Trials

STUDY PROTOCOL

Open Access

# Digital therapeutics approach for young children with myopia using SAT-001 (DAYS): study protocol for a randomized controlled trial

Hae Jung Paik[1*], Byung Joo Lee[2], Dong Hui Lim[3], So Young Han[4], Eun Hye Jung[5], Hyun Jin Shin[6], Hyun Kyung Kim[7], Ungsoo Samuel Kim[8], Won Jae Kim[9], Hee Young Choi[10], Jihae Park[11], Soolienah Rhiu[12], Jihye Lee[13], Moonjeong Kim[13] and Kyunghee Kim[13]

## Abstract

**Background** Myopia is a prevailing refractive disorder and rapidly increases the risk of vision-threatening conditions. Earlier intervention is crucial to suppress myopia progression; however, the pharmacological and non-pharmacological therapies currently available have limitations. SAT-001 is a novel digital therapeutic software developed for myopia control and is designed to overcome the limitations of existing therapies. The present study aims to evaluate the efficacy and safety of the software as a medical device, SAT-001, for the inhibition of myopia progression and treatment in pediatric patients with myopia.

**Methods** This clinical trial is a two-arm, prospective, randomized, open-label study with a duration of approximately 25 months, comprising a maximum of 52 weeks of participant participation. We will enroll 110 pediatric patients with myopia aged 5 to < 9 years, each with a spherical equivalent of − 0.75 D to − 5.75 D in each eye. Eligible participants will be randomly assigned in a 1:1 ratio to either the study group using SAT-001 with single-vision spectacles or the control group using single-vision spectacles alone. The change in the spherical equivalent refractive error (SER) at 48 weeks from baseline serves as the primary endpoint. The change in SER at 24 weeks and axial length at every 12 weeks from baseline will be the secondary endpoints. Each change will be assessed depending on the myopic severity. Treatment emergent adverse events will be evaluated for the safety analysis.

**Discussion** This randomized controlled trial aims to confirm the efficacy and safety of SAT-001 in slowing pediatric myopia progression. The findings of this study could establish SAT-001 as an easily accessible, convenient, and non-invasive treatment option with minimal side effects, offering long-term myopia control from an early stage. Further research is needed to validate the effectiveness of SAT-001 for moderate to high myopia and concurrent conditions like astigmatism and to improve user engagement, diversify the program, and integrate with hospital-based treatments.

**Trial registration** ClinicalTrials.gov: NCT06344572; date of registration: April 12, 2024 (retrospectively registered).

**Keywords** *Trials* guidance: pediatric myopia, Digital therapeutics, SAT-001, Software as a medical device (SaMD), Randomized controlled trial (RCT)

*Correspondence:
Hae Jung Paik
hjpaik@gilhospital.com
Full list of author information is available at the end of the article

## Administrative information

Note: the numbers in curly brackets in this protocol refer to SPIRIT checklist item numbers. The order of the items has been modified to group similar items (see http://www.equator-network.org/reporting-guidelines/spirit-2013-statement-defining-standard-protocol-items-for-clinical-trials/).

| | |
|---|---|
| Title {1} | Digital therapeutics Approach for Young children with myopia using SAT-001 (DAYS): study protocol for a randomized controlled trial. |
| Trial registration {2a and 2b}. | ClinicalTrials.gov: NCT06344572; date of registration: April 12, 2024 (retrospectively registered). |
| Protocol version {3} | Version 2.0, April 23, 2024 |
| Funding {4} | S-Alpha Therapeutics, Inc. provided funding for this clinical trial. |
| Author details {5a} | *Hae Jung Paik*[1]*, *Byung Joo Lee*[2], *Dong Hui Lim*[3], *So Young Han*[4], *Eun Hye Jung*[5], *Hyun Jin Shin*[6], *Hyun Kyung Kim*[7], *Ungsoo Samuel Kim*[8], *Won Jae Kim*[9], *Hee Young Choi*[10], *Jihae Park*[11], *Soolienah Rhiu*[12], *Jihye Lee*[13], *Moonjeong Kim*[13], *and Kyunghee Kim*[13]<br>1 Department of Ophthalmology, Gachon University Gil Medical Center, Incheon, Republic of Korea<br>[2] Department of Ophthalmology, Asan Medical Center, Seoul, Republic of Korea<br>[3] Department of Ophthalmology, Samsung Medical Center, Seoul, Republic of Korea<br>[4] Department of Ophthalmology, Kangbuk Samsung Hospital, Seoul, Republic of Korea<br>[5] Department of Ophthalmology, Nowon Eulji Medical Center, Seoul, Republic of Korea<br>[6] Department of Ophthalmology, Konkuk University Medical Center, Seoul, Republic of Korea<br>[7] Department of Ophthalmology, HanGil Eye Hospital, Incheon, Republic of Korea<br>[8] Department of Ophthalmology, Chung-Ang University Gwangmeyong Hospital, Gwangmeyong, Republic of Korea<br>[9] Department of Ophthalmology, Yeungnam University Medical Center, Daegu, Republic of Korea,<br>[10] Department of Ophthalmology, Pusan National University Hospital, Busan, Republic of Korea,<br>[11] Department of Ophthalmology, Daegu Fatima Hospital, Daegu, Republic of Korea<br>[12] Department of Ophthalmology, Hallym University Dongtan Sacred Heart Hospital, Hwaseong, Republic of Korea<br>[13] S-Alpha Therapeutics, Inc., Seoul, Republic of Korea<br>***Correspondence to***<br>*Professor Hae Jung Paik, Department of Ophthalmology, Gachon University Gil Medical Center, Incheon, Republic of Korea* |
| Name and contact information for the trial sponsor {5b} | S-Alpha Therapeutics, Inc.<br>17th F., 311, Gangnam-daero, Seocho-gu, Seoul, Republic of Korea<br>salpha@salphadtx.com<br>+82–2–3487–3923 |
| Role of sponsor {5c} | The sponsor is responsible for research sponsorship and funding, has participated in the study design, and holds the decision making and ultimate authority over the publication of the report. |

## Introduction

### Background and rationale {6a}

Myopia is the most common refractive error and affects approximately 30% of the global population [1, 2]. The prevalence of myopia increases markedly from approximately 6 years of age, with East Asians having the highest prevalence, reaching 34.5% by 10 years of age [3]. This high incidence has made myopia a public health issue owing to its potential yet serious risks. Early-onset myopia is more prone to escalate into high myopia, which can manifest pathological complications, such as glaucoma, cataracts, retinal detachment, and even more detrimental, permanent vision loss [4–9].

