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

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Keywords:	Randomized Controlled Trial, OPHTHALMOLOGY, Glaucoma < OPHTHALMOLOGY

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4 1 **Effect of Intraocular Pressure Reduction on Progressive High**
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6 2 **Myopia (PHM study): Study Protocol of a Randomized**
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8 3 **Controlled Trial**
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17 37 **Competing Interest Statement and Financial Disclosure:**

18
19 38 Jost B. Jonas: European patent EP 3,271,392, JP 2021-119187, and US 2021

20
21 39 0340237 A1: Agents for use in the therapeutic or prophylactic treatment of myopia

22
23 40 or hyperopia; European patent application 23196899.1 “EGFR Antagonists for the

24
25 41 treatment of diseases involving unwanted migration, proliferation, and metaplasia

26
27 42 of retinal pigment epithelium (RPE) cells”.
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30
31 44 **Ethics Statement:** The study was approved by the ethical committee of the

32
33 45 Zhongshan Ophthalmic Center and adhered to the tenets of the Declaration of

34
35 46 Helsinki. Written informed consent was obtained from all subjects.
36

37 47

38
39 48 **Key Words:** High myopia, Axial length, Intraocular pressure, Randomized

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4 59 **ABSTRACT**

5
6 60 **Background** In adult patients with high myopia (HM), progressive axial elongation
7
8 61 poses a significant risk for the development of subsequent ocular's complications that
9
10 62 may lead to visual impairment. Effective strategies to reduce or prevent further axial
11
12 63 elongation in highly myopic adult patients have not been available so far. Recent studies
13
14 64 suggested that medically lowering intraocular pressure (IOP) may reduce axial
15
16 65 elongation. This clinical randomized controlled trial (RCT) aims to evaluate the
17
18 66 efficacy of medical IOP reduction in adult patients with progressive HM (PHM).

19
20 67 **Methods and analysis** This single-center, open-label, prospective RCT will recruit 152
21
22 68 participants with PHM at the Zhongshan Ophthalmic Center (ZOC). Randomized in a
23
24 69 ratio of 1:1, participants will receive IOP-lowering eyedrops (intervention group) or
25
26 70 will be followed without treatment (control group) for 12 months. Follow-up visits will
27
28 71 be conducted at 1, 6, and 12 months after baseline. Only one eye per participant will be
29
30 72 eligible. The primary outcome is the change in axial length (AL) within the study period
31
32 73 of 12 months. Secondary outcomes include the incidence and progression of visual field
33
34 74 (VF) defects, changes in optic disc morphology and incidence and progression of
35
36 75 myopic maculopathy. Difference in AL changes between the two groups will be
37
38 76 analyzed using linear regression analysis. For the secondary outcomes, a multifactor
39
40 77 Poisson regression within a generalized linear model will be utilized to estimate the
41
42 78 relative risk of progression in VF defects and myopic maculopathy, and the rate of
43
44 79 thinning in retinal nerve fiber layer and ganglion cell-inner plexiform will be assessed
45
46 80 through Kaplan-Meier curves and log-rank tests.

47
48 81 **Ethics and dissemination** Full ethics approval for this trial has been obtained from the
49
50 82 Ethics Committee of ZOC, Sun Yat-sen University, China (ID: 2023KYPJ110). Results
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52 83 of this trial will be disseminated through peer-reviewed journals and conference
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54 84 presentations.

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56 85 **Trial registration number** NCT05850936 *clinicaltrials.gov*

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4 87 **Strengths and limitations of this study**

5 88 1. The primary objective of this study is to address a global healthcare concern:

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7 89 effectively mitigating further axial elongation in highly myopic adult patients.

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9 90 2. Due to practical constraints, a double-masking in the study design cannot be

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11 91 achieved.

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For peer review only

115 **Introduction**

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

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

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

136 Building upon these findings, we hypothesize that medically IOP-lowering may
137 slow axial elongation by potentially three pathways related to the sclera and choroid¹⁶.
138 We therefore aim to conduct a randomized controlled trial (RCT) to assess the efficacy
139 of medical IOP-lowering in managing axial elongation in patients with progressive HM
140 (PHM). Additionally, this study should generate data on the effects of IOP-lowering
141 treatment on the incidence and changes in the visual field (VF), changes in the optic
142 nerve head morphology and myopic maculopathy. The outcomes of the study may

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4 143 establish a basis for treatment recommendations for preventing axial elongation of
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6 144 highly myopic eyes.

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11 147 **Methods and Analysis**

12 148 **Study design**

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16 149 The PHM study is an open-label, single-center RCT. The study will be conducted at
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18 150 the Zhongshan Ophthalmic Center (ZOC), Sun Yat-Sen University, a tertiary
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20 151 specialized hospital in Guangzhou, China. All examinations and interventions will be
21
22 152 carried out in the Clinical Research Center at ZOC. **Figure 1** summarizes the design of
23
24 153 the PHM study.

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27 155 **Objective**

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30 156 The primary aim of this trial is to evaluate the effectiveness of medically IOP-lowering
31
32 157 therapy, targeting a 10% decrease from baseline levels, in managing axial elongation
33
34 158 in patients with PHM over a 12-month observation period. Additionally, the trial will
35
36 159 assess alterations in VF, optic disc morphology, thickness of the retinal nerve fiber layer
37
38 160 (RNFL) and retinal ganglion cell-inner plexiform layer (GC-IPL), and the occurrence
39
40 161 or advancement of myopic maculopathy.

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43 163 **Recruitment**

44 164 *Inclusion criteria*

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48 165 1. Age ≥ 18 years and ≤ 65 years.
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50 166 2. Diagnosed with HM¹⁷⁻¹⁸: spherical equivalent ≤ -6.00 diopters or AL ≥ 26.5 mm.
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52 167 3. Diagnosed with PHM: axial elongation ≥ 0.05 mm in the past 6 months or ≥ 0.1 mm
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54 168 in the past 12 months.
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4 169 4. IOP: ≥ 10 mmHg and ≤ 21 mmHg on at least 2 visits using Goldmann applanation
5
6 170 tonometry with correction for the dependence of the IOP-reading on corneal thickness
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8 171 ¹⁹.

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10 172 5. Best corrected visual acuity (BCVA) $\geq 6/12$, ability to undergo AL measurement,
11
12 173 fundus photography, optical coherence tomography (OCT), and complete VF
13
14 174 examination.

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17
18 176 *Exclusion criteria*

19
20 177 1. Allergy to any kind of IOP-lowering eyedrops.

21
22 178 2. Presence of serious fundus pathologies like proliferative diabetic retinopathy, retinal
23
24 179 detachment, central retinal artery occlusion, etc.

25
26 180 3. Presence of chronic, recurrent, or severe ocular inflammatory lesions such as chronic
27
28 181 or recurrent uveitis.

29
30 182 4. Significant corneal or iris lesions, severe cataract affecting fundus examination, or
31
32 183 patients with only one eye.

33
34 184 5. Intraocular surgery or laser treatment within the last year, such as cataract surgery.

35
36 185 6. With a history of previous refractive surgery or prior treatment for myopia-related
37
38 186 conditions (e.g., orthokeratology lens wear, low-intensity red light therapy, or low-
39
40 187 concentration atropine treatment).

41
42 188 7. Presence of other serious systemic diseases (e.g., hypertension, heart disease,
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44 189 diabetes, rheumatic immune system disease) that hinder long-term follow-up and eye
45
46 190 treatment.

