observations after use of prohibited or escape medications will be censored. Observations post treatment discontinuation due to a related AE will also be censored. Observations after study discontinuation will not be imputed.

8.2. Secondary Efficacy Endpoints

The hypothesis testing of secondary endpoints will be conducted using a gatekeeping procedure based on a closed fixed-sequence test order and will be applied separately for the EMA and FDA submissions. The order of testing of secondary efficacy endpoints is defined in Section 3.3 For each endpoint, except for the EMA submission Subgroup analyses as detailed below, the truncated Hochberg adjustment, if required, will be applied if more than one dose of SYD-101 is to be compared to vehicle in order to control type I error for multiple comparisons for each endpoint.

The proposed procedure is detailed below.

- For the primary efficacy endpoint, statistical significance will be achieved for both dose comparisons if both comparisons have p-values < 0.045 [based on truncation $\alpha \times (1+\gamma)/2$]. If one dose comparison has as p-value ≥ 0.045, then the other dose comparison p-value must be less than 0.025 [$\alpha/2$] to be significant.

- The key secondary efficacy endpoint will be assessed for statistical significance dependent on the prior primary efficacy endpoint comparison outcomes.

    - If both dose comparisons were considered statistically significant for the primary efficacy endpoint, then the key secondary efficacy endpoint will be assessed at $\alpha = 0.05$ and statistical significance will be assessed as per the primary efficacy endpoint. (e.g., both comparisons are significant if both p-

values < 0.045, otherwise if one p-value ≥ 0.045, the other much be < 0.025 to be significant.)

- If only one dose comparison was considered statistically significant for the primary efficacy endpoint, then for the key secondary efficacy endpoint, only that dose comparison will be assessed for statistical significance and the comparison will be statistically significant for p-value < 0.005 [based on truncation $\alpha \times (1-\gamma)/2$]. The dose comparisons for all subsequent endpoints of the significant dose will be assessed at 0.005. The other dose comparison for the endpoint (and all subsequent endpoints for the non-significant dose) will be considered descriptive/nominal.

- If neither dose comparison was statistically significant for the primary efficacy endpoint, then both dose comparisons for the key secondary efficacy endpoint (and all subsequent endpoints) will be considered descriptive/nominal.

- The steps above for the key secondary efficacy endpoint will be repeated for each subsequent secondary endpoint as applicable. If both dose comparisons are significant for all endpoints, the last secondary endpoint will utilize the untruncated Hochberg procedure with $\alpha = 0.05$.

The gatekeeping procedure above will be applied for all primary and secondary endpoints in the FDA submission.

The gatekeeping procedure for the EMA submission is the same as described above through Endpoint 5 (time to progression of myopia), namely a truncated Hochberg procedure is used to test both doses for each endpoint. For Secondary Endpoint 6 for Fast Progressor Subgroup 1 and Endpoint 7 Fast Progressor Subgroup 2, the variable estimands depend on the outcomes for endpoints higher in the testing hierarchy.

- If both dose comparisons are statistically significant for all endpoints higher in the testing hierarchy, the active SYD-101 arms will be pooled for analysis of Endpoints 6 and 7, the annual progression rate for Fast Progressor Subgroup 1 and Fast Progression Subgroup 2, respectively.
  - The pooled comparison of SYD-101 to vehicle for Endpoint 6 will be performed at the retained alpha level of 0.05, and if statistically significant, the pooled comparison of SYD-010 to vehicle for Endpoint 7 will also be performed and assessed at $\alpha = 0.05$.
  - If both Endpoints 6 and 7 are statistically significant, then Endpoint 8 (axial length) each dose of SYD-101 will be compared to vehicle and the untruncated Hochberg procedure with $\alpha = 0.05$ will be used.
  - If Endpoint 6 (or Endpoint 7) is not statistically significant, then all subsequent endpoint(s) will be considered descriptive/nominal.

- If only one dose comparison was statistically significant for Endpoint 5, then only that dose of SYD-101 will be statistically compared to vehicle for Endpoint 6 and subsequent endpoints.)
    - The one dose comparison of SYD-101 to vehicle for Endpoint 6 will be performed at the retained alpha level of 0.005, and if statistically significant, the pooled comparison of SYD-010 to vehicle for Endpoint 7 will also be performed and assessed at $\alpha = 0.005$. The other dose comparison will be considered descriptive/nominal.
    - If both Endpoints 6 and 7 are statistically significant for the one dose comparison, then Endpoint 8 (axial length) will be compared to vehicle for that SYD-101 at $\alpha = 0.005$.
    - If Endpoint 6 (or Endpoint 7) is not statistically significant, then all subsequent endpoint(s) will be considered descriptive/nominal.

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 **Error! Reference source not found.**.

For the 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 **Error! Reference source not found.**.

