PROTECT Study: A Prospective Study to Optimize the Atropine Concentration Staircase Protocol for Myopia Prevention in Children Version: V1.0 Version Date: January 19,2026

PROTECT Study: A Prospective Study on Optimizing the Atropine Concentration Staircase Protocol for Myopia Prevention in Children

PROTECT-Study: Prospective Research on Optimizing Atropine Concentration Escalation for Children′ s Myopia Prevention

Study drug: Atropine Sulfate Eye Drops (0.01%,0.02%,0.04%)

Version date: 2026-01-19

Version: V1.0

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catalogue

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1. List of Participating Institutions and Principal Investigators

province	Hospital Name	investigator
Tianjin	**Ophthalmology Hospital of Tianjin Medical University**	**Wei Ruihua**
Guizhou	Affiliated Hospital of Guizhou Medical University	Gu Hao
Guangdong	Foshan First People's Hospital	Shen Peiyang
Anhui	The First Affiliated Hospital of South Anhui Medical College	Wu Changfan
Yunnan	The First Affiliated Hospital of Dali University	Liu Fang
Hubei	Xiangyang Central Hospital	Mao Xiaochun
Hubei	Yellowstone City Central Hospital	Luo Steel
Jiangsu	Nanjing Maternal and Child Health Hospital	Wu Guangqiang
Shaanxi Province	Baoji People's Hospital	megacarp
Shaanxi Province	Xijing Hospital, Air Force Medical University	Dou Guorui
Tianjin	Tianjin Children's Hospital	Guo Zhen
Jiangsu	Affiliated Hospital of Jiangnan University	Wang Jihong
Fujian	Quanzhou Children's Hospital	Chen Yinhua
Sichuan	Chengdu Third People's Hospital	Huang Keke

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province	Hospital Name	investigator
Hubei	Union Hospital Affiliated to Tongji Medical College, Huazhong University of Science and Technology	Cheng Yang
Hunan	Chenzhou First People's Hospital	Li Zheng

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2、Abstract

2.1 Overview

research design	Prospective, multicenter clinical trial.
purpose of research	1. The efficacy of switching to higher-concentration (0.02% and 0.04%) atropine eye drops for delaying myopia progression in children with insufficient hyperopia reserve who show poor response to 0.01% atropine eye drops was clearly demonstrated. 2. To explore the threshold of myopia progression in children using 0.01% atropine eye drops when transitioning to higher concentrations (0.02% and 0.04%) of atropine eye drops.
Selection criteria	Subjects must meet all the following criteria to be enrolled 1. A written informed consent form signed by the child and their legal guardian has been obtained. 2. Children aged 6 to 9 years (inclusive). 3. Equivalent spherical diopter of computerized refraction after bilateral ciliary muscle paralysis: 0D<SE. The upper limit standards for SE are set as follows for different age groups: 6 years old: P25 = +1.13D,7 years old: P25 = +1.00D,8 years old: P25 = +0.88D,9 years old: P25 = +0.63D. 4. After bilateral ciliary muscle paralysis, the astigmatism detected by computerized refraction is ≤1.00D. 5. Anisometropia ≤1.5D. 6. No other organic lesions affecting visual acuity in both eyes. 7. Unaided visual acuity ≥0.8. 8. Ocular intraocular pressure (IOP) ≤21 mmHg.
exclusion criteria	Participants who meet any of the following criteria will not be eligible for enrollment: 1. Subjects who may have ocular diseases affecting vision or refractive errors (such as lens damage diseases like cataract, glaucoma, macular degeneration, corneal lesions, uveitis, retinal detachment, severe vitreous opacity, etc.). 2. Systemic diseases: Immune system disorders, central nervous system diseases, Down syndrome, asthma, severe cardiopulmonary dysfunction, and a history of severe hepatic or

	renal dysfunction. 3. Bilateral or unilateral ocular involvement with dominant strabismus or any other pathological ocular changes or acute inflammatory eye diseases. 4. Patients who have undergone myopia control treatments, including pharmacological therapy (e.g., atropine or piperazine), orthokeratology, multifocal soft lenses, multifocal hard lenses, functional eyeglass frames, or red light therapy. 5. Exclude patients who have used drugs affecting efficacy evaluation (e.g., anticholinergic agents: atropine, piperazine; cholinergic agents: pilocarpine) for systemic or local use within the preceding 3 months. 6. Patients with hypersensitivity to atropine, cipretosil, or other drugs used in this study. 7. Exclude participants who have participated in other drug clinical trials within the past 3 months. 8. Other circumstances deemed unsuitable by the investigator. 9. Individuals with chronic mental disorders or psychiatric abnormalities. 10. Those with an adjustment range below 8D.
trial group	1. Phase 1: 0-24 weeks (0-6 months) 0.01% Atropine Eye Drops, once daily, instill into both eyes. 2. Phase 2: 24-48 weeks (6-12 months) Adjust the atropine concentration in a stepwise manner based on the myopia progression rate from 0 to 24 weeks (6 months), administered once daily with instillation into both eyes. Group A: Good response ($\Delta SE \leq 0.25D$), continue to maintain 0.01% atropine. Group B: Moderate response ($0.25D < \Delta SE \leq 0.375D$), switched to 0.02% atropine. Group C: Poor response ($\Delta SE > 0.375D$), switched to 0.04% atropine.
trial PERIOD AND FOLLOW @-@ UP	1. The trial lasted a total of 12 months, with Phase I involving 6 months of self-administered medication follow-up for patients, and Phase II including follow-up with research support medications. 2. Drug retrieval, distribution, and follow-up examinations were conducted at the 3rd, 6th, 9th, and 12th months post-administration (time windows: 3rd month ± 2 weeks, 6th