Early intervention for myopia can improve the quality of life for children, reduce the economic burden, and prevent the progression to more severe consequences [10, 11]. Various interventions are currently being used to slow the progression of myopia, including low-dose atropine, orthokeratology, and peripheral defocus contact lenses. However, these methods have limitations, such as side effects, cost burden, and insufficient effectiveness in some patients [12]. SAT-001 is software designed to non-invasively suppress the progression of myopia in children by employing eye activity in a well-lit environment through a game format. It also provides modules that promote appropriate relaxation effects.

We hypothesized that the use of SAT-001 would induce extracellular matrix remodeling to help maintain the tensile strength of the sclera, thereby inhibiting axial elongation [13]. A pilot study conducted prior to this trial reviewed the potential efficacy and safety of SAT-001 in slowing the progression of myopia. Therefore, this clinical trial was planned to confirmatively evaluate the efficacy and safety of SAT-001. Schematic illustration showing theoretical hypothesis of SAT-001 is presented in Fig. 1.

### Objectives {7}

The objective of this clinical investigation is to confirm the efficacy and safety of SAT-001, designed as Software as a Medical Device (SaMD) for slowing myopia progression and treatment in pediatric patients with myopia.

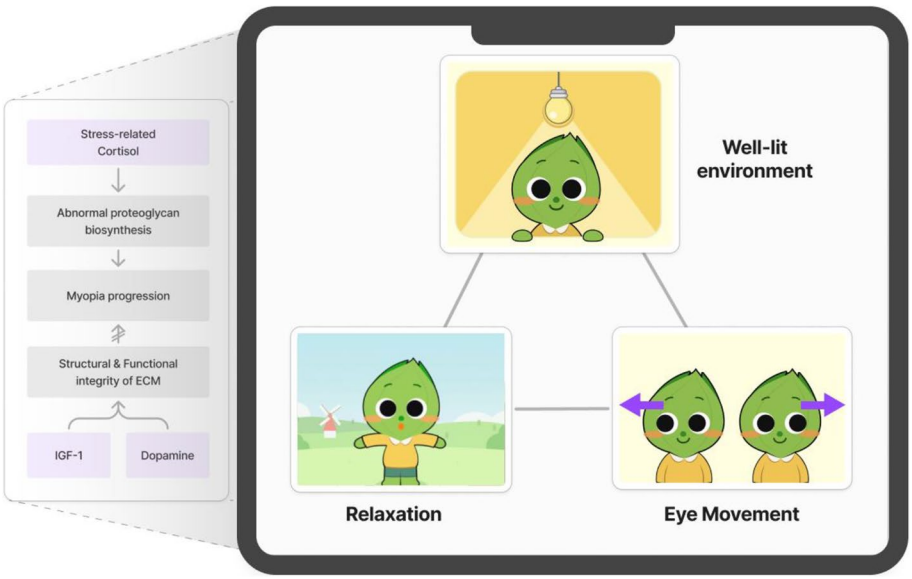


**Fig. 1** Theoretical hypothesis of SAT-001: examples of NHFs affecting myopia progression and corresponding digital tasks for NHF regulation. Progression of myopia might slow down via maintaining of scleral integrity and biosynthesis of ECM components via adjustments of NHFs such as insulin-like growth factor (IGF), cortisol, or dopamine. To adjust NHFs, SAT-001, translated into digital tasks, has been implemented within the investigational medical device, comprising three modules

### Trial design {8}

This trial is a multicenter, open-label, randomized superiority trial designed to evaluate the efficacy and safety of SAT-001 for slowing myopia progression in children. The total study duration will be approximately 25 months, during which patients will participate for a maximum of 52 weeks. A total of 110 participants will be included in this trial, with the study group receiving SAT-001 treatment for 48 weeks. Eligible participants will be randomly assigned in a 1:1 ratio to either the study group or the control group. In this study, participants in the study group will use SAT-001 in combination with single-vision spectacles, while participants in the control group will use single-vision spectacles alone. The trial is designed as a *superiority* study, meaning the primary objective is to demonstrate that the study group (receiving SAT-001 treatment) shows superior efficacy in slowing myopia progression compared to the control group (receiving single-vision spectacles only). Participants will be recruited from 12 different study sites, with each site independently enrolling eligible participants. The recruitment will follow a competitive enrollment approach, where each center will actively recruit participants based on their capacity and recruitment timelines. Randomization will occur centrally via the Interactive Web-based Response System (IWRS), which will assign participants in a 1:1 ratio to either the study group or the control group. This approach ensures efficient participant enrollment across all sites while maintaining the integrity of the randomization process. Figure 2 provides an outline of the trial.

## Methods: participants, interventions, and outcomes

### Study setting {9}

This study will be conducted in 12 centers in the Republic of Korea. A detailed list of study sites can be obtained from the study registry.

### Eligibility criteria {10}

This clinical trial will target patients with mild to moderate myopia aged 5 to 8 years old, excluding concurrent conditions that may affect the progression of myopia. Detailed criteria are specified in Table 1.

### Who will take informed consent? {26a}

The principal investigators (PIs) or their assigned delegates will obtain informed consent or assent from the participants and their legal guardians.

### Additional consent provisions for collection and use of participant data and biological specimens {26b}

For additional consent provisions regarding the collection and use of participant data and biological specimens, please refer to the attached informed consent form. This form includes detailed information about the collection, usage, storage, and sharing of participant data and biological

