Study Protocol

A Randomized, Controlled, Multi-centre Clinical Study on the Effectiveness and Safety of repeated low-level red-light (RLRL) in Controlling High Myopia in Children and Adolescents

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Sponsor: Zuoguan Medical Equipment Co., Ltd. at Suzhou Industrial Park

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Abbreviation

Abbreviation	English	Chinese
AE	Adverse Event	不良事件
CFDA	China Food and Drug Administration	国家食品药品监督管理总局（旧称）
CRF	Case Report Form	病例报告表
CRO	Contract Research Organization	合同研究组织
FAS	Full Analysis Set	全分析集
GCP	Good Clinical Practice	临床试验质量管理规范
ICH	International Conference of Harmonization	人用药品注册技术要求国际技术协调会
ITT	Intention-to treat	意向性分析
LOCF	Last observation carried forward	最接近一次观察的结转
Min	Minute	分钟
NMPA	National Medical Products Administration	国家药品监督管理局
PPS	Per Protocol Set	符合方案集
SAE	Serious Adverse Event	严重不良事件
SAP	Statistical Analysis Plan	统计分析计划
SOP	Standard Operating Procedure	标准操作程序
SS	Safety Analysis Set	安全性数据集

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1. ABSTRACT

Basic information on clinical practice of medical devices: Device Classification: Class II medical devices Specification Model: RS-200-1A Date: September 20, 2020 Sponsor: Zuoguan Medical Devices Co., Ltd. at Suzhou Industrial Park
Practice Title A Randomized, Controlled, Multi-centre Clinical Study on the Effectiveness and Safety of repeated low-level red-light (RLRL) for myopia control in children and adolescents with high myopia
Practice Purpose A Study on assessing the effectiveness and safety of RLRL for myopia control in children and adolescents with high myopia.
Subject Population Subject: Children aged 6-16 with at least one eye with myopia of cycloplegic spherical equivalent refraction (SER) at least –4.0 D Sample size: 192 subjects are planned to be enrolled and assigned to the intervention group or control group according to a ratio of 1:1
Practice Design **Overall design:** This prospective, single-blind, parallel-group, multi-center randomized clinical trial was conducted at six tertiary hospitals. Participants between 6 and 16 years old with at least one eye with a spherical equivalent refraction (SER) of –4.0 D or greater were recruited. The enrolled participants were randomly placed at a 1:1 ratio into

intervention (RLRL treatment plus single-vision spectacles) or control (single-vision spectacles) groups. The participants attended follow-up appointments 1, 3, 6, 9, and 12 months after the baseline evaluation.

Outcomes:

1. Primary Outcome: Change of Axial length (AL, mm) at 12-month follow-up
2. Secondary Outcome: Change of cycloplegic spherical equivalent (SE, D) at 12-month follow-up
3. Optional Indicators：

   Changes of uncorrected visual acuity （UCVA），best-corrected visual acuity （BCVA），intraocular pressure, etc.;

   Changes of corneal thickness（CT）, anterior chamber depth（ACD） and lens thickness（LT）;

   Observe macula and the structure of fundus around the optic disc;

   Observe the choroid/retinal thickness of the fundus;

   Compliance index: frequency of equipment uses.

Safety assessment

①Sudden vision loss；

②Afterimage time over 5 minutes;

③Side effects such as glare, photophobia and flickering;

④Structural damage to retina: tissue disruption or discontinuity, edema, or other abnormalities in the photosensory layer of the SS-OCT images;

⑤Increased intraocular pressure etc.

Participants selection and exclusion criteria:

Eligibility criteria:

Inclusion criteria:

①Age 6-16 years old, no gender limit;

②Either eye meets the diagnosis of myopic refractive error and the myopia of cycloplegic spherical equivalent refraction (SER) at least –4.0 D, astigmatism 2.0 D

or less, anisometropia 3.0 D or less, and best-corrected visual acuity (BCVA) of LogMAR 0.2 or better. ③Have normal thinking and language communication skills, and be able to actively cooperate with the required treatment; ④ No contraindications to the treatment of atropine such as acute ocular inflammation, dry eye, keratoconus, diabetes, etc.; ⑤Written informed consent of the guardian and the child. **Exclusion criteria:** 1. History of photosensitivity, glaucoma, glaucoma syndrome, ocular hypertension, and macular pathology or damage in the fundus; 2. The average K value of the anterior surface of the cornea is ≥45 in corneal curvature examination; 3. Patients with systemic diseases such as heart, liver, kidney, and congenital hereditary myopia; 4. Patients with chronic eye diseases such as eye trauma and strabismus or surgical eye, atopic keratoconjunctivitis; 5. People who have had other eye diseases such as inverted trichiasis, severe corneal and conjunctival infections in the past; 6. People with neurological diseases and allergies or contraindications to atropine drugs or other therapeutic drugs; 7. Patients with immune system and systemic diseases such as albinism, psoriasis, nephrotic syndrome, systemic lupus erythematosus, diabetes, etc.; 8. People with epilepsy and mental disorders who cannot communicate normally; 9. Individuals who have previously received other treatments to control the development of myopia, such as the use of anticholinergic drugs such as atropine within 3 months, or participated in other related researches such as functional frame mirrors, multifocal soft mirrors, etc.; 10. Other situations that the researcher judges are not suitable for participating in the study.
Control type: Comparison of the effect of routine single vision spectacle lenses

Statistical analysis plan：

The intention-to-treat (ITT) population comprised participants randomly assigned to either group. Data from all participants who attended at least one subsequent follow-up visit were included in the analysis. Individuals who switched to other myopia treatment modalities or discontinued the RLRL treatment, were censored.