All other secondary endpoints will be analyzed at both Month 24 and Month 36 except for the Fast Progressor Subgroup 1 and Subgroup 2 analyses for the EU submission which is analyzed at Month 24. For Fast Progressor Subgroups 1 and 2, data after receipt of prohibited treatment or escape medication will be censored and multiple imputation will not be performed for this endpoint. The censoring and MMRM analysis methods will be utilized for study discontinuation (regardless of reason) and receipt of prohibited treatment or escape medication. The analyses at Month 24 will be considered the primary timepoint for assessment of secondary endpoints for the EMA submission with analyses generated at Month 36 being considered exploratory. Conversely, the analyses at Month 36 will be considered the primary timepoint for assessment of secondary endpoints for the FDA submission, and the results generated at Month 24 being considered exploratory.

The mean change from baseline in axial length will be analyzed similar to the annual progression rate 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 axial length as a covariate. No explicit structure will be assumed for the covariance among the repeated measures. However, in case there is a convergence problem with the unstructured covariance, then a compound symmetry covariance structure will be assumed. The Kenward-Roger Method will be used to calculate the denominator degrees of freedom for the test of fixed effects. For analysis at Month 24, all through Month 24 will be included in the model. Observations after receipt of prohibited treatment or escape therapy will be censored. Observations after treatment discontinuation will be included as observed. Multiple imputation will not be performed. A single average axial length for the right and left eyes will be used for analysis.

Proportionate progression rate endpoints using different cutoffs to define myopic progression (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 endpoint using pairwise CMH tests; however, sensitivity analyses, other than PPS analyses, will not be performed.

Time to progression of myopia will be calculated in days as the date of first confirmed SE measurement that represents a reduction 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. Observations after treatment discontinuation will be included as observed. 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 all secondary endpoints excepting axial length, time to progression, and the Fast Progression subgroups, intercurrent events will be handled as specified in Table 3-5 Data will be multiple imputed assuming MAR for intermittent missing data. Observations after prohibited or escape treatments will be multiply imputed assuming MAR. Observations after discontinuation of treatment or study due to a related AE will be multiply imputed assuming MNAR using a sequential vehicle-based pattern regression. Observations after discontinuation of treatment or study not due to a related AE will be multiply imputed assuming MAR.

8.3. Other Efficacy Endpoints

Data collected after Month 36 will be considered exploratory analysis and summarized separately using descriptive statistics only and based on observed data. 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-assigned 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 after Month 36. Changes in continuous measures will be relative to the data collection at the Month 36 visit, unless otherwise specified.

Summaries to be provided for the grouping above include:

- Mean change from Month 36 in SE
- Mean annual progression rate from Month 36 to Month 48
- Proportion of participants with myopic progression from Month 36 >0.75 D
- Proportion of participants with annual myopia progression rate from baseline to Month 48 ⩽0.50 D/year
- Proportion of participants with annual myopia progression rate from baseline to Month 48 ⩽0.25 D/year
- Proportion of participants with increase from baseline of myopia of >0.50 D at Month 48
- Mean change in axial length from Month 36 to Month 48

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 and 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. For comparison, the same summaries will be presented for participants randomized SYD-101 therapy and who are not re-randomized to Vehicle at Month 36. Summary statistics will be presented by initial randomization group.

To evaluate the potential rebound and re-treatment 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 and 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 to investigate rebound. For comparison, the time intervals will be summarized for participants randomized SYD-101 therapy and who are not re-randomized to Vehicle at Month 36. Additionally, these summaries will also be subset by receipt of escape medication after Month 36.

To evaluate the escape medication effect, select summaries and plots will be provided by numerically comparing the participants who never received escape medication and the participants who received escape medication at Month 24, Month 30 and Month 36 by initial randomization group. Summaries and plots will be presented from Baseline to Month 36, and will include:

- Mean change from baseline in SE
- Mean annual progression rate

- Mean change from baseline in axial length

Select summaries will be provided for the subset 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 efficacy profile of those participants receiving up to 48 months of SYD-101 treatment. Summaries to be presented for this subset of participants includes:

- Mean change from baseline in SE
- Mean annual progression rate from baseline to Month 48
- Proportion of participants with myopic progression >0.75 D at or before Month 48
- Proportion of participants with annual myopia progression rate from baseline to Month 48 ⩽0.50 D/year
- Proportion of participants with annual myopia progression rate from baseline to Month 48 ⩽0.25 D/year
- Proportion of participants with increase from baseline of myopia of >0.50 D at Month 48
- Mean change from baseline in axial length at Month 48

Time spent on various activities (e.g., time spent on near activities, time spent outdoors, etc.) will be descriptively summarized by timepoint for each treatment group.

Time on activities will be collected separately for school/workdays. For analysis, the average hours per day for the week will be calculated as (5 × school/workday value + 2 × weekend value) / 7. Responses of "none" will be considered 0 hours and responses of "3 or more hours" will be included as 3 hours. The mean and 95% confidence intervals for time on activities by treatment, visit and subgroups defined in Section 8.1.3 will be provided if applicable.

As noted in Section 8.1.3 proportion of participants with myopic progression and the mean annual progression rate will be summarized numerically by subgroups defined by the time spent on various activities. For each type of activity, time outdoors and near work, the weekly average responses will be averaged to calculate an overall average per participant, and the median of the per participant overall averaged responses will be used to define the subgroups.