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48 191 8. Pregnancy, lactation, or plans to have children during the follow-up period.

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51
52 193 In this study, only one eye per participant will be eligible for inclusion. If both eyes
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54 194 meet the inclusion criteria, the eye with a higher rate of axial elongation, a worse mean
55
56 195 perimetric deviation (MD) value, and a worse BCVA will be selected.

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197 **Randomization and blinding**

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

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

210 **Interventions**

211 *Wash out*

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

221 *Intervention group*

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

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4 225 medication for reducing IOP is Xalacom[®] eye drops (a fixed latanoprost and timolol
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6 226 combination). If the target IOP (reducing baseline IOP by 10%) is not achieved after
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8 227 one month of treatment, 1% brinzolamide eye drops (Azopt[®]) will be added. If the
9
10 228 target IOP is still not achieved after an additional month of treatment, brimonidine
11
12 229 tartrate eye drops (Alphagan[®] 0.2% or Alphagan-P[®] 0.15%) will be added. If the
13
14 230 patient is allergic to prostaglandin analogs, the preferred alternative is Azarga[®] eye
15
16 231 drops (a fixed brinzolamide with timolol combination). If the target IOP is not
17
18 232 achieved after one month of treatment, brimonidine tartrate eye drops (Alphagan[®]
19
20 233 0.2% or Alphagan-P[®] 0.15%) will be added (**Figure 2**).

21
22 234 The treatment protocol will involve the instillation of a single drop of
23
24 235 prostaglandin ophthalmic solution in the study eye once daily in the evening for
25
26 236 medications such as Xalacom. For medications like timolol, Alphagan (or Alphagan-
27
28 237 P), brinzolamide, or Azarga, the study eye will receive one drop twice daily. To
29
30 238 ensure the standardization of medication usage among participants, subjects will be
31
32 239 provided with medication logbooks, which will be collected and recorded by the
33
34 240 investigators during the study visits.

35
36 241 Regular assessment of IOP will be conducted on a weekly basis following the
37
38 242 initiation or addition of medication until the target value is achieved in the study eye.
39
40 243 If the study eye fails to reach the target IOP even after escalating the medication, the
41
42 244 medication will be discontinued, but the subsequent follow-up visits will continue as
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44 245 planned.

45 46 246 47 48 247 *Control group*

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50 248 Participants assigned to the control group will be followed up for 12 months or until
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52 249 they reach the endpoint without medical IOP-lowering therapy.

53 54 250 55 56 251 **Outcome measures**

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58 252 *Primary outcome*
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4 253 The primary outcome is the change of AL at 12-month from baseline measured by
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6 254 IOLMaster.

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10 256 *Secondary outcomes*

11 257 1. Incidence and progression of VF defects at 12 months from baseline based on

12
13 258 Humphrey 24-2 standard VF. Under the premise of reliable VF examination,

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15 259 compared to the baseline, two consecutive perimetric examinations reveal the

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17 260 incidence of VF defects or significant perimetric progression in at least three points at

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19 261 a significance level of $p < 0.05$. Furthermore, two subsequent diagnostic VF

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21 262 examinations conducted within one month also confirm the progression at the

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23 263 locations. The time of progression is defined as the time of the initial diagnostic VF

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25 264 examination²⁰⁻²¹.

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27 265 2. Changes in optic disc morphology (including thinning of RNFL and GC-IPL) at

28
29 266 12-month from baseline based on fundus photography and OCT²²⁻²⁴.

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31 267 3. Incidence and progression of myopic maculopathy at 12 months from baseline based

32
33 268 on fundus photography and OCT. The determination of incidence and progression of

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35 269 myopic maculopathy is based on the META-PM classification system²⁵⁻²⁶.

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39 271 **Study assessments**

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41 272 *Visual acuity*

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43 273 Visual acuity assessment will be conducted prior to any procedures that may potentially

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45 274 impact vision, such as pupil dilation or VF examination. The measurement of visual

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47 275 acuity will be performed using an ETDRS (Early Treatment of Diabetic Retinopathy

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49 276 Study) LogMAR chart (Precision Vision, Villa Park, Illinois, USA) under standard

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51 277 illumination conditions at 4 meters²⁷. For BCVA, a trial frame will be positioned and

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53 278 adjusted on the participant's face based on auto refractometric readings and subsequent

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55 279 subjective refinement.

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4 281 *Refractometry*

5 282 Following pupil dilation using 0.25% compound tropicamide (Zhuobian®; Sinqi,
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7 283 China), three measurements will be taken for each eye using an auto refractometer
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9 284 (KR800, TOPCON, Tokyo, Japan). The average values for spherical refractive error,
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11 285 cylindrical refractive error, and astigmatic axis will be recorded for further analysis and
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13 286 documentation.
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18 288 *Slit-lamp biomicroscopy*

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20 289 The evaluation of the anterior segment with the pupil undilated will be performed using
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22 290 a slit lamp (BQ-900, Haag Streit, Koeniz, Switzerland). After medical pupillary dilation,
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24 291 a slit lamp-based grading of lens opacities is conducted, and using a 90D indirect
25
26 292 ophthalmoscopic lens (Ocular 90D Slit Lamp Lenses, Ocular, Washington, DC, USA),
27
28 293 the optic disc, macula, and peripheral retina will be examined.
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32 295 *Tonometry*

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34 296 IOP measurements will be performed by Goldmann applanation tonometry (AT900,
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36 297 Haag Streit, Koeniz, Switzerland). Prior to enrollment, all participants will undergo
37
38 298 three baseline IOP readings during specific time intervals: 9 am to 10 am, 1 pm to 2
39
40 299 pm, and 4 pm to 5 pm. During follow-up visits, tonometry will be conducted between
41
42 300 9 am and 11 am or between 2 pm and 4 pm. Results from three consecutive
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44 301 measurements will be documented during each visit, and the mean value of these
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46 302 measurements will be utilized for assessment purposes.
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50 304 *AL measurement*

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52 305 AL measurement will be performed using the IOLMaster (IOLmaster 700, Carl Zeiss
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54 306 Meditec, Jena, Germany). Results from five consecutive measurements will be
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56 307 documented during each visit, and the mean value of these measurements will be
57
58 308 utilized for further analysis.
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5 310 *Central corneal thickness (CCT) measurement*

7 311 CCT measurement will be performed with IOLMaster (IOLmaster 700, Carl Zeiss
9 312 Meditec, Jena, Germany). Results from five consecutive measurements will be
11 313 documented during each visit, and the mean value of these measurements will be taken
13 314 for further analysis.

15 315

17 316 *Perimetry*

19 317 The perimetric examination will be performed applying the Humphrey Field Analyzer
21 318 Mark 3 (Carl Zeiss Meditec, Dublin, CA, USA) and the Swedish Interactive Threshold
23 319 Algorithm Standard (SITA) 24-2 program. A reliable VF report is defined as having
25 320 false-positive and false-negative errors below 15%, as well as fixation losses below
27 321 20%.

29 322

31 323 *Fundus photography*

33 324 Using fundus cameras (KOWA, Nonmyd, WX3D, Nagoya, Japan; TRC-NW400,
35 325 TOPCON, Tokyo, Japan), two fundus images centered on the optic disc will be taken
37 326 for each eye under both standardized stereoscopic and non-standardized conditions.
39 327 Additionally, a single image focused on the macula will be obtained after pupil dilation.