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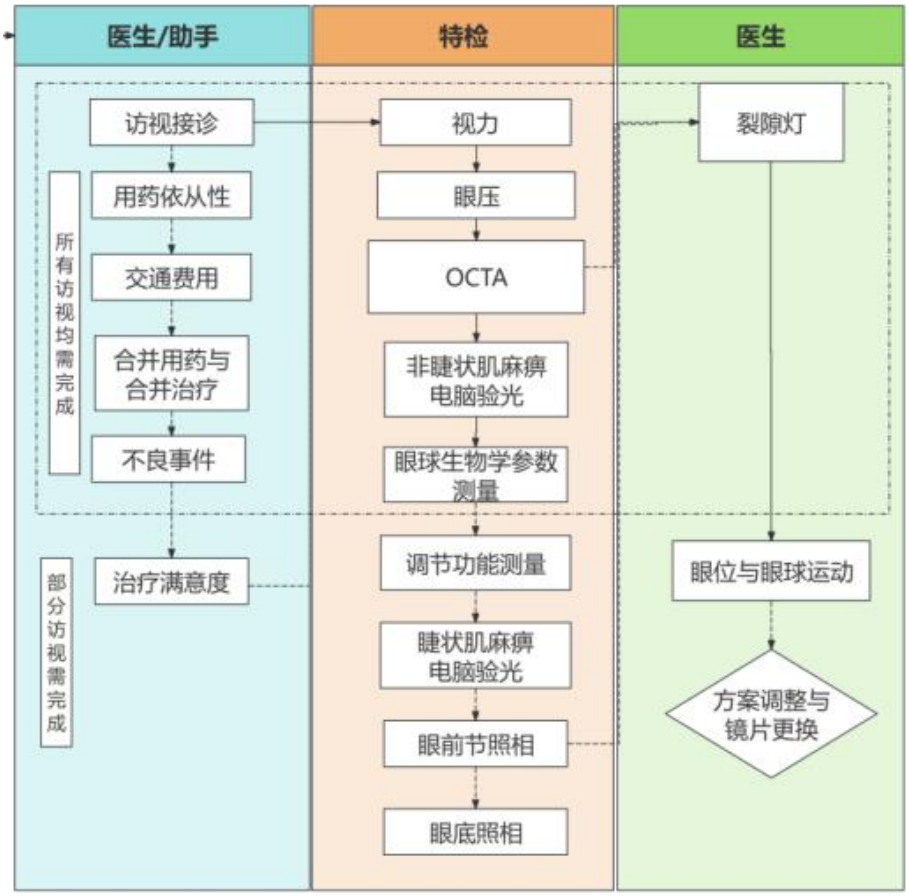
	month-2 weeks, 9th month ±2 weeks, 12th month-2 weeks). 3. Children with pre-existing myopia (ciliary muscle paralysis refraction SE ≤-0.5D) who exhibited a decline in uncorrected visual acuity below 0.8, requiring monocular glasses, were enrolled in the follow-up and continued medication monitoring.
evaluating indicator	1. Primary endpoint: Change in equivalent spherical refraction from baseline at 12 months. 2. Secondary endpoints: (1) Change in axial length from baseline at 12 months. (2) 12-month rapid myopia progression rate. (3) Safety: Incidence of adverse reactions. * Rapid myopia drift rate, defined as the percentage of children with a 6-month SER change < −0.25D
	3. Exploratory indicators: Pharmacoeconomic evaluation indicators (1) Cost-effectiveness Ratio (CER) (2) Incremental Cost-Effectiveness Ratio (ICER)
sample capacity	1. According to previous studies, during the first stage (0−6 months), there were significant differences in the change of SER between the three groups compared to baseline: Group A showed a decrease of −0.03 D (SD = 0.18), Group B a decrease of −0.31 D (SD = 0.07), and Group C a decrease of −0.53 D (SD = 0.12). To achieve Research Objective 1 (significant differences among the three groups in the first stage), a one-way ANOVA (assuming homogeneity of variance) was used for sample size estimation. The population variance was set at 0.5, the significance level at $\alpha = 0.05$, and the statistical power at $1-\beta = 0.80$. The calculation results indicated that at least 21 cases per group were required. Considering that the proportion of children with myopia progression>0.375 D (Group C) was the smallest among the three groups, the sample size for this group determined the total sample size. Assuming that the proportion of Group C was at least 10%, the study required at least 210 children to be enrolled. 2. To achieve Research Objective 2 (Phase 2: No significant differences among the three

	groups at 6－12 months), based on previous studies, the change in SER from June to December was －0.19 D (SD=0.22) in Group A, －0.09 D (SD=0.22) in Group B, and －0.02 D (SD=0.18) in Group C. Under the sample size conditions (21 cases per group), the statistical power of one-way ANOVA was 0.58, and the ANOVA test failed to reject the null hypothesis, indicating that the differences among the three groups were not statistically significant. Therefore, 21 cases per group can simultaneously meet the research objective of "no significant differences" in Phase 2. Considering an attrition rate of approximately 10%, a total of 233 children are required.

2.2 Flowchart



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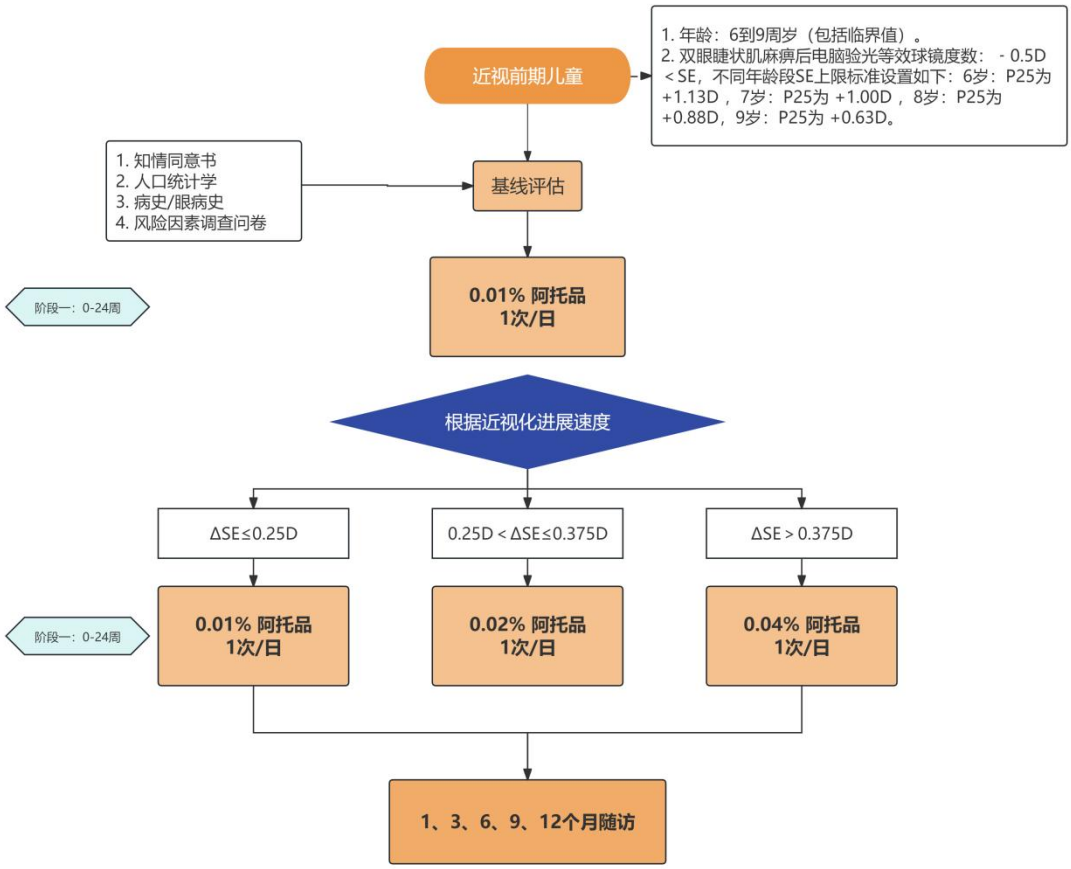