8.4. Quality of Life (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 QOL. Responses will be marked as strongly agree, agree, neither agree or disagree, disagree, strongly disagree. There are eight questions in all. Questions 2 to 7 will be scored from 5 for strongly agree to 1 for strongly disagree and questions 1 and 8 will be reversed scored from 1 for strongly agree to 5 for strongly disagree so that higher values consistently indicate a "worse" outcome for the participant. Summary statistics will be presented for each question as well as for the per participant average of the 8 questions. Participants will be included in the analysis of average question score if they have at least 4 non-missing question responses. For the average question score, missing question responses will be imputed from the mean of the available question responses. Additionally, a Wilcoxon Rank Sum test and frequency tables will be presented summarizing

results and individual participants responses will be listed. The Wilcoxon Rank Sum test will be performed in a pairwise manner comparing each treatment dose (SYD-101 0.01%, SYD-101 0.03%) to vehicle. The ranks are based on the observations of the two groups that are compared, p-values from the exact Wilcoxon Rank Sum test as well as the Hodges-Lehman estimates (Hodges, J. L.; Lehmann, E. L. (1963)). and Moses 95% CI (Moses, Lincoln E. (1965)) will also be presented for supportive use. No adjustment for type 1 error will be made for the multiple dose comparisons or multiple timepoints.

9. Safety Analysis

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 Set.

In general, for ocular assessments, safety will be summarized using the average of both eyes averages, with a few exceptions where presenting data for the eye with the worse response for the given assessment. Percentages, if applicable, will be calculated based on the number of participants in the Safety Set. For analysis of event data, participants will be counted once for given event if the event occurs in at least one eye.

For safety analyses from baseline to Month 24, the baseline will be considered the start of study prior to dose of any study medication. Unless otherwise specified, for safety analyses at Month 36, at Month 48, or from Month 36 to Month 48, data will be summarized based on treatment being taken at the time of event occurrence/assessment, including those who take SYD 101 0.03% as escape medication or who are re-randomized to Vehicle at Month 36. Participants who receive escape medication or who are re-randomized at Month 36 will be included under each treatment received during the analysis period. Percentages, if applicable, will be calculated based on the number of participants in the Safety Set who received at least one dose of the given treatment. For each treatment received, the baseline value will be the last non-missing assessment prior to initiation of the given treatment. (For participants originally randomized to SYD 101 0.03%, who are rerandomized o Vehicle at Month 36, and then subsequently switch to open label SYD 101 0.03% as escape medication, assessments made on SYD 101 0.03% will use the last non-missing value on or prior to Day 1/date of first SYD 101 0.03% treatment as baseline.) Total summaries will include data from assessments during the first 24 months while participants should be on their original randomized treatment only.

9.1. Adverse Events

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) according to treatment taken at the time of event. Adverse events with onset set more than 30 days from date study treatment discontinuation will be summarized separately. In addition, all SAEs, including deaths, will be listed and summarized separately.

For the purpose of inclusion in TEAE tables, incomplete AE start and end dates will be imputed as follows:

Missing onset dates (where UK and UKN indicate unknown or missing day and month respectively):

- UK-MMM-YYYY: If the month and year are different from the month and year of the date of first dose, assume 01-MMM-YYYY. If the month and year are the same as the month and year for the date of first dose, and the end date (after any imputation) is on or after the date of first dose, then assume the date of first dose (Day 1). If the month and year are the same as the date of first dose, and the end date (after any imputation) is prior to the date of first dose, then assume the end date for the start date.
- DD-UKN-YYYY/UK-UKN-YYYY: If the year is different from the year of the date of first dose, assume 01-JAN-YYYY of the collected year. If the year is the same as the date of first dose year, and the end date (after any imputation) is on or after the date of first dose, then assume the date of first dose (Day 1). If the year is the same as the date of first dose, and the end date (after any imputation) is prior to the date of first dose, then assume the end date for the start date.

Missing end dates (where UK and UKN indicate unknown or missing day and month respectively):

- UK-MMM-YYYY: Assume the last day of the month;
- DD-UKN-YYYY/UK-UKN-YYYY: Assume 31-DEC-YYYY

All adverse events will be classified by System Organ Class and Preferred Term (PT) according to the Medical Dictionary for Regulatory Activities (MedDRA, Version 21.0 or higher).

An overview summary of the number and percentage of participants with any TEAE, serious TEAE, treatment-related TEAE, treatment-related serious TEAE, TEAE leading to drug withdrawal, TEAE leading to study discontinuation, and AE leading to death will be provided by treatment group. The overall summaries will be presented for all adverse events, all ocular events, and all non-ocular events.

9.1.1. Incidence of Adverse Events

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. Incidence summaries will be presented separately for ocular and non-ocular events. For ocular summaries,

a participant will be counted once for the given level of summary if the participant experiences the event in either eye. Summaries of the following types will be presented:

- Overall summary of number of unique TEAEs and treatment-emergent SAEs
- Overall summary of number of unique TEAEs and treatment-emergent SAEs by subgroup (Age, Sex, Race and Iris Color)
- Participant incidence of TEAEs by MedDRA SOC and preferred term
- 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
- Participant incidence of non-serious AEs by MedDRA SOC and preferred term
- Participant incidence of AEs leading to discontinuation of study drug by MedDRA SOC and preferred term

At each level of summarization (e.g., 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.

