BMJ Open

Effect of Intraocular Pressure Reduction on Progressive High Myopia (PHM study): Study Protocol of a Randomized Controlled Trial

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2024-084068
Article Type:	Protocol
Date Submitted by the Author:	08-Jan-2024

Complete List of Authors:	Gao, Xinbo; Sun Yat-Sen University Zhongshan Ophthalmic Center State Key Laboratory of Ophthalmology Lam, Dennis SC; The Chinese University of Hong Kong Chen, Shida; Sun Yat-Sen University Zhongshan Ophthalmic Center State Key Laboratory of Ophthalmology Zhang, Xiulan; Sun Yat-Sen University Zhongshan Ophthalmic Center State Key Laboratory of Ophthalmology Jiang, Jingwen; Sun Yat-Sen University Zhongshan Ophthalmic Center State Key Laboratory of Ophthalmology, Clinical research center Lin, Tingting; Sun Yat-Sen University Zhongshan Ophthalmic Center State Key Laboratory of Ophthalmology, Clinical research center; Daqing Oilfield General Hospital Lin, Fengbin; Sun Yat-Sen University Zhongshan Ophthalmic Center State Key Laboratory of Ophthalmology Kong, Kangjie; Sun Yat-Sen University Zhongshan Ophthalmic Center State Key Laboratory of Ophthalmology, Clinical research center Wang, Peiyuan; Sun Yat-Sen University Zhongshan Ophthalmic Center State Key Laboratory of Ophthalmology, Clinical research center Chen, Jinmei; Sun Yat-Sen University Zhongshan Ophthalmic Center State Key Laboratory of Ophthalmology, Clinical research center Song, Yunhe; Sun Yat-Sen University Zhongshan Ophthalmic Center State Key Laboratory of Ophthalmology Wang, Zhenyu; Sun Yat-Sen University Zhongshan Ophthalmic Center State Key Laboratory of Ophthalmology Jin, Ling; Sun Yat-Sen University Zhongshan Ophthalmic Center State Key Laboratory of Ophthalmology, Clinical research center Liu, Yuhong; Sun Yat-Sen University Zhongshan Ophthalmic Center State Key Laboratory of Ophthalmology, Clinical research center Chen, Meiling; Sun Yat-Sen University Zhongshan Ophthalmic Center State Key Laboratory of Ophthalmology Jonas, Jost; Heidelberg University, Ophthalmology; Institute of Molecular and Clinical Ophthalmology Basel,

Keywords:	Randomized Controlled Trial, OPHTHALMOLOGY, Glaucoma < OPHTHALMOLOGY

Effect of Intraocular Pressure Reduction on Progressive High Myopia (PHM study): Study Protocol of a Randomized Controlled Trial

Jingwen Jiang, MD[1, *], Tingting Lin, MD[1, *], Fengbin Lin, MD, PhD[1], Kangjie Kong, MD[1], Peiyuan Wang, MD, PhD[1], Yunhe Song, MD, PhD[1], Zhenyu Wang, MSc[1], Ling Jin, MSc[1], Yuhong Liu, MSc[1], Xinbo Gao, MD, PhD[1], Jinmei Chen, MBBS[1], Meiling Chen, MBBS[1], Dennis SC Lam, MD[2], Jost B. Jonas, MD[3,4], Shida Chen, MD, PhD[1, †], Xiulan Zhang, MD, PhD[1, †], for the Glaucoma Suspects with High Myopia Study Group

[1]State Key Laboratory of Ophthalmology, Zhongshan Ophthalmic Center, Sun Yat-sen University, Guangdong Provincial Key Laboratory of Ophthalmology and Visual Science, Guangdong Provincial Clinical Research Center for Ocular Diseases, Guangzhou 510623, China.

[2] The International Eye Research Institute, the Chinese University of Hong Kong (Shenzhen), Shenzhen, China.

[3]Department of Ophthalmology, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany.

[4]Institute of Molecular and Clinical Ophthalmology, Basel, Switzerland.

* Jingwen Jiang and Tingting Lin contributed equally.

Tingting Lin is a visiting doctor at Zhongshan Ophthalmic Center.

[†]Corresponding Author

Xiulan Zhang, MD, PhD

State Key Laboratory of Ophthalmology, Zhongshan Ophthalmic Center, Sun Yat-Sen University, No.7 Jinsui Road, Guangzhou 510060, China.

Phone number:+86 135 7016 6308

Email: zhangxl2@mail.sysu.edu.cn

Shida Chen, MD, PhD
State Key Laboratory of Ophthalmology, Zhongshan Ophthalmic Center, Sun Yat-Sen University, No.7 Jinsui Road, Guangzhou 510060, China.
Email: chenshd3@mail.sysu.edu.cn

Competing Interest Statement and Financial Disclosure:
Jost B. Jonas: European patent EP 3,271,392, JP 2021-119187, and US 2021 0340237 A1: Agents for use in the therapeutic or prophylactic treatment of myopia or hyperopia; European patent application 23196899.1 "EGFR Antagonists for the treatment of diseases involving unwanted migration, proliferation, and metaplasia of retinal pigment epithelium (RPE) cells".

Ethics Statement: The study was approved by the ethical committee of the Zhongshan Ophthalmic Center and adhered to the tenets of the Declaration of Helsinki. Written informed consent was obtained from all subjects.

Key Words: High myopia, Axial length, Intraocular pressure, Randomized controlled trial

ABSTRACT

Background In adult patients with high myopia (HM), progressive axial elongation poses a significant risk for the development of subsequent ocular's complications that may lead to visual impairment. Effective strategies to reduce or prevent further axial elongation in highly myopic adult patients have not been available so far. Recent studies suggested that medically lowering intraocular pressure (IOP) may reduce axial elongation. This clinical randomized controlled trial (RCT) aims to evaluate the efficacy of medical IOP reduction in adult patients with progressive HM (PHM).

Methods and analysis This single-center, open-label, prospective RCT will recruit 152 participants with PHM at the Zhongshan Ophthalmic Center (ZOC). Randomized in a ratio of 1:1, participants will receive IOP-lowering eyedrops (intervention group) or will be followed without treatment (control group) for 12 months. Follow-up visits will be conducted at 1, 6, and 12 months after baseline. Only one eye per participant will be eligible. The primary outcome is the change in axial length (AL) within the study period of 12 months. Secondary outcomes include the incidence and progression of visual field (VF) defects, changes in optic disc morphology and incidence and progression of myopic maculopathy. Difference in AL changes between the two groups will be analyzed using linear regression analysis. For the secondary outcomes, a multifactor Poisson regression within a generalized linear model will be utilized to estimate the relative risk of progression in VF defects and myopic maculopathy, and the rate of thinning in retinal nerve fiber layer and ganglion cell-inner plexiform will be assessed through Kaplan-Meier curves and log-rank tests.

Ethics and dissemination Full ethics approval for this trial has been obtained from the Ethics Committee of ZOC, Sun Yat-sen University, China (ID: 2023KYPJ110). Results of this trial will be disseminated through peer-reviewed journals and conference presentations.

Trial registration number NCT05850936 *clinicaltrials.gov*

Strengths and limitations of this study

1. The primary objective of this study is to address a global healthcare concern: effectively mitigating further axial elongation in highly myopic adult patients.
2. Due to practical constraints, a double-masking in the study design cannot be achieved.

Introduction

High myopia (HM) is an important global public health issue [1-2], with prevalence estimates of approximately 163 million individuals (2.7% of the world population) affected in 2000, and of approximately 938 million (9.8% of the world population) people estimated to be affected in 2050 [3-5]. High myopia-related complications, such as optic neuropathy, myopic maculopathy and retinal detachment, can lead to irreversible visual impairment [6-8].

Recent clinical studies have revealed that highly myopic eyes in adult patients can undergo further axial elongation with a rate up 0.1mm/year [9]. Axial elongation in highly myopic eyes is a major risk for progression of myopic macular degeneration and potentially of high myopia-associated optic neuropathy and subsequent vision impairment [10-11]. Effective strategies to reduce or stop further axial elongation in highly myopic eyes are warranted.

Recent experimental studies have suggested that medical reduction of intraocular pressure (IOP) could be protective against axial elongation in guinea pigs [12-13]. In a clinical observational study, application of IOP-lowering medication, but not the IOP-value itself, was associated with a reduced ongoing axial elongation in highly myopic patients [14]. As a corollary, recent Mendelian research has established a bidirectional association at the genetic level between myopia and primary open-angle glaucoma mediated through IOP [15]. In a recent retrospective clinical study medically IOP-lowering reduced axial elongation in highly myopic eyes (own unpublished data).

Building upon these findings, we hypothesize that medically IOP-lowering may slow axial elongation by potentially three pathways related to the sclera and choroid[16]. We therefore aim to conduct a randomized controlled trial (RCT) to assess the efficacy of medical IOP-lowering in managing axial elongation in patients with progressive HM (PHM). Additionally, this study should generate data on the effects of IOP-lowering treatment on the incidence and changes in the visual field (VF), changes in the optic nerve head morphology and myopic maculopathy. The outcomes of the study may

establish a basis for treatment recommendations for preventing axial elongation of highly myopic eyes.

Methods and Analysis

Study design

The PHM study is an open-label, single-center RCT. The study will be conducted at the Zhongshan Ophthalmic Center (ZOC), Sun Yat-Sen University, a tertiary specialized hospital in Guangzhou, China. All examinations and interventions will be carried out in the Clinical Research Center at ZOC. **Figure 1** summarizes the design of the PHM study.

Objective

The primary aim of this trial is to evaluate the effectiveness of medically IOP-lowering therapy, targeting a 10% decrease from baseline levels, in managing axial elongation in patients with PHM over a 12-month observation period. Additionally, the trial will assess alterations in VF, optic disc morphology, thickness of the retinal nerve fiber layer (RNFL) and retinal ganglion cell-inner plexiform layer (GC-IPL), and the occurrence or advancement of myopic maculopathy.

Recruitment

Inclusion criteria

1. Age ⩾18 years and ⩽65 years.
2. Diagnosed with HM [17-18]: spherical equivalent ⩽-6.00 diopters or AL ⩾26.5 mm.
3. Diagnosed with PHM: axial elongation ⩾0.05mm in the past 6 months or ⩾0.1mm in the past 12 months.

4. IOP: ⩾10 mmHg and ⩽21mmHg on at least 2 visits using Goldmann applanation tonometry with correction for the dependence of the IOP-reading on corneal thickness [19].

5. Best corrected visual acuity (BCVA) ⩾6/12, ability to undergo AL measurement, fundus photography, optical coherence tomography (OCT), and complete VF examination.

Exclusion criteria

1. Allergy to any kind of IOP-lowering eyedrops.
2. Presence of serious fundus pathologies like proliferative diabetic retinopathy, retinal detachment, central retinal artery occlusion, etc.
3. Presence of chronic, recurrent, or severe ocular inflammatory lesions such as chronic or recurrent uveitis.
4. Significant corneal or iris lesions, severe cataract affecting fundus examination, or patients with only one eye.
5. Intraocular surgery or laser treatment within the last year, such as cataract surgery.
6. With a history of previous refractive surgery or prior treatment for myopia-related conditions (e.g., orthokeratology lens wear, low-intensity red light therapy, or low-concentration atropine treatment).
7. Presence of other serious systemic diseases (e.g., hypertension, heart disease, diabetes, rheumatic immune system disease) that hinder long-term follow-up and eye treatment.
8. Pregnancy, lactation, or plans to have children during the follow-up period.

In this study, only one eye per participant will be eligible for inclusion. If both eyes meet the inclusion criteria, the eye with a higher rate of axial elongation, a worse mean perimetric deviation (MD) value, and a worse BCVA will be selected.

Randomization and blinding

In this trial, randomization will be employed to mitigate distribution bias. After confirming all inclusion and exclusion criteria and obtaining signed written informed consent forms, qualified individuals within each block, with a block size of 4, will be assigned in an even (1:1) manner to either the intervention group or the control group. The random sequence will be generated using an electronic data collection (EDC) system to ensure unbiased allocation.

In this trial, the participants and physicians will not be blinded to the intervention assignment. The technicians conducting the examinations and interpreting the images will be unaware of the participants' group assignments during the screening and follow-up stages. The researchers analyzing the data will also be unaware of the information regarding randomization.

Interventions

Wash out

Patients who have been using IOP-lowering medications prior to enrollment need to undergo a drug washout period. Different medications have different washout periods: prostaglandin analogs require a washout period of 4 weeks, beta-blockers require 3 weeks, adrenergic receptor agonists require 2 weeks, cholinergic receptor agonists and carbonic anhydrase inhibitors require 5 days. For patients who have previously discontinued medication and have already satisfied the specific washout period for that medication, or for those who have not received any IOP-lowering medication, a blank washout period is not necessary.

Intervention group

Participants assigned to the intervention group will receive medical IOP-lowering therapy for a duration of 12 months or until they reach the endpoint**.** Only the study eye will receive medication in the enrolled participants. The preferred initial

medication for reducing IOP is Xalacom® eye drops (a fixed latanoprost and timolol combination). If the target IOP (reducing baseline IOP by 10%) is not achieved after one month of treatment, 1% brinzolamide eye drops (Azopt®) will be added. If the target IOP is still not achieved after an additional month of treatment, brimonidine tartrate eye drops (Alphagan® 0.2% or Alphagan-P® 0.15%) will be added. If the patient is allergic to prostaglandin analogs, the preferred alternative is Azarga® eye drops (a fixed brinzolamide with timolol combination). If the target IOP is not achieved after one month of treatment, brimonidine tartrate eye drops (Alphagan® 0.2% or Alphagan-P® 0.15%) will be added (**Figure 2).**

The treatment protocol will involve the instillation of a single drop of prostaglandin ophthalmic solution in the study eye once daily in the evening for medications such as Xalacom. For medications like timolol, Alphagan (or Alphagan-P), brinzolamide, or Azarga, the study eye will receive one drop twice daily. To ensure the standardization of medication usage among participants, subjects will be provided with medication logbooks, which will be collected and recorded by the investigators during the study visits.

Regular assessment of IOP will be conducted on a weekly basis following the initiation or addition of medication until the target value is achieved in the study eye. If the study eye fails to reach the target IOP even after escalating the medication, the medication will be discontinued, but the subsequent follow-up visits will continue as planned.

Control group

Participants assigned to the control group will be followed up for 12 months or until they reach the endpoint without medical IOP-lowering therapy.

Outcome measures

Primary outcome

The primary outcome is the change of AL at 12-month from baseline measured by IOLMaster.

Secondary outcomes

1. Incidence and progression of VF defects at 12 months from baseline based on Humphrey 24-2 standard VF. Under the premise of reliable VF examination, compared to the baseline, two consecutive perimetric examinations reveal the incidence of VF defects or significant perimetric progression in at least three points at a significance level of $p<0.05$. Furthermore, two subsequent diagnostic VF examinations conducted within one month also confirm the progression at the locations. The time of progression is defined as the time of the initial diagnostic VF examination [20-21].

2. Changes in optic disc morphology (including thinning of RNFL and GC-IPL) at 12-month from baseline based on fundus photography and OCT [22-24].

3. Incidence and progression of myopic maculopathy at 12 months from baseline based on fundus photography and OCT. The determination of incidence and progression of myopic maculopathy is based on the META-PM classification system [25-26].

Study assessments

Visual acuity

Visual acuity assessment will be conducted prior to any procedures that may potentially impact vision, such as pupil dilation or VF examination. The measurement of visual acuity will be performed using an ETDRS (Early Treatment of Diabetic Retinopathy Study) LogMAR chart (Precision Vision, Villa Park, Illinois, USA) under standard illumination conditions at 4 meters [27]. For BCVA, a trial frame will be positioned and adjusted on the participant's face based on auto refractometric readings and subsequent subjective refinement.

Refractometry

Following pupil dilation using 0.25% compound tropicamide (Zhuobian@; Sinqi, China), three measurements will be taken for each eye using an auto refractometer (KR800, TOPCON, Tokyo, Japan). The average values for spherical refractive error, cylindrical refractive error, and astigmatic axis will be recorded for further analysis and documentation.

Slit-lamp biomicroscopy

The evaluation of the anterior segment with the pupil undilated will be performed using a slit lamp (BQ-900, Haag Streit, Koeniz, Switzerland). After medical pupillary dilation, a slit lamp-based grading of lens opacities is conducted, and using a 90D indirect ophthalmoscopic lens (Ocular 90D Slit Lamp Lenses, Ocular, Washington, DC, USA), the optic disc, macula, and peripheral retina will be examined.

Tonometry

IOP measurements will be performed by Goldmann applanation tonometry (AT900, Haag Streit, Koeniz, Switzerland). Prior to enrollment, all participants will undergo three baseline IOP readings during specific time intervals: 9 am to 10 am, 1 pm to 2 pm, and 4 pm to 5 pm. During follow-up visits, tonometry will be conducted between 9 am and 11 am or between 2 pm and 4 pm. Results from three consecutive measurements will be documented during each visit, and the mean value of these measurements will be utilized for assessment purposes.

AL measurement

AL measurement will be performed using the IOLMaster (IOLmaster 700, Carl Zeiss Meditec, Jena, Germany). Results from five consecutive measurements will be documented during each visit, and the mean value of these measurements will be utilized for further analysis.

Central corneal thickness (CCT) measurement

CCT measurement will be performed with IOLMaster (IOLmaster 700, Carl Zeiss Meditec, Jena, Germany). Results from five consecutive measurements will be documented during each visit, and the mean value of these measurements will be taken for further analysis.

Perimetry

The perimetric examination will be performed applying the Humphrey Field Analyzer Mark 3 (Carl Zeiss Meditec, Dublin, CA, USA) and the Swedish Interactive Threshold Algorithm Standard (SITA) 24-2 program. A reliable VF report is defined as having false-positive and false-negative errors below 15%, as well as fixation losses below 20%.

Fundus photography

Using fundus cameras (KOWA, Nonmyd, WX3D, Nagoya, Japan; TRC-NW400, TOPCON, Tokyo, Japan), two fundus images centered on the optic disc will be taken for each eye under both standardized stereoscopic and non-standardized conditions. Additionally, a single image focused on the macula will be obtained after pupil dilation.