1. 阶段一：患者自购药随访6个月，阶段二：科研用药支持赠药随访。
2. 随访中已经发生近视的儿童（睫状肌麻痹验光SE≤-0.5D），且裸眼视力下降，低于0.8，配戴单光眼镜，并继续完成用药随访。

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2.3 Research Schedule

project visit	V1	V3	V4	V5	V6
	D-14 to D0	M3±2W	M6-2W	M9±2W	M12±2W
informed consent	X				
demography	X				
Medical history/Ocular history	X				
Risk Factor Survey Questionnaire 1	X				
Computerized refraction for anisocoria	X	X	X	X	X
intra-ocular tension	X	X	X	X	X
Vision 2	X	X	X	X	X
Ocular Biometric Measurements 3	X	X	X	X	X
Adjustment range measurement 4	X	X	X	X	X
slit lamp	X	X	X	X	X
Eye Position and Ocular Movement 5	X		X		X
Ciliary muscle paralysis computerized refraction 6	X		X		X
Ciliary muscle paralysis subjective refraction	X		X		X
eye-ground photography	X		X		X
OCTA7	X	X	X	X	X
orthopedic glasses	X				
compliance		X	X	X	X
Treatment Satisfaction Questionnaire 8			X		X
Visual Quality Questionnaire 9		X	X	X	X
Post-administration ocular tolerance		X	X	X	X
Inquiry about	X	X	X	X	X

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transportation costs					
adverse event		X	X	X	X
Concomitant medication and concurrent therapy 10	X	X	X	X	X

remarks	1. Risk factor questionnaire: Time spent on outdoor activities (exercise, leisure, etc.), time spent on close-up visual tasks (watching TV, using tablets), and parents' myopia levels 2. Visual acuity: including best corrected distance and near vision, recorded in decimal form 3. Biological measurements: IOL master measures anterior chamber depth, axial length, pupillary diameter, and corneal curvature 4. Adjustment range: measure the adjustment range using the approach method 5. Eye position and ocular motility: Assess eye position and ocular motility. If abnormalities are detected, document the specific type of abnormality. 6. Ciliary muscle paralysis computerized refraction: 0.5% compound tropicamylamine eye drops, administered every 5 minutes for a total of 3 times. The final instillation should be followed by a pupillary light reflex examination 30 minutes later. If the pupillary light reflex is absent, refraction should be performed; otherwise, the frequency of instillation should be increased. 7. OCTA: Choroidal Thickness and Blood Flow: Personalized Examination Based on Device Configuration 8. Therapeutic Satisfaction Questionnaire: Drug Therapy Satisfaction Scale-Second Edition (TSQM II) 9. Visual Quality Questionnaire: National Eye Institute Visual Function Questionnaire (NEI-VFQ-25) Chinese Version 10. Inquire whether other myopia prevention interventions are being administered concurrently

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3、background

Myopia is the most common type of refractive error worldwide and has become a major public health issue threatening the eye health of children and adolescents. The World Health Organization predicts that by 2050, the global prevalence of myopia will reach 50%, with high myopia accounting for nearly 10%, and the situation is particularly severe in East Asia. The prevalence of myopia among children in China has already ranked first in the world [1-3]. Myopia not only leads to decreased vision, but high myopia is also more likely to cause irreversible complications such as retinal detachment, choroidal atrophy, and macular degeneration, significantly increasing the risk of blindness [4]. Previous studies have shown that delaying the onset of myopia by one year can reduce the final myopia level by at least 0.75 D. Therefore, it is necessary to adopt effective myopia prevention measures to reduce the prevalence of myopia and the proportion of moderate and high myopia [5]. Thus, exploring safe and effective myopia prevention strategies is imperative.

Among various preventive measures, low-concentration atropine eye drops have garnered significant attention due to their remarkable therapeutic efficacy. As a non-selective muscarinic receptor antagonist, atropine can delay axial length growth by modulating scleral and choroidal signaling pathways. However, the optimal concentration for preventing myopia onset and progression remains inconclusive, with numerous studies focusing on different concentrations, most of which concentrate on 0.01%－0.05% [6-8]. Atropine eye drops at concentrations of 0.01%,0.025%, and 0.05% have been shown to improve refractive error and axial length growth in children with presbyopia, reduce the incidence of myopia in children, and not impair normal daily life or academic performance. Currently, 0.01% atropine eye drops are widely used in clinical practice. However, individual variations in efficacy are observed due to factors such as ethnicity, visual habits, age, and environmental conditions.

It is noteworthy that there are significant individual variations in the progression rate of myopia, and fixed-concentration regimens may fail to meet clinical needs. The stepwise concentration adjustment strategy has emerged, with the core principle being the modulation of drug concentration. Some scholars have proposed that initial use of 0.01% atropine eye drops yields suboptimal responses, and increasing the concentration can

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achieve better outcomes, thereby more effectively controlling the progression of myopia. However, existing "stepwise concentration" protocols lack multicenter evidence, particularly for prophylactic applications in children with early-stage myopia. Therefore, rigorous clinical trials are urgently needed to clarify the efficacy and safety of concentration escalation protocols in preventing myopia onset.