41 328

43 329 *OCT examination*

45 330 All participants will undergo a series of standardized swept-source OCT examinations
47 331 using the DRI-OCT Triton model (TOPCON, Tokyo, Japan), focusing on the optic disc
49 332 and macula. To ensure the reliability and accuracy of the results, a minimum image
51 333 quality score of 60 will be set. In addition to the swept-source OCT, a spectral domain
53 334 OCT examination will be conducted to obtain measurements of the peripapillary RNFL
55 335 and the macular GC-IPL.

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4 337 *Pregnancy test*

5 338 A urine pregnancy test will be performed for women of reproductive age during their
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7 339 initial visit.
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11 341 *Anthropometry and blood pressure*

12 342 Participants' height and weight measurements will be measured using a free-standing
13
14 343 height rod and a calibrated scale (RGZ120, Jiangsu Wujin Weighing Apparatus Factory,
15
16 344 Jiangsu, China). During the baseline visit, blood pressure readings will be obtained
17
18 345 from the participant's left arm while they are seated and have rested for a minimum of
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20 346 five minutes with the Omron M7 Blood Pressure Monitor (Matsusaka, Mie, Japan).
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26 348 **Visit schedule**

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28 349 **Table 1** summarizes the visit schedule for the enrolment, interventions, and
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30 350 assessments of this trial.
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34 352 **Sample size**

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36 353 The sample size calculation for this study was determined based on the primary
37
38 354 outcome and the study hypothesis, taking into account relevant findings from previous
39
40 355 studies. The objective of this study is to evaluate the potential of IOP-lowering therapy
41
42 356 to reduce axial elongation during a study period of one year growth in eyes with PHM.
43
44 357 It is hypothesized that the intervention group receiving IOP-lowering therapy will
45
46 358 exhibit a 70% reduction in axial elongation compared to the control group. The control
47
48 359 group is estimated to experience a 0.1 mm axial elongation over 12 months, while the
49
50 360 intervention group is expected to have a mean axial elongation of 0.03 mm. The
51
52 361 common standard deviation is estimated to be 0.14 mm. To achieve a statistical power
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54 362 of 80% with a two-sided significance level of 0.05, a total of 64 individuals per group
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56 363 is required. Accounting for an estimated 15% loss to follow-up at the 12-months mark,
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58 364 the final sample size is determined to be 76 individuals per group, resulting in a total
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4 365 of 152 participants. The sample size calculation was performed using PASS 16.0
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6 366 software (NCSS, LLC, Kaysville, UT, USA).

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8 367

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10 368 **Statistical analysis**

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12 369 Statistical analysis will be conducted using Stata 16.0 software (StataCorp, College
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14 370 Station, TX, USA). A two-sided P-value of less than 0.05 will be considered
15
16 371 statistically significant, and a 95% confidence interval will be used for parameter
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18 372 estimation.

19
20 373 For the intention-to-treat (ITT) analysis, missing data will be addressed using the
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22 374 multiple imputation method. No simulation will be performed for missing data in the
23
24 375 safety evaluation. Dropout rates in the two groups will be compared using chi-squared
25
26 376 tests or Fisher's exact tests. Descriptive statistics will be reported as mean and standard
27
28 377 deviation for normally distributed continuous data, and as median and interquartile
29
30 378 range for non-normally distributed continuous data. Frequency and percentage will be
31
32 379 provided for categorical data. Baseline data, including demographic and clinical
33
34 380 characteristics, will be analyzed using independent samples t-tests and Wilcoxon rank-
35
36 381 sum tests for continuous data, and chi-squared or Fisher's exact tests for categorical
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38 382 variables.

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40 383 The analysis of primary and secondary outcomes will follow the ITT principle,
41
42 384 including all participants. For the primary outcome, the difference in axial elongation
43
44 385 between the two groups will be analyzed using linear regression analysis. As for the
45
46 386 secondary outcomes, a multifactor Poisson regression within a generalized linear model
47
48 387 will be utilized to estimate the relative risk of progression in perimetric defects and
49
50 388 myopic maculopathy. Additionally, the rate of thinning of the RNFL and the GC-IPL
51
52 389 will be assessed through log-rank tests.

53
54 390 Safety analysis will be performed in participants belonging to the intervention
55
56 391 group, comparing adverse event occurrence between the two groups using the chi-
57
58 392 squared test or Fisher's exact test.

1
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4 393 The missing data will be handled using the Multiple Imputations method. With the
5
6 394 multiple imputation approach, 20 replicas of the dataset will be generated, where
7
8 395 missing values are imputed through chained equations. The final results will be
9
10 396 obtained by averaging these 20 datasets using Rubin's rules.

11
12 397

13 14 398 **Data monitoring**

15
16 399 (1) The Data Monitoring Committee (DMC) will closely monitor the data throughout
17
18 400 the trial using the EDC system to ensure the reliability and integrity of the collected
19
20 401 data. The DMC members are independent individuals who are not affiliated with the
21
22 402 researchers or sponsors, ensuring an impartial assessment. There is no conflict of
23
24 403 interest between the researchers and sponsors, further guaranteeing the transparency
25
26 404 and objectivity of the data monitoring process.

27
28 405 (2) Interim analysis: The study does not include provisions for conducting an interim
29
30 406 analysis.

31
32 407

33 34 408 **Data management**

35
36 409 The collected data will be meticulously recorded and entered into the EDC system. The
37
38 410 EDC system is securely hosted on a password-protected network server, ensuring
39
40 411 digital protection. Only the principal investigators and authorized study team members
41
42 412 will have access to the research data. To ensure confidentiality and integrity, all source
43
44 413 documents will be stored in locked file cabinets with restricted access. Prior to data
45
46 414 collection, all researchers will undergo comprehensive training. The raw data will be
47
48 415 monitored by an independent data and safety monitoring committee. In the event of
49
50 416 queries or uncertainties in the case report form, the data administrator will generate a
51
52 417 data queue request (DRQ) and communicate the query to the researcher through the
53
54 418 clinical monitoring system. The researcher is expected to provide a prompt response to
55
56 419 the data administrator. If necessary, data modifications, confirmations, and entries will
57
58 420 be made, and a new DRQ will be issued.

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5 422 **Drug packaging, management, dispensing and storage**

7 423 *Drug packaging*

10 424 The investigational drugs will be packaged in their own containers with dedicated
11 425 research labels. Each medication package will consist of a single box, and each box will
12 426 contain one unit of the drug. The box packaging will be made of paper and labeled with
13 427 the phrase "For Clinical Research Use Only," along with a drug label indicating a
14 428 unique drug identification number. The drug identification number is composed of the
15 429 first two letters of the drug name followed by a four-digit Arabic numeral.

21 430

23 431 *Drug management*

26 432 The investigator will directly purchase the investigational drugs through the ZOC
27 433 Research Procurement System. The drugs will be received and stored by a dedicated
28 434 medication administrator in the Clinical Research Center. The investigational drugs
29 435 will be managed by the designated medication administrator, who will be responsible
30 436 for:

- 36 437 1. Storing the drugs according to the storage conditions specified in the drug
37 438 instructions.
- 40 439 2. Recording all drug dispensing and retrieval activities.
- 42 440 3. Dispensing the drugs only to the participants as specified in the research protocol.
- 44 441 4. Maintaining a comprehensive record of drug inventory throughout the study and
45 442 providing inventory logs.
- 48 443 5. Maintaining a detailed catalog of the drugs, including information on received
49 444 materials, dispensing dates, and records of drugs provided to participants.
- 52 445 6. Ensuring that the drug dispensing records match the usage and unused drugs and
53 446 providing explanations for any discrepancies. Relevant dispensing and return forms
54 447 must be signed by the medication administrator.