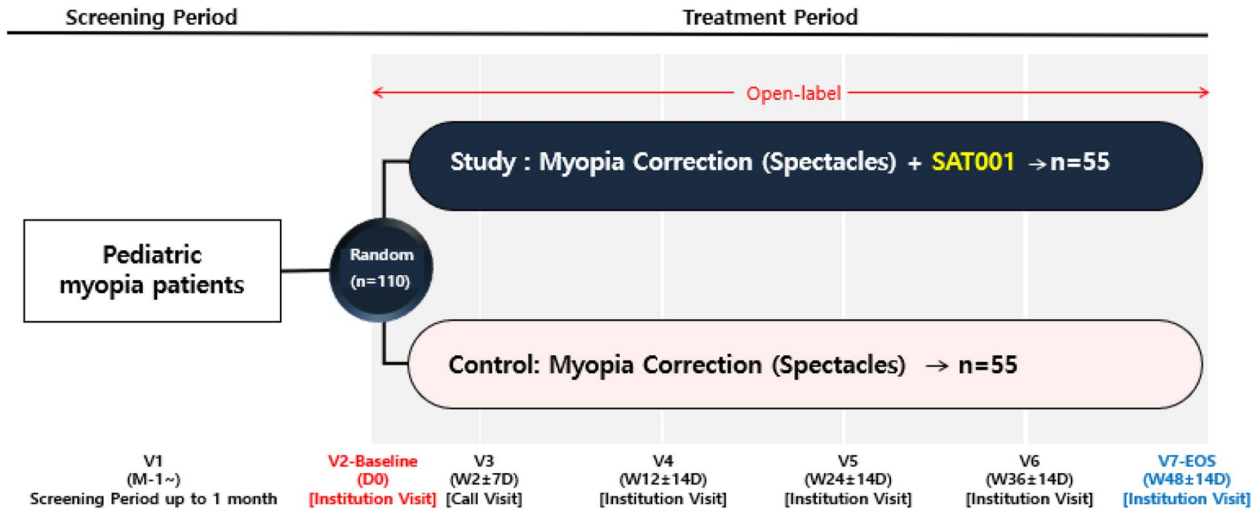


**Fig. 2** Scheme of the study. Figure 2 illustrates the outline of this clinical trial. The timeline is divided into several key phases: Screening visit (M-1 ~): participants will be screened for eligibility based on inclusion and exclusion criteria. ICF will be obtained from participants and their parents. Baseline assessments (D 0): eligible participants will be randomly allocated to either study group or control group. Initial measurements including medical history, physical examinations, and ophthalmic examinations will be conducted. Intervention period (weeks 0–48): participants will receive the assigned intervention. The study group will use SAT-001 and single vision spectacles, while the control group will use single vision spectacles only. Visit 3 will be conducted via phone call, with all other visits taking place at the institution. Each visit is depicted with a corresponding time frame, highlighting the sequence of events and the overall duration of the trial

**Table 1** Eligibility criteria

| | |
|---|---|
| Inclusion criteria | 1. Children aged 5 to < 9 years<br>2. Meeting the following refractive criteria by cycloplegic refraction:<br>- SER: − 0.75 to less than − 6.00 D<br>- Astigmatism: ≤ 1.50 D<br>- Anisometropia: ≤ 2.00 D<br>3. BCVA: 0.2 logMAR or better OU at screening visit (visit 1)<br>4. Able to accomplish SAT-001 (capable of comprehending and executing written and verbal instructions)<br>5. Providing signed informed consent (for < 6 years old, providing agreement with a marked indication after full information and understanding) |
| Exclusion criteria | 1. History of myopia intervention, including atropine use within 3 days prior to baseline (visit 2)<br>2. Current or prior use of multifocal lenses, orthokeratology, or RGP within 1 month prior to baseline (visit 2)<br>3. Ocular abnormalities in the cornea, lens, central retina, iris, or ciliary body or malignant tumors in the orbital area<br>4. History of eye diseases (e.g., strabismus, amblyopia, and nystagmus)<br>5. History of ocular surgery (e.g., eyelid, strabismus, intraocular, or refractive surgery)<br>6. Down's syndrome or cerebral palsy<br>7. Participation in other clinical trial medications or investigational devices within 6 months prior to screening visit (visit 1)<br>8. Significant systemic diseases (e.g., congenital heart disease or respiratory, endocrine, and neurological diseases)<br>9. Systemic diseases that could impact visual acuity and visual field<br>10. History of growth hormone treatment within 1 month prior to baseline (visit 2)<br>11. Other reasons at the discretion of the investigator |

*SER* Spherical equivalent refractive error, *BCVA* Best-corrected visual acuity *logMAR* logarithmic minimum angle of resolution, *OU* Oculi unitas, *RGP* Rigid gas permeable

specimens in accordance with the study protocol as well as the participants' rights to withdraw consent at any time.

## Interventions

### Explanation for the choice of comparators {6b}

Single-vision spectacles are the standard treatment for correcting myopia and are usually the first step in managing myopia; therefore, utilizing refractive correction as a control could show the difference in effect between both interventions most appropriately and provide a stable and robust baseline, allowing any differences in effect between groups to be attributed to the therapeutic intervention. Furthermore, glasses are safe and non-invasive, ensuring the safety of participants in the control group. Therefore, employing glasses as the control is considered the most appropriate approach for assessing the safety and efficacy of this clinical trial.

### Intervention description {11a}

SaMD is software intended to be used for medical purposes without being part of a hardware medical device [14]. SAT-001, SaMD developed by S-Alpha Therapeutics Inc. (Seoul, Republic of Korea) and designated as its code name, is designed to slow down myopia progression. It consists of three modules. The first module is an eye-movement game. Various types of games induce eye movements while holding a participant's interest. Prior to the commencement of the first module, a personalized gaze-tracking process is performed every day to optimize the participant's eye movements. The second module involves a well-designed relaxation module, which follows each eye-movement module. The third module senses light to allow the previous two modules to take place in a well-lit environment.

SAT-001 comprises six 5-min sessions and each session is further divided into 10 modules of 30 s each, including five eye-movement and five relaxation modules. Once 10 modules (five eye-movement modules and five relaxation modules) are completed, one session is completed. The relaxation module can be skipped after 5 s. After completing all six sessions, the daily training is finished. Performing SAT-001 five times a week will be requested. Performance data of SAT-001 in the study group will be provided to the investigator on a session-by-session basis. The key features of the application are presented in Fig. 3.

SAT-001 will be prescribed by the investigator every 12 weeks through the investigator's web portal. After completing the previously prescribed performance for 12 weeks, participants will visit an outpatient clinic or have a telephone consultation to discuss the progression of myopia and the performance of SAT-001 with the investigator. This process will be repeated four times every 12 weeks, for a total of 48 weeks of SAT-001 use.

### Criteria for discontinuing or modifying allocated interventions {11b}

When new information or assessments regarding the safety of an investigational medical device indicate changes in the known risk or benefit profile, rendering a patient's participation in the trial inappropriate, various entities may determine the discontinuation of the trial. These entities include the sponsor, PI, coordinating investigator, Institutional Review Board (IRB), and/or regulatory authority. Additionally, the sponsor may choose to suspend the clinical trial owing to safety-related concerns, such as when the progress of the trial poses a threat to the safety of participants or when changes in the development plan occur. In such cases, recommendations from the data monitoring committee (DMC) may be followed.

### Strategies to improve adherence to interventions {11c}

Investigators can monitor real-time information on participants' application use, check their adherence, and appropriately intervene when necessary. Automatic messaging will help encourage participants' adherence.

### Relevant concomitant care permitted or prohibited during the trial {11d}

Concomitant medications and treatments/therapies that may affect the evaluation of myopia progression during the clinical trial are prohibited, including atropine for myopia treatment and growth hormone. Contraindicated therapies include multifocal lenses, orthokeratology (e.g., Dream Lens), rigid gas-permeable contact lenses, and any other contact lenses used for suppressing myopia progression.