OCT examination

All participants will undergo a series of standardized swept-source OCT examinations using the DRI-OCT Triton model (TOPCON, Tokyo, Japan), focusing on the optic disc and macula. To ensure the reliability and accuracy of the results, a minimum image quality score of 60 will be set. In addition to the swept-source OCT, a spectral domain OCT examination will be conducted to obtain measurements of the peripapillary RNFL and the macular GC-IPL.

Pregnancy test

A urine pregnancy test will be performed for women of reproductive age during their initial visit.

Anthropometry and blood pressure

Participants' height and weight measurements will be measured using a free-standing height rod and a calibrated scale (RGZ120, Jiangsu Wujin Weighing Apparatus Factory, Jiangsu, China). During the baseline visit, blood pressure readings will be obtained from the participant's left arm while they are seated and have rested for a minimum of five minutes with the Omron M7 Blood Pressure Monitor (Matsusaka, Mie, Japan).

Visit schedule

Table 1 summarizes the visit schedule for the enrolment, interventions, and assessments of this trial.

Sample size

The sample size calculation for this study was determined based on the primary outcome and the study hypothesis, taking into account relevant findings from previous studies. The objective of this study is to evaluate the potential of IOP-lowering therapy to reduce axial elongation during a study period of one year growth in eyes with PHM. It is hypothesized that the intervention group receiving IOP-lowering therapy will exhibit a 70% reduction in axial elongation compared to the control group. The control group is estimated to experience a 0.1 mm axial elongation over 12 months, while the intervention group is expected to have a mean axial elongation of 0.03 mm. The common standard deviation is estimated to be 0.14 mm. To achieve a statistical power of 80% with a two-sided significance level of 0.05, a total of 64 individuals per group is required. Accounting for an estimated 15% loss to follow-up at the 12-months mark, the final sample size is determined to be 76 individuals per group, resulting in a total

of 152 participants. The sample size calculation was performed using PASS 16.0 software (NCSS, LLC, Kaysville, UT, USA).

Statistical analysis

Statistical analysis will be conducted using Stata 16.0 software (StataCorp, College Station, TX, USA). A two-sided P-value of less than 0.05 will be considered statistically significant, and a 95% confidence interval will be used for parameter estimation.

For the intention-to-treat (ITT) analysis, missing data will be addressed using the multiple imputation method. No simulation will be performed for missing data in the safety evaluation. Dropout rates in the two groups will be compared using chi-squared tests or Fisher's exact tests. Descriptive statistics will be reported as mean and standard deviation for normally distributed continuous data, and as median and interquartile range for non-normally distributed continuous data. Frequency and percentage will be provided for categorical data. Baseline data, including demographic and clinical characteristics, will be analyzed using independent samples t-tests and Wilcoxon rank-sum tests for continuous data, and chi-squared or Fisher's exact tests for categorical variables.

The analysis of primary and secondary outcomes will follow the ITT principle, including all participants. For the primary outcome, the difference in axial elongation between the two groups will be analyzed using linear regression analysis. As for the secondary outcomes, a multifactor Poisson regression within a generalized linear model will be utilized to estimate the relative risk of progression in perimetric defects and myopic maculopathy. Additionally, the rate of thinning of the RNFL and the GC-IPL will be assessed through log-rank tests.

Safety analysis will be performed in participants belonging to the intervention group, comparing adverse event occurrence between the two groups using the chi-squared test or Fisher's exact test.

The missing data will be handled using the Multiple Imputations method. With the multiple imputation approach, 20 replicas of the dataset will be generated, where missing values are imputed through chained equations. The final results will be obtained by averaging these 20 datasets using Rubin's rules.

Data monitoring

(1) The Data Monitoring Committee (DMC) will closely monitor the data throughout the trial using the EDC system to ensure the reliability and integrity of the collected data. The DMC members are independent individuals who are not affiliated with the researchers or sponsors, ensuring an impartial assessment. There is no conflict of interest between the researchers and sponsors, further guaranteeing the transparency and objectivity of the data monitoring process.

(2) Interim analysis: The study does not include provisions for conducting an interim analysis.

Data management

The collected data will be meticulously recorded and entered into the EDC system. The EDC system is securely hosted on a password-protected network server, ensuring digital protection. Only the principal investigators and authorized study team members will have access to the research data. To ensure confidentiality and integrity, all source documents will be stored in locked file cabinets with restricted access. Prior to data collection, all researchers will undergo comprehensive training. The raw data will be monitored by an independent data and safety monitoring committee. In the event of queries or uncertainties in the case report form, the data administrator will generate a data queue request (DRQ) and communicate the query to the researcher through the clinical monitoring system. The researcher is expected to provide a prompt response to the data administrator. If necessary, data modifications, confirmations, and entries will be made, and a new DRQ will be issued.

Drug packaging, management, dispensing and storage

Drug packaging

The investigational drugs will be packaged in their own containers with dedicated research labels. Each medication package will consist of a single box, and each box will contain one unit of the drug. The box packaging will be made of paper and labeled with the phrase "For Clinical Research Use Only," along with a drug label indicating a unique drug identification number. The drug identification number is composed of the first two letters of the drug name followed by a four-digit Arabic numeral.

Drug management

The investigator will directly purchase the investigational drugs through the ZOC Research Procurement System. The drugs will be received and stored by a dedicated medication administrator in the Clinical Research Center. The investigational drugs will be managed by the designated medication administrator, who will be responsible for:

1. Storing the drugs according to the storage conditions specified in the drug instructions.
2. Recording all drug dispensing and retrieval activities.
3. Dispensing the drugs only to the participants as specified in the research protocol.
4. Maintaining a comprehensive record of drug inventory throughout the study and providing inventory logs.
5. Maintaining a detailed catalog of the drugs, including information on received materials, dispensing dates, and records of drugs provided to participants.
6. Ensuring that the drug dispensing records match the usage and unused drugs and providing explanations for any discrepancies. Relevant dispensing and return forms must be signed by the medication administrator.

Drug dispensing

After randomization, the medication administrator will dispense the corresponding investigational drugs to the participants based on the randomized assignment and document the drug dispensing.

Drug storage

Unopened medications should be stored according to the instructions provided in the drug package insert. For drugs that require refrigeration between 2-8°C, the medication administrator needs to monitor the temperature and humidity daily and document the storage conditions. The research drugs should not be provided to anyone other than the participants in the study. Access to the research drugs is limited to personnel authorized by the principal investigator to dispense them. After opening, medications should be stored according to the instructions provided in the drug package insert and must be used within four weeks of opening the drug package.

Safety assessments

The safety assessments included in this study are as follows:

1. Medication-related safety assessment: The ocular hypotensive medications used in this study are known to have rare occurrences of local and systemic adverse reactions, such as ocular surface irritation, eyelid pigmentation, eyelash growth, and drug allergies. These assessments will be conducted and recorded by the investigators during the study visits using slit lamp examination.

2. High myopia-related safety assessment: This study focuses on individuals with high myopia, and during the natural course of high myopia, retinal pathologies can occur. The investigators will assess and record the complications associated with high myopia based on the examination results during the study visits.

Report and management of adverse events

An adverse event refers to any negative medical occurrence experienced by a participant in the study, regardless of its relation to the treatment. Utmost attention will be given to identifying potential adverse events or unfavorable findings. The primary concern is the safety of the participant, and appropriate medical intervention will be provided in case of an adverse event. All adverse events, whether reported voluntarily by the participant or discovered through questioning, physical examination, or other means by the study staff, will be promptly recorded on an online adverse event form The Safety Supervision Committee will review each form to determine the appropriate coding and reporting procedures.

Serious adverse events, regardless of their connection to the study drug, must be reported within 24 hours to the Institutional Review Board (IRB), the DMC, and the Clinical Research Center. Additionally, a faxed report must be sent to the Drug Administration's drug registration office. The original and fax confirmation forms for serious adverse events should be retained in the research center along with the case report form.

Discussion

This trial is designed to evaluate the effect of intraocular pressure reduction on progressive high myopia. Due to the limited research on the use of IOP reduction medications in highly myopic eyes, the study design was conducted on the preliminary experimental results. It's found that the use of Xalacom in highly myopic eyes resulted in a 10% reduction in baseline IOP for 90% of the cases. Additionally, the use of IOP reduction medications slowed down axial elongation in approximately 70% of highly myopic eyes. Therefore, we set the target IOP reduction at 10% below the baseline, selected Xalacom as the preferred medication, and performed sample size calculations based on these findings.

Study progress

The recruitment period of this study has started in June 2023 in ZOC. As of September 2023, we have included 47 participants.

Acknowledgement: We thank all the members of the Glaucoma Suspects with High Myopia Study Group (GSHM) Study Group for conducting this trial. And also, we thank all staff in clinical research center of ZOC for their effort in this study.

GSHM study group

Principal investigators:

Xiulan Zhang, Yizhi Liu, Lin Lv, David Friedman, Jost B. Jonas, and Tin Aung.

Members:

Shida Chen, Wei Wang, Fengbin Lin, Yunhe Song, Peiyuan Wang, Kangjie Kong, Jingwen Jiang, Fei Li, Kai Gao, Bingqian Liu, Yuhong Liu, and Meiling Chen.

Steering committee:

Neil M. Bressler, Ki Ho Park, Mingguang He, Kyoko Ohno-Matsui, Dennis S.C. Lam, and Robert N. Weinreb.

Data monitoring committee:

Ching-Yu Cheng, Paul Healey, and Linda M. Zangwill.

Safety supervision committee:

Xiang Chen and Guangxian Tang.

Biostatistics and data monitoring center:

Ling Jin.

Funding/Support: This article was supported by the National Key R&D Program of China (2022YFC2502800); the High-level Hospital Construction Project, Zhongshan Ophthalmic Center, Sun Yat-sen University (303020104); the National Natural Science Foundation of China (82070955); the Science and Technology Program of Guangzhou, China (202201020362, 202102010209 2024A03J00515); Natural Science Foundation

of Guangdong Province (2020A1515011282). The funding organizations had no role in the design or conduct of this article.

Contributors: XZ, FL, JBJ, XG and SC participated in the study design. JJ, TL and FL wrote the primary protocol manuscript. XZ, DSL and JBJ revised the manuscript. KK, PW and YS contributed to data collecting. LJ and WZ helped with sample size calculation and were the statistical consultants. YL, JC and MC were clinical research coordinators of the project.

Competing interest: Jost B. Jonas: European patent EP 3,271,392, JP 2021-119187, and US 2021 0340237 A1: Agents for use in the therapeutic or prophylactic treatment of myopia or hyperopia; European patent application 23196899.1 “EGFR Antagonists for the treatment of diseases involving unwanted migration, proliferation, and metaplasia of retinal pigment epithelium (RPE) cells”.

Patient and public involvement: Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication: Not applicable

References

1. Yusufu M, Bukhari J, Yu X, et al. Challenges in eye care in the Asia-Pacific region. *Asia Pac J Ophthalmol (Phila)*. 2021;10(5):423-429. doi:10.1097/APO.0000000000000391.
2. Sankaridurg P, Berntsen DA, Bullimore MA, et al. IMI 2023 Digest. *Invest Ophthalmol Vis Sci*. 2023;64(6):7. doi:10.1167/iovs.64.6.7.
3. Holden BA, Fricke TR, Wilson DA, et al. Global prevalence of myopia and high myopia and temporal trends from 2000 through 2050. *Ophthalmology*. 2016;123:1036-1042. doi: 10.1016/j.ophtha.2016.01.006.
4. Fricke TR, Jong M, Naidoo KS, et al. Global prevalence of visual impairment associated with myopic macular degeneration and temporal trends from 2000 through 2050: systematic review, meta-analysis and modelling. *Br J Ophthalmol*. 2018;102:855-862. doi: 10.1136/bjophthalmol-2017-311266.
5. Morgan IG, Jan CL. China turns to school reform to control the myopia epidemic: a narrative review. *Asia Pac J Ophthalmol (Phila)*. 2022;11:27-35. doi: 10.1097/APO.0000000000000489.
6. Parolini B, Palmieri M, Finzi A, et al. Myopic traction maculopathy: a new perspective on classification and management. *Asia Pac J Ophthalmol (Phila)*. 2021;10:49–59. doi: 10.1097/APO.0000000000000347.
7. Haarman AEG, Enthoven CA, Tideman JWL, et al. The complications of myopia: a review and meta-analysis. *Invest Ophthalmol Vis Sci*. 2020;61:49. doi: 10.1167/iovs.61.4.49.
8. Ha A, Kim CY, Shim SR, et al. Degree of myopia and glaucoma risk: a dose-response meta-analysis. *Am J Ophthalmol*. 2022;236:107-119. doi: 10.1016/j.ajo.2021.10.007.
9. Du R, Xie S, Igarashi-Yokoi T, et al. Continued increase of axial length and its risk factors in adults with high myopia. *JAMA Ophthalmol*. 2021;139(10):1096-1103. doi:10.1001/jamaophthalmol.2021.3303.

10. Jonas JB, Spaide RF, Ostrin LA, Logan NS, Flitcroft I, Panda-Jonas S. IMI-Nonpathological human ocular tissue changes with axial myopia. *Invest Ophthalmol Vis Sci*. 2023;64(6):5. doi:10.1167/iovs.64.6.5.
11. Lee MW, Lee SE, Lim HB, Kim JY. Longitudinal changes in axial length in high myopia: a 4-year prospective study. *Br J Ophthalmol*. 2020;104(5):600-603. doi:10.1136/bjophthalmol-2019-314619.
12. El-Nimri NW, Wildsoet CF. Effects of topical latanoprost on intraocular pressure and myopia progression in young guinea pigs. *Invest Ophthalmol Vis Sci*. 2018;59(6):2644-2651. doi:10.1167/iovs.17-22890.
13. Yang J, Pan M, Reinach PS, et al. Prostaglandin F2α receptor modulation affects eye development in guinea pigs. *Basic Clin Pharmacol Toxicol*. 2018;123(3):263-270. doi:10.1111/bcpt.13017.
14. Igarashi-Yokoi T, Shinohara K, Fang Y, et al. Prognostic factors for axial length elongation and posterior staphyloma in adults with high myopia: a Japanese observational study. *Am J Ophthalmol.* 2021;225:76-85. doi:10.1016/j.ajo.2020.11.023.
15. Chong RS, Li H, Cheong AJY, et al. Mendelian randomization implicates bidirectional association between myopia and primary open-angle glaucoma or intraocular pressure. *Ophthalmology*. 2023;130(4):394-403. doi:10.1016/j.ophtha.2022.11.030.
16. Wang P, Chen S, Liu Y, et al. Lowering intraocular pressure: a potential approach for controlling high myopia progression. *Invest Ophthalmol Vis Sci.* 2021;62(14):17. doi:10.1167/iovs.62.14.17.
17. Flitcroft DI, He M, Jonas JB, et al. IMI - Defining and classifying myopia: a proposed set of standards for clinical and epidemiologic studies. *Invest Ophthalmol Vis Sci*. 2019;60(3):M20-M30. doi:10.1167/iovs.18-25957.
18. Wolf S, Balciuniene VJ, Laganovska G, et al. RADIANCE: a randomized controlled study of ranibizumab in patients with choroidal neovascularization secondary to pathologic myopia. *Ophthalmology*. 2014;121(3):682-92.e2. doi:10.1016/j.ophtha.2013.10.023.

19. Comparison of glaucomatous progression between untreated patients with normal-tension glaucoma and patients with therapeutically reduced intraocular pressures. Collaborative Normal-Tension Glaucoma Study Group. *Am J Ophthalmol*. 1998;126(4):487-497. doi:10.1016/s0002-9394(98)00223-2.

20. Garway-Heath DF, Lascaratos G, Bunce C, et al. The United Kingdom Glaucoma Treatment Study: a multicenter, randomized, placebo-controlled clinical trial: design and methodology. *Ophthalmology*. 2013;120(1):68-76. doi:10.1016/j.ophtha.2012.07.028.

21. Garway-Heath DF, Crabb DP, Bunce C, et al. Latanoprost for open-angle glaucoma (UKGTS): a randomised, multicentre, placebo-controlled trial. *Lancet*. 2015;385(9975):1295-1304. doi:10.1016/S0140-6736(14)62111-5.

22. Leske MC, Heijl A, Hyman L, Bengtsson B. Early Manifest Glaucoma Trial: design and baseline data. *Ophthalmology*. 1999;106(11):2144-2153. doi:10.1016/s0161-6420(99)90497-9.