58 448
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4 449 *Drug dispensing*

5 450 After randomization, the medication administrator will dispense the corresponding
6
7 451 investigational drugs to the participants based on the randomized assignment and
8
9 452 document the drug dispensing.
10

11 453

12
13
14 454 *Drug storage*

15 455 Unopened medications should be stored according to the instructions provided in the
16
17 456 drug package insert. For drugs that require refrigeration between 2-8°C, the medication
18
19 457 administrator needs to monitor the temperature and humidity daily and document the
20
21 458 storage conditions. The research drugs should not be provided to anyone other than the
22
23 459 participants in the study. Access to the research drugs is limited to personnel authorized
24
25 460 by the principal investigator to dispense them. After opening, medications should be
26
27 461 stored according to the instructions provided in the drug package insert and must be
28
29 462 used within four weeks of opening the drug package.
30

31 463

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33
34 464 **Safety assessments**

35
36 465 The safety assessments included in this study are as follows:

37
38 466 1. Medication-related safety assessment: The ocular hypotensive medications used in
39
40 467 this study are known to have rare occurrences of local and systemic adverse reactions,
41
42 468 such as ocular surface irritation, eyelid pigmentation, eyelash growth, and drug
43
44 469 allergies. These assessments will be conducted and recorded by the investigators
45
46 470 during the study visits using slit lamp examination.

47
48 471 2. High myopia-related safety assessment: This study focuses on individuals with high
49
50 472 myopia, and during the natural course of high myopia, retinal pathologies can occur.
51
52 473 The investigators will assess and record the complications associated with high myopia
53
54 474 based on the examination results during the study visits.
55

56 475

57
58 476 **Report and management of adverse events**
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4 477 An adverse event refers to any negative medical occurrence experienced by a
5
6 478 participant in the study, regardless of its relation to the treatment. Utmost attention will
7
8 479 be given to identifying potential adverse events or unfavorable findings. The primary
9
10 480 concern is the safety of the participant, and appropriate medical intervention will be
11
12 481 provided in case of an adverse event. All adverse events, whether reported voluntarily
13
14 482 by the participant or discovered through questioning, physical examination, or other
15
16 483 means by the study staff, will be promptly recorded on an online adverse event form
17
18 484 The Safety Supervision Committee will review each form to determine the appropriate
19
20 485 coding and reporting procedures.

21
22 486 Serious adverse events, regardless of their connection to the study drug, must be
23
24 487 reported within 24 hours to the Institutional Review Board (IRB), the DMC, and the
25
26 488 Clinical Research Center. Additionally, a faxed report must be sent to the Drug
27
28 489 Administration's drug registration office. The original and fax confirmation forms for
29
30 490 serious adverse events should be retained in the research center along with the case
31
32 491 report form.

33
34 492

35 36 493 **Discussion**

37
38 494 This trial is designed to evaluate the effect of intraocular pressure reduction on
39
40 495 progressive high myopia. Due to the limited research on the use of IOP reduction
41
42 496 medications in highly myopic eyes, the study design was conducted on the preliminary
43
44 497 experimental results. It's found that the use of Xalacom in highly myopic eyes resulted
45
46 498 in a 10% reduction in baseline IOP for 90% of the cases. Additionally, the use of IOP
47
48 499 reduction medications slowed down axial elongation in approximately 70% of highly
49
50 500 myopic eyes. Therefore, we set the target IOP reduction at 10% below the baseline,
51
52 501 selected Xalacom as the preferred medication, and performed sample size calculations
53
54 502 based on these findings.

55
56 503

57 58 504 **Study progress**

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4 505 The recruitment period of this study has started in June 2023 in ZOC. As of September
5
6 506 2023, we have included 47 participants.
7
8 507

9
10 508 **Acknowledgement:** We thank all the members of the Glaucoma Suspects with High
11
12 509 Myopia Study Group (GSHM) Study Group for conducting this trial. And also, we
13
14 510 thank all staff in clinical research center of ZOC for their effort in this study.
15

16 511

17
18 512 ***GSHM study group***

19
20 513 Principal investigators:

21
22 514 Xiulan Zhang, Yizhi Liu, Lin Lv, David Friedman, Jost B. Jonas, and Tin Aung.

23
24 515 Members:

25
26 516 Shida Chen, Wei Wang, Fengbin Lin, Yunhe Song, Peiyuan Wang, Kangjie Kong,
27

28 517 Jingwen Jiang, Fei Li, Kai Gao, Bingqian Liu, Yuhong Liu, and Meiling Chen.

29
30 518 Steering committee:

31
32 519 Neil M. Bressler, Ki Ho Park, Mingguang He, Kyoko Ohno-Matsui, Dennis S.C. Lam,
33
34 520 and Robert N. Weinreb.

35
36 521 Data monitoring committee:

37
38 522 Ching-Yu Cheng, Paul Healey, and Linda M. Zangwill.

39
40 523 Safety supervision committee:

41
42 524 Xiang Chen and Guangxian Tang.

43
44 525 Biostatistics and data monitoring center:

45
46 526 Ling Jin.
47

48 527

49
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51
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53
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55
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57
58 532 China (202201020362, 202102010209 2024A03J00515); Natural Science Foundation
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5
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7

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9
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11
12 537 FL wrote the primary protocol manuscript. XZ, DSL and JBJ revised the manuscript.
13
14 538 KK, PW and YS contributed to data collecting. LJ and WZ helped with sample size
15
16 539 calculation and were the statistical consultants. YL, JC and MC were clinical research
17
18 540 coordinators of the project.
19

20 541

21
22 542 **Competing interest:** Jost B. Jonas: European patent EP 3,271,392, JP 2021-
23
24 543 119187, and US 2021 0340237 A1: Agents for use in the therapeutic or
25
26 544 prophylactic treatment of myopia or hyperopia; European patent application
27
28 545 23196899.1 “EGFR Antagonists for the treatment of diseases involving unwanted
29
30 546 migration, proliferation, and metaplasia of retinal pigment epithelium (RPE)
31
32 547 cells”.
33

34 548

35
36 549 **Patient and public involvement:** Patients and/or the public were not involved in the
37
38 550 design, or conduct, or reporting, or dissemination plans of this research.
39