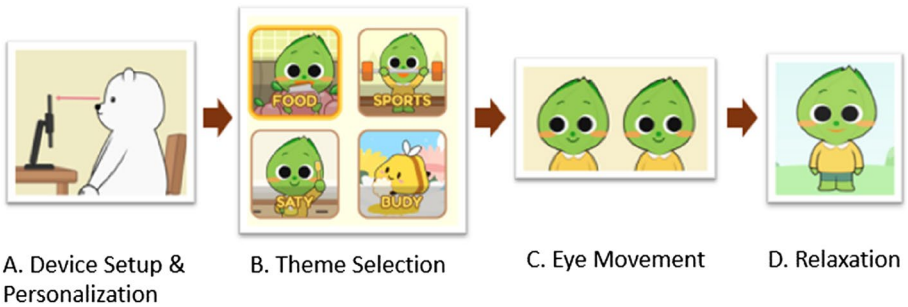


**Fig. 3** Example screens how to use the application. Figure 3 presents brief guidance how to use the application, including the device setup and personalization, theme selection, eye movement and rest session. **A** Device Setup and personalization: Participants can secure the iPad in the cradle and adjust the distance and height from the screen. Personalized Gaze-tracking Process is followed to track and analyze the participant's eye movements. Participants may move their eyes according to the instructions before starting the eye movements and rest sessions to set the maximum range of movement. **B** Theme Selection: An interface allowing participants to choose or change the theme to proceed the game including eye movement modules and rest modules. **C** Eye Movement: A dedicated module designed for activities related to eye movement, including rotation and up-down-left-right movement. **D** Rest: A module focused on guiding participants through relaxation, helping them take effective breaks and reduce eye strain and stress. After rest session, a 30-s eye activity follows

### Provisions for post-trial care {30}

Compensation is provided for adverse events experienced by participants during the clinical trial. It covers not only adverse events but also damages incurred during the treatment of adverse reactions. The sponsor obtained Clinical Trial Liability Insurance to compensate or indemnify participants for any potential health damages that may arise.

### Outcomes {12}

The spherical equivalent refractive error (SER) will be measured to accurately determine the progression of myopia. The SER and axial length (AL) will be assessed to measure the efficacy of the treatment. The SER will be measured at baseline and at every 24-week follow-up visit using the autorefractors KR-1, KR-800A, KR-800, and KR-8800 (Topcon, Tokyo, Japan); HRK-8000A (Huvitz, Anyang, Republic of Korea); and RK-F2 (Canon, Tokyo, Japan) or a retinoscope. AL will be assessed at baseline and at every 12-week follow-up visit using the IOL Master (Carl Zeiss, Oberkochen, Germany), ARGOS (Suntec, Aichi, Japan), or Lenster LS 900 (Haag-Streit AG, Bern, Switzerland). Each institution will consistently use identical devices for measurements throughout the study.

The primary endpoint is the change in the SER at 48 weeks from the baseline. Secondary endpoints include the change in the SER at 24 weeks from baseline and the change in AL at every 12 weeks until 48 weeks from baseline. Changes in the SER and AL at each visit, stratified by myopia severity (mild or moderate), will also be evaluated for subgroup analysis.

We will provide descriptive statistics, including the mean, standard deviation, median, minimum, and maximum of the changes in the SER and AL at each visit. To estimate the difference between the study and control group, the efficacy evaluation variable will serve as the response variable. A mixed-effects model will be employed, incorporating study/control group status (treatment group), categorical week, age, sex, baseline cycloplegic refraction, and the interaction between the treatment group and categorical week as fixed effects. Random effects will be set for the site and participant nested within the site, considering individual variability. An unstructured covariance structure will model within-participant error. The comparison between the study and control group will include presentation of the *p*-value, least squares (LS) mean, standard error, and 95% confidence interval (CI) of the difference.

As safety outcomes, adverse events and ophthalmic examinations will be evaluated. The summary and analysis of adverse events will examine treatment emergent adverse events (TEAEs) occurring in either the study or control group. The frequency and percentage of adverse events, adverse device events (ADEs), serious TEAEs, and serious ADEs that occur during the clinical trial for each group will be presented, compared, and analyzed using the chi-square or Fisher's exact test.

Abnormal findings discovered through ophthalmic examinations, including best-corrected visual acuity, fundus examination, and slit lamp examination, during the clinical trial period will be summarized in Table.

### Participant timeline {13}

The total study duration will be approximately 25 months, depending on enrolment status, including a screening period of 1 month and a treatment period of 48 weeks.

During the screening (visit 1), participants and their parents or legal guardians will be briefed about the clinical trial, and consent will be obtained. Various procedures will follow to confirm eligibility, including demographic surveys, physical examinations, and medical history reviews. Assessments, such as cycloplegic refraction tests, AL measurements, and ophthalmic examinations, will be conducted to establish baseline data.

At the baseline (visit 2), participants will be randomly allocated to either the study or control group, and eligible participants will undergo further assessments, including lifestyle questionnaires and adverse event assessments. Investigational medical device training will be provided to the participants assigned to the study group. For participants in the study group, a call visit (visit 3) will be conducted within 1 week after baseline, focusing on compliance verification and adverse event assessment related to the investigational medical device. Subsequent visits, from visit 4 to visit 6, will follow a similar pattern. These visits will involve a range of assessments, including physical examinations, device prescriptions (if applicable), lifestyle questionnaires, and various eye examinations, such as AL measurements, fundus examination, slit lamp examination, and tonometry. Adverse event assessments and confirmation of adherence will also be part of these visits.

The end of study (EOS) visit will conclude the use of the investigational medical device and will include comprehensive assessments similar to previous visits, ensuring the safety and efficacy of the device throughout the study duration.

The schedule for enrolment, allocation, and assessments is outlined in Table 2, and a schematic timeline of the study is also provided in Fig. 2.

**Table 2** Evaluation schedule

| Visit no | Visit 1 Screening | Visit 2 Baseline | Visit 3 | Visit 4 | Visit 5 | Visit 6 | Visit 7 EOS |
|---|---|---|---|---|---|---|---|
| **Visit weeks** | **M-1** | **0** | **W2 ± 7D** | **W12 ± 14D** | **W24 ± 14D** | **W36 ± 14D** | **W48 ± 14D** |
| Informed consent/assignment of screening number | ○ | | | | | | |
| Demographic information | ○ | | | | | | |
| Height/weight measurement | ○ | | | | ○ | | ○ |
| Physical examination | ○ | | | ○ | ○ | ○ | ○ |
| Medical/medication history | ○ | ○ | | | | | |
| Inclusion/exclusion criteria review | ○ | ○ | | | | | |
| Randomization | | ○ | | | | | |
| Investigational device training | | ○ | ○ | | | | |
| Prescription of investigational device | | ○ | | ○ | ○ | ○ | |
| Lifestyle questionnaire | | ○ | | ○ | ○ | ○ | ○ |
| Myopia history of parents | | ○ | | | | | |
| Spherical equivalent refractive error | ○ | ○ | | | ○ | | ○ |
| Axial length | ○ | ○ | | ○ | ○ | ○ | ○ |
| Best-corrected visual acuity | ○ | ○ | | | △ | | △ |
| Ophthalmic examination (fundus examination; slit lamp examination) | ○ | ○ | | △ | △ | △ | △ |
| Strabismus | ○ | ○ | | △ | △ | △ | △ |
| Intraocular pressure | ○ | ○ | | △ | △ | △ | △ |
| Adverse events | | ○ | ○ | ○ | ○ | ○ | ○ |
| Concomitant medications/therapies | | ○ | ○ | ○ | ○ | ○ | ○ |
| Adherence | | | | ○ | ○ | ○ | ○ |