Treatment efficacy was assessed using longitudinal mixed models for primary (changes in AL) and secondary (changes in SER and IOP) outcomes at multiple follow-up visits. Sensitivity analyses were conducted to assess the treatment effects of therapy in controlling myopia progression, specifically axial elongation and SER progression, across different baseline SER and age groups.

A longitudinal mixed-model analysis was conducted to assess the relationship between treatment efficacy and compliance within the intervention group.

Safety analyses were performed in the ITT population. All adverse events were reported individually.

Ethics:

The practice protocol (including the informed consent form) is submitted to the ethics committee for approval, and all subjects entering the trial screening must sign the informed consent form. Researchers should conduct experiments in strict accordance with the experimental protocol and GCP requirements to fully protect the legal rights and safety of the subjects.

2. INTRODUCTION

2.1 Sponsor Information

Sponsor name：Zuoguan Medical Equipment Co., Ltd. at Suzhou Industrial Park

Sponsor adress：Tonghe Road, Weiting Technology Park, Suzhou Industrial Park, Suzhou, Jiangsu, China

Sponsor Contact: Xianyong Wu, 13801252099

2.2 Study Personnel and institution

Site code	Study Institution	Researchers	professional title	Contact
01	Shanghai Ophthalmopathy Prevention & Treatment Centre	Haidong Zou，Yan Xu	Study Chair，Clinic site PI	13311986528 18621080996
02	Children's Hospital of Soochow University	Kehong Feng	Clinic site PI	18994305527
03	Xinhua Hospital Affiliated to Shanghai Jiaotong University School of Medicine	Huang Zhu	Clinic site PI	13801946402
04	Shanghai East Hospital	Hongping Cui	Clinic site PI	13671900868
05	The Children's Hospital Zhejiang University School of Medicine	Caiping Shi	Clinic site PI	13957125522
06	Shanxi Eye Hospital	Xueliang Feng	Clinic site PI	13934517456

2.3 Study Purpose

Study on effectiveness and safety of repeated low-level red-light in controlling high myopia in children and adolescents.

2.4 Research Background

Myopia, or nearsightedness, is a prevalent refractive error of the eye characterized by the ability to see close objects clearly while distant objects appear blurred. High myopia, defined as a refractive error of -6.00 diopters or more, poses a significant public health concern due to its increasing prevalence, particularly among children and adolescents worldwide[1-4] . High myopia not only impairs visual acuity but also substantially raises the risk of sight-threatening complications such as myopic macular degeneration,

glaucoma or even retinal detachment [5].

Despite the growing prevalence and potential vision-threatening consequences of high myopia, effective strategies for its control and management remain elusive. High myopia is often out of range as an indication for orthokeratology[6]. Low-concentration atropine[7-10] or defocus spectacles[11] have demonstrated reasonable efficacy on controlling low or moderate myopia in multiple randomized controlled trials (RCTs) but no evidence suggests their efficacy among highly myopic eyes.

The Eyerising amblyopia treatment instrument has been widely used in mainland China to treat amblyopia. The instrument utilizes repeated low-level red-light (RLRL) for treatment. Some studies confirm that it can improve the vision of patients, and no local or systemic side effects have been found [12]. Low-intensity lasers can cause photochemical reactions in the retina, including increasing the activity of cytochrome C oxidase [13,14] changing gene expression to regulate the mitochondrial respiratory chain [15], and increasing the biological activity of nitric oxide [16]. Preliminary trial data shows that it has a significant effect on slowing down the progression of myopia. This study will explore the effect of RLRL therapy in the prevention and treatment of high myopia for the first time. If successful, it will provide new ideas for effectively controlling myopia.

3. STUDY DESIGN

This trial is a randomized, controlled, multi-centre clinical trial. The subjects selected 192 children aged 6-16 who had developed high myopia, and divided them into intervention group and control group with 96 cases each. The intervention group was treated with the Eyerising RLRL and single vision spectacle lenses, and the control group was treated with single vision spectacle lenses. Then, we compare the changes of myopia during the observation period between the two groups, and evaluate the safety and effectiveness of the test device.

Subjects will be screened after signing the informed consent form (as early as 7 days before the randomization day). The screening test can use the results of the ophthalmological examination in hospital within 1 week, and subjects enter the group after confirming that they meet the selection conditions. On the day of enrolment, the group is confirmed after consultation with the parents, and determine whether to receive

equipment for treatment based on the results of the grouping. Visits were conducted 30±14 days, 90±14 days, 180±14 days, 270±14 days, and 365±14 days after enrolment.