In conclusion, low-concentration atropine eye drops represent a critical option for myopia prevention and control. Further research is required to evaluate the efficacy of switching to higher-concentration (0.02% and 0.04%) atropine eye drops in children with insufficient hyperopia reserve who exhibit poor response to 0.01% atropine eye drops, as a means to delay myopia progression. Additionally, it remains necessary to investigate the threshold for myopia progression in children using 0.01% atropine eye drops when transitioning to higher-concentration (0.02% and 0.04%) formulations.

4、purpose

Clarify the efficacy of switching to higher-concentration (0.02% and 0.04%) atropine eye drops for delaying myopia progression in children with insufficient hyperopia reserve who exhibit poor response to 0.01% atropine eye drops. Explore the threshold for myopia progression in children using 0.01% atropine eye drops when transitioning to higher-concentration (0.02% and 0.04%) atropine eye drops.

5、research technique

5.1 Experimental Design

Prospective, multicenter clinical trial.

5.2 Eligibility Criteria

5.2.1 Eligibility Criteria

(1) Written informed consent was obtained from the child and legal guardian.

(2) Children aged 6 to 9 years (inclusive).

(3) After bilateral ciliary muscle paralysis, the equivalent spherical diopter of computerized refraction is: 0D<SE. The upper limit standards for SE are set as follows for different age groups: 6 years old: P25 is +1.13D,7 years old: P25 is +1.00D,8 years old: P25 is +0.88D,9 years old: P25 is +0.63D.

(4) The astigmatism degree detected by computerized refraction after bilateral ciliary

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muscle paralysis was ≤1.00D.

(5) The anisometropia of both eyes was ≤1.5D.

(6) No other organic lesions affecting visual acuity were found in both eyes.

(7) The eyes had the visual acuity of ≥0.8.

(8) The intraocular pressure in both eyes was ≤21 mmHg.

5.2.2 Exclusion Criteria

Participants who meet any of the following criteria will not be eligible for enrollment:

(1) Subjects who may have ocular diseases affecting vision or refractive errors (such as lens damage diseases like cataracts, glaucoma, macular degeneration, corneal lesions, uveitis, retinal detachment, severe vitreous opacity, etc.).

(2) Systemic diseases: immune system disorders, central nervous system diseases, Down syndrome, asthma, severe cardiopulmonary dysfunction, and a history of severe hepatic or renal dysfunction.

(3) Bilateral or unilateral ocular involvement with dominant strabismus or any other pathological ocular changes or acute inflammatory eye diseases.

(4) Treatment methods for myopia control include: pharmacological therapy (e.g., atropine or pilocarpine); orthokeratology lenses, multifocal soft lenses, multifocal hard lenses, or functional eyeglass frames; and red light therapy.

(5) Use of drugs affecting efficacy evaluation (e.g., anticholinergic agents: atropine, piperazine; cholinergic agents: pilocarpine) systemically or topically within the preceding 3 months.

(6) Patients with hypersensitivity to atropine, cyclopentolide, or other drugs used in this study.

(7) Participants who had participated in other drug clinical trials within the first 3 months prior to screening.

(8) Other circumstances deemed unsuitable by the investigator.

(9) Individuals with chronic mental disorders or psychiatric abnormalities.

(10) The adjustment range was lower than 8D.

5.3 Trial Grouping

(1) Phase 1: 0-24 weeks (0-6 months). 0.01% atropine eye drops, once daily, instilled into both eyes.

(2) Phase 2: 24-48 weeks (6-12 months). Based on the progression rate of myopia from 0-24 weeks (6 months), the atropine concentration is incrementally increased; administered once daily, instilled into both eyes.

Group A: Good response ($\Delta SE \leq 0.25D$), continue to maintain 0.02% atropine.

Group B: General response ($0.25D < \Delta SE \leq 0.375D$), switched to 0.02% atropine.

Group C: Poor response ($\Delta SE > 0.375D$), switched to 0.04% atropine.

5.4 Sample Size

(1) According to previous studies, during the first stage (0－6 months), there were significant differences in the change of SER between the three groups compared to baseline: Group A showed a decrease of －0.03 D (SD = 0.18), Group B a decrease of －0.31 D (SD = 0.07), and Group C a decrease of －0.53 D (SD = 0.12). To achieve Research Objective 1 (significant differences among the three groups in the first stage), a one-way ANOVA (assuming homogeneity of variance) was used for sample size estimation. The population variance was set at 0.5, the significance level at $\alpha = 0.05$, and the statistical power at $1-\beta = 0.80$. The calculation results indicated that at least 21 cases per group were required. Considering that the proportion of children with myopia progression>0.375 D (Group C) was the smallest among the three groups, the sample size for this group determined the total sample size. Assuming that the proportion of Group C was at least 10%, the study required at least 210 children to be enrolled.

(2) To achieve Research Objective 2 (Phase 2: No significant differences among the three groups at 6−12 months), based on previous studies, the change in SER from June to December was －0.19 D (SD=0.22) in Group A, －0.09 D (SD=0.22) in Group B, and －0.02 D (SD=0.18) in Group C. Under the sample size conditions (21 cases per group), the statistical power of one-way ANOVA was 0.58, and the

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ANOVA test failed to reject the null hypothesis, indicating that the differences among the three groups were not statistically significant. Therefore, 21 cases per group can simultaneously meet the research objective of "no significant differences" in Phase 2. Considering an attrition rate of approximately 10%, a total of 233 children are required.

5.5 Process

v.1 Baseline Assessment

For subjects intended for inclusion, the investigator shall explain the purpose, methodology, effects of the investigational drug, and potential adverse effects of the trial, obtain consent from the subject and their parent/guardian, and obtain a signed informed consent form. Subsequently, screening tests shall be conducted to determine whether the subject meets the case selection criteria.