At the Month 36 and Month 48 analysis, adverse events will be assigned based on the treatment being taken at the time of the event. If an event occurs after a participant is on escape medication, the event will be assigned to the SYD-101 0.03% treatment group regardless of the randomized treatment.

Additionally, adverse events will be summarized separately for those events with onset after Month 36. Events will be assigned based on the treatment being taken at the time of the event.

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.

9.1.2. Adverse Events Related to Study Drug

A summary of related TEAEs, either possibly related or related, to study drug will be presented in a table by total number of TEAE and incidence of occurrence. The investigator will provide an assessment of the relationship of the event to the study drug. If a participant reports multiple occurrences of the same TEAE, only the most closely related occurrence will be presented in the incidence count. TEAEs that are missing a relationship will be presented in the summary table

as “Related” but will be presented in the data listing with a missing relationship. Percentages will be calculated out of the number of participants in the Safety set.

The TEAE data will be categorized and presented by SOC, PT, and relationship in a manner similar to that described in Section 9.1.1.

9.1.3. Severity of Adverse Event

A summary of TEAEs by severity will be presented in a table by total number of TEAE and incidence of occurrence. The severity that will be presented represents the most extreme severity captured on the CRF page. The possible severities are “Mild,” “Moderate,” and “Severe.” In the TEAE severity table, if a participant reported multiple occurrences of the same TEAE, only the most severe will be presented in the incidence count. TEAEs that are missing severity will be presented in tables as “Severe” but will be presented in the data listing with a missing severity. Percentages will be calculated out of the number of participants in the Safety set. Additionally, a summary of TEAE related to study drug by severity will be presented.

9.1.4. Serious Adverse Events

Treatment-emergent SAEs will be presented in a table. At each level of participant summarization, a participant is counted once for the incidence if the participant reported one or more events. Percentages will be calculated out of the number of participants in the Safety set. The treatment-emergent SAE data will be categorized and presented by SOC and PT in a manner similar to that described in Section 9.1.1.

9.1.5. Death or Adverse Events Leading to Treatment or Study Discontinuation

All AEs leading to treatment or study discontinuation will be summarized. All discontinuations will be assessed based on data recorded in the AE eCRF page. AEs leading to treatment discontinuation will be identified as AEs where the action taken with study drug is “Drug Withdrawn”. AEs leading to study discontinuation will be identified as AEs where the caused study discontinuation field is marked as “Yes”. In addition, all deaths will be listed. Participant deaths will be identified as AEs where the outcome is “Fatal”.

9.1.6. Adverse Event by Annual Period

A summary of AEs by annual period: Year 1 (Study days 1- 409 inclusive), Year 2 (Study days 410- 773 inclusive), Year 3 (Study days 774- 1137 inclusive), and Year 4 (Study days 1138- 1516 inclusive), will be presented. Each period summary will be include AEs occurring in the period, either as a new onset event or a prior event ongoing into the period, including AEs with onset date within the period start and end dates (inclusive), AEs with a start date prior to the period start date and AE stop date after period start date, and AEs with start date prior to period start date and ongoing after period start date. Note, for the Month 24 and Month 36 analyses, the data of the data cut will also be taken into account for ongoing events to ensure that a participant had been followed so that the data cutoff date for the participant would be after the annual period start date. (e.g., if the data cut was taking on date that would be only 28 months of

follow-up for a participant, ongoing AEs for that participant would be counted in the Year 3 annual period but not be included in the Year 4 annual period.)

At each level of participant summarization, a participant is counted once for the incidence if the participant reported on or more events in that period. If an AE is ongoing across multiple periods, it will be counted in each period in which the AE was ongoing. Percentages will be calculated out of the number of Participants in the Safety set. The treatment-emergent SAE data will be categorized and presented by SOC and PT in a manner similar to that described in Section 9.1.1.

9.1.7. Adverse events after Treatment Discontinuation

All AEs after more than 30 days after the date of last does of study treatment discontinuation will be presented in a table. At each level of participant summarization, a participant is counted once for the incidence if the participant reported on or more events. Percentages will be calculated out of the number of Participants in the Safety set. The treatment-emergent SAE data will be categorized and presented by SOC and PT in a manner similar to that described in Section 9.1.1. All AEs after treatment discontinuation data by participant will be presented in a listing.

9.2. Vital Sign Measurements

Summary tables will be presented for vital sign data, including systolic blood pressure (mmHg), diastolic blood pressure (mmHg), temperature (C), heart rate (bpm), height(cm) and body weight(kg) by treatment group and overall for participants in the Safety set. Observed results at each visit and changes from baseline to each scheduled post-baseline visit will be presented. All vital sign data by participant will be presented in a listing.

9.3. Ocular Safety Data

9.3.1. Best Corrected Visual Acuity (BCVA)

Best-Corrected Visual Acuity (BCVA) will be measured in each eye prior to cycloplegia with the participant wearing current correction using the Early Treatment of Diabetic Retinopathy Study (ETDRS) testing protocol. If the vision is more than 1 line (≥5 letters) worse than baseline, the testing will be redone using trial frames or phoropter with the most recent subjective refraction.