3.1 Eligibility criteria

Inclusion criteria

①Age 6-16 years old, no gender limit;

②Either eye meets the diagnosis of myopic refractive error and the myopia of cycloplegic spherical equivalent refraction (SER) at least –4.0 D, astigmatism 2.0 D or less, anisometropia 3.0 D or less, and best-corrected visual acuity (BCVA) of LogMAR 0.2 or better.

③Have normal thinking and language communication skills, and be able to actively cooperate with the required treatment;

④ No contraindications to the treatment of atropine such as acute ocular inflammation, dry eye, keratoconus, diabetes, etc.;

⑤Written informed consent of the guardian and the child.

Exclusion criteria

①A history of photosensitivity, glaucoma, glaucoma syndrome, ocular hypertension, and macular pathology or damage in the fundus;

② Corneal curvature examination, the average K value of the anterior surface of the cornea is ≥45;

③Patients with heart, liver, kidney and other systemic diseases and congenital hereditary myopia;

④Patients with chronic eye diseases such as ocular trauma and oblique or surgical eyes, atopic keratoconjunctivitis;

⑤Patients with previous eye diseases such as inverted trichiasis, severe corneal and conjunctival infections;

⑥Patients with neurological diseases and allergies or contraindications to atropine drugs or other therapeutic drugs;

⑦Patients with immune system and systemic diseases such as albinism, psoriasis, nephrotic syndrome, systemic lupus erythematosus, diabetes, etc.;

⑧ People with epilepsy, mental disorders and unable to communicate normally;

⑨ Those who have previously received other treatments to control the development of myopia, such as the use of anticholinergic drugs such as atropine within 3 months, or participated in other functional frame mirrors, multifocal soft mirrors and other related researchers;

⑩ Other situations that the researcher judges are not suitable for participating in the research.

Participant withdrawal or termination

A study investigator will terminate participation in the study for the following reasons:

1) The patient receives other myopia control treatments;
2) Patients continuously stop using Eyerising equipment for more than 14 days;
3) Severe comorbidities or adverse events: patients cannot tolerate light, have obvious eye allergies such as tearing, skin rash, and the after-image time after low-energy laser treatment exceeds 5 minutes;
4) Serious safety problems occurred repeatedly during the test (such as serious adverse events related to the test);
5) China Food and Drug Administration ordered the suspension of the test for some reason;
6) Sponsor requests suspension (such as funding reasons, management reasons, etc.).

3.2 Recruitment and informed consent

Children who met the Inclusion criteria and their parents or guardians will be invited to participate in the study at the refractive clinic and optometry center of the research hospital through poster advertisements and physician referrals. Prior to collecting baseline data, written informed consent will be obtained from the parents/guardians of all participants.

3.3 Randomization and masking

A statistician without contacts with the participants generated the randomization sequence using SAS software (version 9.4; Cary, NC, USA). All eligible participants were randomly assigned to the intervention (RLRL plus SVS) or control (SVS only) groups at a 1:1 ratio. The randomization process adopted central stratification block randomization with block sizes of four or six. Each eligible participant was assigned a number based on their study entry sequence. Random assignment outcomes were

recorded in sealed envelopes with the corresponding sequential numbers written on the covers. Then, an investigator at the main center took custody of the envelopes. Each time an eligible participant's informed consent was acquired, the investigators responsible for group allocation at the six centers contacted the investigator holding the envelopes by telephone. The investigator immediately opened the envelopes and provided information on the group allocation of the newly enrolled participants. Owing to the nature of the intervention, the participants were aware of their assigned treatment groups. However, outcome assessors, including clinical examination technicians, optometrists, ophthalmologists, and statisticians, were blinded to the treatment allocation.

3.4 Intervention

1. Intervention group: Use the Eyerising RLRL device to treat with the treatment device twice a day, three minutes each time, with an interval of 4 hours. The method of use is as follows:

A. Put the instrument on a stable desktop, confirm the interface before connecting accessories;

B. Connect the power supply and turn on the power switch;

C. Let the user sit in a suitable position, loosen the hand-wheel on the side of the treatment device, and adjust it up and down to the most suitable angle to make the eyes relatively comfortable when resting on the goggles, and fix the hand-wheel to a fixed angle;

D. Enter the subject's unique account and password, and click Confirm to log in;

E. After logging in, the first interface enters the photo-kinetic energy treatment item by default, take off the glasses, click OK. Then, making sure that there is visible red light in the eye position corresponding to the instrument, and put the eyes close to the blue eye mask;

F. For the first use, please place your hands on the top of the treatment device and adjust the interpupillary wheel on the top at the same time. It is better to regard the two light points as one light point. If not, the brightest light also can be used.