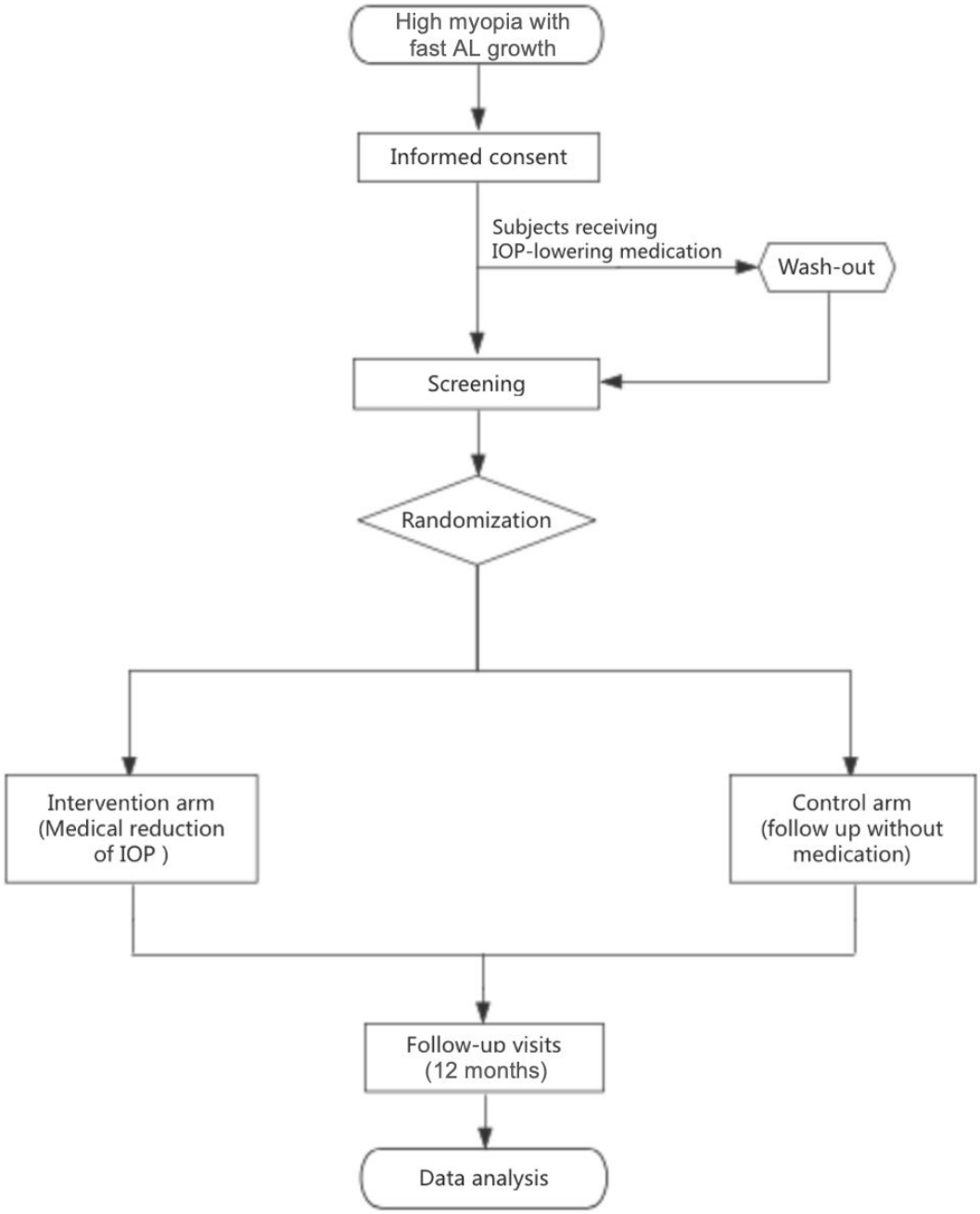
23. Lalezary M, Medeiros FA, Weinreb RN, et al. Baseline optical coherence tomography predicts the development of glaucomatous change in glaucoma suspects. *Am J Ophthalmol*. 2006;142(4):576-582. doi:10.1016/j.ajo.2006.05.004.

24. Keltner JL, Johnson CA, Anderson DR, et al. The association between glaucomatous visual fields and optic nerve head features in the Ocular Hypertension Treatment Study. *Ophthalmology*. 2006;113(9):1603-1612. doi:10.1016/j.ophtha.2006.05.061.

25. Ohno-Matsui K, Kawasaki R, Jonas JB, et al. International photographic classification and grading system for myopic maculopathy. *Am J Ophthalmol*. 2015;159(5):877-83.e7. doi:10.1016/j.ajo.2015.01.022.

26. Li Z, Liu R, Xiao O, et al. Progression of myopic maculopathy in highly myopic Chinese eyes. *Invest Ophthalmol Vis Sci*. 2019;60(4):1096-1104. doi:10.1167/iovs.18-25800.

27. Farida FM, Hassan Farahat HG, Salem MS. Refraction errors in school children. *Menoufia Med J*. 2018;31(1):293-298. doi:10.4103/mmj.mmj_115_17.



643

644 **Figure 1** Schematic of the PHM study design.

645

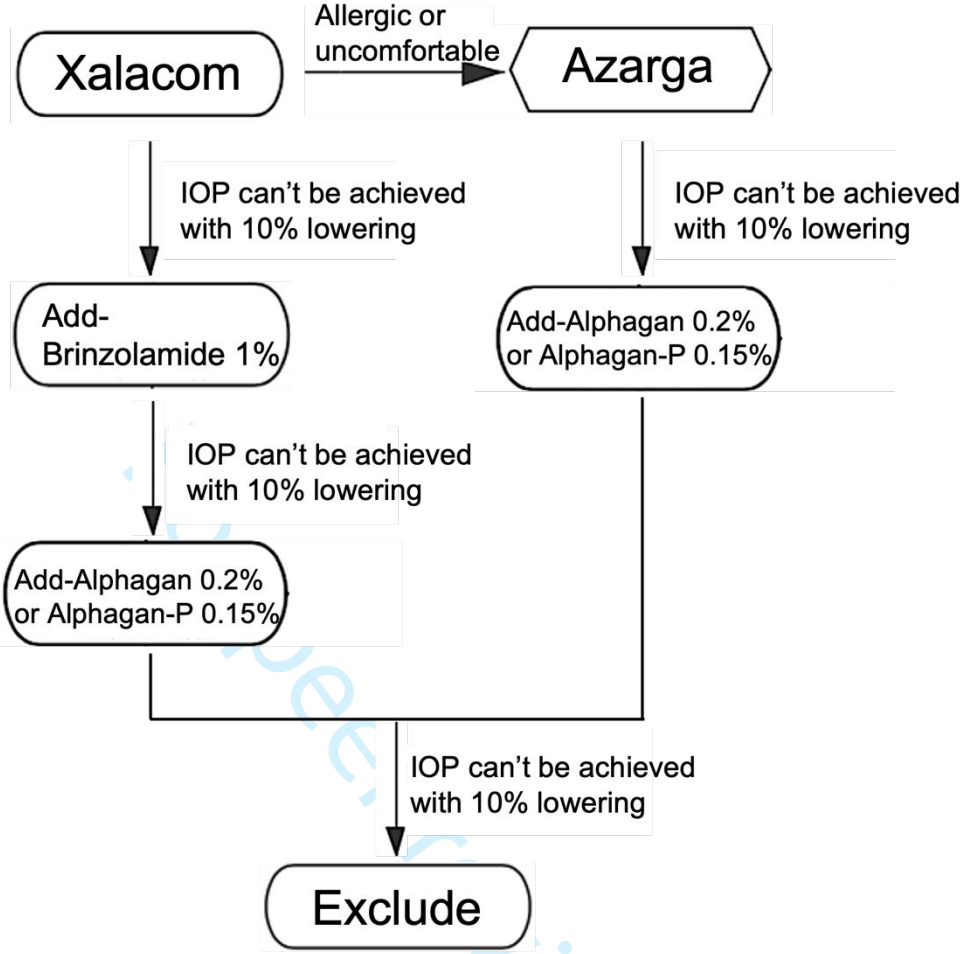


Figure 2 The schematic of the intervention design.

Table 1 Visit schedule

Periods	**Screening**	**Baseline visit**	**Follow-up visits**		
Visit	**V_0**	**V_1**	**V_2**	**V_3**	**V_4**
Timepoint	**Day -14 to -1**	**Day 0**	**Week 4 (±7d)**	**Week 26 (±14d)**	**Week 52 (±28d)**
Enrolment					
Eligibility screen	x				
Informed consent	x				
History information	x				
Allocation		x			
Interventions		x	x	x	x
Assessments					
Physical examination		x			
Pregnancy test		x			
Visual acuity		x	x	x	x
Refraction		x	x	x	x
Slip lamp biomicroscopy		x	x	x	x
Intraocular pressure	x	x	x	x	x
Axial length		x	x	x	x
Visual field		x	x	x	x
Fundus photography		x	x	x	x
Optical coherence tomography		x	x	x	x
Central corneal thickness		x	x	x	x
Adverse events	x	x	x	x	x
Combination drugs	x	x	x	x	x
Drug distribution		x	x	x	
Drug recovery and investigation			x	x	x

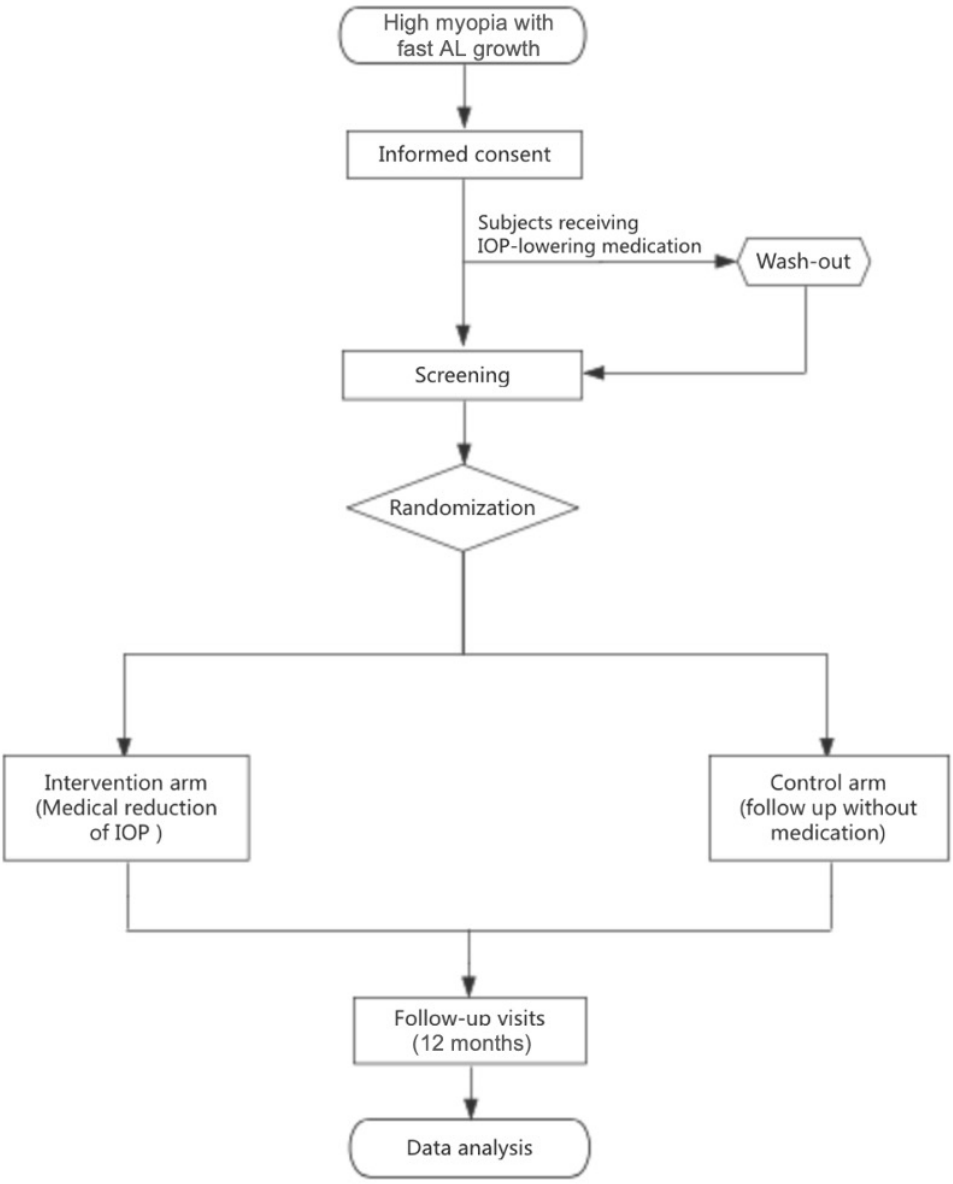


Figure 1

146x174mm (144 x 144 DPI)

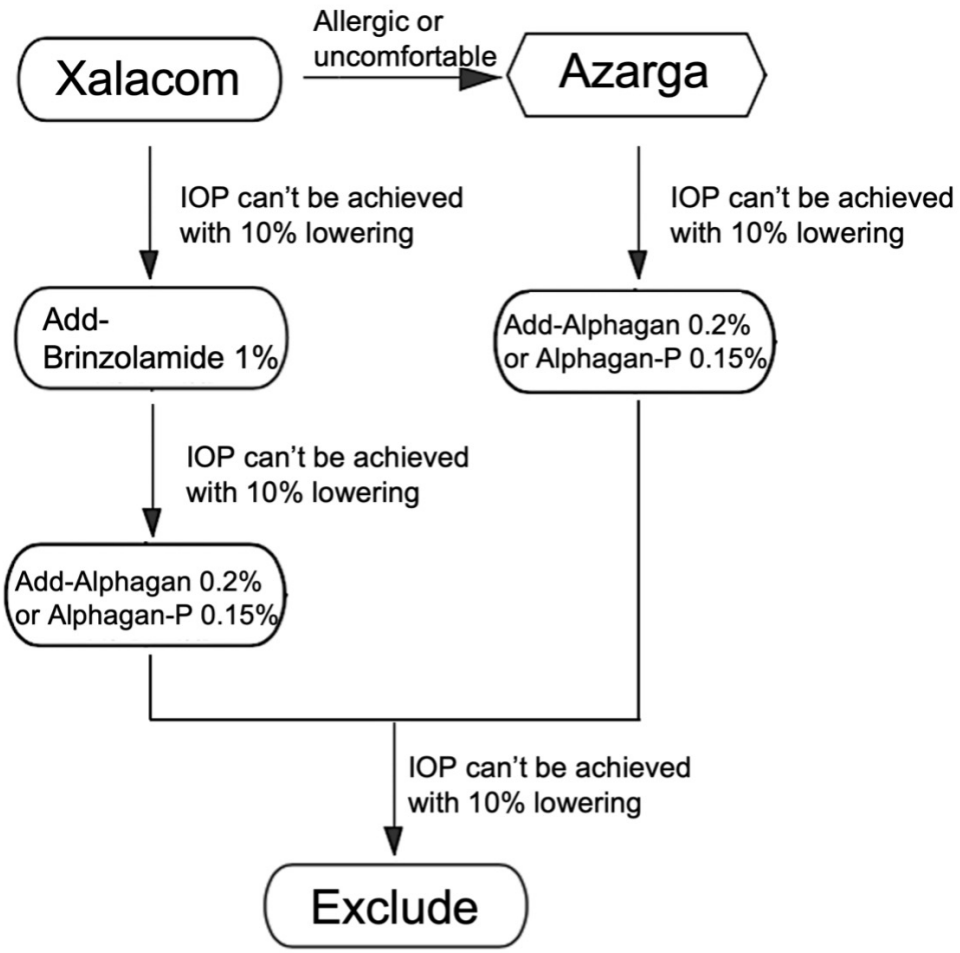


Figure 2

133x129mm (220 x 220 DPI)

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry
	2b	All items from the World Health Organization Trial Registration Data Set
Protocol version	3	Date and version identifier
Funding	4	Sources and types of financial, material, and other support
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors
	5b	Name and contact information for the trial sponsor
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)
Introduction		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention
	6b	Explanation for choice of comparators
Objectives	7	Specific objectives or hypotheses
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)

Methods: Participants, interventions, and outcomes		
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size
Methods: Assignment of interventions (for controlled trials)		
Allocation:		
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions

Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial
Methods: Data collection, management, and analysis		
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)
Methods: Monitoring		
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed

	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions
	31b	Authorship eligibility guidelines and any intended use of professional writers
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code

Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Effect of Intraocular Pressure Reduction on Progressive High Myopia (PHM study): Study Protocol of a Randomized Controlled Trial

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2024-084068.R1
Article Type:	Protocol
Date Submitted by the Author:	23-Mar-2024
Complete List of Authors:	Jiang, Jingwen; Sun Yat-Sen University Zhongshan Ophthalmic Center State Key Laboratory of Ophthalmology, Clinical research center Lin, Tingting; Sun Yat-Sen University Zhongshan Ophthalmic Center State Key Laboratory of Ophthalmology, Clinical research center; Daqing Oilfield General Hospital Lin, Fengbin; Sun Yat-Sen University Zhongshan Ophthalmic Center State Key Laboratory of Ophthalmology Kong, Kangjie; Sun Yat-Sen University Zhongshan Ophthalmic Center State Key Laboratory of Ophthalmology, Clinical research center Wang, Peiyuan; Sun Yat-Sen University Zhongshan Ophthalmic Center State Key Laboratory of Ophthalmology, Clinical research center Song, Yunhe; Sun Yat-Sen University Zhongshan Ophthalmic Center State Key Laboratory of Ophthalmology Zhou, Fengqi; Mayo Clinic College of Medicine and Science Wang, Zhenyu; Sun Yat-Sen University Zhongshan Ophthalmic Center State Key Laboratory of Ophthalmology Jin, Ling; Sun Yat-Sen University Zhongshan Ophthalmic Center State Key Laboratory of Ophthalmology, Clinical research center Liu, Yuhong; Sun Yat-Sen University Zhongshan Ophthalmic Center State Key Laboratory of Ophthalmology, Clinical research center Gao, Xinbo; Sun Yat-Sen University Zhongshan Ophthalmic Center State Key Laboratory of Ophthalmology Chen, Jinmei; Sun Yat-Sen University Zhongshan Ophthalmic Center State Key Laboratory of Ophthalmology, Clinical research center Chen, Meiling; Sun Yat-Sen University Zhongshan Ophthalmic Center State Key Laboratory of Ophthalmology Lam, Dennis SC; The Chinese University of Hong Kong Jonas, Jost; Heidelberg University, Ophthalmology; Institute of Molecular and Clinical Ophthalmology Basel, Chen, Shida; Sun Yat-Sen University Zhongshan Ophthalmic Center State Key Laboratory of Ophthalmology Zhang, Xiulan; Sun Yat-Sen University Zhongshan Ophthalmic Center State Key Laboratory of Ophthalmology
Primary Subject Heading:	Ophthalmology
Secondary Subject Heading:	Ophthalmology

Keywords:	Randomized Controlled Trial, OPHTHALMOLOGY, Glaucoma < OPHTHALMOLOGY

Effect of Intraocular Pressure Reduction on Progressive High Myopia (PHM study): Study Protocol of a Randomized Controlled Trial

Jingwen Jiang, MD[1, *], Tingting Lin, MD[1, *], Fengbin Lin, MD, PhD[1], Kangjie Kong, MD[1], Peiyuan Wang, MD, PhD[1], Yunhe Song, MD, PhD[1], Fengqi Zhou, OD[2], Zhenyu Wang, MSc[1], Ling Jin, MSc[1], Yuhong Liu, MSc[1], Xinbo Gao, MD, PhD[1], Jinmei Chen, MBBS[1], Meiling Chen, MBBS[1], Dennis SC Lam, MD[3], Jost B. Jonas, MD[4,5], Shida Chen, MD, PhD[1, †], Xiulan Zhang, MD, PhD[1, †], for the Glaucoma Suspects with High Myopia Study Group

[1]State Key Laboratory of Ophthalmology, Zhongshan Ophthalmic Center, Sun Yat-sen University, Guangdong Provincial Key Laboratory of Ophthalmology and Visual Science, Guangdong Provincial Clinical Research Center for Ocular Diseases, Guangzhou 510623, China.