The relevant processes include:

(1) Sign the informed consent form

(2) Collect demographic data (including age, gender, date of birth, and ethnicity)

(3) Medical history/Ocular history

(4) Risk Factor Questionnaire

(5) Computerized refraction for anisocoria

(6) intra-ocular tension

(7) Visual acuity: best corrected distance and near vision

(8) Ocular biometric measurements: axial length, anterior chamber depth, pupillary diameter, corneal curvature

(9) amplitude of accommodation

(10) Slit-lamp and anterior segment photography: external eye and conjunctiva, tear film, cornea, lens

(11) Eye Position and Ocular Movement

(12) Ciliary muscle paralysis (specific medication standards refer to SOP)

(13) Ciliary muscle paralysis computerized refraction

(14) Ciliary muscle paralysis subjective refraction

(15) eye-ground photography

(16) OCTA

(17) orthopedic glasses

(18) Record concomitant medications and combined therapies

(19) Inquiry on transportation costs to the hospital

For eligible participants who meet the enrollment criteria, schedule an appointment for the next planned visit.

v.2 1 month after medication (M1 ±2 weeks)

(1) Computerized refraction for anisocoria

(2) intra-ocular tension

(3) Visual acuity: best corrected distance and near vision

(4) Ocular biometric measurements: axial length, anterior chamber depth, pupillary diameter, corneal curvature

(5) amplitude of accommodation

(6) Slit-lamp and anterior segment photography: external eye and conjunctiva, tear film, cornea, lens

(7) OCTA

(8) orthopedic glasses

(9) compliance

(10) Visual Quality Questionnaire

(11) Post-administration ocular tolerance

(12) adverse event

(13) Record concomitant medications and combined therapies

(14) Inquiry on transportation costs to the hospital

v.3 3 months after medication (M3±2W)

(1) Computerized refraction for anisocoria

(2) intra-ocular tension

(3) Visual acuity: best corrected distance and near vision

(4) Ocular biometric measurements: axial length, anterior chamber depth, pupillary diameter, corneal curvature

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(5) amplitude of accommodation

(6) Slit-lamp and anterior segment photography: external eye and conjunctiva, tear film, cornea, lens

(7) OCTA

(8) orthopedic glasses

(9) compliance

(10) Visual Quality Questionnaire

(11) Post-administration ocular tolerance

(12) adverse event

(13) Record concomitant medications and combined therapies

(14) Inquiry on transportation costs to the hospital

v.4 6 months after medication (M6-2W)

(1) Treatment Satisfaction Questionnaire

(2) Computerized refraction for anisocoria

(3) intra-ocular tension

(4) Visual acuity: best corrected distance and near vision

(5) Ocular biometric measurements: axial length, anterior chamber depth, pupillary diameter, corneal curvature

(6) amplitude of accommodation

(7) Slit-lamp and anterior segment photography: external eye and conjunctiva, tear film, cornea, lens

(8) Eye Position and Ocular Movement

(9) Ciliary muscle paralysis (specific medication standards refer to SOP)

(10) Ciliary muscle paralysis computerized refraction

(11) Ciliary muscle paralysis subjective refraction

(12) eye-ground photography

(13) OCTA

(14) orthopedic glasses

(15) compliance

(16) Visual Quality Questionnaire

(17) Post-administration ocular tolerance

(18) adverse event

(19) Record concomitant medications and combined therapies

(20) Inquiry on transportation costs to the hospital

v.5 9 months after medication (M9±2W)

(1) Computerized refraction for anisocoria

(2) intra-ocular tension

(3) Visual acuity: best corrected distance and near vision

(4) Ocular biometric measurements: axial length, anterior chamber depth, pupillary diameter, corneal curvature

(5) amplitude of accommodation

(6) Slit-lamp and anterior segment photography: external eye and conjunctiva, tear film, cornea, lens

(7) OCTA

(8) orthopedic glasses

(9) compliance

(10) Visual Quality Questionnaire

(11) Post-administration ocular tolerance

(12) adverse event

(13) Record concomitant medications and combined therapies

(14) Inquiry on transportation costs to the hospital

v.6 12 months after medication (M12±2W)

(1) Treatment Satisfaction Questionnaire

(2) Computerized refraction for anisocoria

(3) intra-ocular tension

(4) Visual acuity: best corrected distance and near vision

(5) Ocular biometric measurements: axial length, anterior chamber depth, pupillary diameter, corneal curvature

(6) amplitude of accommodation

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(7) Slit-lamp and anterior segment photography: external eye and conjunctiva, tear film, cornea, lens

(8) Eye Position and Ocular Movement

(9) Ciliary muscle paralysis (specific medication standards refer to SOP)

(10) Ciliary muscle paralysis computerized refraction

(11) Ciliary muscle paralysis subjective refraction

(12) eye-ground photography

(13) OCTA

(14) orthopedic glasses

(15) compliance

(16) Visual Quality Questionnaire

(17) Post-administration ocular tolerance

(18) adverse event

(19) Record concomitant medications and combined therapies

(20) Inquiry on transportation costs to the hospital

5.6 Evaluation of Research Findings

5.6.1 Key Evaluation Indicators

The change of equivalent spherical diopter at 12 months was compared with that at baseline.

5.6.2 Secondary Indicators

(1) The change of axial length at 12 months compared with baseline.

(2) 12-month rapid myopia progression rate (percentage of 6-month SER change < −0.25D).

(3) Safety: Incidence of adverse reactions.

5.6.3 Economic Evaluation Indicators

① Cost-effectiveness Ratio (CER)

② Incremental Cost-Effectiveness Ratio (ICER)

6、Combined therapeutic measures

Children who have developed myopia during follow-up (ciliary muscle paralysis

refraction SE ≤ -0.5D) and whose uncorrected visual acuity has decreased below 0.8, wearing monocular glasses, should continue to complete medication follow-up and be noted in the case report form.

7、compliance

During each follow-up visit, inquire about the actual medication use of the subject and calculate the subject's medication adherence.

Medication adherence = (actual number of doses administered/theoretical number of doses administered) × 100%

Theoretical medication frequency = daily medication frequency × theoretical medication days.

8、Trial Duration and Follow-up

The trial lasted a total of 12 months. Phase 1: Patients self-purchased medications and underwent 6-month follow-up. Phase 2: Scientific research medication support and free medication follow-up. Drug retrieval, distribution, and inspection follow-ups were conducted at the 3rd, 6th, 9th, and 12th months post-administration (time windows: 3rd month ±2 weeks, 6th month-2 weeks, 9th month ±2 weeks, 12th month-2 weeks).

9、Observation, Recording, and Management of Adverse Events

9.1 Definition of Adverse Event (AE)

Any adverse medical event occurring during the follow-up study period (from the time of the subject's signing of the informed consent form to the last follow-up) is classified as an adverse event, regardless of whether there is a causal relationship with the study product. Therefore, an adverse event may be any adverse or unexpected signs, symptoms, or diseases that are temporally related to the study treatment, irrespective of whether they are treatment-related.