G. After three minutes of use, the light kinetic energy will automatically stop, leave the blue eye mask, close your eyes and rest for 3-5 minutes, until the front and back image spots disappear;

H. After using the instrument, turn it off.

2. Control group: single vision spectacle lenses

3.5 Outcomes

1. Primary Outcome: Change of Axial length (AL, mm) at 12-month follow-up
2. Secondary Outcome: Change of cycloplegic spherical equivalent (SE, D) at 12-month follow-up
3. Optional Indicators：

   Changes of uncorrected visual acuity （UCVA），best-corrected visual acuity （BCVA），intraocular pressure, etc.;

   Changes of corneal thickness（CT）, anterior chamber depth（ACD） and lens thickness（LT）;

   Observe macula and the structure of fundus around the optic disc;

   Observe the choroid/retinal thickness of the fundus;

   Compliance index: frequency of equipment uses.

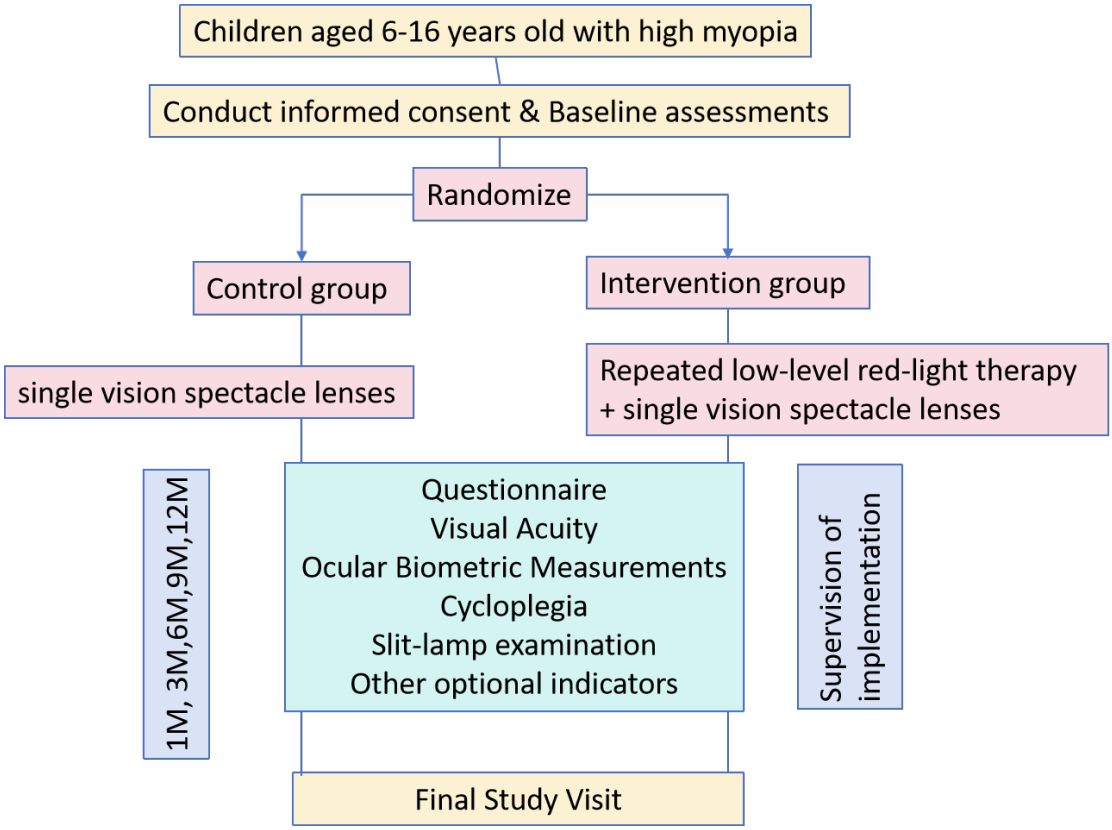
3.6 Study sample size

Sample size calculation

The sample size estimation was conducted assuming an α level of 0.05, 90% power, an annual axial elongation of 0.40 mm with a standard deviation of 0.40 mm over 12 months (based on previous results from our study group), and a 50% treatment effect (reducing axial elongation by 0.20 mm). The required sample size was 86 participants per group, totaling 172 participants. After adjusting for a 10% loss to follow-up, the total sample size was 192 participants.

4. FIELD WORK PROCEDURES

4.1 Summary flow chart



4.2 Baseline and Follow-up Examination

1. Baseline examinations

Standardized case report form (CRF) will be administered. The measurements outlined below will be performed at the baseline examination.

1）Registration: Name, date of birth, gender, ethnicity, contact information, and history of ocular disease or surgery, outdoor activities, time and habits of using eyes at close range, history and treatment of myopia, history of general medical conditions, history of allergies, will be obtained from questionnaire interviews and input into the EDC system.

2）Visual acuity: An ETDRS chart (Guangzhou Xieyi Weishikang, Guangzhou, China) with standard illumination will be used to measure distance visual acuity. Visual acuity measurement is performed at a distance of 4 meters. Uncorrected and best corrected visual acuity will be measured.

3）Cover-uncover test: Children will be asked to focus on a near object. The cover-

uncover test will be used to confirm strabismus and determine the type of ocular deviation

4）Ocular biometric measurements via IOL Master: Before cycloplegia, IOL Master (version 5.02, Carl Zeiss, Jena, Germany) is used to measure axial length. Using model eye to calibrate before measurement. Taking the average of 3 consecutive measurements. The difference between any two measurements cannot exceed 0.05mm, otherwise the measurement shall be performed again.