40 551

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42 552 Patient consent for publication: Not applicable
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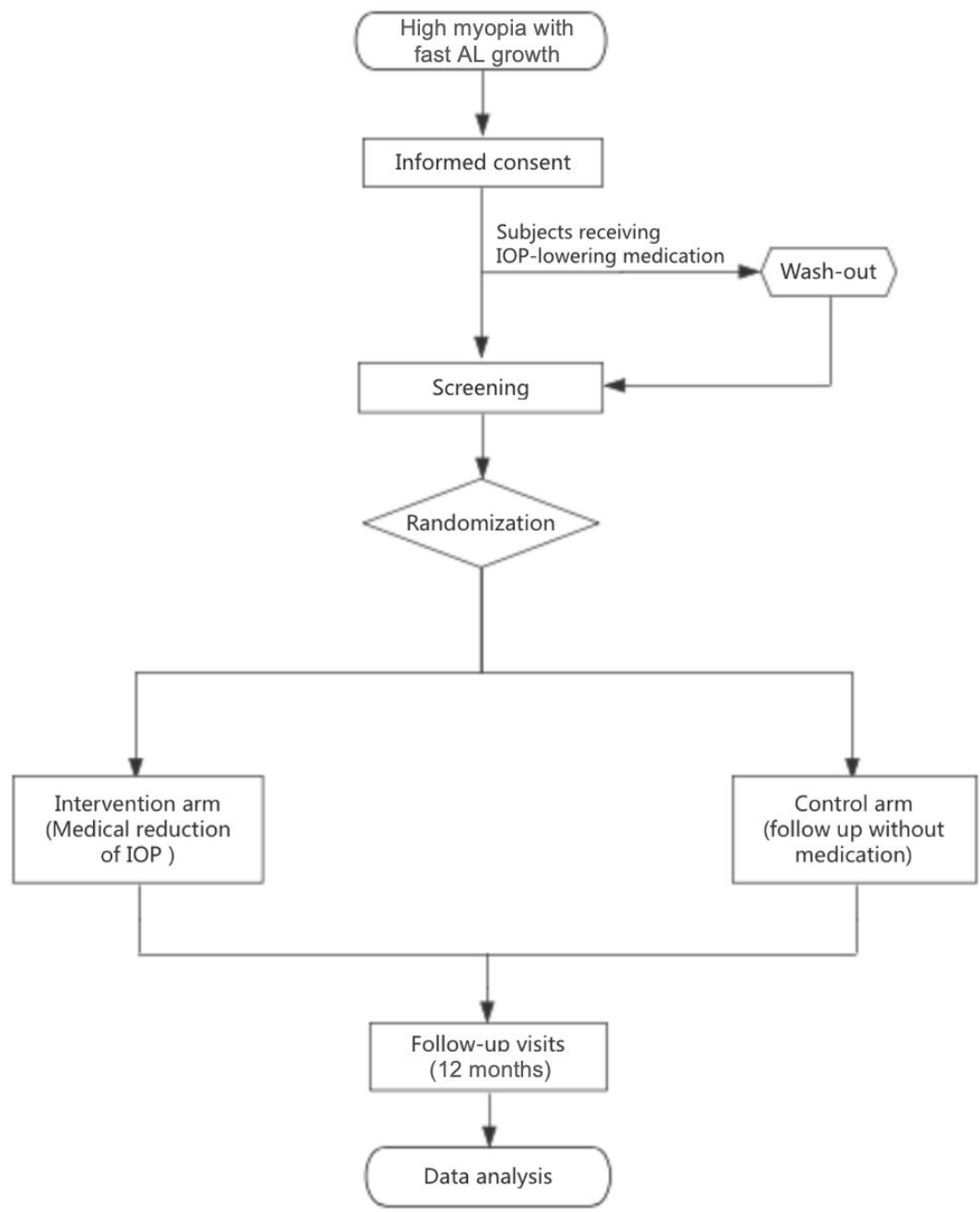
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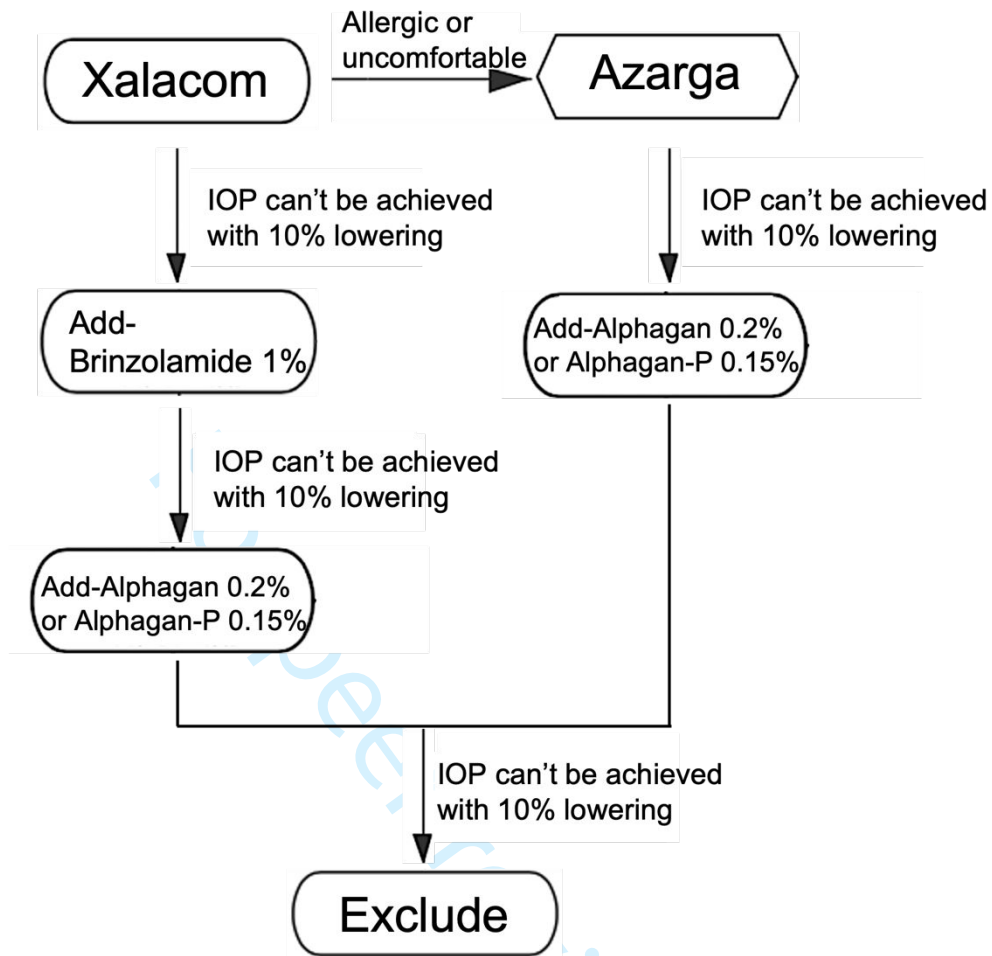
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Figure 1 Schematic of the PHM study design.



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647 **Figure 2** The schematic of the intervention design.