[2]Mayo Clinic College of Medicine, Rochester, MN 55902, USA.

[3]The International Eye Research Institute, the Chinese University of Hong Kong (Shenzhen), Shenzhen, China.

[4]Department of Ophthalmology, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany.

[5]Institute of Molecular and Clinical Ophthalmology, Basel, Switzerland.

* Jingwen Jiang and Tingting Lin contributed equally.

Tingting Lin is a visiting doctor at Zhongshan Ophthalmic Center.

[†]Corresponding Author

Xiulan Zhang, MD, PhD

State Key Laboratory of Ophthalmology, Zhongshan Ophthalmic Center, Sun Yat-Sen University, No.7 Jinsui Road, Guangzhou 510060, China.

Phone number:+86 135 7016 6308
Email: zhangxl2@mail.sysu.edu.cn

Shida Chen, MD, PhD
State Key Laboratory of Ophthalmology, Zhongshan Ophthalmic Center, Sun Yat-Sen University, No.7 Jinsui Road, Guangzhou 510060, China.
Email: chenshd3@mail.sysu.edu.cn

Competing Interest Statement and Financial Disclosure:

Jost B. Jonas: European patent EP 3,271,392, JP 2021-119187, and US 2021 0340237 A1: Agents for use in the therapeutic or prophylactic treatment of myopia or hyperopia; European patent application 23196899.1 "EGFR Antagonists for the treatment of diseases involving unwanted migration, proliferation, and metaplasia of retinal pigment epithelium (RPE) cells".

Ethics Statement: The study was approved by the ethical committee of the Zhongshan Ophthalmic Center and adhered to the tenets of the Declaration of Helsinki. Written informed consent was obtained from all subjects.

Key Words: High myopia, Axial length, Intraocular pressure, Randomized controlled trial

ABSTRACT

Background In adult patients with high myopia (HM), progressive axial elongation poses a significant risk for the development of subsequent ocular complications that may lead to visual impairment. Effective strategies to reduce or prevent further axial elongation in highly myopic adult patients have not been available so far. Recent studies suggested that medically lowering intraocular pressure (IOP) may reduce axial elongation.

Objective This clinical randomized controlled trial (RCT) aims to evaluate the efficacy of medical IOP reduction in adult patients with progressive HM (PHM).

Trial Design Single-center, open-label, prospective RCT.

Methods This RCT will recruit 152 participants with PHM at the Zhongshan Ophthalmic Center (ZOC). Randomized in a ratio of 1:1, participants will receive IOP-lowering eyedrops (intervention group) or will be followed without treatment (control group) for 12 months. Follow-up visits will be conducted at 1, 6, and 12 months after baseline. Only one eye per eligible participant will be included for analysis. The primary outcome is the change in axial length (AL) within the study period of 12 months. Secondary outcomes include the incidence and progression of visual field (VF) defects, changes in optic disc morphology and incidence and progression of myopic maculopathy. Difference in AL changes between the two groups will be analyzed using linear regression analysis. For the secondary outcomes, a multifactor Poisson regression within a generalized linear model will be utilized to estimate the relative risk of progression in VF defects and myopic maculopathy, and the rate of thinning in retinal nerve fiber layer and ganglion cell-inner plexiform will be assessed through Kaplan-Meier curves and log-rank tests.

Ethics and dissemination Full ethics approval for this trial has been obtained from the Ethics Committee of ZOC, Sun Yat-sen University, China (ID: 2023KYPJ110). Results of this trial will be disseminated through peer-reviewed journals and conference presentations.

Trial registration number NCT05850936 *clinicaltrials.gov*

Strengths and limitations of this study

1. This study is to address a global healthcare concern: effectively mitigating further axial elongation in highly myopic adult patients.
2. We performed this RCT based on an on-going highly myopic cohort.
3. Due to practical constraints, a double-masking in the study design cannot be achieved.
4. Participants are recruited from a single center.

Introduction

High myopia (HM) is an important global public health issue [1-2], with prevalence estimates of approximately 163 million individuals (2.7% of the world population) affected in 2000, and of approximately 938 million (9.8% of the world population) people estimated to be affected in 2050 [3-5]. High myopia-related complications, such as optic neuropathy, myopic maculopathy and retinal detachment, can lead to irreversible visual impairment [6-11].

Recent clinical studies have revealed that highly myopic eyes in adult patients can undergo further axial elongation with a rate up 0.1mm/year [12]. Axial elongation in highly myopic eyes is a major risk for progression of myopic macular degeneration and potentially of high myopia-associated optic neuropathy and subsequent vision impairment [13-14]. Effective strategies to reduce or stop further axial elongation in highly myopic eyes are warranted.

Recent experimental studies have suggested that medical reduction of intraocular pressure (IOP) could be protective against axial elongation in guinea pigs [15-16]. In a clinical observational study, application of IOP-lowering medication, but not the IOP-value itself, was associated with a reduced ongoing axial elongation in highly myopic patients [17]. As a corollary, recent Mendelian research has established a bidirectional association at the genetic level between myopia and primary open-angle glaucoma mediated through IOP [18]. In a recent retrospective clinical study medically IOP-lowering reduced axial elongation in highly myopic eyes (own unpublished data).

Building upon these findings, we hypothesize that medically IOP-lowering may slow axial elongation by potentially three pathways related to the sclera and choroid [19]. We therefore aim to conduct a randomized controlled trial (RCT) to assess the efficacy of medical IOP-lowering in managing axial elongation in patients with progressive HM (PHM). Additionally, this study should generate data on the effects of IOP-lowering treatment on the incidence and changes in the visual field (VF), changes in the optic nerve head morphology and myopic maculopathy. The outcomes of the

study may establish a basis for treatment recommendations for preventing axial elongation of highly myopic eyes.

Methods and Analysis

Study design

The PHM study is an open-label,-single-center RCT. The study will be conducted at the Zhongshan Ophthalmic Center (ZOC), Sun Yat-Sen University, a tertiary specialized hospital in Guangzhou, China. All examinations and interventions will be carried out in the Clinical Research Center at ZOC. This study does not permit blinding and is therefore designed as an open-label trial. **Figure 1** summarizes the design of the PHM study.

Objective

The primary aim of this trial is to evaluate the effectiveness of medically IOP-lowering therapy in managing axial elongation in patients with PHM over a 12-month observation period. Additionally, the trial will assess alterations in VF, optic disc morphology, thickness of the retinal nerve fiber layer (RNFL) and retinal ganglion cell-inner plexiform layer (GC-IPL), and the occurrence or advancement of myopic maculopathy.

Recruitment

Inclusion criteria

1. Age ⩾18 years and ⩽65 years.

2. Diagnosed with HM [20-21]: spherical equivalent ⩽-6.00 diopters or AL ⩾26.5 mm.

3. Diagnosed with PHM: axial elongation ⩾0.05mm in the past 6 months or ⩾0.1mm in the past 12 months.

4. IOP: ⩾10 mmHg and ⩽21mmHg on at least 2 visits using Goldmann applanation tonometry with correction for the dependence of the IOP-reading on corneal thickness [22].

5. Best corrected visual acuity (BCVA) ⩾6/12, ability to undergo AL measurement, fundus photography, optical coherence tomography (OCT), and complete VF examination.

Exclusion criteria

1. Patients who have been using IOP-lowering medications within the last year.

2. Allergy to any kind of IOP-lowering eyedrops.

3. Presence of serious fundus pathologies like proliferative diabetic retinopathy, retinal detachment, central retinal artery occlusion, etc.

4. Presence of chronic, recurrent, or severe ocular inflammatory lesions such as chronic or recurrent uveitis.

5. Significant corneal or iris lesions, severe cataract affecting fundus examination, or patients with only one eye.

6. Intraocular surgery or laser treatment within the last year, such as cataract surgery.

7. With a history of previous refractive surgery or prior treatment for myopia-related conditions (e.g., orthokeratology lens wear, low-intensity red light therapy, or low-concentration atropine treatment).

8. Presence of other serious systemic diseases (e.g., hypertension, heart disease, diabetes, rheumatic immune system disease) that hinder long-term follow-up and eye treatment.

9. Pregnancy, lactation, or plans to have children during the follow-up period.

In this study, only one eye per eligible participant will be included. If both eyes meet the inclusion criteria, the eye with a higher rate of axial elongation, a worse mean perimetric deviation (MD) value, and a worse BCVA will be selected.

Randomisation and blinding

In this trial, randomisation will be employed to mitigate distribution bias. After confirming all inclusion and exclusion criteria and obtaining signed written informed consent forms, qualified individuals within each block, with a block size of 4, will be assigned in an even (1:1) manner to either the intervention group or the control group. The random sequence will be generated using an electronic data collection (EDC) system to ensure unbiased allocation.

In this trial, the participants and physicians will not be blinded to the intervention assignment. The technicians conducting the examinations and interpreting the images will be unaware of the participants' group assignments during the screening and follow-up stages. The researchers analyzing the data will also be unaware of the information regarding randomisation.

Interventions

Intervention group

Participants assigned to the intervention group will receive medical IOP-lowering therapy for a duration of 12 months or until they reach the endpoint**.** Only the study eye will receive medication in the enrolled participants. The preferred medication for reducing IOP is Xalacom® eye drop (Pfizer Inc., New York, NY, USA), a fixed latanoprost and timolol combination.

The treatment protocol will involve the instillation of a single drop of prostaglandin ophthalmic solution in the study eye once daily in the evening for medications such as Xalacom. To ensure the standardisation of medication usage among participants, subjects will be provided with medication logbooks, which will be collected and recorded by the investigators during the study visits.

Control group

Participants assigned to the control group will be followed up for 12 months or until they reach the endpoint without medical IOP-lowering therapy.

Outcome measures

Primary outcome

The primary outcome is the change of AL at 12-month from baseline measured by IOLMaster.

Secondary outcomes

1. Incidence and progression of VF defects at 12 months from baseline based on Humphrey 24-2 standard VF. Under the premise of reliable VF examination, compared to the baseline, two consecutive perimetric examinations reveal the incidence of VF defects or significant perimetric progression in at least three points at a significance level of $p<0.05$. Furthermore, two subsequent diagnostic VF examinations conducted within one month also confirm the progression at the locations. The time of progression is defined as the time of the initial diagnostic VF examination [23-24].

2. Changes in optic disc morphology (including thinning of RNFL and GC-IPL) at 12-month from baseline based on fundus photography and OCT [25-27].

3. Incidence and progression of myopic maculopathy at 12 months from baseline based on fundus photography and OCT. The determination of incidence and progression of myopic maculopathy is based on the META-PM classification system [28-29].

Study assessments

Visual acuity

Visual acuity assessment will be conducted prior to any procedures that may potentially impact vision, such as pupil dilation or VF examination. The measurement of visual

acuity will be performed using an ETDRS (Early Treatment of Diabetic Retinopathy Study) LogMAR chart (Precision Vision, Villa Park, Illinois, USA) under standard illumination conditions at 4 meters [30]. For BCVA, a trial frame will be positioned and adjusted on the participant's face based on auto refractometric readings and subsequent subjective refinement.

Refractometry

Following pupil dilation using 0.25% compound tropicamide (Zhuobian@; Sinqi, China), three measurements will be taken for each eye using an auto refractometer (KR800, TOPCON, Tokyo, Japan). The average values for spherical refractive error, cylindrical refractive error, and astigmatic axis will be recorded for further analysis and documentation.

Slit-lamp biomicroscopy

The evaluation of the anterior segment with the pupil undilated will be performed using a slit lamp (BQ-900, Haag Streit, Koeniz, Switzerland). After medical pupillary dilation, a slit lamp-based grading of lens opacities is conducted and using a 90D indirect ophthalmoscopic lens (Ocular 90D Slit Lamp Lenses, Ocular, Washington, DC, USA), the optic disc, macula, and peripheral retina will be examined.

Tonometry

IOP measurements will be performed by Goldmann applanation tonometry (AT900, Haag Streit, Koeniz, Switzerland). Prior to enrollment, all participants will undergo three baseline IOP readings during specific time intervals: 9 am to 10 am, 1 pm to 2 pm, and 4 pm to 5 pm. During follow-up visits, tonometry will be conducted between 9 am and 11 am. Results from three consecutive measurements will be documented during each visit, and the mean value of these measurements will be utilized for assessment purposes.

AL measurement

AL measurement will be performed using the IOLMaster (IOLmaster 700, Carl Zeiss Meditec, Jena, Germany). Results from five consecutive measurements will be documented during each visit, and the mean value of these measurements will be utilized for further analysis.

Central corneal thickness (CCT) measurement

CCT measurement will be performed with IOLMaster (IOLmaster 700, Carl Zeiss Meditec, Jena, Germany). Results from five consecutive measurements will be documented during each visit, and the mean value of these measurements will be taken for further analysis.

Perimetry

The perimetric examination will be performed applying the Humphrey Field Analyzer Mark 3 (Carl Zeiss Meditec, Dublin, CA, USA) and the Swedish Interactive Threshold Algorithm Standard (SITA) 24-2 program. A reliable VF report is defined as having false-positive and false-negative errors below 15%, as well as fixation losses below 20%.

Fundus photography

Using fundus cameras (KOWA, Nonmyd, WX3D, Nagoya, Japan; TRC-NW400, TOPCON, Tokyo, Japan), two fundus images centered on the optic disc will be taken for each eye under both standardized stereoscopic and non-standardized conditions. Additionally, a single image focused on the macula will be obtained after pupil dilation.

OCT examination

All participants will undergo a series of standardized swept-source OCT examinations using the DRI-OCT Triton model (TOPCON, Tokyo, Japan), focusing on the optic disc and macula. To ensure the reliability and accuracy of the results, a minimum image quality score of 60 will be set. In addition to the swept-source OCT, a spectral domain OCT examination will be conducted to obtain measurements of the peripapillary RNFL and the macular GC-IPL.

Pregnancy test

A urine pregnancy test will be performed for women of reproductive age during their initial visit.

Anthropometry and blood pressure

Participants' height and weight measurements will be measured using a free-standing height rod and a calibrated scale (RGZ120, Jiangsu Wujin Weighing Apparatus Factory, Jiangsu, China). During the baseline visit, blood pressure readings will be obtained from the participant's left arm while they are seated and have rested for a minimum of five minutes with the Omron M7 Blood Pressure Monitor (Matsusaka, Mie, Japan).

Visit schedule

Table 1 summarizes the visit schedule for the enrolment, interventions, and assessments of this trial.

Sample size

The sample size calculation for this study is determined based on the primary outcome and the study hypothesis, taking into account relevant findings from previous studies. The objective of this study is to evaluate the potential of IOP-lowering therapy to reduce axial elongation during a study period of one year growth in eyes with PHM. It is hypothesized that the intervention group receiving IOP-lowering therapy will exhibit a

70% reduction in axial elongation compared to the control group. The control group is estimated to experience a 0.1 mm axial elongation over 12 months, while the intervention group is expected to have a mean axial elongation of 0.03 mm. The common standard deviation is estimated to be 0.14 mm. To achieve a statistical power of 80% with a two-sided significance level of 0.05, a total of 64 individuals per group is required. Accounting for an estimated 15% loss to follow-up at the 12-months mark, the final sample size is determined to be 76 individuals per group, resulting in a total of 152 participants. The sample size calculation was performed using PASS 16.0 software (NCSS, LLC, Kaysville, UT, USA).

Statistical analysis

Statistical analysis will be conducted using Stata 16.0 software (StataCorp, College Station, TX, USA). A two-sided P-value of less than 0.05 will be considered statistically significant, and a 95% confidence interval will be used for parameter estimation.

For the intention-to-treat (ITT) analysis, missing data will be addressed using the multiple imputation method. No simulation will be performed for missing data in the safety evaluation. Dropout rates in the two groups will be compared using chi-squared tests or Fisher's exact tests. Descriptive statistics will be reported as mean and standard deviation for normally distributed continuous data, and as median and interquartile range for non-normally distributed continuous data. Frequency and percentage will be provided for categorical data. Baseline data, including demographic and clinical characteristics, will be analyzed using independent samples t-tests and Wilcoxon rank-sum tests for continuous data, and chi-squared or Fisher's exact tests for categorical variables.

The analysis of primary and secondary outcomes will follow the ITT principle, including all participants. For the primary outcome, the difference in axial elongation between the two groups will be analyzed using linear regression analysis. As for the

secondary outcomes, a multifactor Poisson regression within a generalized linear model will be utilized to estimate the relative risk of progression in perimetric defects and myopic maculopathy. Additionally, the rate of thinning of the RNFL and the GC-IPL will be assessed through log-rank tests.

Safety analysis will be performed in participants belonging to the intervention group, comparing adverse event occurrence between the two groups using the chi-squared test or Fisher's exact test.

The missing data will be handled using the Multiple Imputations method. With the multiple imputation approach, 20 replicas of the dataset will be generated, where missing values are imputed through chained equations. The final results will be obtained by averaging these 20 datasets using Rubin's rules.

Data monitoring

(1) The Data Monitoring Committee (DMC) will closely monitor the data throughout the trial using the EDC system to ensure the reliability and integrity of the collected data. The DMC members are independent individuals who are not affiliated with the researchers or sponsors, ensuring an impartial assessment. There is no conflict of interest between the researchers and sponsors, further guaranteeing the transparency and objectivity of the data monitoring process.

(2) Interim analysis: The study does not include provisions for conducting an interim analysis.

Data management

The collected data will be meticulously recorded and entered into the EDC system. The EDC system is securely hosted on a password-protected network server, ensuring digital protection. Only the principal investigators and authorized study team members will have access to the research data. To ensure confidentiality and integrity, all source documents will be stored in locked file cabinets with restricted access. Prior to data

collection, all researchers will undergo comprehensive training. The raw data will be monitored by an independent data and safety monitoring committee. In the event of queries or uncertainties in the case report form, the data administrator will generate a data queue request (DRQ) and communicate the query to the researcher through the clinical monitoring system. The researcher is expected to provide a prompt response to the data administrator. If necessary, data modifications, confirmations, and entries will be made, and a new DRQ will be issued.