5）Cycloplegia: 1% cyclopentolate hydrochloride (Cyclogyl) is used as a mydriatic agent. Each time, the patient firstly puts 1 drop of Proparacaine Hydrochloride, 1 drop of Cyclogyl after 15 seconds, and 1 drop Cyclogyl 5 minutes later. 45 minutes after the last drop, checking the degree of pupil dilation and light reflection. Dilation and light reflex status will be recorded and full cycloplegia will be justified if the pupil dilates to 6 mm or greater and the light reflex is absent. If the requirements for cycloplegia are not met, the third drop of Cyclogyl will be given. Then the cycloplegia will be reconfirmed after 15 minutes.

6）Cycloplegic auto-refraction: Cycloplegic auto-refraction will be conducted using an auto-refractor (KR-8900, Topcon, Tokyo, Japan). The same auto-refractor will be used throughout the study. It will be calibrated before each examination session to ensure there is no equipment drift during the long follow-up process.

7）Slit-lamp examination: Slit-lamp examination will be used to examine the anterior segment, lens, vitreous, and fundus, and any abnormalities will be recorded.

8）Optical coherence tomography (optional): SS-OCT fundus image acquisition and data processing: using swept source OCT (DRI OCT-1 Atlantis, Topcon) 9 Line Radial follow-up mode to scan and collect images to obtain fundus pictures and fundus tissue tomographic images. Before the collection, the subjects should be asked to sit still for a while, avoid taking coffee and drinks; during collection, doctors should pay attention to correct the axial magnification; researchers should concentrate on collection time to avoid the influence of the time rhythm fluctuation of choroidal thickness. After the choroidal boundary is automatically segmented by the machine's built-in software,

manual verification and correction are carried out, and the choroidal thickness data of 9 regions of the fovea and the inner, middle and outer rings (upper, lower, nasal, and temporal) are obtained.

2. Follow-up Examinations:

1) Questionnaire: A questionnaire on adverse events following the intervention will be administered at each follow-up visit and unexpected visits for children in the intervention group. Children and their parents/guardians will be asked about the side effects, including but not limited to short-term glare, flash blindness, and afterimages.

2) Visual acuity: An ETDRS chart (Guangzhou Xieyi Weishikang, Guangzhou, China) with standard illumination will be used to measure distance visual acuity. Visual acuity measurement is performed at a distance of 4 meters. Uncorrected visual acuity will be measured for each follow-up visit, best corrected visual acuity will be measured for the baseline, 6-month and 12-month follow-up visit.

3) Ocular biometric measurements via IOLMaster: IOLMaster will be used to measure the axial length of both eyes. Five measurements will be taken for each eye. The axial length measurement will be based on the mean of these five values if the desired precision (<0.05 mm) is achieved.

4) Cycloplegia: Cycloplegia will be induced with three drops of 1% cyclopentolate administered at the 0, 5th, and 20th minute to each eye. The light reflex and pupil dilation will be checked after an additional 15 minutes. Dilation and light reflex status will be recorded and full cycloplegia will be justified if the pupil dilates to 6 mm or greater and the light reflex is absent.

5) Cycloplegic auto-refraction: Cycloplegic auto-refraction will be conducted using an auto-refractor (KR-8800, Topcon, Tokyo, Japan). The same auto-refractor will be used throughout the study. It will be calibrated before each examination session to ensure there is no equipment drift during the long follow-up process.

6) Slit-lamp examination: Slit-lamp examination will be used to examine the anterior segment, lens, vitreous, and fundus, and any abnormalities will be recorded.

7) Optical coherence tomography (optional): Swept Source-OCT (DRI OCT-1 Atlantis, Topcon) will be used to capture the macular scan. Shooting mode: 12 mm radial scan mode (follow up mode).

8）Safety assessment

①The incidence of allergic reactions;

②Afterimage duration exceeds 5 minutes;

③Decreased near visual acuity；

④ Levels of side effects such as photophobia and blurred vision;

⑤Increased intraocular pressure, headache, nausea and vomiting, etc.

Follow-up Schedule

(1) Visit 1: Screening period (-7～0 days)

1) Sign the "Informed Consent";

2) Record the general information of the patient;

3) Record the medical history;

4) Perform visual inspection, axial inspection, intraocular pressure inspection, equivalent spherical lens measurement, slit lamp inspection, OCT inspection;

5) Review the inclusion and exclusion criteria;

6) Record the combined/concomitant medication;

(2) Visit 2: Enrolment and randomization (day 0)

1) Randomly group, and the intervention group will receive experimental devices;

2) Record device defects;

3) Record the combined/concomitant medication;

(3) Visit 3: Day 30±14

1) Perform visual inspection, axial inspection, and intraocular pressure inspection;

2) Record the combined/concomitant medication;

3) Record adverse events/device defects.

(4) Visit 4: Day 90±14

1) Perform visual inspection, axial inspection, and intraocular pressure inspection;

2) Record the combined/concomitant medication;

3) Record adverse events/device defects.