9.2 Observation and Evaluation of Adverse Events

The safety of post-marketing follow-up studies is evaluated through adverse event reporting by subjects or direct observation by investigators. During visits, investigators will inquire about adverse events in a non-inductive manner. Additionally, investigators are responsible for verifying test results. For abnormal (outside the normal range) test results,

they must confirm whether there is a deviation from baseline levels. If necessary, repeat testing or additional tests may be performed.

To confirm the original test results. If the test results show a meaningful abnormality compared to the baseline level, it should be classified as an adverse event.

9.3 Assessment of Adverse Event Severity

When completing the adverse event form, investigators will refer to the grading criteria of the "Common Terminology Criteria for Adverse Events (CTCAE) 5.0 (Chinese Version)" (November 27,2017) issued by HHS/NIH/NCI to comprehensively assess the severity of adverse events. To standardize the criteria, the grading of AE event severity is as follows:

Level 1:	Mild, asymptomatic or mild; only clinically or diagnostically apparent; no treatment required.
Level 2:	Moderate, requiring minor, localized, or non-invasive treatment; limited instrumental
Level 3:	Severe or medically significant but not immediately life-threatening; resulting in
Level 4:	Life-threatening; requires urgent treatment.
Level 5:	AE-related deaths.
Note: Activities of Daily Living (ADL) *: Instrumental activities of daily living refer to the use of telephones, etc.	

9.4 Determination of Correlation Between Adverse Reactions/Adverse Events and the Investigational Drug

Adverse reactions refer to adverse events associated with the investigational drug.

Low-concentration atropine eye drops are known to occasionally cause the following adverse reactions: ocular irritation, blurred vision, photophobia, allergic conjunctivitis, etc. If these occur, they will be closely monitored and quantitatively assessed, and recorded in the adverse event form.

Investigators should endeavor to explain each adverse event and establish their relationship with the investigational drug. Potential associations between adverse events, the investigational drug, and concomitant medications should be evaluated using the following five-level classification criteria:

(1) Negative correlation: The adverse event occurs at a time inconsistent with the

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rational sequence after medication administration, and the event does not match the suspected type of drug reaction. However, the clinical status of the subject or other treatments may have caused the reaction, or the disease improved or other treatments were discontinued, leading to the resolution of the event.

(2) Possible unrelated: The occurrence of adverse events does not align with the reasonable temporal sequence after medication administration, the event does not correspond to the known reaction type of the suspected drug, and the clinical status of the subject or other treatment modalities may also have contributed to the reaction.

(3) May be related: The occurrence of adverse events follows a reasonable temporal sequence after medication administration, and the events correspond to known types of reactions associated with the suspected drug. However, the clinical status of the subject or other treatment modalities may also have contributed to the observed reactions.

(4) Highly probable: The adverse event occurred in a reasonable temporal sequence after medication administration, the event corresponds to the known reaction type of the suspected drug, the symptoms alleviated after discontinuation of the drug, and the event cannot be reasonably explained by the known clinical status characteristics of the subject.

(5) Relevance confirmation: The adverse event occurs in a reasonable temporal sequence after medication administration, matches the known reaction type of the suspected drug, improves after discontinuation, and reappears upon repeated administration.

In this clinical study, adverse events classified as definitely related, very likely related, and possibly related were counted as the drug adverse reaction rate. Investigators should follow up on adverse reactions until symptoms resolve or stabilize.

9.5 Pharmacovigilance (PV) and Safety Data Reporting

(1) Scope of Reporting: The sponsor (healthcare institution) shall provide the sponsor/farmaceutically active substance (FAS) provider with the following safety data (including but not limited to): adverse reactions (ARs) occurring in subjects after administration of the investigational product (defined as harmful reactions unrelated to the intended use of the product under normal dosage and administration, including those potentially caused by product quality issues or associated with off-label use, overdose, etc.).

(2) Reporting timeline and method: During the study, if any drug safety information

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related to the product is identified, it should be reported to the sponsor/pharmaceutical provider's pharmacovigilance department within 3 calendar days via the Wenjuanxing mini-program (scan the QR code below).

Note: All shared data must undergo subject privacy desensitization.

Wenjuanxing Mini Prog

10、Compliance with ethical principles and relevant regulations

10.1 Medical Ethics Requirements

In compliance with the ethical review guidelines for biomedical research involving humans (2016) issued by the Ministry of Health, the WMA Declaration of Helsinki (2013), the CIOMS International Ethical Guidelines for Health-Related Research Involving Human Subjects (2016), and the ethical principles of Good Clinical Practice (GCP), the study will be conducted under the guidance of Good Clinical Practice (GCP) and in accordance with the protocol approved by the ethics committee. This ensures the scientific rigor of the study and protects the health rights of the participants.

10.2 Subject Protection

The informed consent process provides continuous explanations to participants and their parents/guardians, enabling them to make informed decisions about whether to initiate or continue participation in the study after thorough understanding and consideration. Investigators will discuss the study content with participants and their parents/guardians. Participants and their parents/guardians have the opportunity to raise questions before, during, and after the study. Participants and their parents/guardians are entitled to the right to be informed throughout the study and may withdraw from the study at any time without justification. The informed consent form provides an overview of the study, including its purpose, procedures and planned activities, potential risks and benefits, as well as alternative

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treatments available. The informed consent form also explains the rights of participants once they have participated in the study. Participants and their parents/guardians should be given sufficient time to consider whether to participate in the study. If they agree to participate, they must sign the informed consent form for the participant and their parents/guardians.

10.3 Benefits and Risks

Participants who enroll in this study will receive a free medication box per follow-up visit. During the follow-up period, investigators will provide one-on-one priority medical consultations, and personalized treatment plans will be formulated based on the examination results.

At the initial stage of low-concentration atropine eye drops administration, patients may experience varying degrees of photophobia, glare, blurred near vision, and localized allergic reactions. Relevant parameter changes should be monitored through pupil diameter measurement, accommodation function assessment, and intraocular pressure examination. For subjects intolerant to photophobia or glare, corrective measures such as wearing photochromic lenses can be implemented. Those with blurred near vision due to inadequate accommodation function may benefit from specialized accommodation training.