Drug packaging, management, dispensing and storage

Drug packaging

The investigational drugs will be packaged in their own containers with dedicated research labels. Each medication package will consist of a single box, and each box will contain one unit of the drug. The box packaging will be made of paper and labeled with the phrase "For Clinical Research Use Only," along with a drug label indicating a unique drug identification number. The drug identification number is composed of the first two letters of the drug name followed by a four-digit Arabic numeral.

Drug management

The investigator will directly purchase the investigational drugs through the ZOC Research Procurement System. The drugs will be received and stored by a dedicated medication administrator in the Clinical Research Center. The investigational drugs will be managed by the designated medication administrator, who will be responsible for:

1. Storing the drugs according to the storage conditions specified in the drug instructions.
2. Recording all drug dispensing and retrieval activities.
3. Dispensing the drugs only to the participants as specified in the research protocol.

4. Maintaining a comprehensive record of drug inventory throughout the study and providing inventory logs.

5. Maintaining a detailed catalog of the drugs, including information on received materials, dispensing dates, and records of drugs provided to participants.

6. Ensuring that the drug dispensing records match the usage and unused drugs and providing explanations for any discrepancies. Relevant dispensing and return forms must be signed by the medication administrator.

Drug dispensing

After randomisation, the medication administrator will dispense the corresponding investigational drugs to the participants based on the randomized assignment and document the drug dispensing.

Drug storage

Unopened medications should be stored according to the instructions provided in the drug package insert. For drugs that require refrigeration between 2-8°C, the medication administrator needs to monitor the temperature and humidity daily and document the storage conditions. The research drugs should not be provided to anyone other than the participants in the study. Access to the research drugs is limited to personnel authorized by the principal investigator to dispense them. After opening, medications should be stored according to the instructions provided in the drug package insert and must be used within four weeks of opening the drug package.

Safety assessments

The safety assessments included in this study are as follows:

1. Medication-related safety assessment: The ocular hypotensive medications used in this study are known to have rare occurrences of local and systemic adverse reactions, such as ocular surface irritation, eyelid pigmentation, eyelash growth, and drug

allergies. These assessments will be conducted and recorded by the investigators during the study visits using slit lamp examination.

2. High myopia-related safety assessment: This study focuses on individuals with high myopia, and during the natural course of high myopia, retinal pathologies can occur. The investigators will assess and record the complications associated with high myopia based on the examination results during the study visits.

Report and management of adverse events

An adverse event refers to any negative medical occurrence experienced by a participant in the study, regardless of its relation to the treatment. Utmost attention will be given to identifying potential adverse events or unfavorable findings. The primary concern is the safety of the participant, and appropriate medical intervention will be provided in case of an adverse event. All adverse events, whether reported voluntarily by the participant or discovered through questioning, physical examination, or other means by the study staff, will be promptly recorded on an online adverse event form The Safety Supervision Committee will review each form to determine the appropriate coding and reporting procedures.

Serious adverse events, regardless of their connection to the study drug, must be reported within 24 hours to the Institutional Review Board (IRB), the DMC, and the Clinical Research Center. Additionally, a faxed report must be sent to the Drug Administration's drug registration office. The original and fax confirmation forms for serious adverse events should be retained in the research center along with the case report form.

Discussion

This trial is designed to evaluate the effect of intraocular pressure reduction on progressive high myopia. Due to the limited research on the use of IOP reduction medications in highly myopic eyes, the design of this study is based on a retrospective

analysis of a large cohort of highly myopic individuals. It is found that the use of IOP reduction medications slowed down axial elongation in approximately 70% of highly myopic eyes. Therefore, we performed sample size calculations based on these findings.

Study progress

The recruitment period of this study has started in June 2023 in ZOC. As of February 2024, we have included 73 participants.

Acknowledgement: We thank all the members of the Glaucoma Suspects with High Myopia Study Group (GSHM) Study Group for conducting this trial. And also, we thank all staff in clinical research center of ZOC for their effort in this study.

GSHM study group

Principal investigators:

Xiulan Zhang, Yizhi Liu, Lin Lv, David Friedman, Jost B. Jonas, and Tin Aung.

Members:

Shida Chen, Wei Wang, Fengbin Lin, Yunhe Song, Peiyuan Wang, Kangjie Kong, Jingwen Jiang, Fei Li, Kai Gao, Bingqian Liu, Yuhong Liu, and Meiling Chen.

Steering committee:

Neil M. Bressler, Ki Ho Park, Mingguang He, Kyoko Ohno-Matsui, Dennis S.C. Lam, and Robert N. Weinreb.

Data monitoring committee:

Ching-Yu Cheng, Paul Healey, and Linda M. Zangwill.

Safety supervision committee:

Xiang Chen and Guangxian Tang.

Biostatistics and data monitoring center:

Ling Jin.

Funding/Support: This article was supported by the National Key R&D Program of China (2022YFC2502800); the High-level Hospital Construction Project, Zhongshan Ophthalmic Center, Sun Yat-sen University (303020104); the National Natural Science Foundation of China (82070955); the Science and Technology Program of Guangzhou, China (202201020362, 202102010209 2024A03J00515); Natural Science Foundation of Guangdong Province (2020A1515011282). The funding organisations had no role in the design or conduct of this article.

Contributors: XZ, FL, JBJ, XG and SC participated in the study design. JJ, TL and FL wrote the primary protocol manuscript. XZ, FZ, DSL and JBJ revised the manuscript. KK, PW and YS contributed to data collecting. LJ and WZ helped with sample size calculation and were the statistical consultants. YL, JC and MC were clinical research coordinators of the project.

Competing interest: Jost B. Jonas: European patent EP 3,271,392, JP 2021-119187, and US 2021 0340237 A1: Agents for use in the therapeutic or prophylactic treatment of myopia or hyperopia; European patent application 23196899.1 “EGFR Antagonists for the treatment of diseases involving unwanted migration, proliferation, and metaplasia of retinal pigment epithelium (RPE) cells”.

Patient and public involvement: Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication: Not applicable

Protocol Version: 5.0

Figure 1 Diagram of the PHM study design.

References

1. Yusufu M, Bukhari J, Yu X, et al. Challenges in eye care in the Asia-Pacific region. *Asia Pac J Ophthalmol (Phila)*. 2021;10(5):423-429. doi:10.1097/APO.0000000000000391.
2. Sankaridurg P, Berntsen DA, Bullimore MA, et al. IMI 2023 Digest. *Invest Ophthalmol Vis Sci*. 2023;64(6):7. doi:10.1167/iovs.64.6.7.
3. Holden BA, Fricke TR, Wilson DA, et al. Global prevalence of myopia and high myopia and temporal trends from 2000 through 2050. *Ophthalmology*. 2016;123:1036-1042. doi: 10.1016/j.ophtha.2016.01.006.
4. Fricke TR, Jong M, Naidoo KS, et al. Global prevalence of visual impairment associated with myopic macular degeneration and temporal trends from 2000 through 2050: systematic review, meta-analysis and modelling. *Br J Ophthalmol*. 2018;102:855-862. doi: 10.1136/bjophthalmol-2017-311266.
5. Morgan IG, Jan CL. China turns to school reform to control the myopia epidemic: a narrative review. *Asia Pac J Ophthalmol (Phila)*. 2022;11:27-35. doi: 10.1097/APO.0000000000000489.
6. Parolini B, Palmieri M, Finzi A, et al. Myopic traction maculopathy: a new perspective on classification and management. *Asia Pac J Ophthalmol (Phila)*. 2021;10:49–59. doi: 10.1097/APO.0000000000000347.
7. Haarman AEG, Enthoven CA, Tideman JWL, et al. The complications of myopia: a review and meta-analysis. *Invest Ophthalmol Vis Sci*. 2020;61:49. doi: 10.1167/iovs.61.4.49.
8. Ha A, Kim CY, Shim SR, et al. Degree of myopia and glaucoma risk: a dose-response meta-analysis. *Am J Ophthalmol*. 2022;236:107-119. doi: 10.1016/j.ajo.2021.10.007.
9. Jiang J, Song Y, Kong K, et al. Optic Nerve Head Abnormalities in Nonpathologic High Myopia and the Relationship With Visual Field. *Asia-Pacific Journal of Ophthalmology*. 2023;12: 460-467. doi: 10.1097/APO.0000000000000636.

10. He HL, Liu YX, Chen XY, et al. Fundus Tessellated Density of Pathologic Myopia. *Asia-Pacific Journal of Ophthalmology*. 2023; 12: 604-613. doi: https://doi.org/10.1097/APO.0000000000000642.

11. Yasushi I. Overview of the complications of high myopia. *Retina*. 2017;37:2347-2351. doi: 10.1097/IAE.0000000000001489.

12. Du R, Xie S, Igarashi-Yokoi T, et al. Continued increase of axial length and its risk factors in adults with high myopia. *JAMA Ophthalmol*. 2021;139(10):1096-1103. doi:10.1001/jamaophthalmol.2021.3303.

13. Jonas JB, Spaide RF, Ostrin LA, Logan NS, Flitcroft I, Panda-Jonas S. IMI-Nonpathological human ocular tissue changes with axial myopia. *Invest Ophthalmol Vis Sci*. 2023;64(6):5. doi:10.1167/iovs.64.6.5.

14. Lee MW, Lee SE, Lim HB, Kim JY. Longitudinal changes in axial length in high myopia: a 4-year prospective study. *Br J Ophthalmol*. 2020;104(5):600-603. doi:10.1136/bjophthalmol-2019-314619.

15. El-Nimri NW, Wildsoet CF. Effects of topical latanoprost on intraocular pressure and myopia progression in young guinea pigs. *Invest Ophthalmol Vis Sci*. 2018;59(6):2644-2651. doi:10.1167/iovs.17-22890.

16. Yang J, Pan M, Reinach PS, et al. Prostaglandin F2α receptor modulation affects eye development in guinea pigs. *Basic Clin Pharmacol Toxicol*. 2018;123(3):263-270. doi:10.1111/bcpt.13017.

17. Igarashi-Yokoi T, Shinohara K, Fang Y, et al. Prognostic factors for axial length elongation and posterior staphyloma in adults with high myopia: a Japanese observational study. *Am J Ophthalmol.* 2021;225:76-85. doi:10.1016/j.ajo.2020.11.023.

18. Chong RS, Li H, Cheong AJY, et al. Mendelian randomization implicates bidirectional association between myopia and primary open-angle glaucoma or intraocular pressure. *Ophthalmology*. 2023;130(4):394-403. doi:10.1016/j.ophtha.2022.11.030.

19. Wang P, Chen S, Liu Y, et al. Lowering intraocular pressure: a potential approach for controlling high myopia progression. *Invest Ophthalmol Vis Sci.* 2021;62(14):17. doi:10.1167/iovs.62.14.17.

20. Flitcroft DI, He M, Jonas JB, et al. IMI - Defining and classifying myopia: a proposed set of standards for clinical and epidemiologic studies. *Invest Ophthalmol Vis Sci*. 2019;60(3):M20-M30. doi:10.1167/iovs.18-25957.

21. Wolf S, Balciuniene VJ, Laganovska G, et al. RADIANCE: a randomized controlled study of ranibizumab in patients with choroidal neovascularization secondary to pathologic myopia. *Ophthalmology*. 2014;121(3):682-92.e2. doi:10.1016/j.ophtha.2013.10.023.

22. Comparison of glaucomatous progression between untreated patients with normal-tension glaucoma and patients with therapeutically reduced intraocular pressures. Collaborative Normal-Tension Glaucoma Study Group. *Am J Ophthalmol*. 1998;126(4):487-497. doi:10.1016/s0002-9394(98)00223-2.

23. Garway-Heath DF, Lascaratos G, Bunce C, et al. The United Kingdom Glaucoma Treatment Study: a multicenter, randomized, placebo-controlled clinical trial: design and methodology. *Ophthalmology*. 2013;120(1):68-76. doi:10.1016/j.ophtha.2012.07.028.

24. Garway-Heath DF, Crabb DP, Bunce C, et al. Latanoprost for open-angle glaucoma (UKGTS): a randomised, multicentre, placebo-controlled trial. *Lancet*. 2015;385(9975):1295-1304. doi:10.1016/S0140-6736(14)62111-5.

25. Leske MC, Heijl A, Hyman L, Bengtsson B. Early Manifest Glaucoma Trial: design and baseline data. *Ophthalmology*. 1999;106(11):2144-2153. doi:10.1016/s0161-6420(99)90497-9.

26. Lalezary M, Medeiros FA, Weinreb RN, et al. Baseline optical coherence tomography predicts the development of glaucomatous change in glaucoma suspects. *Am J Ophthalmol*. 2006;142(4):576-582. doi:10.1016/j.ajo.2006.05.004.

27. Keltner JL, Johnson CA, Anderson DR, et al. The association between glaucomatous visual fields and optic nerve head features in the Ocular Hypertension Treatment Study. *Ophthalmology*. 2006;113(9):1603-1612. doi:10.1016/j.ophtha.2006.05.061.

28. Ohno-Matsui K, Kawasaki R, Jonas JB, et al. International photographic classification and grading system for myopic maculopathy. *Am J Ophthalmol*. 2015;159(5):877-83.e7. doi:10.1016/j.ajo.2015.01.022.

29. Li Z, Liu R, Xiao O, et al. Progression of myopic maculopathy in highly myopic Chinese eyes. *Invest Ophthalmol Vis Sci*. 2019;60(4):1096-1104. doi:10.1167/iovs.18-25800.

30. Farida FM, Hassan Farahat HG, Salem MS. Refraction errors in school children. *Menoufia Med J*. 2018;31(1):293-298. doi:10.4103/mmj.mmj_115_17.

Table 1 Visit schedule

Periods	**Screening**	**Baseline visit**	**Follow-up visits**		
Visit	**V_0**	**V_1**	**V_2**	**V_3**	**V_4**
Timepoint	**Day -14 to -1**	**Day 0**	**Week 4 (±7d)**	**Week 26 (±14d)**	**Week 52 (±28d)**
Enrolment					
Eligibility screen	x				
Informed consent	x				
History information	x				
Allocation		x			
Interventions		x	x	x	x
Assessments					
Physical examination		x			
Pregnancy test		x			
Visual acuity		x	x	x	x
Refraction		x	x	x	x
Slip lamp biomicroscopy		x	x	x	x
Intraocular pressure	x	x	x	x	x
Axial length		x	x	x	x
Visual field		x	x	x	x
Fundus photography		x	x	x	x
Optical coherence tomography		x	x	x	x
Central corneal thickness		x	x	x	x
Adverse events	x	x	x	x	x
Combination drugs	x	x	x	x	x
Drug distribution		x	x	x	
Drug recovery and investigation			x	x	x

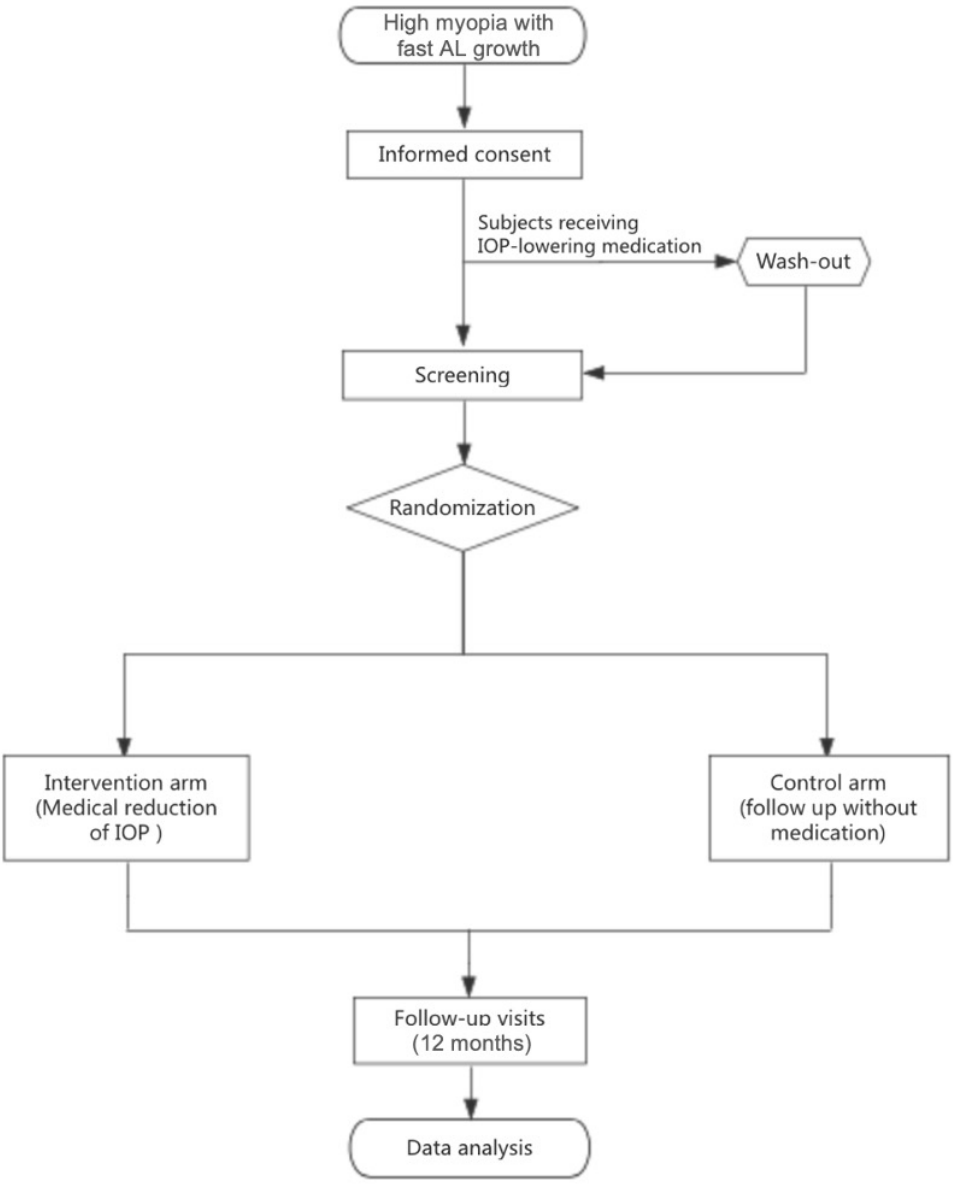


Figure 1

146x174mm (144 x 144 DPI)