△: Additional assessments may be conducted at the investigator's discretion during each institution visit

*EOS*, end of study

#### Sample size {14}

The sample size was calculated based on the previous clinical trial, which is currently in preparation. The effect size and the standard deviation of the patients ages 5 to 8 (SAT-001 group, $n = 15$; control group, $n = 11$, with one control patient excluded as an outlier beyond mean ± 2SD) were used, comparable to the current study. To obtain conservative estimate on sample size, four imputation methods including multiple imputation to calculate target effect size and standard deviation. A value within the range of estimates obtained through imputation methods, which is more conservative than the results from the previous clinical study, was selected: effect size: − 0.3 D, standard deviation: 0.465 D. The final sample size was calculated as 55 participants per arm (two-sample $t$-test, $\alpha = 0.25$ (one-tailed), power = 80%, dropout rate = 30%) to assess efficacy.

#### Recruitment {15}

To facilitate the recruitment of participants for this clinical trial, we are promoting the trial by posting recruitment advertisements within the institution.

## Assignment of interventions: allocation

#### Sequence generation {16a}

The computer- and web-based randomization process will employ the stratified block-randomization method. Randomization numbers will be generated using SAS (Version 9.4 or higher, SAS Institute, Cary, NC, USA) to create a centralized ratio of participants to the test and control groups based on myopia severity (mild or moderate) and site. Enrolled participants will be assigned to the test or control group in a 1:1 ratio according to the randomization number.

#### Concealment mechanism {16b}

Although this trial was conducted as an open-label study, method to minimize the bias, including randomization, is implemented. The randomization was managed independently of the data analyst or clinical operation to avoid bias. Stratified block randomization will be employed, and random allocation codes will be generated using the PROC PLAN procedure of SAS, version 9.4 or higher. Registered participants will be assigned to the study or control group in a 1:1 ratio based on the random allocation code.

#### Implementation {16c}

At each institution, when investigators confirm participant eligibility, randomization numbers will be automatically generated via the Interactive Web-based Response System (IWRS). The IWRS will sequentially assign participants to the test or control group in a 1:1 ratio. Myopia severity (mild or moderate) and the institution are factors for stratified random allocation. Participants in the study group will receive conventional myopia correction methods (single-vision spectacles) and investigational medical devices, while those in the control group will receive only conventional myopia correction methods.

Similarly, the allocation of participants to the test or control group is also carried out automatically by the IWRS, ensuring unbiased assignment. As the system handles the random allocation, there is no specific individual responsible for assigning participants to the groups.

### Assignment of interventions: blinding

#### Who will be blinded {17a}

This clinical trial is open-labeled, and the involved people are unblinded.

#### Procedure for unblinding if needed {17b}

N/A. This study is an open-label trial, meaning both the participants and investigators are aware of the treatment allocation. Therefore, unblinding is not necessary.

### Data collection and management

#### Plans for assessment and collection of outcomes {18a}

To ensure the integrity and quality of outcome data, protocols are in place for the assessment and collection of outcome, baseline, and other trial data. These protocols include measures to promote data quality, such as the performance of tests by skilled technicians and the use of duplicate measurements to reduce errors. Data will be recorded in the electronic case report form by the investigator and monitored by the clinical research associate (CRA) at each monitoring visit. Ongoing validation of clinical data will be conducted through automated edit checks at the point of entry. Manual queries can be raised by the study monitor for discrepant data identified during source data verification. All queries will be recorded, tracked, and managed by data management and the CRA until resolution. Further details are outlined in the data management plan (DMP).

#### Plans to promote participant retention and complete follow-up {18b}

In order to enhance participant retention and ensure completion of follow-up, we will implement early support measures. To assist participants in adapting to the protocol, particularly early participants and those allocated to the study group, a telephone consult will be scheduled 1 month after the baseline visit and before the next institution visit. During this telephone consult, participants will be provided with feedback and training on application usage, aiming to prevent early clinical dropout. Throughout the clinical trial, adherence to the intervention protocols will be closely monitored. If a participant's adherence falls below an appropriate level, an automatic alarm will be triggered and sent to the participant's parents. This serves as a prompt to encourage the participant's continued participation in the trial. Participants who discontinue or drop out of the trial will still be included in the efficacy and safety evaluation, unless there is a valid reason or basis for exclusion.

#### Data management {19}

Data will be entered directly into the electronic data capture system by authorized site staff. Each datum will time-stamped and stored securely within the system. The system complies with the 21 Code of Federal Regulations part 11 standards for clinical database management hosting and security. Compliance statements and validation certificates will be reviewed and maintained by the contract research organization. Security measures include regular checks on system details, quarterly reviews of security system changes, and vulnerability checks on servers and networks. Daily data backups will be performed, and backup results will be verified for completeness and reliability. Ongoing validation of clinical data will be conducted through automated edit checks with manual query management. Further details on data management procedures are provided in the DMP.

#### Confidentiality {27}

Information collected from participants in this clinical trial is protected under relevant laws, including the Personal Information Protection Act. The purpose of collecting personal and sensitive information is for the execution of the trial and reporting of results. Participants' identities will be kept confidential through anonymization. Clinical trial data will be stored for a minimum of 10 years, and participant information will be disposed of according to regulations after this period. Monitoring and verification of trial procedures may involve accessing participant medical records within regulatory limits to ensure data reliability without compromising confidentiality.

#### Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in this trial/future use {33}

N/A. This trial will utilize a software device for the intervention and no biological specimens will be collected for genetic or molecular analysis.

## Statistical methods

### Statistical methods for primary and secondary outcomes {20a}

The primary endpoint will be assessed as the change in the SER at 48 weeks from baseline. Descriptive statistics, including mean, standard deviation, median, minimum, and maximum of the change in cycloplegic refraction (D) at 48 weeks from baseline, will be provided.

To estimate the difference between the study and control group regarding the change in the SER at 48 weeks from baseline, the efficacy-evaluation variable will serve as the response variable. A mixed-effects model will be employed, incorporating treatment, visit, age, sex, baseline SER, and the interaction between the treatment group and visit as fixed effects. Random effects will be set for the site and participant nested within the site, considering individual variability. The comparison between the study and control group will provide the *p*-value, LS mean, standard error, and 95% CI of the difference.