Changes in BCVA will be summarized for the Safety Set and subgroups (Age, Sex, Race and Iris Color) based on the following categories:

- ⩾15 letters gained
- ⩾10 letters but <15 letters gained
- ⩾5 but <10 letters gained
- No change (<5 letters change)
- ⩾5 but <10 letters lost
- ⩾10 but <15 letters lost
- ⩾15 letters lost

Shift in BCVA from baseline will be measured for most recent assessment (i.e., the last available assessment prior to or on the analysis cut-off of Month 24, Month 36, Month 48) and worst-post baseline assessment at Month 24, Month 36 and Month 48 for each treatment received. The average of BCVA from the right and left eyes will be used for analysis.

9.3.2. Binocular Near Visual Acuity

Binocular Near Visual Acuity will be measured using the ATS4 Near Acuity Test with participants wearing current refractive correction prior to administration of cycloplegia on a bi-annual basis and results in Snellen equivalents will be recorded on the eCRF. Changes in near visual acuity at most recent post-baseline visit (i.e., the last available assessment prior to or on the analysis cut-off of Month 24, Month 36, Month 48) and for the worst post baseline assessment will be summarized based on the following categories:

- ⩾3 lines gained
- ⩾2 but <3 lines gained
- ⩾1 but <2 lines gained
- No change (<1 line change)
- ⩾1 but <2 lines lost
- ⩾2 but <3 lines lost
- ⩾3 lines lost

Line changes will be derived from the LogMAR equivalent scores using the following formula such that a positive value indicates a worsening/loss and a negative value indicates an improvement/gain:

LogMAR = -log(20/denominator of Snellen fraction)

Line change = 10 x [-log (20/dfollow-up) – (- log (20/dbaseline))],

where follow-up is the denominator of the Snellen fraction at a post-baseline visit
dbaseline is the denominator of the Snellen fraction at Baseline
log is logarithm base 10.

For example, the line change for a Snellen visual acuity at Baseline of 20/20 followed by a Snellen VA of 20/15 would be 10 x [- log(20/15) – (- log(20/20))] = -1.25 and represent an improvement/gain of 1.25 lines in visual acuity.

The number and percentage of participants with categorized line change will be summarized by treatment group. The eye with the most lines lost/least lines gained will be summarized.

9.3.3. Dilated Ophthalmoscopy

An ophthalmoscopy examination will be performed with pupil dilation using an indirect ophthalmoscope as per the current standard of practice to evaluate the condition of the vitreous, macula, retina, optic nerve, choroid, and retinal periphery.

Ocular findings will be evaluated by the following criteria:

- Normal
- Abnormal (not clinically significant [NCS])
- Abnormal with clinical significance (clinically significant [CS])

The number and percentage of participants with at least 1 treatment-emergent clinically significant abnormality for any parameter and for each parameter will be summarized for each treatment group. At each level of summarization, a participant will be counted once even if the participant experiences more than one treatment-emergent clinically significant abnormality summarizing data for the worse eye. For analysis, the worse eye will be defined as the eye with the greater degree of abnormality where Abnormal CS > Abnormal NCS > Normal. An abnormality will be deemed treatment emergent if the onset date is on or after the date of first treatment. Data from all ophthalmoscopy assessments will be listed.

At Month 36 and Month 48 analyses, findings will be summarized for participants by current treatment at time of abnormality.

9.3.4. Pupil Diameter

Pupil Diameter will be measured prior to any cycloplegia using a hand-held pupil card provided to the sites and the result in 0.5 mm increments will be recorded on the eCRF. Descriptive statistics for pupil diameter and changes from baseline at each assessment time point will be presented by randomized treatment. For analysis, the average of the right and left eyes will be used.

9.3.5. Binocular Accommodative Amplitude

Binocular accommodative amplitude will be measured with the participant wearing current refractive correction prior to cycloplegia with a study-specified accommodation near-point rule and results in diopter will be recorded on the eCRF. Descriptive statistics for amplitude and changes from baseline at each assessment time point will be presented by randomized treatment.

9.3.6. Corneal Endothelial Cell Density

Corneal endothelial cell count data will be obtained using specular microscopy at selected sites with the required equipment (approximately 25% of study participants). Three measurements in units of cells/mm^2 will be obtained for each eye at each visit and analysis will be performed using the mean of the 3 assessments, first averaged by eye, then averaged over both eyes.

Descriptive statistics for the mean central endothelial cell density and changes from baseline at each assessment time point will be presented by treatment group.

9.3.7. Biomicroscopy

Biomicroscopy (with corneal fluorescein staining) will be performed by slit-lamp examination of lids, conjunctiva, cornea, iris and lens evaluated as follows:

- Normal
- Abnormal (not clinically significant [NCS])
- Abnormal with clinical significance (clinically significant [CS])

The number and percentage of participants with at least 1 treatment-emergent clinically significant abnormality for any parameter and for each parameter will be summarized for each treatment group. At each level of summarization, a participant will be counted once even if the participant experiences more than one treatment-emergent clinically significant abnormality summarizing data for the worse eye. For analysis, the worse eye will be defined as the eye with the greater degree of abnormality where Abnormal CS > Abnormal NCS > Normal. An abnormality will be deemed treatment emergent if the onset date is on or after the date of first treatment At Month 36 and Month 48 analyses, findings will be summarized by current treatment at the time of abnormality to visit. Data from all ophthalmoscopy assessments will be listed.