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym (P1 L1-3)
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry (P3 L85)
	2b	All items from the World Health Organization Trial Registration Data Set
Protocol version	3	Date and version identifier (P20 L554)
Funding	4	Sources and types of financial, material, and other support (P19 L528-534)
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors (P1 L5-21,P20 L536-540)
	5b	Name and contact information for the trial sponsor
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)
Introduction		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention (P3 L60-65)
	6b	Explanation for choice of comparators
Objectives	7	Specific objectives or hypotheses (P3 L66-67)

Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) (P3 L68)
Methods: Participants, interventions, and outcomes		
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained (P3 L69-70)
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) (P3 L69-70)
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered (P3 L70-72)
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended (P3 L73-77)
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) (P25)
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations (P3 L69)
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size (P3 L69)
Methods: Assignment of interventions (for controlled trials)		
Allocation:		

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions (P8 L198-209)
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how (P8 L198-209)
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial
Methods: Data collection, management, and analysis		
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol (P10-P13 L271-346)
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol (P15 L408-240)
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol(P14 L368-396)
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)

	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)
Methods: Monitoring		
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed (P15 L398-406)
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct (P17 L464-474)
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor(P15 L398-406)
Ethics and dissemination		
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval(P2 L45-47)
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators

Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions(P3 L83-86)
	31b	Authorship eligibility guidelines and any intended use of professional writers
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code
Appendices		
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates(P8 L200)
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Effect of Intraocular Pressure Reduction on Progressive High Myopia (PHM study): Study Protocol of a Randomized Controlled Trial

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2024-084068.R2
Article Type:	Protocol
Date Submitted by the Author:	11-Apr-2024
Complete List of Authors:	Jiang, Jingwen; Sun Yat-Sen University Zhongshan Ophthalmic Center State Key Laboratory of Ophthalmology, Clinical research center Lin, Tingting; Sun Yat-Sen University Zhongshan Ophthalmic Center State Key Laboratory of Ophthalmology, Clinical research center; Daqing Oilfield General Hospital Lin, Fengbin; Sun Yat-Sen University Zhongshan Ophthalmic Center State Key Laboratory of Ophthalmology Kong, Kangjie; Sun Yat-Sen University Zhongshan Ophthalmic Center State Key Laboratory of Ophthalmology, Clinical research center Wang, Peiyuan; Sun Yat-Sen University Zhongshan Ophthalmic Center State Key Laboratory of Ophthalmology, Clinical research center Song, Yunhe; Sun Yat-Sen University Zhongshan Ophthalmic Center State Key Laboratory of Ophthalmology Zhou, Fengqi; Mayo Clinic College of Medicine and Science Wang, Zhenyu; Sun Yat-Sen University Zhongshan Ophthalmic Center State Key Laboratory of Ophthalmology Jin, Ling; Sun Yat-Sen University Zhongshan Ophthalmic Center State Key Laboratory of Ophthalmology, Clinical research center Liu, Yuhong; Sun Yat-Sen University Zhongshan Ophthalmic Center State Key Laboratory of Ophthalmology, Clinical research center Gao, Xinbo; Sun Yat-Sen University Zhongshan Ophthalmic Center State Key Laboratory of Ophthalmology Chen, Jinmei; Sun Yat-Sen University Zhongshan Ophthalmic Center State Key Laboratory of Ophthalmology, Clinical research center Chen, Meiling; Sun Yat-Sen University Zhongshan Ophthalmic Center State Key Laboratory of Ophthalmology Lam, Dennis SC; The Chinese University of Hong Kong Jonas, Jost; Heidelberg University, Ophthalmology; Institute of Molecular and Clinical Ophthalmology Basel, Chen, Shida; Sun Yat-Sen University Zhongshan Ophthalmic Center State Key Laboratory of Ophthalmology Zhang, Xiulan; Sun Yat-Sen University Zhongshan Ophthalmic Center State Key Laboratory of Ophthalmology
Primary Subject Heading:	Ophthalmology
Secondary Subject Heading:	Ophthalmology

Keywords:	Randomized Controlled Trial, OPHTHALMOLOGY, Glaucoma < OPHTHALMOLOGY

Effect of Intraocular Pressure Reduction on Progressive High Myopia (PHM study): Study Protocol of a Randomized Controlled Trial

Jingwen Jiang, MD[1, *], Tingting Lin, MD[1, *], Fengbin Lin, MD, PhD[1], Kangjie Kong, MD[1], Peiyuan Wang, MD, PhD[1], Yunhe Song, MD, PhD[1], Fengqi Zhou, OD[2], Zhenyu Wang, MSc[1], Ling Jin, MSc[1], Yuhong Liu, MSc[1], Xinbo Gao, MD, PhD[1], Jinmei Chen, MBBS[1], Meiling Chen, MBBS[1], Dennis SC Lam, MD[3], Jost B. Jonas, MD[4,5], Shida Chen, MD, PhD[1, †], Xiulan Zhang, MD, PhD[1, †], for the Glaucoma Suspects with High Myopia Study Group

[1]State Key Laboratory of Ophthalmology, Zhongshan Ophthalmic Center, Sun Yat-sen University, Guangdong Provincial Key Laboratory of Ophthalmology and Visual Science, Guangdong Provincial Clinical Research Center for Ocular Diseases, Guangzhou 510623, China.

[2]Mayo Clinic College of Medicine, Rochester, MN 55902, USA.

[3]The International Eye Research Institute, the Chinese University of Hong Kong (Shenzhen), Shenzhen, China.

[4]Department of Ophthalmology, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany.

[5]Institute of Molecular and Clinical Ophthalmology, Basel, Switzerland.

* Jingwen Jiang and Tingting Lin contributed equally.

Tingting Lin is a visiting doctor at Zhongshan Ophthalmic Center.

[†]Corresponding Author

Xiulan Zhang, MD, PhD

State Key Laboratory of Ophthalmology, Zhongshan Ophthalmic Center, Sun Yat-Sen University, No.7 Jinsui Road, Guangzhou 510060, China.

Phone number:+86 135 7016 6308
Email: zhangxl2@mail.sysu.edu.cn

Shida Chen, MD, PhD
State Key Laboratory of Ophthalmology, Zhongshan Ophthalmic Center, Sun Yat-Sen University, No.7 Jinsui Road, Guangzhou 510060, China.
Email: chenshd3@mail.sysu.edu.cn

Competing Interest Statement and Financial Disclosure:

Jost B. Jonas: European patent EP 3,271,392, JP 2021-119187, and US 2021 0340237 A1: Agents for use in the therapeutic or prophylactic treatment of myopia or hyperopia; European patent application 23196899.1 "EGFR Antagonists for the treatment of diseases involving unwanted migration, proliferation, and metaplasia of retinal pigment epithelium (RPE) cells".

Ethics Statement: The study was approved by the ethical committee of the Zhongshan Ophthalmic Center and adhered to the tenets of the Declaration of Helsinki. Written informed consent was obtained from all subjects.

Key Words: High myopia, Axial length, Intraocular pressure, Randomized controlled trial

ABSTRACT

Background In adult patients with high myopia (HM), progressive axial elongation poses a significant risk for the development of subsequent ocular complications that may lead to visual impairment. Effective strategies to reduce or prevent further axial elongation in highly myopic adult patients have not been available so far. Recent studies suggested that medically lowering intraocular pressure (IOP) may reduce axial elongation.

Objective This clinical randomized controlled trial (RCT) aims to evaluate the efficacy of medical IOP reduction in adult patients with progressive HM (PHM).

Trial Design Single-center, open-label, prospective RCT.

Methods This RCT will recruit 152 participants with PHM at the Zhongshan Ophthalmic Center (ZOC). Randomized in a ratio of 1:1, participants will receive IOP-lowering eyedrops (intervention group) or will be followed without treatment (control group) for 12 months. Follow-up visits will be conducted at 1, 6, and 12 months after baseline. Only one eye per eligible participant will be included for analysis. The primary outcome is the change in axial length (AL) within the study period of 12 months. Secondary outcomes include the incidence and progression of visual field (VF) defects, changes in optic disc morphology and incidence and progression of myopic maculopathy. Difference in AL changes between the two groups will be analyzed using linear regression analysis. For the secondary outcomes, a multifactor Poisson regression within a generalized linear model will be utilized to estimate the relative risk of progression in VF defects and myopic maculopathy, and the rate of thinning in retinal nerve fiber layer and ganglion cell-inner plexiform will be assessed through Kaplan-Meier curves and log-rank tests.

Ethics and dissemination Full ethics approval for this trial has been obtained from the Ethics Committee of ZOC, Sun Yat-sen University, China (ID: 2023KYPJ110). Results of this trial will be disseminated through peer-reviewed journals and conference presentations.

Trial registration number NCT05850936 *clinicaltrials.gov*

Strengths and limitations of this study

1. Prospective, interventional, randomized controlled trial to evaluate the effect of intraocular pressure-lowering medications for controlling axial elongation in adult patients.
2. Designing and performing this randomized controlled trial based on an on-going large-scale highly myopic cohort.
3. Study does not include a placebo group and blinding is not applicated.
4. Participants are recruited from a single center.

Introduction

High myopia (HM) is an important global public health issue [1-2], with prevalence estimates of approximately 163 million individuals (2.7% of the world population) affected in 2000, and of approximately 938 million (9.8% of the world population) people estimated to be affected in 2050 [3-5]. High myopia-related complications, such as optic neuropathy, myopic maculopathy and retinal detachment, can lead to irreversible visual impairment [6-11].

Recent clinical studies have revealed that highly myopic eyes in adult patients can undergo further axial elongation with a rate up 0.1mm/year [12]. Axial elongation in highly myopic eyes is a major risk for progression of myopic macular degeneration and potentially of high myopia-associated optic neuropathy and subsequent vision impairment [13-14]. Effective strategies to reduce or stop further axial elongation in highly myopic eyes are warranted.

Recent experimental studies have suggested that medical reduction of intraocular pressure (IOP) could be protective against axial elongation in guinea pigs [15-16]. In a clinical observational study, application of IOP-lowering medication, but not the IOP-value itself, was associated with a reduced ongoing axial elongation in highly myopic patients [17]. As a corollary, recent Mendelian research has established a bidirectional association at the genetic level between myopia and primary open-angle glaucoma mediated through IOP [18]. In a recent retrospective clinical study medically IOP-lowering reduced axial elongation in highly myopic eyes (own unpublished data).

Building upon these findings, we hypothesize that medically IOP-lowering may slow axial elongation by potentially three pathways related to the sclera and choroid [19]. We therefore aim to conduct a randomized controlled trial (RCT) to assess the efficacy of medical IOP-lowering in managing axial elongation in patients with progressive HM (PHM). Additionally, this study should generate data on the effects of IOP-lowering treatment on the incidence and changes in the visual field (VF), changes in the optic nerve head morphology and myopic maculopathy. The outcomes of the

study may establish a basis for treatment recommendations for preventing axial elongation of highly myopic eyes.

Methods and Analysis

Study design

The PHM study is an open-label,-single-center RCT. The study will be conducted at the Zhongshan Ophthalmic Center (ZOC), Sun Yat-Sen University, a tertiary specialized hospital in Guangzhou, China. All examinations and interventions will be carried out in the Clinical Research Center at ZOC. This study does not permit blinding and is therefore designed as an open-label trial. **Figure 1** summarizes the design of the PHM study.

Objective

The primary aim of this trial is to evaluate the effectiveness of medically IOP-lowering therapy in managing axial elongation in patients with PHM over a 12-month observation period. Additionally, the trial will assess alterations in VF, optic disc morphology, thickness of the retinal nerve fiber layer (RNFL) and retinal ganglion cell-inner plexiform layer (GC-IPL), and the occurrence or advancement of myopic maculopathy.

Recruitment

Inclusion criteria

1. Age ⩾18 years and ⩽65 years.

2. Diagnosed with HM [20-21]: spherical equivalent ⩽-6.00 diopters or AL ⩾26.5 mm.

3. Diagnosed with PHM: axial elongation ⩾0.05mm in the past 6 months or ⩾0.1mm in the past 12 months.

4. IOP: ⩾10 mmHg and ⩽21mmHg on at least 2 visits using Goldmann applanation tonometry with correction for the dependence of the IOP-reading on corneal thickness [22].

5. Best corrected visual acuity (BCVA) ⩾6/12, ability to undergo AL measurement, fundus photography, optical coherence tomography (OCT), and complete VF examination.

Exclusion criteria

1. Patients who have been using IOP-lowering medications within the last year.

2. Allergy to any kind of IOP-lowering eyedrops.

3. Presence of serious fundus pathologies like proliferative diabetic retinopathy, retinal detachment, central retinal artery occlusion, etc.

4. Presence of chronic, recurrent, or severe ocular inflammatory lesions such as chronic or recurrent uveitis.

5. Significant corneal or iris lesions, severe cataract affecting fundus examination, or patients with only one eye.

6. Intraocular surgery or laser treatment within the last year, such as cataract surgery.

7. With a history of previous refractive surgery or prior treatment for myopia-related conditions (e.g., orthokeratology lens wear, low-intensity red light therapy, or low-concentration atropine treatment).

8. Presence of other serious systemic diseases (e.g., hypertension, heart disease, diabetes, rheumatic immune system disease) that hinder long-term follow-up and eye treatment.

9. Pregnancy, lactation, or plans to have children during the follow-up period.

In this study, only one eye per eligible participant will be included. If both eyes meet the inclusion criteria, the eye with a higher rate of axial elongation, a worse mean perimetric deviation (MD) value, and a worse BCVA will be selected.

Randomisation and blinding

In this trial, randomisation will be employed to mitigate distribution bias. After confirming all inclusion and exclusion criteria and obtaining signed written informed consent forms (see supplemental material), qualified individuals within each block, with a block size of 4, will be assigned in an even (1:1) manner to either the intervention group or the control group. The random sequence will be generated using an electronic data collection (EDC) system to ensure unbiased allocation.

In this trial, the participants and physicians will not be blinded to the intervention assignment. The technicians conducting the examinations and interpreting the images will be unaware of the participants' group assignments during the screening and follow-up stages. The researchers analyzing the data will also be unaware of the information regarding randomisation.

Interventions

Intervention group

Participants assigned to the intervention group will receive medical IOP-lowering therapy for a duration of 12 months or until they reach the endpoint**.** Only the study eye will receive medication in the enrolled participants. The preferred medication for reducing IOP is Xalacom® eye drop (Pfizer Inc., New York, NY, USA), a fixed latanoprost and timolol combination.

The treatment protocol will involve the instillation of a single drop of prostaglandin ophthalmic solution in the study eye once daily in the evening for medications such as Xalacom. To ensure the standardisation of medication usage among participants, subjects will be provided with medication logbooks, which will be collected and recorded by the investigators during the study visits.

Control group

Participants assigned to the control group will be followed up for 12 months or until they reach the endpoint without medical IOP-lowering therapy.

Outcome measures

Primary outcome

The primary outcome is the change of AL at 12-month from baseline measured by IOLMaster.

Secondary outcomes

1. Incidence and progression of VF defects at 12 months from baseline based on Humphrey 24-2 standard VF. Under the premise of reliable VF examination, compared to the baseline, two consecutive perimetric examinations reveal the incidence of VF defects or significant perimetric progression in at least three points at a significance level of $p<0.05$. Furthermore, two subsequent diagnostic VF examinations conducted within one month also confirm the progression at the locations. The time of progression is defined as the time of the initial diagnostic VF examination [23-24].

2. Changes in optic disc morphology (including thinning of RNFL and GC-IPL) at 12-month from baseline based on fundus photography and OCT [25-27].

3. Incidence and progression of myopic maculopathy at 12 months from baseline based on fundus photography and OCT. The determination of incidence and progression of myopic maculopathy is based on the META-PM classification system [28-29].

Study assessments

Visual acuity

Visual acuity assessment will be conducted prior to any procedures that may potentially impact vision, such as pupil dilation or VF examination. The measurement of visual

acuity will be performed using an ETDRS (Early Treatment of Diabetic Retinopathy Study) LogMAR chart (Precision Vision, Villa Park, Illinois, USA) under standard illumination conditions at 4 meters [30]. For BCVA, a trial frame will be positioned and adjusted on the participant's face based on auto refractometric readings and subsequent subjective refinement.

Refractometry

Following pupil dilation using 0.25% compound tropicamide (Zhuobian@; Sinqi, China), three measurements will be taken for each eye using an auto refractometer (KR800, TOPCON, Tokyo, Japan). The average values for spherical refractive error, cylindrical refractive error, and astigmatic axis will be recorded for further analysis and documentation.

Slit-lamp biomicroscopy

The evaluation of the anterior segment with the pupil undilated will be performed using a slit lamp (BQ-900, Haag Streit, Koeniz, Switzerland). After medical pupillary dilation, a slit lamp-based grading of lens opacities is conducted and using a 90D indirect ophthalmoscopic lens (Ocular 90D Slit Lamp Lenses, Ocular, Washington, DC, USA), the optic disc, macula, and peripheral retina will be examined.

Tonometry

IOP measurements will be performed by Goldmann applanation tonometry (AT900, Haag Streit, Koeniz, Switzerland). Prior to enrollment, all participants will undergo three baseline IOP readings during specific time intervals: 9 am to 10 am, 1 pm to 2 pm, and 4 pm to 5 pm. During follow-up visits, tonometry will be conducted between 9 am and 11 am. Results from three consecutive measurements will be documented during each visit, and the mean value of these measurements will be utilized for assessment purposes.

AL measurement

AL measurement will be performed using the IOLMaster (IOLmaster 700, Carl Zeiss Meditec, Jena, Germany). Results from five consecutive measurements will be documented during each visit, and the mean value of these measurements will be utilized for further analysis.

Central corneal thickness (CCT) measurement

CCT measurement will be performed with IOLMaster (IOLmaster 700, Carl Zeiss Meditec, Jena, Germany). Results from five consecutive measurements will be documented during each visit, and the mean value of these measurements will be taken for further analysis.

Perimetry

The perimetric examination will be performed applying the Humphrey Field Analyzer Mark 3 (Carl Zeiss Meditec, Dublin, CA, USA) and the Swedish Interactive Threshold Algorithm Standard (SITA) 24-2 program. A reliable VF report is defined as having false-positive and false-negative errors below 15%, as well as fixation losses below 20%.