Secondary endpoints comprise the change in the SER at 24 weeks from baseline and the change in AL at 12, 24, 36, and 48 weeks from baseline. Descriptive statistics, both for the change in the SER (D) at week 24 and for the change in AL at each time point from baseline, will be provided. Similarly, a mixed-effects model will be applied to estimate the difference between the study and control group for the change in the SER at 24 weeks and for the change in AL at each time point from baseline. As for the primary endpoint, random effects will be set for the site and participant nested within the site. In results, the *p*-value, LS mean, standard error, and 95% CI of the difference between the study and control group will be included.

### Interim analyses {21b}

N/A. In this trial, interim analysis is not planned.

### Methods for additional analyses (e.g., subgroup analyses) {20b}

The SER values at baseline, which distinguish myopia severity as mild or moderate, will be used as a random stratification. Based on this, participants will be divided into mild- or moderate-severity groups, and subgroup analyses for efficacy and safety will be conducted accordingly. Descriptive statistics of the change in the SER at 24 and 48 weeks and of the change in AL at 12, 24, 36, and 48 weeks from baseline will be presented, stratified by myopia severity (mild or moderate). A mixed effects model will be used to estimate differences between the test and control groups, with variables including treatment, visit, age, sex, baseline SER, and their interaction. The site and participant nested within the site are considered as random effects. Results will include the *p*-value, LS mean, standard error, and 95% CI.

### Methods in analysis to handle protocol non-adherence and any statistical methods to handle missing data {20c}

Any protocol deviations must be promptly reported to the sponsor, documented, and reviewed for their impact on the results. Significant deviations may result in the exclusion of participants from the analysis, such as violations of inclusion or exclusion criteria, concurrent administration of prohibited medications/therapies, or other major violations. In the case of protocol deviation, participants are designated for exclusion from the per protocol set during the analysis.

Missing data in the trial will be managed using the last observation carried forward (LOCF) method. This approach ensures that the last available measurement for each participant is carried forward to address missing values, maintaining consistency in the dataset.

### Plans to give access to the full protocol, participant-level data, and statistical code {31c}

The main content of the protocol is publicly available on ClinicalTrials.gov and accessible to everyone; any changes will also be disclosed through this registry. Furthermore, the protocol will also be published in this paper, and it will be disclosed before the completion of the study enrollment. There are no plans to separately disclose participant-level data and statistical codes.

## Oversight and monitoring

### Composition of the coordinating center and trial steering committee {5d}

This project is coordinated by the clinical trial coordination team at S-Alpha Therapeutics, Inc. Some tasks related to clinical trial design, conduct, and data management and analysis are outsourced to a clinical research organization (CRO). The CRO's progress and activities are reported to the clinical trial coordination team on a monthly basis. The coordinating team meets at least twice a month to ensure close monitoring and oversight of the trial's progress. At each participating institution, the principal investigator (PI) is responsible for ensuring that the trial is conducted in accordance with the approved protocol. Investigator meetings are held with PIs at each site prior to the start of the trial to ensure consistency and adherence to the study protocol. Additionally, monitoring meetings with the CRO are held at least once every 3 months during the trial to ensure ongoing compliance and address any emerging issues. An independent data management committee (DMC) has been established to oversee the management of the study data. The DMC operates separately from the clinical trial

coordinating team to maintain impartiality and objectivity in data review. The committee consists of an external statistician and an ophthalmologist. The DMC meets regularly every 3 months to evaluate data integrity and monitor the safety and progress of the trial.

#### Composition of the data monitoring committee, its role and reporting structure {21a}

The DMC comprises a chairperson, who is a statistician, and two clinician members. The role of the DMC includes monitoring the performance of the clinical trial, including reviewing cases of project deviation, ensuring data integrity, and reviewing safety data. The responsibility also includes analyzing trial completion, such as confirming analysis groups; monitoring safety and efficacy; establishing recommendations where they determine whether to continue or terminate the trial; reviewing trial integrity; and reviewing participants' recruitment, selection, retention, and management. The DMC will maintain meeting records, with open meeting discussions documented and forwarded to the sponsor and closed meeting discussions documented and delivered to the sponsor.

The DMC will anticipatedly review the protocol and quarterly reviews of participant registration status, protocol violations, and cumulative safety data. After data verification, participant selection for each group will be reviewed. After database lock, investigational medical device efficacy and safety data for final recommendations will be reviewed at the EOS meeting. Irregular meetings may be held at the sponsor's request to address severe study quality, safety, and data issues.

The DMC is independent from the sponsor and competing interests. Further details about DMC are described in the DMC charter.

#### Adverse event reporting and harms {22}

All adverse events, ADEs, serious TEAEs, and serious ADEs that occur during the clinical trial period will be collected. All adverse events will be followed until resolution, the condition stabilizes, the event is otherwise explained, or the participant dies or is lost to follow-up.

All serious adverse events (SAEs) and serious device adverse reactions (SADRs), regardless of their relationship to the investigational medical device, must be recorded during the period from the time the participant signs the written consent form until the end of the study. If the PI recognizes a SAE/SADR, the pharmacovigilance team will be notified within 24 h of recognizing the case and will also report to the IRB. Cases of serious and unexpected adverse device effects will be reported to regulatory authorities in accordance with the Ministry of Food and Drug Safety (MFDS) guidelines.

Additionally, for the safety of users, all medical device defects will be reported within 24 h after the researcher becomes aware of the defect. Medical device defects include, but are not limited to, device errors, malfunctions, and user errors. Appropriate corrective precautions will be taken when necessary for reported medical device defects.

#### Frequency and plans for auditing trial conduct {23}

A delegate approved by the sponsor, regulatory authority, or IRB may visit the institution and conduct an audit or inspection, including review of source documents. The purpose of the sponsor audit is to systematically and independently examine all trial-related activities and documentation and determine whether these activities were performed and that clinical data were recorded, analyzed, and reported accurately in accordance with the trial protocol, International Council for Harmonisation Good Clinical Practice guidelines, and applicable regulatory requirements. If contacted by a regulatory authority regarding an inspection, the PI must immediately contact the sponsor.

#### Plans for communicating important protocol amendments to relevant parties (e.g., trial participants, ethical committees) {25}

A major amendment in this clinical trial refers to substantial changes to the protocol that significantly affect the safety, ethics, or scientific validity of the study. These changes can include adjustments to address new safety information, changes to primary objectives or endpoints, or revisions to the informed consent process. Such amendments should first be discussed with the clinical investigator and the opinions of each institution's PI should be considered before proceeding with the protocol amendment. The DMC will review each amendment to the protocol. The MFDS and the IRB of each institution must approve these amendments. The changes must also be communicated to the participants and their parents or legal guardians. When a major amendment occurs, the participants and their parents or legal guardians will be notified of the changes as soon as possible, and the consent process for participating under the amended protocol will be conducted. When amending a clinical trial protocol, details such as the date of amendment, reason for amendment, and content of amendments must be recorded and retained. Small amendments or details that do not affect the trial may require only administrative changes and may not necessarily require approval.