11、statistical analysis

11.1 Statistical Analysis Data Set

(1) Full Analysis Set (FAS): Conduct efficacy analysis on all subjects who received at least one dose of the drug, in accordance with the intention-to-treat (ITT) principle.

(2) Per-protocol Set: All cases that comply with the trial protocol, demonstrate good adherence, do not use prohibited medications during the trial period, and complete the required content in the case report form. The efficacy of the drugs is statistically analyzed simultaneously in both the FAS and PPS.

(3) Safety Analysis Set (SAS): All enrolled cases that have received at least one dose of the investigational drug and have complete post-administration safety records are included in the Safety Analysis Set. This dataset is used for safety analysis.

11.2 Statistical Analysis Plan

For each subject, the right eye was included in the analysis.

12、economics evaluation

12.1 Data Definition and Data Sources

(1) Direct costs: Focus on the consumption of medical resources directly related to the use of low-concentration atropine eye drops

(2) Indirect costs: Non-medical expenses (transportation costs) incurred by families due to children's participation in this study and the use of low-concentration atropine eye drops.

To clearly delineate the components of this evaluation metric, all relevant parameters were systematically collected and documented in a self-designed form (see Appendix 2).

12.2 Cost Estimation Formula

Total cost of investigational drug = unit price × total number of required boxes

Total required boxes = Total required units / Units per box. If the total is less than one box, it is rounded up to one box.

Total required quantity = Daily usage frequency × Number of usage days

If the drug packaging specifications change during the research process, the 'number of units per box' parameter must be updated immediately, and the total required number of boxes and costs must be recalculated to avoid deviations from the actual procurement costs.

12.3 Cost-Effectiveness Analysis

Based on the clinical efficacy indicators established in this study protocol, the cost-effectiveness relationship of low-concentration atropine eye drops was quantified without setting up an additional control group, with economic evaluation solely based on its own efficacy data:

1. Effectiveness indicators:

1) Reduction rate of equivalent spherical error progression within 12 months (ΔSE, unit: D)

2) Reduction in axial length growth within 12 months (△AL, unit: mm)

3) Adverse reaction incidence rate (refer to the adverse reaction type statistics in the package insert), with "1-Adverse reaction incidence rate" serving as a supplementary safety efficacy indicator

Key indicator calculation

Unit efficacy cost = Total input cost of low-concentration atropine / Corresponding efficacy index value

2. Analytical Methods

The following analyses were conducted using "external real-world controls" as the benchmark for comparison.

(1) Cost-Effectiveness Ratio (CER): Calculate the "cost per 0.25D delay in equivalent spherical lens progression" and "cost per 0.1mm delay in axial length growth" for the trial group, and compare these with the CER of the external control to evaluate the cost-effectiveness of the product.

(2) Incremental cost-effectiveness ratio (ICER): ICER = (total cost of the trial group-total cost of the control group) / (effect of the trial group-effect of the control group). Using 3 times China's per capita GDP as the economic threshold, if the ICER is below this threshold, the trial drug is considered to have economic advantages.

3. Sensitivity Analysis

The robustness of the results was verified through single-factor sensitivity analysis (fluctuation simulation of ±10% for product procurement price, ±5% for diagnosis and treatment costs, and ±15% for efficacy indicators) and probabilistic sensitivity analysis (Monte Carlo simulation 1000 times, assuming costs follow a Gamma distribution and efficacy follows a Beta distribution).

12.4 Long-term Economic Value Prediction Model (Markov Model)

Based on the clinical characteristics of low-dose atropine treatment for pediatric myopia (long-term progression and dynamic changes in complication risk with myopia severity) and the "China Pharmacoeconomic Evaluation Guidelines (2011 Edition)", the Markov model (for long-term cost-effectiveness analysis) and the Budget Impact Analysis

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(BIA) model (for short-term health insurance budget prediction) were selected as core prediction tools.

1. Health Status Classification

health status	Definition (SER range/clinical characteristics)
S1: Mild myopia	SER (Equivalent Sphere Refractive Power): -0.5 to>-3.0D, no complications
S2: Moderate myopia	SER: -3.0 to>-6.0D, no complications
S3: High myopia	SER ≤-6.0D, no complications
S4: Myopia-Related Complications	concomitant with one or more complications such as retinal detachment, macular degeneration, or glaucoma
S5: Death	All-cause death (model termination state)

2. Key Model Assumptions

1) Basic case analysis

- Core outputs: Incremental cost-effectiveness ratio (ICER) (formula: ICER = (total cost of low-concentration atropine group-total cost of SVL group) / (total QALY of low-concentration atropine group-total QALY of SVL group)), lifetime QALY gain, and lifetime cost difference.
- Predictive logic: Low-dose atropine reduces the incidence of high myopia and its subsequent complications by decreasing the transition probability from S1 to S2 to S3, thereby achieving "cost increment ≤ health benefit increment".

2) Sensitivity Analysis

- Single-factor sensitivity analysis: Testing the impact of key parameter fluctuations on ICER, with key parameters including low-concentration atropine efficacy, drug price, and high myopia complication risk
- Probability sensitivity analysis: Monte Carlo simulation (1000 iterations) was employed to randomly sample all parameters (cost parameters followed a gamma distribution, utility/transit probabilities followed a beta distribution), generating cost-effectiveness acceptable curves (CEACs) to evaluate the probability of low-concentration atropine being cost-effective under different payment thresholds.

3) Subgroup Analysis

Calculate the ICER separately for key subgroups in clinical practice that may affect cost-effectiveness:

- Age: 4–8 years (early-onset myopia) vs. 9–16 years (late-onset myopia)
- Combined optical interventions: monocular glasses vs combined orthokeratology (OK) lenses vs combined defocused spectacle frames
- Medication adherence: High adherence (adherence rate ≥ 70%) vs. Moderate adherence (70%> adherence rate ≥30%) vs. Low adherence (adherence rate <30%)

13、Analysis of drug proportion effect

13.1 Definitions and Scope of Measurement

Definition of drug cost proportion: The proportion of "drug expenses" incurred by subjects during the trial period (from screening to 6-month follow-up, potentially extended to 48 weeks as appropriate) relative to the "total medical expenses" during the same period.