Fundus photography

Using fundus cameras (KOWA, Nonmyd, WX3D, Nagoya, Japan; TRC-NW400, TOPCON, Tokyo, Japan), two fundus images centered on the optic disc will be taken for each eye under both standardized stereoscopic and non-standardized conditions. Additionally, a single image focused on the macula will be obtained after pupil dilation.

OCT examination

All participants will undergo a series of standardized swept-source OCT examinations using the DRI-OCT Triton model (TOPCON, Tokyo, Japan), focusing on the optic disc and macula. To ensure the reliability and accuracy of the results, a minimum image quality score of 60 will be set. In addition to the swept-source OCT, a spectral domain OCT examination will be conducted to obtain measurements of the peripapillary RNFL and the macular GC-IPL.

Pregnancy test

A urine pregnancy test will be performed for women of reproductive age during their initial visit.

Anthropometry and blood pressure

Participants' height and weight measurements will be measured using a free-standing height rod and a calibrated scale (RGZ120, Jiangsu Wujin Weighing Apparatus Factory, Jiangsu, China). During the baseline visit, blood pressure readings will be obtained from the participant's left arm while they are seated and have rested for a minimum of five minutes with the Omron M7 Blood Pressure Monitor (Matsusaka, Mie, Japan).

Visit schedule

Table 1 summarizes the visit schedule for the enrolment, interventions, and assessments of this trial.

Sample size

The sample size calculation for this study is determined based on the primary outcome and the study hypothesis, taking into account relevant findings from previous studies. The objective of this study is to evaluate the potential of IOP-lowering therapy to reduce axial elongation during a study period of one year growth in eyes with PHM. It is hypothesized that the intervention group receiving IOP-lowering therapy will exhibit a

70% reduction in axial elongation compared to the control group. The control group is estimated to experience a 0.1 mm axial elongation over 12 months, while the intervention group is expected to have a mean axial elongation of 0.03 mm. The common standard deviation is estimated to be 0.14 mm. To achieve a statistical power of 80% with a two-sided significance level of 0.05, a total of 64 individuals per group is required. Accounting for an estimated 15% loss to follow-up at the 12-months mark, the final sample size is determined to be 76 individuals per group, resulting in a total of 152 participants. The sample size calculation was performed using PASS 16.0 software (NCSS, LLC, Kaysville, UT, USA).

Statistical analysis

Statistical analysis will be conducted using Stata 16.0 software (StataCorp, College Station, TX, USA). A two-sided P-value of less than 0.05 will be considered statistically significant, and a 95% confidence interval will be used for parameter estimation.

For the intention-to-treat (ITT) analysis, missing data will be addressed using the multiple imputation method. No simulation will be performed for missing data in the safety evaluation. Dropout rates in the two groups will be compared using chi-squared tests or Fisher's exact tests. Descriptive statistics will be reported as mean and standard deviation for normally distributed continuous data, and as median and interquartile range for non-normally distributed continuous data. Frequency and percentage will be provided for categorical data. Baseline data, including demographic and clinical characteristics, will be analyzed using independent samples t-tests and Wilcoxon rank-sum tests for continuous data, and chi-squared or Fisher's exact tests for categorical variables.

The analysis of primary and secondary outcomes will follow the ITT principle, including all participants. For the primary outcome, the difference in axial elongation between the two groups will be analyzed using linear regression analysis. As for the

secondary outcomes, a multifactor Poisson regression within a generalized linear model will be utilized to estimate the relative risk of progression in perimetric defects and myopic maculopathy. Additionally, the rate of thinning of the RNFL and the GC-IPL will be assessed through log-rank tests.

Safety analysis will be performed in participants belonging to the intervention group, comparing adverse event occurrence between the two groups using the chi-squared test or Fisher's exact test.

The missing data will be handled using the Multiple Imputations method. With the multiple imputation approach, 20 replicas of the dataset will be generated, where missing values are imputed through chained equations. The final results will be obtained by averaging these 20 datasets using Rubin's rules.

Data monitoring

(1) The Data Monitoring Committee (DMC) will closely monitor the data throughout the trial using the EDC system to ensure the reliability and integrity of the collected data. The DMC members are independent individuals who are not affiliated with the researchers or sponsors, ensuring an impartial assessment. There is no conflict of interest between the researchers and sponsors, further guaranteeing the transparency and objectivity of the data monitoring process.

(2) Interim analysis: The study does not include provisions for conducting an interim analysis.

Data management

The collected data will be meticulously recorded and entered into the EDC system. The EDC system is securely hosted on a password-protected network server, ensuring digital protection. Only the principal investigators and authorized study team members will have access to the research data. To ensure confidentiality and integrity, all source documents will be stored in locked file cabinets with restricted access. Prior to data

collection, all researchers will undergo comprehensive training. The raw data will be monitored by an independent data and safety monitoring committee. In the event of queries or uncertainties in the case report form, the data administrator will generate a data queue request (DRQ) and communicate the query to the researcher through the clinical monitoring system. The researcher is expected to provide a prompt response to the data administrator. If necessary, data modifications, confirmations, and entries will be made, and a new DRQ will be issued.

Drug packaging, management, dispensing and storage

Drug packaging

The investigational drugs will be packaged in their own containers with dedicated research labels. Each medication package will consist of a single box, and each box will contain one unit of the drug. The box packaging will be made of paper and labeled with the phrase "For Clinical Research Use Only," along with a drug label indicating a unique drug identification number. The drug identification number is composed of the first two letters of the drug name followed by a four-digit Arabic numeral.

Drug management

The investigator will directly purchase the investigational drugs through the ZOC Research Procurement System. The drugs will be received and stored by a dedicated medication administrator in the Clinical Research Center. The investigational drugs will be managed by the designated medication administrator, who will be responsible for:

1. Storing the drugs according to the storage conditions specified in the drug instructions.
2. Recording all drug dispensing and retrieval activities.
3. Dispensing the drugs only to the participants as specified in the research protocol.

4. Maintaining a comprehensive record of drug inventory throughout the study and providing inventory logs.

5. Maintaining a detailed catalog of the drugs, including information on received materials, dispensing dates, and records of drugs provided to participants.

6. Ensuring that the drug dispensing records match the usage and unused drugs and providing explanations for any discrepancies. Relevant dispensing and return forms must be signed by the medication administrator.

Drug dispensing

After randomisation, the medication administrator will dispense the corresponding investigational drugs to the participants based on the randomized assignment and document the drug dispensing.

Drug storage

Unopened medications should be stored according to the instructions provided in the drug package insert. For drugs that require refrigeration between 2-8°C, the medication administrator needs to monitor the temperature and humidity daily and document the storage conditions. The research drugs should not be provided to anyone other than the participants in the study. Access to the research drugs is limited to personnel authorized by the principal investigator to dispense them. After opening, medications should be stored according to the instructions provided in the drug package insert and must be used within four weeks of opening the drug package.

Safety assessments

The safety assessments included in this study are as follows:

1. Medication-related safety assessment: The ocular hypotensive medications used in this study are known to have rare occurrences of local and systemic adverse reactions, such as ocular surface irritation, eyelid pigmentation, eyelash growth, and drug

allergies. These assessments will be conducted and recorded by the investigators during the study visits using slit lamp examination.

2. High myopia-related safety assessment: This study focuses on individuals with high myopia, and during the natural course of high myopia, retinal pathologies can occur. The investigators will assess and record the complications associated with high myopia based on the examination results during the study visits.

Report and management of adverse events

An adverse event refers to any negative medical occurrence experienced by a participant in the study, regardless of its relation to the treatment. Utmost attention will be given to identifying potential adverse events or unfavorable findings. The primary concern is the safety of the participant, and appropriate medical intervention will be provided in case of an adverse event. All adverse events, whether reported voluntarily by the participant or discovered through questioning, physical examination, or other means by the study staff, will be promptly recorded on an online adverse event form The Safety Supervision Committee will review each form to determine the appropriate coding and reporting procedures.

Serious adverse events, regardless of their connection to the study drug, must be reported within 24 hours to the Institutional Review Board (IRB), the DMC, and the Clinical Research Center. Additionally, a faxed report must be sent to the Drug Administration's drug registration office. The original and fax confirmation forms for serious adverse events should be retained in the research center along with the case report form.

Discussion

This trial is designed to evaluate the effect of intraocular pressure reduction on progressive high myopia. Due to the limited research on the use of IOP reduction medications in highly myopic eyes, the design of this study is based on a retrospective

analysis of a large cohort of highly myopic individuals. It is found that the use of IOP reduction medications slowed down axial elongation in approximately 70% of highly myopic eyes. Therefore, we performed sample size calculations based on these findings.

Study progress

The recruitment period of this study has started in June 2023 in ZOC. As of February 2024, we have included 73 participants.

Acknowledgement: We thank all the members of the Glaucoma Suspects with High Myopia Study Group (GSHM) Study Group for conducting this trial. And also, we thank all staff in clinical research center of ZOC for their effort in this study.

GSHM study group

Principal investigators:

Xiulan Zhang, Yizhi Liu, Lin Lv, David Friedman, Jost B. Jonas, and Tin Aung.

Members:

Shida Chen, Wei Wang, Fengbin Lin, Yunhe Song, Peiyuan Wang, Kangjie Kong, Jingwen Jiang, Fei Li, Kai Gao, Bingqian Liu, Yuhong Liu, and Meiling Chen.

Steering committee:

Neil M. Bressler, Ki Ho Park, Mingguang He, Kyoko Ohno-Matsui, Dennis S.C. Lam, and Robert N. Weinreb.

Data monitoring committee:

Ching-Yu Cheng, Paul Healey, and Linda M. Zangwill.

Safety supervision committee:

Xiang Chen and Guangxian Tang.

Biostatistics and data monitoring center:

Ling Jin.

Funding/Support: This article was supported by the National Key R&D Program of China (2022YFC2502800); the High-level Hospital Construction Project, Zhongshan Ophthalmic Center, Sun Yat-sen University (303020104); the National Natural Science Foundation of China (82070955); the Science and Technology Program of Guangzhou, China (202201020362, 202102010209 2024A03J00515); Natural Science Foundation of Guangdong Province (2020A1515011282). The funding organisations had no role in the design or conduct of this article.

Contributors: XZ, FL, JBJ, XG and SC participated in the study design. JJ, TL and FL wrote the primary protocol manuscript. XZ, FZ, DSL and JBJ revised the manuscript. KK, PW and YS contributed to data collecting. LJ and WZ helped with sample size calculation and were the statistical consultants. YL, JC and MC were clinical research coordinators of the project.

Competing interest: Jost B. Jonas: European patent EP 3,271,392, JP 2021-119187, and US 2021 0340237 A1: Agents for use in the therapeutic or prophylactic treatment of myopia or hyperopia; European patent application 23196899.1 “EGFR Antagonists for the treatment of diseases involving unwanted migration, proliferation, and metaplasia of retinal pigment epithelium (RPE) cells”.

Patient and public involvement: Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication: Not applicable

Protocol Version: 5.0

Figure 1 Diagram of the PHM study design.

References

1. Yusufu M, Bukhari J, Yu X, et al. Challenges in eye care in the Asia-Pacific region. *Asia Pac J Ophthalmol (Phila)*. 2021;10(5):423-429. doi:10.1097/APO.0000000000000391.
2. Sankaridurg P, Berntsen DA, Bullimore MA, et al. IMI 2023 Digest. *Invest Ophthalmol Vis Sci*. 2023;64(6):7. doi:10.1167/iovs.64.6.7.
3. Holden BA, Fricke TR, Wilson DA, et al. Global prevalence of myopia and high myopia and temporal trends from 2000 through 2050. *Ophthalmology*. 2016;123:1036-1042. doi: 10.1016/j.ophtha.2016.01.006.
4. Fricke TR, Jong M, Naidoo KS, et al. Global prevalence of visual impairment associated with myopic macular degeneration and temporal trends from 2000 through 2050: systematic review, meta-analysis and modelling. *Br J Ophthalmol*. 2018;102:855-862. doi: 10.1136/bjophthalmol-2017-311266.
5. Morgan IG, Jan CL. China turns to school reform to control the myopia epidemic: a narrative review. *Asia Pac J Ophthalmol (Phila)*. 2022;11:27-35. doi: 10.1097/APO.0000000000000489.
6. Parolini B, Palmieri M, Finzi A, et al. Myopic traction maculopathy: a new perspective on classification and management. *Asia Pac J Ophthalmol (Phila)*. 2021;10:49–59. doi: 10.1097/APO.0000000000000347.
7. Haarman AEG, Enthoven CA, Tideman JWL, et al. The complications of myopia: a review and meta-analysis. *Invest Ophthalmol Vis Sci*. 2020;61:49. doi: 10.1167/iovs.61.4.49.
8. Ha A, Kim CY, Shim SR, et al. Degree of myopia and glaucoma risk: a dose-response meta-analysis. *Am J Ophthalmol*. 2022;236:107-119. doi: 10.1016/j.ajo.2021.10.007.
9. Jiang J, Song Y, Kong K, et al. Optic Nerve Head Abnormalities in Nonpathologic High Myopia and the Relationship With Visual Field. *Asia-Pacific Journal of Ophthalmology*. 2023;12: 460-467. doi: 10.1097/APO.0000000000000636.

10. He HL, Liu YX, Chen XY, et al. Fundus Tessellated Density of Pathologic Myopia. *Asia-Pacific Journal of Ophthalmology*. 2023; 12: 604-613. doi: https://doi.org/10.1097/APO.0000000000000642.
11. Yasushi I. Overview of the complications of high myopia. *Retina*. 2017;37:2347-2351. doi: 10.1097/IAE.0000000000001489.
12. Du R, Xie S, Igarashi-Yokoi T, et al. Continued increase of axial length and its risk factors in adults with high myopia. *JAMA Ophthalmol*. 2021;139(10):1096-1103. doi:10.1001/jamaophthalmol.2021.3303.
13. Jonas JB, Spaide RF, Ostrin LA, Logan NS, Flitcroft I, Panda-Jonas S. IMI-Nonpathological human ocular tissue changes with axial myopia. *Invest Ophthalmol Vis Sci*. 2023;64(6):5. doi:10.1167/iovs.64.6.5.
14. Lee MW, Lee SE, Lim HB, Kim JY. Longitudinal changes in axial length in high myopia: a 4-year prospective study. *Br J Ophthalmol*. 2020;104(5):600-603. doi:10.1136/bjophthalmol-2019-314619.
15. El-Nimri NW, Wildsoet CF. Effects of topical latanoprost on intraocular pressure and myopia progression in young guinea pigs. *Invest Ophthalmol Vis Sci*. 2018;59(6):2644-2651. doi:10.1167/iovs.17-22890.
16. Yang J, Pan M, Reinach PS, et al. Prostaglandin F2α receptor modulation affects eye development in guinea pigs. *Basic Clin Pharmacol Toxicol*. 2018;123(3):263-270. doi:10.1111/bcpt.13017.
17. Igarashi-Yokoi T, Shinohara K, Fang Y, et al. Prognostic factors for axial length elongation and posterior staphyloma in adults with high myopia: a Japanese observational study. *Am J Ophthalmol.* 2021;225:76-85. doi:10.1016/j.ajo.2020.11.023.
18. Chong RS, Li H, Cheong AJY, et al. Mendelian randomization implicates bidirectional association between myopia and primary open-angle glaucoma or intraocular pressure. *Ophthalmology*. 2023;130(4):394-403. doi:10.1016/j.ophtha.2022.11.030.

19. Wang P, Chen S, Liu Y, et al. Lowering intraocular pressure: a potential approach for controlling high myopia progression. *Invest Ophthalmol Vis Sci.* 2021;62(14):17. doi:10.1167/iovs.62.14.17.

20. Flitcroft DI, He M, Jonas JB, et al. IMI - Defining and classifying myopia: a proposed set of standards for clinical and epidemiologic studies. *Invest Ophthalmol Vis Sci*. 2019;60(3):M20-M30. doi:10.1167/iovs.18-25957.

21. Wolf S, Balciuniene VJ, Laganovska G, et al. RADIANCE: a randomized controlled study of ranibizumab in patients with choroidal neovascularization secondary to pathologic myopia. *Ophthalmology*. 2014;121(3):682-92.e2. doi:10.1016/j.ophtha.2013.10.023.

22. Comparison of glaucomatous progression between untreated patients with normal-tension glaucoma and patients with therapeutically reduced intraocular pressures. Collaborative Normal-Tension Glaucoma Study Group. *Am J Ophthalmol*. 1998;126(4):487-497. doi:10.1016/s0002-9394(98)00223-2.

23. Garway-Heath DF, Lascaratos G, Bunce C, et al. The United Kingdom Glaucoma Treatment Study: a multicenter, randomized, placebo-controlled clinical trial: design and methodology. *Ophthalmology*. 2013;120(1):68-76. doi:10.1016/j.ophtha.2012.07.028.

24. Garway-Heath DF, Crabb DP, Bunce C, et al. Latanoprost for open-angle glaucoma (UKGTS): a randomised, multicentre, placebo-controlled trial. *Lancet*. 2015;385(9975):1295-1304. doi:10.1016/S0140-6736(14)62111-5.

25. Leske MC, Heijl A, Hyman L, Bengtsson B. Early Manifest Glaucoma Trial: design and baseline data. *Ophthalmology*. 1999;106(11):2144-2153. doi:10.1016/s0161-6420(99)90497-9.

26. Lalezary M, Medeiros FA, Weinreb RN, et al. Baseline optical coherence tomography predicts the development of glaucomatous change in glaucoma suspects. *Am J Ophthalmol*. 2006;142(4):576-582. doi:10.1016/j.ajo.2006.05.004.

27. Keltner JL, Johnson CA, Anderson DR, et al. The association between glaucomatous visual fields and optic nerve head features in the Ocular Hypertension Treatment Study. *Ophthalmology*. 2006;113(9):1603-1612. doi:10.1016/j.ophtha.2006.05.061.

28. Ohno-Matsui K, Kawasaki R, Jonas JB, et al. International photographic classification and grading system for myopic maculopathy. *Am J Ophthalmol*. 2015;159(5):877-83.e7. doi:10.1016/j.ajo.2015.01.022.

29. Li Z, Liu R, Xiao O, et al. Progression of myopic maculopathy in highly myopic Chinese eyes. *Invest Ophthalmol Vis Sci*. 2019;60(4):1096-1104. doi:10.1167/iovs.18-25800.