(5) Visit 5: Day 180±14

1) Perform vision examination, axial examination, intraocular pressure examination, equivalent spherical lens, slit lamp examination, and OCT;

2) Record the combined/concomitant medication;

3) Record adverse events/device defects.

(6) Visit 6: Day 270±14

1) Perform visual inspection, axial inspection, and intraocular pressure inspection;

2) Record the combined/concomitant medication;

3) Record adverse events/device defects.

(7) Visit 7: Day 365±14

1) Perform vision examination, axial examination, intraocular pressure examination, equivalent spherical lens, slit lamp examination, and OCT;

2) Record the combined/concomitant medication;

3) Record adverse events/device defects.

4.3 Process of the practice

Schedule of events table

Phase	**Period of Filter**	**Enroll and random**	**Period of Treatment**				
Visit Time	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**
Observed Time Point	Day-7~0	Day 0	Day 30±14	Day 90±14	Day 180±14	Day 270±14	Day 365±14 天
Demographic data	√						
History-taking	√						
Examination of Distant Vision	√		√	√	√	√	√
Examination of Axial	√		√	√	√	√	√

Intraocular Pressure (IOP)	√		√	√	√	√	√
Spherical Equivalent (SE)	√				√		√
Examination with Slit-lamp	√				√		√
OCT	√				√		√
Sign Informed Consent	√						
Determine Inclusion/Exclusion Criteria	√						
Random Grouping	√						
Distribute Equipment		√					
Record Device Defects		√	√	√	√	√	√
Record Concomitant Medications	√		√	√	√	√	√
Record Adverse Events	√		√	√	√	√	√
End of Practice							√

5. Data entry and Analysis

5.1 Data collection

The case report forms (CRFs) will serve as the means to document and collect clinical data throughout the trial. These forms will be in physical paper format, ensuring that the original material remains intact. It is important to note that the CRFs should not be altered or modified arbitrarily.

All pertinent information regarding the patients involved in the trial will be recorded accurately and promptly on the CRFs. This includes any relevant data related to their medical condition, treatment received, and any observed outcomes or adverse events. It is crucial that this information is recorded truthfully to maintain the integrity and validity of the trial results.

Data collected on site will be entered on a real-time basis using the EDC system to ensure that all required items are entered. The EDC will automatically verify that there are no missing values during submission. After examinations are completed, the paper examination forms will be stored in a locker of the research center to protect the privacy

of participants and ensure access for data review and audit.

5.2 Statistical analysis plan

The intention-to-treat (ITT) population comprised participants randomly assigned to either group. Data from all participants who attended at least one subsequent follow-up visit were included in the analysis, regardless of treatment or follow-up visit compliance. No imputation was used for the missing data. Individuals who switched to other myopia treatment modalities, such as orthokeratology or atropine eye drops, or discontinued the RLRL treatment, were censored. If a participant had only one eye with a SER exceeding –4.0 D, that eye was selected for the statistical analysis. In cases where both eyes were exceeding –4.0 D, the right eye was chosen for the analysis.

Treatment efficacy was assessed using longitudinal mixed models for primary (changes in AL) and secondary (changes in SER and IOP) outcomes at multiple follow-up visits. The mixed effects model was fitted with a random intercept and random slope for the participant, where the group, visit, group-by-visit interaction, baseline age, sex, and baseline AL were fixed effects. Estimated mean treatment differences and corresponding 95% confidence intervals (CIs) were derived from mixed models. UCVA alterations were classified into three categories: decline by two or more lines, stable (within a line), or improvement by two or more lines. The BCVA at the 12-month and baseline was evaluated against the 20/25 standard.

Sensitivity analyses were conducted to assess the treatment effects of therapy in controlling myopia progression, specifically axial elongation and SER progression, across different baseline SER and age groups.

A longitudinal mixed-model analysis was conducted to assess the relationship between treatment efficacy and compliance within the intervention group. Treatment compliance in the intervention group was measured as a percentage of the total number of assigned treatment sessions.

Safety analyses were performed in the ITT population. All adverse events were reported individually. Six ophthalmologists, one from each center, independently scrutinized the OCT scans for potential structural anomalies.

6.MONITORING

Monitoring begins immediately after initiation. The first case from each participating center is enrolled, followed by monitoring at 30% and 50% of enrollment, and finally after completion of enrollment. The duration of surveillance is determined by the occurrence of serious adverse events. If there are abnormal enrollment situations or a high frequency of program violations, the frequency of monitoring will be increased accordingly. The monitoring focuses on subjects, investigators, and equipment used, primarily assessing the following aspects:

1. Informed consent status: Ensuring that the number of signed informed consent forms matches the number of cases in the clinical trial report (including cases of screening failure), verifying that the version of the signed informed consent form aligns with the version approved by the ethics review, confirming that the ethics review was conducted prior to the signing of the informed consent form, assessing the completeness and standardization of the informed consent form (including inclusion of the clinical trial personnel's contact information, signing date, etc.), and verifying that the subject's signed informed consent form was signed by the subject or their legal representative (if necessary, confirming the actual participation of subjects in the trial).