9.3.7.1. Corneal Staining

Corneal staining will be graded as 0 = none, 0.5 = trace, 1 = mild, 2 = moderate, and 3 = severe. The number and percentage of participants for each grade will be summarized via shift from baseline tables for the worse eye for each treatment group. For analysis, the worse eye is the eye with the higher grade. Tables will be presented for baseline to worst visit (defined as highest grade) and baseline to most recent visit for Month 24 and Month 36 analyses. For Month 36 and Month 48, participants will be summarized by each treatment received (e.g., if a participant receives more than one treatment, the participant will be included under each treatment)

In addition, to investigate the recovery of any emergent corneal staining, the above analyses showing the shift from baseline to the most recent visit (e.g., last available visit prior to analysis cut-off) will be performed on the subset of participants who had a post-baseline value of 1 or greater based. Participants will be summarized by the treatment taken at the time of assessment.

9.3.8. Intraocular Presssure (IOP)

IOP will be measured with a tonometer per study site's standard operating procedures and results recorded in units of mmHg on the eCRF. For analysis, the frequency of increase greater than 10 mmHg from baseline to any post-baseline timepoint will be measured by treatment received at

the time of the increase. Participants will be counted under each treatment received. The average of the right and left eyes will be used for analysis.

9.3.9. Tolerability

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) with severity scored on a 0 to 3 scale (none, mild, moderate, severe) and frequency indicated as Intermittent or Continuous. The number and percentage of participants for each level of response for each parameter will be summarized at each visit based on current treatment.

The frequency distribution of severity score by visit will be presented by a bar chart.

The instructions to study investigators regarding tolerability assessments and adverse event reporting was inconsistent during the study duration. Only tolerability assessments that were reported as moderate or severe were required to be reported as an AE. Tolerability assessments that where mild were not to be considered AEs. However, some investigative sites were instructed to report any tolerability assessment greater than none as an AE. Investigators were not asked to remove adverse events once reported.

To investigate the potential reporting bias from incorrect site instructions, participants who have an adverse event for selected preferred terms will have their maximum tolerability severity score while on the same treatment as date of ae onset for corresponding assessment summarized. Table *9-1* below summarizes the assessments to be summarized and the AE preferred terms to define subset for summary. Reported Adverse events will be reviewed as the study progresses and terms to be included for each assessment will be updated as needed.

Table 9-1 Selected Preferred Terms for Tolerability

Assessment	**AE Preferred Terms**
Blurred Vision	VISION BLURRED, VISUAL ACUITY REDUCED
Burning/Stinging	EYE IRRITATION, OCULAR DISCOMFORT
Eye Pain	EYE PAIN, INSTILLATION SITE PAIN
Grittiness in Eye	FOREIGN BODY SENSATION IN EYES
Sensitivity to Light	PHOTOPHOBIA
Headache	HEADACHE, MIGRAINE, MIGRAINE WITH AURA, TENSION HEADACHE

9.4. Pregnancy Test

Serum pregnancy testing will be performed on an annual basis using human chorionic gonadotropin pregnancy urine dipstick test (female participants of childbearing potential only.) Pregnancy testing results will be listed.

10. Interim Analysis

There are no interim analyses planned for this study. Analyses performed at Month 24 for the EMA Submission are considered the final analysis of primary efficacy for that submission. Analyses performed at Month 36 for the FDA Submission are considered the final analysis of primary efficacy for that submission.

11. Changes in Planned Analysis

With protocol amendment 3, intercurrent event analysis has been expanded to include 6 sensitivity analyses per FDA and EMA primary and key secondary efficacy endpoint and the intercurrent event approaches for all endpoints have been modified from original protocol incorporating regulatory feedback from the FDA and EMA. An additional subgroup for fast-progressors has been added to the EMA endpoint to be included in secondary analysis. Statistical testing will be performed for QOL assessments for informational purposes.

12. Impact of COVID-19 on the Planned Analyses

On January 31, 2020, the Department of Health and Human Services issued a declaration of a public health emergency related to the Coronavirus Disease 2019 (COVID-19) acute respiratory disease, and on March 13, 2020, the President declared a national state of emergency. The Food and Drug Administration has recognized that the COVID-19 pandemic may impact the conduct, evolution, and statistical analyses of clinical trials across therapeutic areas (March and June 2020). Participants with missing clinic visits due to COVID-19 will be listed; participants were able to complete questionnaires via phone.

13. REFERENCES

Aldrich M. Too much screen time is raising rate of childhood myopia. 2018. https://keck.usc.edu/too-much-screen-time-is-raising-rate-of-childhood-myopia/. Accessed 18 May 2018.

Chua W-H, Balakrishnan V, Chan Y-H, et al. Atropine for the treatment of childhood myopia. Ophthalmology. 2006;113(12):2285-2291.