#### Dissemination plans {31a}

Publication, presentation, or other disclosure of trial results (each a "Publication of Materials") will be accurate

and honest, and will be done with integrity and transparency, as approved by the sponsor. The publication of results is subject to impartial peer-review. Copyright belongs to the sponsor. Any conflicts arising from disputes regarding copyright will be reviewed by the sponsor. Copyright must comply with domestic regulations. The data will not be released publicly until the manuscript has been accepted for publication. If the data is not published, the information will be released to the public and media only upon approval by the sponsor. Trial data that are not published, presented, or otherwise disclosed pursuant to the clinical trial agreement will remain the confidential information of the sponsor. PIs should not disclose or permit disclosure of such unpublished data and should not disclose or permit disclosure of study data to third parties in more detail than is disclosed in permitted publications, presentations, or other disclosures.

## Discussion

The Digital therapeutics Approach for Young children with myopia using SAT-001 (DAYS) study is a multicenter, randomized clinical trial on SAT-001, an investigational medical device developed to slow the progression of myopia in children. This pivotal study aims to gather confirmatory evidence for the efficacy and safety of SAT-001 by comparing SER and AL changes at 48 weeks from the baseline between pediatric patients using SAT-001 and those not using SAT-001.

According to previous exploratory clinical trial results, SAT-001 shows the potential for consistent and reliable efficacy over 48 weeks. In an analysis of pediatric patients with myopia aged 5 to 8 years with prespecified subanalysis, the treatment group compared with the control group showed a statistically significant difference in the amount of change in the SER and AL compared to baseline. Additionally, no SAEs or adverse medical device reactions were reported during the 48-week treatment period [15].

The DAYS study was designed to be conducted on patients with mild to moderate myopia aged 5 to 8 years, as this patient group can most accurately confirm the effectiveness of SAT-001 based on the results obtained in previous exploratory clinical trials. Randomization is planned to stratify the severity of myopia, assuming that the degree of myopia progression in the test and control groups would be similar. Other risk factors believed to affect the progression of myopia in children, such as lifestyle, sex, and parental myopia as genetic factors [16], are assumed to be equally distributed by registering a sufficient number of participants. However, all of these elements will be included as collected information items to be used for comprehensive results analysis after the clinical trial is completed.

Clinical trials involving children must be conducted with the highest ethical standards owing to the vulnerability of the participants. The DAYS study will obtain verbal consent (under 6 years of age) or written consent from the participants based on a consent form written in terms that are easy for children to understand. Additionally, consent will be obtained from the participant's parents or legal representatives after fully explaining their children's rights and the benefits and disadvantages of participating in the clinical trial. The entire clinical trial plan, including consent procedures and participant protection measures, will be reviewed and conducted by each institution's IRB.

The DAYS study, a clinical trial targeting children, will be conducted under an open-label design. SAT-001, digital therapeutic software, involves exposure to digital devices for 17.5–30 min per day. Because near-field work involving electronic devices is known to be a risk factor for myopia [17], the open-label design was chosen after discussion with Korean regulatory agencies.

After onset, myopia in children continues to deteriorate with growth. In particular, early onset of the disease increases the likelihood of progressing to high myopia, underscoring the importance of early intervention [18]. However, interventions currently being used or under development in clinical settings cannot be used in young children or have some limitations. SAT-001 is a newly developed medical device that applies digital treatment technology, which aims to address these challenges. We believe our study will establish SAT-001 as a safe and effective treatment option for pediatric patients with myopia, thereby making a substantial contribution to the literature. The results of this study may be utilized for regulatory approval of SAT-001. The findings will highlight its advantages in home care convenience and safety with non-invasive therapy, and its potential for long-term use for myopia control from an early stage, distinguishing it as a safe, convenient, and effective myopia suppression treatment. A separate 6-month follow-up study is planned for consenting patients in this study, the purpose of which is to determine the effect of discontinuation of SAT-001 on myopia progression.

Further study is warranted to validate its efficacy in cases requiring more intensive myopia management, such as moderate to high degrees of myopia or concurrent conditions like astigmatism. In addition, enhancing the device to maintain user engagement and interest and diversifying its program are crucial considerations. As a software medical device, connecting the device's myopia control status to actual clinical practice will be a necessary for product development challenge in the future.

## Trial status

The recent protocol was updated to Version 2.0 on April 23, 2024. Participant recruitment commenced on September 27, 2023, and is anticipated to conclude on November 9, 2024.

**Abbreviations**

| | |
|---|---|
| ADE | Adverse device event |
| AL | Axial length |
| CI | Confidence interval |
| CRA | Clinical research associate |
| DAYS | Digital therapeutics Approach for Young children with myopia using SAT-001 |
| DMC | Data monitoring committee |
| DMP | Data management plan |
| EOS | End of study |
| IRB | Institutional Review Board |
| LS | Least squares |
| MFDS | Ministry of Food and Drug Safety |
| PI | Principal investigator |
| SADR | Serious adverse device reaction |
| SAE | Serious adverse event |
| SaMD | Software as a Medical Device |
| SER | Spherical equivalent refractive error |
| TEAE | Treatment emergent adverse event |

## Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13063-025-08717-w.

Supplementary Material 1.

**Acknowledgements**

The authors gratefully acknowledge the expertise and oversight provided by the data monitoring committee throughout the duration of this study. Additionally, the authors acknowledge the significant contributions of the Data Science Team, who are affiliated with S-Alpha Therapeutics, Inc. [the sponsor], in shaping the study protocol, particularly in advising on sample size determination and optimizing data collection and analysis strategies. Special thanks are also extended to the sponsor for their invaluable contributions beyond financial support, including their collaboration in study design and logistical assistance.

**Authors' contributions {31b}**

HJ Paik, as the coordinating investigator, conceptualized the study and led the proposal and protocol development. Principal investigators BJ Lee, DH Lim, SY Han, EH Jung, HJ Shin, HK Kim, US Kim, WJ Kim, HY Choi, J Park, and S Rhiu contributed to the study design and proposal development. All investigators, who are ophthalmologists, contributed to the refinement of the study protocol and approved the final paper. J Lee, MJ Kim, and KH Kim provided expertise in both protocol and proposal development. All authors have read and approved the final manuscript.

**Funding {4}**

S-Alpha Therapeutics, Inc., provided funding for this clinical trial.

**Data availability {29}**

All PIs, DMC, and the sponsor will have access to the final trial dataset.