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660 **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
Slit 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

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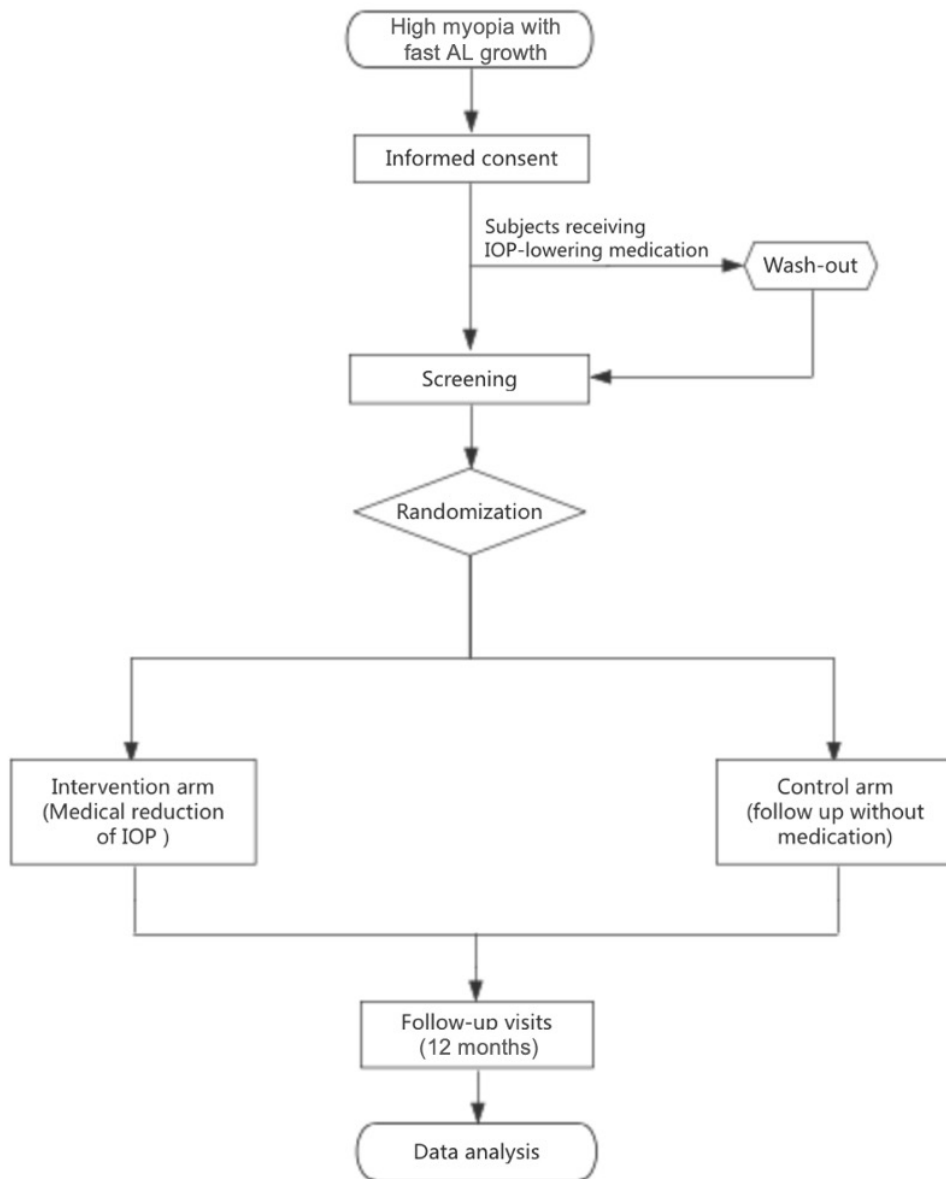


Figure 1

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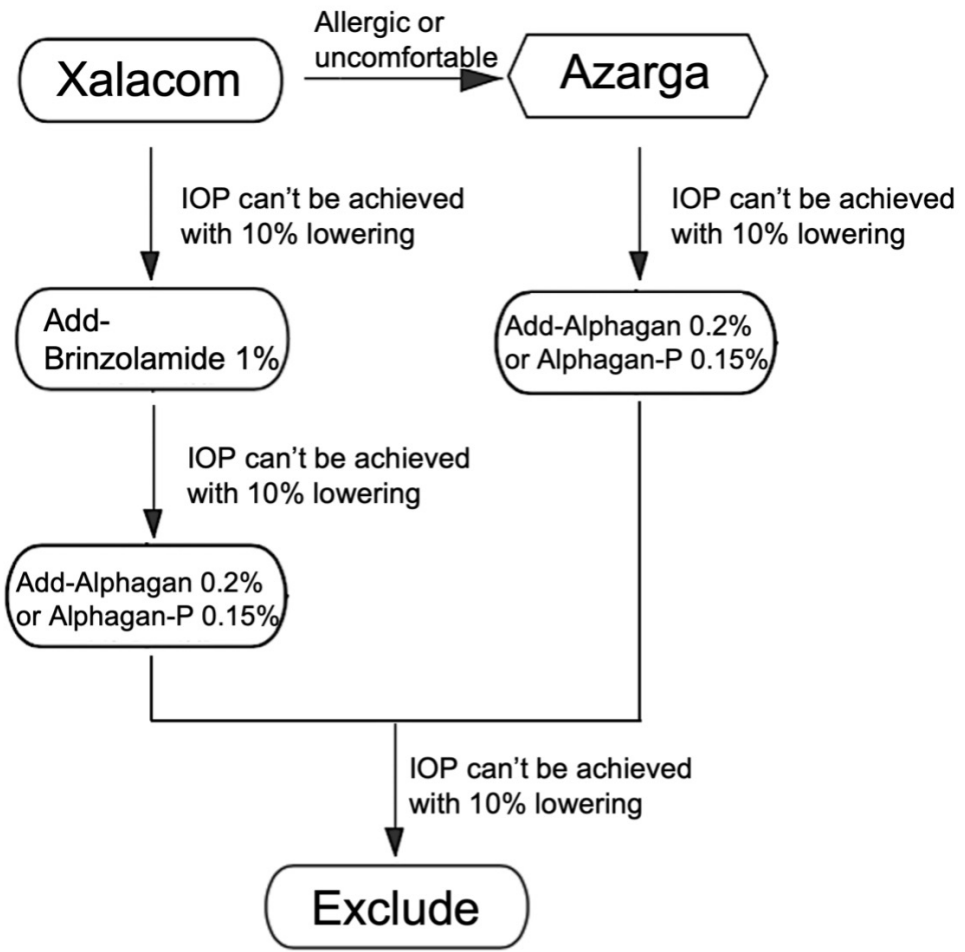


Figure 2

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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
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1			
2	Allocation	16b	Mechanism of implementing the allocation sequence (eg, central
3	concealment		telephone; sequentially numbered, opaque, sealed envelopes),
4	mechanism		describing any steps to conceal the sequence until interventions are
5			assigned
6			
7	Implementation	16c	Who will generate the allocation sequence, who will enrol participants,
8			and who will assign participants to interventions
9			
10	Blinding	17a	Who will be blinded after assignment to interventions (eg, trial
11	(masking)		participants, care providers, outcome assessors, data analysts), and
12			how
13		17b	If blinded, circumstances under which unblinding is permissible, and
14			procedure for revealing a participant's allocated intervention during
15			the trial
16			
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Methods: Data collection, management, and analysis

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21	Data collection	18a	Plans for assessment and collection of outcome, baseline, and other
22	methods		trial data, including any related processes to promote data quality (eg,
23			duplicate measurements, training of assessors) and a description of
24			study instruments (eg, questionnaires, laboratory tests) along with
25			their reliability and validity, if known. Reference to where data
26			collection forms can be found, if not in the protocol
27		18b	Plans to promote participant retention and complete follow-up,
28			including list of any outcome data to be collected for participants who
29			discontinue or deviate from intervention protocols
30			
31	Data	19	Plans for data entry, coding, security, and storage, including any
32	management		related processes to promote data quality (eg, double data entry;
33			range checks for data values). Reference to where details of data
34			management procedures can be found, if not in the protocol
35			
36	Statistical	20a	Statistical methods for analysing primary and secondary outcomes.
37	methods		Reference to where other details of the statistical analysis plan can be
38			found, if not in the protocol
39		20b	Methods for any additional analyses (eg, subgroup and adjusted
40			analyses)
41		20c	Definition of analysis population relating to protocol non-adherence
42			(eg, as randomised analysis), and any statistical methods to handle
43			missing data (eg, multiple imputation)
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Methods: Monitoring