Dmitrienko A1, Soulakova JN, Millen BA. Three methods for constructing parallel gatekeeping procedures in clinical trials. J Biopharm Stat. 2011 Jul;21(4):768-86.

Eye Diseases Prevalence Research Group. The prevalence of refractive errors among adults in the United States, Western Europe, and Australia. Arch Ophthalmol.2004;122(4):495-505.

Goria, M.N. 1992. On the forth root transformation of chi-square. Australian Journal of Statistics, 34 (1), 55-64.

Hodges, J. L.; Lehmann, E. L. (1963). "Estimation of location based on ranks". Annals of Mathematical Statistics. 34 (2): 598–611. doi:10.1214/aoms/1177704172. JSTOR 2238406. MR 0152070. Zbl 0203.21105. PE euclid.aoms/1177704172.

Holden BA, Fricke TR, Wilson DA, et al. Global prevalence of myopia and high myopia and temporaltrends from 2000 through 2050. Ophthalmology. 2016;123(5):1036-1042.

Hollander, Myles and Douglas A. Wolfe. (1973),
Nonparametric Statistical Methods, New York: John Wiley &
Sons, 75-82.

Huang HM, Chang DS, Wu PC. The association between near work activities and myopia in children: a systematic review and meta-analysis. PLoS One. 2015;10(10):e0140419.

Lehmann, E. L. (1963). “Nonparametric Confidence Intervals for a Shift Parameter.” Annals of Mathematical Statistics 34:1507–1512.

Leo SW; Scientific Bureau of World Society of Paediatric Ophthalmology and Strabismus (WSPOS). Current approaches to myopia control. Curr Opin Ophthalmol. 2017;28(3):267-275.

Leo SW and Young TL. An evidence-based update on myopia and interventions to retard its progression. J AAPOS. 2011;15(2):181-189.

Matsumura H and Hirai H. Prevalence of myopia and refractive changes in students from 3 to 17 years of age. Surv Ophthalmol. 1999;44:S109-S115.

Morgan IG, Ohno-Matsui K, Saw SM. Myopia. Lancet. 2012;379(9827):1739-1748.

Moses, Lincoln E. (1965). Confidence Limits from Rank Tests. Technometrics 7(2), 257-260. https://doi.org/10.1080/00401706.1965.10490254

Pan CW, Ramamurthy D, Saw SM. Worldwide prevalence and risk factors for myopia. Ophthalmic Physiol Opt. 2012;32(1):3-16.

Prepas SB. Light, literacy and the absence of ultraviolet radiation in the development of myopia. Med Hypotheses. 2008;70(3):635-637.

Ratitch, B., O'Kelly, M. (2011). "Implementation of Pattern-Mixture Models Using Standard SAS/STAT Procedures." *In Proceedings of PharmaSUG 2011 (Pharmaceutical Industry SAS Users Group). Paper SP04*. Nashville.

Vitale S, Sperduto RD, Ferris FL III. Increased prevalence of myopia in the United States between 1971-1972 and 1999-2004. Arch Ophthalmol. 2009;127(12):1632-1639.

Williams KM, Bertelsen G, Cumberland P, et al.; European Eye Epidemiology (E(3)) Consortium. Increasing prevalence of myopia in Europe and the impact of education. Ophthalmology.
2015;122(7):1489-1497.

Wilson, E.B., Hilferty, M.M. 1931. The distribution of chi-squared. Proceedings of the National Academy of Sciences, Washington, 17, 684–688.

Wong TY, Ferreira A, Hughes R, Carter G, Mitchell P. Epidemiology and disease burden of pathologic myopia and myopic choroidal neovascularization: an evidence-based systematic review. Am J Ophthalmol. 2014 Jan;157(1):9-25.

World Health Organization. The impact of myopia and high myopia: report of the Joint World Health Organization-Brien Holden Vision Institute Global Scientific Meeting on Myopia, University of New South Wales, Sydney, Australia, 16-18 March 2015. Geneva: World Health Organization; 2017.

Xiong S, Sankaridurg P, Naduvilath T, et al. Time spent in outdoor activities in relation to myopia prevention and control: a meta-analysis and systematic review. Acta Ophthalmol. 2017;95(6):551 566.

14. APPENDICES

14.1. Summary of Analyses including Primary, Key Secondary, Secondary and Sensitivity

	Intercurrent Events					
Analysis	Intermittent Missing Data	Receipt of Prohibited Treatment	Receipt of Escape Therapy	Treatment Discontinuation	Study Discontinuation	Invalid SE Values
Primary Analysis FAS While on Treatment/ Hypothetical EMA Endpoint is Annualized Progression Rate at Month 24 FDA Endpoint is Confirmed Progression at Month 36	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 Participants who receive 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 Participants who receive escape medication will be considered non-responders (e.g., have progressed)	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 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	Treatment Policy Use observed data