2. Implementation assessment: Whether the clinical trial procedures adhere to the clinical trial protocol, including the subject selection and exclusion criteria, sample size, selection of control devices, trial duration, observation endpoints, and the management and documentation of adverse events; verifying that the original data collection and case report forms are signed by the clinical trial personnel.

3. Equipment assessment: Whether the delivered equipment product has a valid product inspection report issued by a qualified testing agency, and whether the management record of the tested product (including transportation, reception, processing, storage, distribution, recycling, and disposal) is complete; verifying if the quantity is consistent; assessing if the transportation conditions, storage temperature, storage conditions, storage duration, and safety validity period of the tested product meet the requirements; confirming if the tested product matches the product name, specification, and model

stated in the test report and clinical practice report. After each inspection, the inspector will generate an inspection report based on the findings.

7. QUALITY ASSURANCE

To ensure that this trial can be carried out in strict accordance with the clinical research protocol, clinical investigators, sponsors, and supervisors should strictly adhere to the requirements of the “Good Clinical Practice” (GCP) throughout the entire process of the clinical trial. This will help achieve standardized test procedures, accurate data, and reliable research conclusions.

1. Investigator's Responsibility

1) Ensure that the “Informed Consent” is obtained and signed by each subject or their authorized representative.
2) Carefully complete the case report form (CRF) as per the specified requirements.
3) Collaborate with the regular visits of clinical monitors assigned by the sponsor.
4) Maintain comprehensive records of laboratory inspections, clinical records, and original medical records of the subjects.

2. Clinical Practice records

The investigator is responsible for accurately and diligently documenting all cases according to the design requirements of the "case report form". The case report form serves as the original record and should not be altered. If any corrections are necessary, the original record should not be obscured. Instead, a horizontal line should be drawn at the location of the correction, accompanied by an explanation of the reason for the correction. This should be signed and dated by the physician who was involved in the clinical practice.

3. Training

The personnel involved in the clinical research should have a consistent and stable team. Prior to the commencement of the clinical trial, all personnel involved should undergo standardized training to ensure that they have a consistent understanding and knowledge of the clinical trial protocol. They should also be familiar with the recording method and judgment criteria of the case report form (CRF) in a uniform manner.

4. Supervision

1) The sponsor appoints qualified monitors to regularly visit each study site during the trial period. Their role is to ensure that the investigator accurately completes the case report form, adheres to the research plan, conducts clinical trials, and collects completed case report forms.
2) Monitors should be granted direct access to source documents, including original documents, data, and records. This access allows them to inspect, analyze, and verify any important records and reports related to the evaluation of clinical trials.
3) The investigator should be able to contact the monitor at any time for discussions. The original data that the monitor should verify include (but are not limited to):
   - ✓ Subjects' information (subject's phone number, date of birth);
   - ✓ The confirmation of participation in the clinical trial should include the subject's identity, the test device number, and the date of signing the informed consent form;
   - ✓ Whether it meets the criteria for participating in clinical trials;
   - ✓ Date of visit.

5. Data validation

1) The investigator should verify the data that significantly deviates from or is outside the acceptable range, and provide necessary explanations.
2) Each test item must indicate the unit of measurement used.
3) All observations and findings in clinical practice should be verified to ensure the reliability of the data and to ensure that all conclusions are derived from the original data.

8. ETHICS

Ethical approval

This study will undergo review and approval from the Ethics Committee of Shanghai General Hospital. The study protocol must be granted approval by the ethics committee prior to its implementation. The implementation process must adhere to the regulations and requirements set by relevant institutions and study sites, and may require additional approval from the clinical site if necessary. Any modifications to the study protocol after ethical approval has been obtained will need to be submitted to the ethics

committee for re-approval before implementation.

Plan modification

Modifications to the study plan must be submitted to the sponsor and the ethics committee for review and approval before implementation, except for necessary modifications that intend to handle immediate hazards to subjects, or for modifications that are relevant for administrative management and/or related (such as changing the contact number).

Informed consent

The procedures and documentation for obtaining informed consent in the research study will be reviewed and approved by the ethics committee prior to implementation. The informed consent process will ensure that participants are provided with comprehensive information to make an informed decision about their participation, including the potential benefits and risks involved. The researcher will engage in discussions with the participants and their parents/guardians, allowing them to ask questions before, during, and after the study. Participants and their parents/guardians will have the right to be informed throughout the study and can withdraw their participation at any time without providing a reason.

The informed consent process will provide an overview of the study, including the purpose of the study, procedures and scheduled plans, potential risks and benefits, and other treatment options. The informed consent should include an explanation of the subjects' rights once they participate in the study. Subjects should be given enough time to consider whether to participate in the study. If they agree to become volunteers, they need to sign off on the subjects' informed consent.

Confidentiality

According to the relevant agreement, all parties involved must keep study data confidential throughout the study process. All data related to the test cannot be accessed without authorization. The private information of research subjects will be protected in the report and the publication of any clinical research data.