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53	Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role
54			and reporting structure; statement of whether it is independent from
55			the sponsor and competing interests; and reference to where further
56			details about its charter can be found, if not in the protocol.
57			Alternatively, an explanation of why a DMC is not needed
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2		21b	Description of any interim analyses and stopping guidelines, including
3			who will have access to these interim results and make the final
4			decision to terminate the trial
5			
6	Harms	22	Plans for collecting, assessing, reporting, and managing solicited and
7			spontaneously reported adverse events and other unintended effects
8			of trial interventions or trial conduct
9			
10	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and
11			whether the process will be independent from investigators and the
12			sponsor
13			
14			

Ethics and dissemination

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16			
17	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval
18			
19			
20	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)
21			
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25			
26	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)
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29		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable
30			
31			
32	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
33			
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36			
37	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site
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40	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
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45	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
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48	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
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54		31b	Authorship eligibility guidelines and any intended use of professional writers
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57		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code
58			
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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.

For peer review only

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

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Primary Subject Heading:	Ophthalmology
Secondary Subject Heading:	Ophthalmology

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Keywords:	Randomized Controlled Trial, OPHTHALMOLOGY, Glaucoma < OPHTHALMOLOGY

SCHOLARONE™
Manuscripts

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4 1 **Effect of Intraocular Pressure Reduction on Progressive High**
5 **Myopia (PHM study): Study Protocol of a Randomized**
6 **Controlled Trial**
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12 5 Jingwen Jiang, MD^{1, *}, Tingting Lin, MD^{1, *}, Fengbin Lin, MD, PhD¹, Kangjie
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17 10 Glaucoma Suspects with High Myopia Study Group
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18 38 **Competing Interest Statement and Financial Disclosure:**

19
20 39 Jost B. Jonas: European patent EP 3,271,392, JP 2021-119187, and US 2021
21 0340237 A1: Agents for use in the therapeutic or prophylactic treatment of myopia
22 or hyperopia; European patent application 23196899.1 “EGFR Antagonists for the
23 treatment of diseases involving unwanted migration, proliferation, and metaplasia
24 of retinal pigment epithelium (RPE) cells”.

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26 44

27 45 **Ethics Statement:** The study was approved by the ethical committee of the
28 Zhongshan Ophthalmic Center and adhered to the tenets of the Declaration of
29 Helsinki. Written informed consent was obtained from all subjects.

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32 49 **Key Words:** High myopia, Axial length, Intraocular pressure, Randomized
33 controlled trial

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4 59 **ABSTRACT**

5
6 60 **Background** In adult patients with high myopia (HM), progressive axial elongation
7
8 61 poses a significant risk for the development of subsequent ocular complications that
9
10 62 may lead to visual impairment. Effective strategies to reduce or prevent further axial
11
12 63 elongation in highly myopic adult patients have not been available so far. Recent studies
13
14 64 suggested that medically lowering intraocular pressure (IOP) may reduce axial
15
16 65 elongation.

17
18 66 **Objective** This clinical randomized controlled trial (RCT) aims to evaluate the efficacy
19
20 67 of medical IOP reduction in adult patients with progressive HM (PHM).

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22 68 **Trial Design** Single-center, open-label, prospective RCT.

23
24 69 **Methods** This RCT will recruit 152 participants with PHM at the Zhongshan
25
26 70 Ophthalmic Center (ZOC). Randomized in a ratio of 1:1, participants will receive IOP-
27
28 71 lowering eyedrops (intervention group) or will be followed without treatment (control
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30 72 group) for 12 months. Follow-up visits will be conducted at 1, 6, and 12 months after
31
32 73 baseline. Only one eye per eligible participant will be included for analysis. The
33
34 74 primary outcome is the change in axial length (AL) within the study period of 12
35
36 75 months. Secondary outcomes include the incidence and progression of visual field (VF)
37
38 76 defects, changes in optic disc morphology and incidence and progression of myopic
39
40 77 maculopathy. Difference in AL changes between the two groups will be analyzed using
41
42 78 linear regression analysis. For the secondary outcomes, a multifactor Poisson
43
44 79 regression within a generalized linear model will be utilized to estimate the relative risk
45
46 80 of progression in VF defects and myopic maculopathy, and the rate of thinning in retinal
47
48 81 nerve fiber layer and ganglion cell-inner plexiform will be assessed through Kaplan-
49
50 82 Meier curves and log-rank tests.

51
52 83 **Ethics and dissemination** Full ethics approval for this trial has been obtained from the
53
54 84 Ethics Committee of ZOC, Sun Yat-sen University, China (ID: 2023KYPJ110). Results
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56 85 of this trial will be disseminated through peer-reviewed journals and conference
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58 86 presentations.

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4 87 **Trial registration number** NCT05850936 *clinicaltrials.gov*

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8 89 **Strengths and limitations of this study**

9
10 90 1. This study is to address a global healthcare concern: effectively mitigating
11 91 further axial elongation in highly myopic adult patients.

12
13
14 92 2. We performed this RCT based on an on-going highly myopic cohort.

15
16 93 3. Due to practical constraints, a double-masking in the study design cannot be
17 94 achieved.

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20 95 4. Participants are recruited from a single center.

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115 **Introduction**

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

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

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

136 Building upon these findings, we hypothesize that medically IOP-lowering may
137 slow axial elongation by potentially three pathways related to the sclera and choroid
138 [19]. We therefore aim to conduct a randomized controlled trial (RCT) to assess the
139 efficacy of medical IOP-lowering in managing axial elongation in patients with
140 progressive HM (PHM). Additionally, this study should generate data on the effects of
141 IOP-lowering treatment on the incidence and changes in the visual field (VF), changes
142 in the optic nerve head morphology and myopic maculopathy. The outcomes of the

1
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4 143 study may establish a basis for treatment recommendations for preventing axial
5
6 144 elongation of highly myopic eyes.

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8 145

9
10 146 **Methods and Analysis**

11
12 147 **Study design**

13
14 148 The PHM study is an open-label, single-center RCT. The study will be conducted at
15
16 149 the Zhongshan Ophthalmic Center (ZOC), Sun Yat-Sen University, a tertiary
17
18 150 specialized hospital in Guangzhou, China. All examinations and interventions will be
19
20 151 carried out in the Clinical Research Center at ZOC. This study does not permit blinding
21
22 152 and is therefore designed as an open-label trial. **Figure 1** summarizes the design of the
23
24 153 PHM study.

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27
28 155 **Objective**

29
30 156 The primary aim of this trial is to evaluate the effectiveness of medically IOP-lowering
31
32 157 therapy in managing axial elongation in patients with PHM over a 12-month
33
34 158 observation period. Additionally, the trial will assess alterations in VF, optic disc
35
36 159 morphology, thickness of the retinal nerve fiber layer (RNFL) and retinal ganglion cell-
37
38 160 inner plexiform layer (GC-IPL), and the occurrence or advancement of myopic
39
40 161 maculopathy.