	Intercurrent Events					
Analysis	Intermittent Missing Data	Receipt of Prohibited Treatment	Receipt of Escape Therapy	Treatment Discontinuation	Study Discontinuation	Invalid SE Values
Key Secondary FAS Multiple Imputation/ Composite EMA Endpoint is Confirmed Progression Annualized Progression Rate at Month 24 FDA Endpoint is Annualized Progression Rate at Month 36	Hypothetical Multiple imputation assuming MAR	EMA Endpoint: Composite Participants who receive prohibited treatment will be considered non-responders FDA Endpoint: Hypothetical Observations after receipt of prohibited treatment will be multiple imputed assuming MNAR; using a sequential vehicle-based pattern regression	EMA Endpoint: Composite Participants who receive escape medication will be considered non-responders FDA Endpoint: Hypothetical Observations after receipt of escape medication will be multiple imputed assuming MNAR; using a sequential vehicle-based pattern regression	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 Observations after discontinuation (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	Treatment Policy Use observed data
Secondary Endpoints FAS Multiple Imputation Same methodology employed at Month 24 and Month 36 for any secondary endpoints derived from SE	Hypothetical Multiple imputation assuming MAR	Hypothetical Observations after receipt of prohibited treatment will be multiple imputed assuming MAR	Hypothetical Observations after receipt of escape medication will be multiple imputed assuming MAR	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 Observations after discontinuation (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	Treatment Policy Use observed data

	Intercurrent Events					
Analysis	Intermittent Missing Data	Receipt of Prohibited Treatment	Receipt of Escape Therapy	Treatment Discontinuation	Study Discontinuation	Invalid SE Values
Secondary Endpoints PPS Multiple Imputation Same methodology employed at Month 24 and Month 36 for any secondary endpoints derived from SE	Hypothetical Multiple imputation assuming MAR	Hypothetical Observations after receipt of prohibited treatment will be multiple imputed assuming MAR	Hypothetical Observations after receipt of escape medication will be multiple imputed assuming MAR	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 Observations after discontinuation (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	Treatment Policy Use observed data
Sensitivity Analysis 1 PPS Primary Efficacy Endpoints While on Treatment/ Hypothetical EMA Endpoint is Annualized Progression Rate at Month 24 FDA Endpoint is Confirmed Progression at Month 36	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)	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	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 DC for other reasons will be multiply imputed assuming MAR FDA Endpoint: Composite	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
				Participants with discontinuation (DC) due to a related AE are non-responders Observations after DC for other reasons will be multiply imputed assuming MAR	Participants with discontinuation (DC) due to a related AE are non-responders Observations after DC for other reasons will be multiply imputed assuming MAR	
Sensitivity Analysis 1 PPS Key Secondary Endpoints FAS Multiple Imputation/ Composite EMA Endpoint is Confirmed Progression Annualized Progression Rate at Month 24 FDA Endpoint is Annualized Progression Rate at Month 36	Hypothetical Multiple imputation assuming MAR	EMA Endpoint: Composite Participants who receive prohibited treatment will be considered non-responders FDA Endpoint: Hypothetical Observations after receipt of prohibited treatment will be multiple imputed assuming MNAR; using a sequential vehicle-based pattern regression	EMA Endpoint: Composite Participants who receive escape medication will be considered non-responders FDA Endpoint: Hypothetical Observations after receipt of escape medication will be multiple imputed assuming MNAR; using a sequential vehicle-based pattern regression	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 Observations after discontinuation (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	Hypothetical Multiple imputation assuming MAR
Sensitivity Analysis 2 FAS Treatment Policy for Prohibited and Rescue Treatments EMA Endpoint is Annualized Progression Rate at	Hypothetical Multiple imputation assuming MAR	Treatment Policy Use observed data	Treatment Policy Use observed data	Treatment Policy Use observed data	EMA Endpoint: Hypothetical Observations after discontinuation (DC) due to a related AE will be multiply imputed assuming MNAR	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
Month 24 and Month 36 FDA Endpoint is Confirmed Progression at Month 24 and Month 36					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	
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	Hypothetical Observations after receipt of escape medication will be multiply imputed assuming MNAR	Treatment Policy Use observed data	Hypothetical Observations after study discontinuation will be multiply imputed assuming MNAR	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	Treatment policy for vehicle Use observed data Hypothetical for SYD	Treatment Policy Use observed data	Hypothetical Observations after study discontinuation will be multiply imputed assuming MNAR	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
		Observations after receipt of prohibited medication will be multiply imputed assuming MNAR	Observations after receipt of escape medication will be multiply imputed assuming MNAR			
Sensitivity Analysis 6 FAS for confirmed progression only – all 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 escape 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 regardless of reason for discontinuation Where X = Month 36 for FDA submission, 24 for EMA submission	Treatment Policy Use observed data
Sensitivity Analysis 7 FAS for annual progression rate 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

14.2. Schedule of Events

	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 [ba]	X						X				X				X			
Inclusion/Exclusion Review	X	X																
Demographics/Med Hx [d]	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 [e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs [f]	X						X				X				X			X
Urine Pregnancy Test Error! Reference source not found.		X					X				X				X			X
Tolerability Questionnaire [j]		X		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							
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 Questionnaireo	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.
m. Axial length will be measured by cycloplegic biometry (selected sites only; approximately 25% 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 (through Week 27) and then monthly from Month 7 until Month 48/End of Study.