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Introduction to Treatment Device and Data Managements System

Specifications for the use of machinery

After the start of the research, the sponsor will send special personnel to directly deliver the test materials to each research centre. The research centre and the sponsor will establish a complete test equipment handover procedure. Each research institution shall set up a test material administrator and establish a special "Clinical Practice Medical Device Use Record Form", register the device number, the name of the subject, and be signed by the device administrator.

The management, issuance, and recycling of clinical devices in this practice are managed by special personnel. Researchers must ensure that all experimental devices are used only for subjects participating in the clinical practice. Their usage should follow the practice protocol and instructions. The sponsor shall contract with the hospital for disposal, and shall not transfer the clinical trial equipment to any non-clinical practice participant. The supervisor is responsible for supervising the supply, use, storage of clinical trial equipment and the processing of the trial equipment.

1. Features, structure, working principle, mechanism of action, and test scope of Eyerising products

Eyerising amblyopia comprehensive treatment instrument is mainly composed of treatment module, housing, eye mask, interpupillary distance adjustment knob, locking hand wheel, touch screen, control circuit, and electrical interface (as shown in Figure 1). The functions of each component structure are as follows:

1) Treatment module: an electronic module that realizes four treatment functions;
2) Shell: fix and install each component module, which is convenient for users to use the instrument;
3) Eye mask: The user's eyes are close to the eye mask during treatment, and the eye mask has a good wrapping property to prevent the interference of external light;
4) Interpupillary distance knob: The treatment device is a binocular product, and the user can adjust the distance of the emission window of the treatment device to be consistent with their own interpupillary distance, to achieve the best treatment effect;
5) Hand wheel lock: The user adjusts the pitch angle of the treatment head to the best position according to his height and posture, and then locks it with the hand wheel

lock to prevent loosening.

6) Touch screen: the user operates the machine through the touch screen;
7) Circuit control: control each electronic module;
8) Electrical interface: including power switch, power interface, USB interface and LAN interface.
9) Power switch: use for starting and closing the machine;
10) Power interface: connect the adapter for power supply;
11) USB interface: used for manufacturers to detect and debug internal circuits;
12) LAN interface: help machine connect to the external Internet.

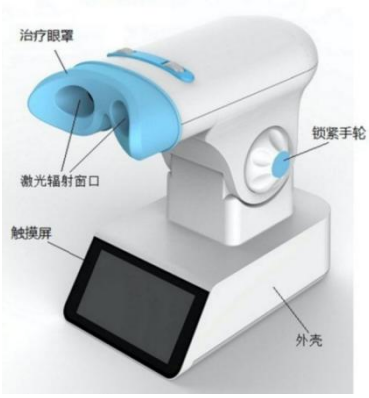

Figure 1:
治疗眼罩：Treatment Eye Mask
激光辐射窗口：Laser Radiation Window
锁紧手轮：Hand Wheel Lock
触摸屏：Touch Screen
外壳：Shell

2. Specifications and models

RS-200-1A

3. Working principle and mechanism

The potential of low-intensity photochemical conversion can cause photochemical reactions in the retina, including increasing the activity of cytochrome C oxidase, changing gene expression to regulate the mitochondrial respiratory chain , and increasing the biological activity of nitric oxide . Also, it can increase Choroidal metabolism rate and circulation to improve scleral hypoxia, prevent or slow down the progression of myopia.

4. product indications and contraindications, precautions,

Indications:

1) It is suitable for patients with ametropia, anisometropia and strabismus amblyopia.
2) It is suitable for the treatment of juvenile myopia.

3) Applicable age for this product: 3-16 years old.

Contraindications:

1) Patients with a history of photosensitivity.

2) Patients with fundus retinopathy, cataracts or other intraocular diseases.

3) Patients with optic nerve damage or congenital optic nerve dysfunction.

Precautions:

1) Laser safety matters

This product is classified as a Class 3R laser product according to GB7247.1-2012. For non-patients, direct vision may cause dazzling, flash blindness, and after-eye imaging and other adverse reactions. Non-patient users are requested not to look directly into the laser window (as shown in Figure 1). If you need to look directly into the laser for special reasons, please wear laser protective glasses and laser protective glasses with optical density OD≥3 in the visible light range.

The laser parameters emitted by the treatment device are as follows:

a) Wavelength: 650nm

b) Divergence angle: 2.5°

c) Pulse width and repetition frequency: continuous emission

d) Power: 2.0mW±0.5mW

2) Pay attention to eye hygiene during treatment, and stop using this product if you have eye diseases such as eye inflammation and swelling.

3) To use this product, please follow the doctor's instructions and select appropriate functions for treatment.

4) If discomfort occurs while using this product, stop using it or follow the doctor's advice.

5) After each use, please turn off the power switch, and then unplug the power plug.

6) If the external network voltage suddenly increases or the operator deliberately frequently starts and stops the equipment, the laser radiation of the equipment may exceed the maximum radiant power specified by this product.

7) If the treatment device is expected to be used by more than one person in a hospital or clinic, a non-woven eye mask should be put on the eye mask of the treatment device to ensure that one person has a new eye mask.

8) Please strictly follow the operation method in this manual for operation and treatment. If this operation method is not followed, it may cause harmful laser irradiation.