- Medication costs: including the cost of low-concentration atropine eye drops, medications for adverse reaction management (e.g., anti-allergic eye drops), and ocular medications permitted for concomitant therapy (to be noted in the case report form).
- Total treatment cost: Medication cost + Examination cost (essential/optional examinations for this study) + Basic orthodontic consumables cost (e.g., off-focus frame lenses, OK lenses, only for combined treatment-related purposes) (see Appendix 1)

13.2 Data Collection and Methods

(1) Data Sources

- Hospital system data: Extract "drug revenue" and "examination revenue" for subjects at each visit point (screening period, 1M,3M,6M) through the hospital HIS system, and cross-reference with the "Cost Detail Record Form" in the CRF to ensure data traceability.
- Manual verification: For consumables expenses related to combined therapies (e.g., OK lenses), the brand, procurement date, and amount must be recorded in the CRF to exclude non-study period consumable replacement costs.

(2) Collection Time Nodes

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Visit stage	Collect content
Screening period (D-14 to D0)	Basic examination fee, initial prescription fee (if required)
3M follow-up (M3±2W)	Drug costs (adjusted accounting), follow-up examination fees, and combined treatment consumables costs (if newly added)
6-month follow-up (M6-2W)	Drug costs (adjusted accounting), follow-up examination fees, and combined treatment consumables costs (if newly added)
9M follow-up (M9±2W)	Drug costs (adjusted accounting), follow-up examination fees, and combined treatment consumables costs (if newly added)
12-month follow-up (M12-2W)	Summary of drug costs, end-of-life examination fees, and cumulative drug/examination/consumable expenses over 6 months

13.3 Comparison Benchmark

(1) Internal benchmark: The average proportion of medication costs for myopic patients aged 4-16 years in the pediatric ophthalmology outpatient department of the hospital during 2024-2025 (provided by the hospital's medical insurance office, excluding cases of non-standard medications such as systemic anti-infective drugs)

(2) External benchmark: The "Target for Controlling the Proportion of Pediatric Outpatient Medications in Secondary and Above Hospitals by 2025" issued by the National Health Commission (NHC) (subject to the latest policy documents)

13.4 Analytical Methods

(1) Descriptive analysis: Calculate the mean proportion of medication (±standard deviation) for all subjects, and perform subgroup analysis based on "frequency of medication (once daily/twice daily)" and "whether adverse reactions occurred (yes/no)", to observe differences in the proportion of medication among subgroups and their underlying causes.

(2) Compliance assessment: Compare the proportion of trial drugs with internal benchmarks and external control targets

- If the proportion of trial drugs is ≤ the control target, it is determined to comply with the hospital's drug proportion management requirements;

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- If the proportion of trial drugs exceeds the control target, a detailed analysis of the reasons for the overrun (e.g., increased dosage of trial drugs, increased use of medications for adverse event management, etc.) should be conducted, and optimization recommendations should be proposed.

14、test schedule

Upon receiving the ethics committee approval and the investigational drug, each clinical unit shall conduct clinical studies in accordance with the clinical research protocol, aiming to complete the assigned number of clinical trial cases within 14 months.

Principal Investigator: Date: Year Month Day

Principal Investigator: Date: Year Month Day

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Appendix 1 Basic Medical Related Cost Record Form

order number	cost item	unit	Fill in by center (RMB)	Data source/Notes
1	Unit purchase price of low-concentration atropine eye drops	Yuan per box		Hospital Drug Procurement Ledger/HIS System Drug Outbound Record
2	Total medication cost for a 6-month basic medication cycle	Yuan		Hospital Drug Procurement Ledger/HIS System Drug Outbound Record
3	Cost of cycloplegic refraction	CNY per session		Hospital Medical Service Price List/Patient Visit Fee Details
4	Number of cycloplegic refraction tests	Next		Patient Visit Fee Details/Medical Record
5	Cost of ocular biological parameter measurements	CNY per session		Hospital Medical Service Price List/Patient Visit Fee Details
6	Number of ocular biometric parameter measurements	Next		Patient Visit Fee Details/Medical Record
7	Intraocular pressure measurement cost	CNY per session		Hospital Medical Service Price List/Patient Visit Fee Details
8	Number of intraocular pressure measurements	Next		Patient Visit Fee Details/Medical Record
9	Fundus photography cost	CNY per session		Hospital Medical Service Price List/Patient Visit Fee Details
10	Number of fundus photographs	Next		Patient Visit Fee Details/Medical Record
11	cost of anterior segment	CNY		Hospital Medical Service

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	photography	per session		Price List/Patient Visit Fee Details
12	Number of anterior segment photographs	Next		Patient Visit Fee Details/Medical Record
13	Cost of slit lamp examination	CNY per session		Hospital Medical Service Price List/Patient Visit Fee Details
14	Number of slit lamp examinations	Next		Patient Visit Fee Details/Medical Record
15	Adjustment fee for functional testing	CNY per session		Hospital Medical Service Price List/Patient Visit Fee Details
16	Adjust the number of function tests	Next		Patient Visit Fee Details/Medical Record
17	OCTA cost	CNY per session		Hospital Medical Service Price List/Patient Visit Fee Details
18	OCTA number of times	Next		Patient Visit Fee Details/Medical Record
19	Cost of glasses	CNY per session		Patient Visit Fee Details/Medical Record
20	Number of glasses fitted	Next		Patient Visit Fee Details/Medical Record
21	Other related examinations, training costs, and frequency	CNY per session		Hospital Medical Service Price List/Patient Visit Fee Details

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Appendix 2 Record Form of Economic Indicators

definition		**unit**	**Fill in by center**	**statistical description**
direct cost	Drug cost	Yuan		Total medication cost for a 6-month basic medication cycle
	Cost of spectacles	Yuan		Total cost of glasses for 6 months
	check cost	Yuan		Total number of required examinations during the follow-up period (ciliary muscle paralysis computerized refraction, axial length measurement, intraocular pressure testing, fundus photography) and associated costs
	adverse reaction management cost	Yuan		Additional medical expenses incurred due to adverse drug reactions (e.g., photophobia, allergic conjunctivitis), including costs for symptomatic medications (e.g., antihistamine eye drops) and adjunctive interventions (e.g., tinted contact lens fitting).
indirect cost	family transportation expenses	Yuan		Transportation costs for children and accompanying parents to visit the research center for follow-up
Incremental Cost-Effectiveness Ratio (ICER)		Yuan /QALY		ICER = Incremental Cost/Preventive Effect, between groups