30. Farida FM, Hassan Farahat HG, Salem MS. Refraction errors in school children. *Menoufia Med J*. 2018;31(1):293-298. doi:10.4103/mmj.mmj_115_17.

Table 1 Visit schedule

Periods	**Screening**	**Baseline visit**	**Follow-up visits**		
Visit	**V_0**	**V_1**	**V_2**	**V_3**	**V_4**
Timepoint	**Day -14 to -1**	**Day 0**	**Week 4 (±7d)**	**Week 26 (±14d)**	**Week 52 (±28d)**
Enrolment					
Eligibility screen	x				
Informed consent	x				
History information	x				
Allocation		x			
Interventions		x	x	x	x
Assessments					
Physical examination		x			
Pregnancy test		x			
Visual acuity		x	x	x	x
Refraction		x	x	x	x
Slip lamp biomicroscopy		x	x	x	x
Intraocular pressure	x	x	x	x	x
Axial length		x	x	x	x
Visual field		x	x	x	x
Fundus photography		x	x	x	x
Optical coherence tomography		x	x	x	x
Central corneal thickness		x	x	x	x
Adverse events	x	x	x	x	x
Combination drugs	x	x	x	x	x
Drug distribution		x	x	x	
Drug recovery and investigation			x	x	x

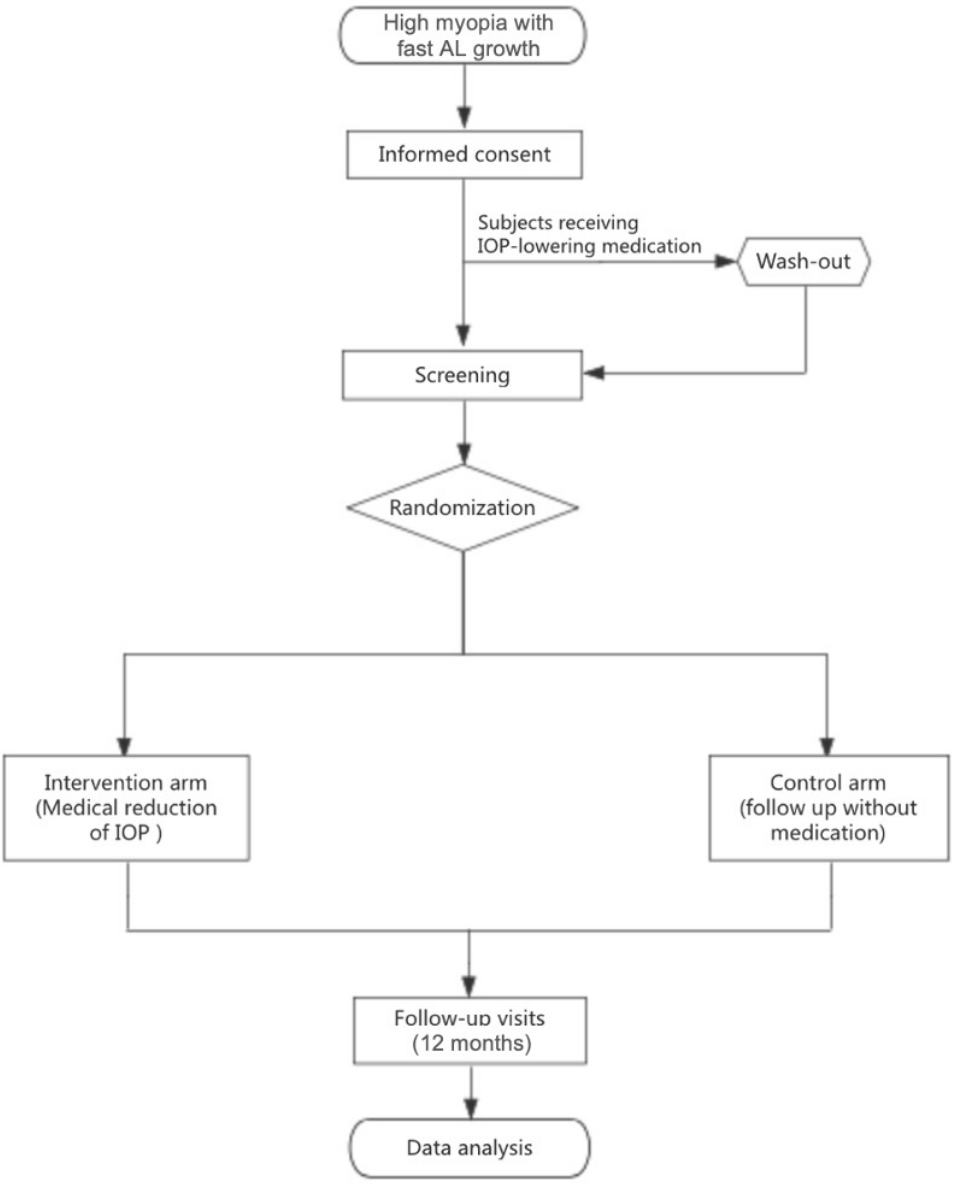


Figure 1

146x174mm (144 x 144 DPI)

Informed Consent Form · Informed Consent Page

Dear Participant,

Greetings!

You have been diagnosed with "high myopia (HM)," and we cordially invite you to participate in a research study titled " Effect of Intraocular Pressure Reduction on Progressive High Myopia (PHM study): a Randomized Controlled Trial". The purpose of this informed consent form is to provide you with comprehensive research information, enabling you to make an informed decision regarding your participation in this trial. We kindly request you to read this document attentively and direct any inquiries to the responsible researchers.

Please note that participation in this study is entirely voluntary. The research protocol has undergone rigorous review and approval by the Ethics Committee of Zhongshan Ophthalmic Center, Sun Yat-sen University, ensuring compliance with ethical standards for conducting clinical research.

1. Why is this study being conducted?

HM, particularly pathological myopia, can lead to various severe complications that significantly impact visual function. The axial elongation of the eye in adult patients with HM is a risk factor for the progression of pathological myopia. Therefore, finding ways to delay the continuous axial elongation in adult patients with HM has become a pressing clinical issue. Research indicates that lowering intraocular pressure (IOP) serves as a protective factor against axial elongation in adult patients with high myopia. Animal experiments and our previous small-scale retrospective study have shown that localized IOP reduction can effectively slow down the progression of HM. However, there is currently a lack of robust clinical randomized controlled trials providing substantial evidence in this regard. Hence, it is imperative to conduct this research to establish a strong foundation for determining treatment strategies for patients with progressive high myopia (PHM).

2. Who is eligible to participate in this study?

Inclusion criteria

1. Age ≥18 years and ≤65 years.

2. Diagnosed with HM: spherical equivalent ≤-6.00 diopters or axial length ≥26.5 mm.

3. Diagnosed with PHM: axial elongation ≥0.05mm in the past 6 months or ≥0.1mm in the past 12 months.

4. IOP: ≥10 mmHg and ≤21mmHg on at least 2 visits using Goldmann applanation tonometry with correction for the dependence of the IOP-reading on corneal thickness.

5. Best corrected visual acuity (BCVA) ≥6/12, ability to undergo axial length measurement, fundus

photography, optical coherence tomography (OCT), and complete visual field examination.

Exclusion criteria

1. Patients who have been using IOP-lowering medications within the last year.

2. Allergy to any kind of IOP-lowering eyedrops.

3. Presence of serious fundus pathologies like proliferative diabetic retinopathy, retinal detachment, central retinal artery occlusion, etc.

4. Presence of chronic, recurrent, or severe ocular inflammatory lesions such as chronic or recurrent uveitis.

5. Significant corneal or iris lesions, severe cataract affecting fundus examination, or patients with only one eye.

6. Intraocular surgery or laser treatment within the last year, such as cataract surgery.

7. With a history of previous refractive surgery or prior treatment for myopia-related conditions (e.g., orthokeratology lens wear, low-intensity red light therapy, or low-concentration atropine treatment).

8. Presence of other serious systemic diseases (e.g., hypertension, heart disease, diabetes, rheumatic immune system disease) that hinder long-term follow-up and eye treatment.

9. Pregnancy, lactation, or plans to have children during the follow-up period.

In this study, only one eye per eligible participant will be included. If both eyes meet the inclusion criteria, the eye with a higher rate of axial elongation, a worse mean perimetric deviation (MD) value, and a worse BCVA will be selected.

3. How is the study conducted?

Once you are diagnosed with PHM, we will provide you with the above explanation. If you agree to participate in this study, we will proceed with the following research procedures after you have signed this informed consent form. These procedures involve collecting your research data and relevant examination results as specified in the research protocol. The study process is as follows:

1) Informed consent and screening for eligibility, with medication washout if necessary.

2) The study physician will select the appropriate eye for research observation based on the requirements of the research protocol and the patient's individual circumstances.

3) Randomization: Participants will be randomly assigned in a 1:1 ratio to either the intraocular pressure-lowering medication group or the control group (no medication).

Participants assigned to the intervention group will receive medical IOP-lowering therapy for a duration of 12 months or until they reach the endpoint**.** Only the study eye will receive medication in the enrolled participants. The preferred medication for reducing IOP is Xalacom® eye drop (Pfizer Inc., New York, NY, USA), a fixed latanoprost and timolol combination.

The treatment protocol will involve the instillation of a single drop of prostaglandin ophthalmic solution in the study eye once daily in the evening for medications such as Xalacom. To ensure the standardisation of medication usage among participants, subjects will be provided with medication logbooks, which will be collected and recorded by the investigators during the study visits.

Control group

Participants assigned to the control group will be followed up for 12 months or until they reach the endpoint without medical IOP-lowering therapy.

- Medication Administration:

Xalacom: One drop once daily at 22:00 (±1 hour), with lacrimal sac compression for one minute after administration.

- Medication Follow-up Duration: 1 year (Participants are required to complete three visits within one year, scheduled at approximately 1 month (±1 week), 6 months (±2 weeks), and 12 months (±4 weeks) respectively).
- Follow-up Examinations: Visual acuity (uncorrected visual acuity, BCVA), computerized auto-refraction, Goldmann tonometry, central corneal thickness, axial length, visual field, fundus photography, OCT examination, quality of life questionnaire, etc.

Throughout the study, we will closely monitor any changes in your condition and make necessary adjustments to the follow-up plan in order to ensure your rights and safety.

4. What is required to participate in the study?

1) Understand the details of this study and voluntarily agree to participate.

2) Adhere to the medication regimen (for the IOP-lowering medication group) and follow-up visits as specified in the protocol. Provide accurate information regarding medication response and changes in your condition.

5. Impact on daily life by participating in the study

1) You may experience inconvenience due to the study visits and examinations. Additionally, some tests may cause discomfort. If you have any concerns or questions about the examinations and procedures during the study, you can consult the research physician.

2) During the study period, please consult your research physician before using any new prescription medications to avoid conflicts.

3) To ensure your safety and the validity of the study results, you will not be able to participate in any other clinical studies involving medications or medical devices during the study.

6. Potential benefits of participating in the study:

Participation in the study will not directly benefit the participants. However, as part of the study, you will receive close follow-up for one year, and the study-related costs, such as the IOP-lowering medication and examinations, will be provided free of charge. This allows for timely detection and treatment of disease progression or other complications. The application of the study results may contribute to improving treatment recommendations for controlling axial elongation in HM.

7. Risks of participating in the study

1) Risks if enrolled in the IOP-lowering medication group:

- The medication used in this study for lowering IOP is a commonly used glaucoma medication approved by the regulatory authority. Known local and systemic adverse reactions are rare and include eye redness, eyelid pigmentation, eyelash growth, and medication allergies, which are detailed in the drug's package insert.

- Low IOP: During the first week after administering the medication, the participants' IOP will be monitored. If low IOP or other related conditions occur, dose reduction or discontinuation of the medication will be implemented. However, based on previous studies, even when the IOP of normal-tension glaucoma patients is lowered to 30% of baseline, excessively low IOP has not been observed. Therefore, this risk is extremely low.

2) Risks if enrolled in the control group:

- The control group in this study does not receive medication. Only a small number of highly myopic participants may have suspected glaucoma, and there is a possibility of worsening of the suspected glaucoma condition during the follow-up. If the examination reveals suspected glaucoma and there is progression of visual field defects during the follow-up, the study will be terminated, and participants will receive further glaucoma-related treatment according to clinical guidelines. The visit intervals in this study are 3-6 months, during which any potential progression would be mild and manageable.

3) Risks associated with HM itself:

- This study focuses on individuals with HM. In the natural course of HM, retinal pathologies associated with high myopia such as chorioretinal atrophy, retinal tears, macular holes, retinal detachment, and choroidal neovascularization may occur. Therefore, before enrollment, participants will undergo a detailed dilated fundus examination to exclude individuals at high risk of developing severe complications in the short term. These individuals will be referred to relevant clinical departments for further diagnosis and treatment. If a participant experiences severe retinal complications, such as retinal detachment, during the follow-up period, and it is determined to be unrelated to the medication, the participant will be responsible for the related treatment costs, and the participant will be provided with convenient access to medical care. At the same time, the participant will discontinue the study.

4) Risks associated with examinations:

- Risks associated with the examination instruments: All the ophthalmic examinations used in this study have been widely used in clinical practice and do not pose adverse effects on participants. The Goldmann tonometry examination involves contact with the cornea, but with skilled technicians performing precise operations and strict disinfection protocols, the risk is minimized.

- Risks associated with examination medications: The study requires the use of compound tropicamide eye drops for pupil dilation, which is a commonly used mydriatic in clinical practice. Due to pupil dilation, participants may experience blurred vision and mild photosensitivity, which naturally resolves within 4-5 hours. After this examination, participants should avoid engaging in activities such as driving that require visual acuity for about half a day. In rare cases, localized reactions such as allergic conjunctivitis or eyelid inflammation may occur. Therefore, before administering the medication, participants' medical history and allergies will be thoroughly assessed and explained to minimize the occurrence of risks.

8. What happens if harm occurs during participation in the study?

Except for unforeseeable circumstances, this study will not cause harm to the participants. The researchers will provide insurance services to the participants involved in the clinical study, as required by Good Clinical Practice (GCP), to protect their rights and interests in participating in the study. Compensation for any harm related to the clinical research will be carried out in accordance with applicable laws and regulations in China.

9. Is personal information kept confidential?

Yes. Your medical records (medical history, examination results, etc.) will be securely stored at the hospital where you receive treatment. The doctor will record the examination results in your medical records. Researchers, ethics committees, and regulatory authorities will be allowed to access your medical records. Any public reports regarding the results of this study will not disclose your personal identity. We will make every effort to protect the privacy of your personal medical information within the limits permitted by law.

10. Is participation in this study mandatory?

Participation in this study is completely voluntary, and it is entirely up to your discretion whether to participate. You have the right to refuse to participate in this study or withdraw from the study at any time without affecting your relationship with the doctor or any other medical or personal interests.

If you decide to withdraw from this study, please inform your research doctor in advance. If you experience any abnormal symptoms during the study, please inform your research doctor or study staff.

For your best interests, the research doctor may suspend your participation in this study at any time if: 1) continuing the study may be detrimental to you, 2) you need treatment that is prohibited by this study, 3) you fail to follow instructions, or 4) the study is terminated.

11. What should I do now?

Whether or not to participate in this study is a decision for you (and your family) to make. Before making a decision to participate in the study, please ask your doctor any questions you may have.T hank you for reading the above information. If you decide to participate in this study, please inform your doctor, who will arrange all the necessary matters related to the study. Please keep this information for your reference.

Contact number for the Ethics Committee of Sun Yat-sen Eye Center, Sun Yat-sen University: 020-66610729.

Informed Consent Form - Consent Signature Page

Consent Statement:

I have read the above information regarding this study and have had the opportunity to discuss it with the doctor and ask questions. All the questions I have raised have been satisfactorily answered.

I am aware of the risks and benefits associated with participating in this study. I understand that participation is voluntary and confirm that I have had sufficient time to consider it. Furthermore, I understand that:

- I can consult the doctor for additional information at any time.
- I can withdraw from this study at any time without discrimination or retaliation, and my medical treatment and rights will not be affected.
- I also understand that if I withdraw from the study, I should inform the doctor about changes in my medical condition and complete the necessary physical and laboratory examinations, as this would be beneficial to the overall study.
- If I require any other medication treatment due to changes in my medical condition, I will either seek the doctor's advice in advance or truthfully inform the doctor afterward.
- I agree that regulatory authorities, ethics committees, or representatives of the sponsor may access my research data.

Finally, I have decided to consent to participate in this study and commit to following the medical advice to the best of my ability.

Signature of Participant (or Guardian)：_____ Date: _____

Contact Phone Number：_____

I confirm that I have explained the details of this trial to the patient, including their rights and the potential benefits and risks involved.

Signature of Researcher：_____ Date: _____

Contact Phone Number：_____

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym (P1 L1-3)
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry (P3 L85)
	2b	All items from the World Health Organization Trial Registration Data Set
Protocol version	3	Date and version identifier (P20 L554)
Funding	4	Sources and types of financial, material, and other support (P19 L528-534)
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors (P1 L5-21,P20 L536-540)
	5b	Name and contact information for the trial sponsor
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)
Introduction		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention (P3 L60-65)
	6b	Explanation for choice of comparators
Objectives	7	Specific objectives or hypotheses (P3 L66-67)

Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) (P3 L68)
Methods: Participants, interventions, and outcomes		
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained (P3 L69-70)
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) (P3 L69-70)
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered (P3 L70-72)
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended (P3 L73-77)
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) (P25)
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations (P3 L69)
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size (P3 L69)
Methods: Assignment of interventions (for controlled trials)		
Allocation:		

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions (P8 L198-209)
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how (P8 L198-209)
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial
Methods: Data collection, management, and analysis		
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol (P10-P13 L271-346)
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol (P15 L408-240)
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol(P14 L368-396)
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)

	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)
Methods: Monitoring		
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed (P15 L398-406)
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct (P17 L464-474)
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor(P15 L398-406)
Ethics and dissemination		
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval(P2 L45-47)
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators

Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions(P3 L83-86)
	31b	Authorship eligibility guidelines and any intended use of professional writers
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code
Appendices		
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates(P8 L200)
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.