## Declarations

**Ethics approval and consent to participate {24}**

The study was approved by the following Institutional Review Boards with their reference numbers listed. Written, informed consent to participate will be obtained from all participants and their parents or legal guardians.

**Consent for publication {32}**

In accordance with Article 10 (Ownership and Publication of Study Results) of the Clinical Trial Agreement, all tangible and intangible results, including intellectual property rights arising from this study, are owned by the Sponsor. The Institution acknowledges that any publication or public disclosure of study results shall be made solely at the discretion of the Sponsor. Prior to presenting or publishing any study results, data, or findings from this study through academic journals, conferences, or other forums, the Institution or the principal investigator shall submit all presentation or publication materials to the Sponsor for review at least 1 month before the scheduled presentation or publication date. The Institution and the principal investigator agree that any presentation or publication of study results shall occur only within the scope agreed upon in writing by the Sponsor. Additionally, the Institution and the principal investigator shall mention the Sponsor's financial support in any presentation or publication of the study results, as requested by the Sponsor. The Sponsor may also use the content of any presentation or publication for promotional, advertising, or press release purposes.

**Competing interests {28}**

The authors declare that they have no competing interests.

**Author details**

[1]Department of Ophthalmology, Gachon University Gil Medical Center, Incheon, Republic of Korea. [2]Department of Ophthalmology, Asan Medical Center, Seoul, Republic of Korea. [3]Department of Ophthalmology, Samsung Medical Center, Seoul, Republic of Korea. [4]Department of Ophthalmology, Kangbuk Samsung Hospital, Seoul, Republic of Korea. [5]Department of Ophthalmology, Nowon Eulji Medical Center, Seoul, Republic of Korea. [6]Department of Ophthalmology, Konkuk University Medical Center, Seoul, Republic of Korea. [7]Department of Ophthalmology, HanGil Eye Hospital, Incheon, Republic of Korea. [8]Department of Ophthalmology, Chung-Ang University Gwangmeyong Hospital, Gwangmeyong, Republic of Korea. [9]Department of Ophthalmology, Yeungnam University Medical Center, Daegu, Republic of Korea. [10]Department of Ophthalmology, Pusan National University Hospital, Busan, Republic of Korea. [11]Department of Ophthalmology, Daegu Fatima Hospital, Daegu, Republic of Korea. [12]Department of Ophthalmology, Hallym University Dongtan Sacred Heart Hospital, Hwaseong, Republic of Korea. [13]S-Alpha Therapeutics, Inc., Seoul, Republic of Korea.

Received: 8 August 2024 Accepted: 2 January 2025
Published online: 08 April 2025

**References**

1. Baird PN, Saw SM, Lanca C, Guggenheim JA, Smith EL III, Zhou X, et al. Myopia Nat Rev Dis Primers. 2020;6:99.
2. Holden BA, Fricke TR, Wilson DA, Jong M, Naidoo KS, Sankaridurg P, et al. Global prevalence of myopia and high myopia and temporal trends from 2000 through 2050. Ophthalmology. 2016;123:1036–42.
3. Rudnicka AR, Kapetanakis VV, Wathern AK, Logan NS, Gilmartin B, Whincup PH, et al. Global variations and time trends in the prevalence of childhood myopia, a systematic review and quantitative meta-analysis: implications for aetiology and early prevention. Br J Ophthalmol. 2016;100:882–90.
4. Flitcroft DI. The complex interactions of retinal, optical and environmental factors in myopia aetiology. Prog Retin Eye Res. 2012;31:622–60.
5. Morgan IG, French AN, Ashby RS, Guo X, Ding X, He M, et al. The epidemics of myopia: aetiology and prevention. Prog Retin Eye Res. 2018;62:134–49.
6. Mitchell P, Hourihan F, Sandbach J, Wang JJ. The relationship between glaucoma and myopia: the Blue Mountains Eye Study. Ophthalmology. 1999;106:2010–5.
7. Younan C, Mitchell P, Cumming RG, Rochtchina E, Wang JJ. Myopia and incident cataract and cataract surgery: the blue mountains eye study. Invest Ophthalmol Vis Sci. 2002;43:3625–32.
8. Mitry D, Charteris DG, Fleck BW, Campbell H, Singh J. The epidemiology of rhegmatogenous retinal detachment: geographical variation and clinical associations. Br J Ophthalmol. 2010;94:678–84.

9. Chua SY, Sabanayagam C, Cheung YB, Chia A, Valenzuela RK, Tan D, et al. Age of onset of myopia predicts risk of high myopia in later childhood in myopic Singapore children. Ophthalmic Physiol Opt. 2016;36:388–94.
10. Dudovitz RN, Izadpanah N, Chung PJ, Slusser W. Parent, teacher, and student perspectives on how corrective lenses improve child wellbeing and school function. Matern Child Health J. 2016;20:974–83.
11. Sankaridurg P, Tahhan N, Kandel H, Naduvilath T, Zou H, Frick KD, et al. IMI impact of myopia. Invest Ophthalmol Vis Sci. 2021;62:2.
12. Lawrenson JG, Shah R, Huntjens B, Downie LE, Virgili G, Dhakal R, et al. Interventions for myopia control in children: a living systematic review and network meta-analysis. Cochrane Database Syst Rev. 2023;2:CD014758.
13. Lee YS, Choi SE, Hahm J, Kim MJ, Bae HS, Yi K, et al. Digital therapeutics: exploring the possibilities of digital intervention for myopia. Front Digit Health. 2021;3: 710644.
14. IMDRF SaMD Working Group. Software as a Medical Device (SaMD): key definitions. (2013). https://www.imdrf.org/sites/default/files/docs/imdrf/final/technical/imdrf-tech-131209-samd-key-definitions-140901.pdf. Accessed 21 Jun 2024.
15. Lee BJ, Han SY, Choi S, Kim K, Huh Y, Lee J. Randomized controlled trial of eye movement exercise based digital therapeutics for inhibiting myopia progression. Invest Ophthalmol Vis Sci. 2024;65:2750.
16. Yu M, Hu Y, Han M, Song J, Wu Z, Xu Z, et al. Global risk factor analysis of myopia onset in children: a systematic review and metaanalysis. PLoS ONE. 2023;18: e0291470.
17. Dutheil F, Oueslati T, Delamarre L, Castanon J, Maurin C, Chiambaretta F, et al. Myopia and near work: a systematic review and meta-analysis. Int J Environ Res Public Health. 2023;20:875.
18. Hu Y, Ding X, Guo X, Chen Y, Zhang J, He M. Association of age at myopia onset with risk of high myopia in adulthood in a 12-year follow-up of a Chinese cohort. JAMA Ophthalmol. 2020;138:1129–34.

## Publisher's Note