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43
44 163 **Recruitment**

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46 164 *Inclusion criteria*

- 47
48 165 1. Age ≥ 18 years and ≤ 65 years.
49
50 166 2. Diagnosed with HM [20-21]: spherical equivalent ≤ -6.00 diopters or AL ≥ 26.5 mm.
51
52 167 3. Diagnosed with PHM: axial elongation ≥ 0.05 mm in the past 6 months or ≥ 0.1 mm
53
54 168 in the past 12 months.
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4 169 4. IOP: ≥ 10 mmHg and ≤ 21 mmHg on at least 2 visits using Goldmann applanation
5
6 170 tonometry with correction for the dependence of the IOP-reading on corneal thickness
7
8 171 [22].

9
10 172 5. Best corrected visual acuity (BCVA) $\geq 6/12$, ability to undergo AL measurement,
11
12 173 fundus photography, optical coherence tomography (OCT), and complete VF
13
14 174 examination.

15
16 175

17
18 176 *Exclusion criteria*

19
20 177 1. Patients who have been using IOP-lowering medications within the last year.

21
22 178 2. Allergy to any kind of IOP-lowering eyedrops.

23
24 179 3. Presence of serious fundus pathologies like proliferative diabetic retinopathy, retinal
25
26 180 detachment, central retinal artery occlusion, etc.

27
28 181 4. Presence of chronic, recurrent, or severe ocular inflammatory lesions such as chronic
29
30 182 or recurrent uveitis.

31
32 183 5. Significant corneal or iris lesions, severe cataract affecting fundus examination, or
33
34 184 patients with only one eye.

35
36 185 6. Intraocular surgery or laser treatment within the last year, such as cataract surgery.

37
38 186 7. With a history of previous refractive surgery or prior treatment for myopia-related
39
40 187 conditions (e.g., orthokeratology lens wear, low-intensity red light therapy, or low-
41
42 188 concentration atropine treatment).

43
44 189 8. Presence of other serious systemic diseases (e.g., hypertension, heart disease,
45
46 190 diabetes, rheumatic immune system disease) that hinder long-term follow-up and eye
47
48 191 treatment.

49
50 192 9. Pregnancy, lactation, or plans to have children during the follow-up period.

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53
54 194 In this study, only one eye per eligible participant will be included. If both eyes meet
55
56 195 the inclusion criteria, the eye with a higher rate of axial elongation, a worse mean
57
58 196 perimetric deviation (MD) value, and a worse BCVA will be selected.

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4 1975 198 **Randomisation and blinding**

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7
8 199 In this trial, randomisation will be employed to mitigate distribution bias. After
9
10 200 confirming all inclusion and exclusion criteria and obtaining signed written informed
11
12 201 consent forms, qualified individuals within each block, with a block size of 4, will be
13
14 202 assigned in an even (1:1) manner to either the intervention group or the control group.
15
16 203 The random sequence will be generated using an electronic data collection (EDC)
17
18 204 system to ensure unbiased allocation.

19
20 205 In this trial, the participants and physicians will not be blinded to the intervention
21
22 206 assignment. The technicians conducting the examinations and interpreting the images
23
24 207 will be unaware of the participants' group assignments during the screening and follow-
25
26 208 up stages. The researchers analyzing the data will also be unaware of the information
27
28 209 regarding randomisation.

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30 21031
32 211 **Interventions**33
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36 213 *Intervention group*

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38 214 Participants assigned to the intervention group will receive medical IOP-lowering
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40 215 therapy for a duration of 12 months or until they reach the endpoint. Only the study
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42 216 eye will receive medication in the enrolled participants. The preferred medication for
43
44 217 reducing IOP is Xalacom[®] eye drop (Pfizer Inc., New York, NY, USA), a fixed
45
46 218 latanoprost and timolol combination.

47
48 219 The treatment protocol will involve the instillation of a single drop of
49
50 220 prostaglandin ophthalmic solution in the study eye once daily in the evening for
51
52 221 medications such as Xalacom. To ensure the standardisation of medication usage
53
54 222 among participants, subjects will be provided with medication logbooks, which will
55
56 223 be collected and recorded by the investigators during the study visits.

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4 225 *Control group*

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6 226 Participants assigned to the control group will be followed up for 12 months or until
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8 227 they reach the endpoint without medical IOP-lowering therapy.
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12 229 **Outcome measures**

13
14 230 *Primary outcome*

15
16 231 The primary outcome is the change of AL at 12-month from baseline measured by
17
18 232 IOLMaster.
19

20 233

21
22 234 *Secondary outcomes*

23
24 235 1. Incidence and progression of VF defects at 12 months from baseline based on
25
26 236 Humphrey 24-2 standard VF. Under the premise of reliable VF examination,
27
28 237 compared to the baseline, two consecutive perimetric examinations reveal the
29
30 238 incidence of VF defects or significant perimetric progression in at least three points at
31
32 239 a significance level of $p < 0.05$. Furthermore, two subsequent diagnostic VF
33
34 240 examinations conducted within one month also confirm the progression at the
35
36 241 locations. The time of progression is defined as the time of the initial diagnostic VF
37
38 242 examination [23-24].
39

40 243 2. Changes in optic disc morphology (including thinning of RNFL and GC-IPL) at
41
42 244 12-month from baseline based on fundus photography and OCT [25-27].
43

44 245 3. Incidence and progression of myopic maculopathy at 12 months from baseline based
45
46 246 on fundus photography and OCT. The determination of incidence and progression of
47
48 247 myopic maculopathy is based on the META-PM classification system [28-29].
49

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52 249 **Study assessments**

53
54 250 *Visual acuity*

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56 251 Visual acuity assessment will be conducted prior to any procedures that may potentially
57
58 252 impact vision, such as pupil dilation or VF examination. The measurement of visual
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4 253 acuity will be performed using an ETDRS (Early Treatment of Diabetic Retinopathy
5
6 254 Study) LogMAR chart (Precision Vision, Villa Park, Illinois, USA) under standard
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8 255 illumination conditions at 4 meters [30]. For BCVA, a trial frame will be positioned
9
10 256 and adjusted on the participant's face based on auto refractometric readings and
11
12 257 subsequent subjective refinement.

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14 258

15
16 259 *Refractometry*

17
18 260 Following pupil dilation using 0.25% compound tropicamide (Zhuobian@; Sinqi,
19
20 261 China), three measurements will be taken for each eye using an auto refractometer
21
22 262 (KR800, TOPCON, Tokyo, Japan). The average values for spherical refractive error,
23
24 263 cylindrical refractive error, and astigmatic axis will be recorded for further analysis and
25
26 264 documentation.

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28 265

29
30 266 *Slit-lamp biomicroscopy*

31
32 267 The evaluation of the anterior segment with the pupil undilated will be performed using
33
34 268 a slit lamp (BQ-900, Haag Streit, Koeniz, Switzerland). After medical pupillary dilation,
35
36 269 a slit lamp-based grading of lens opacities is conducted and using a 90D indirect
37
38 270 ophthalmoscopic lens (Ocular 90D Slit Lamp Lenses, Ocular, Washington, DC, USA),
39
40 271 the optic disc, macula, and peripheral retina will be examined.

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44 273 *Tonometry*

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46 274 IOP measurements will be performed by Goldmann applanation tonometry (AT900,
47
48 275 Haag Streit, Koeniz, Switzerland). Prior to enrollment, all participants will undergo
49
50 276 three baseline IOP readings during specific time intervals: 9 am to 10 am, 1 pm to 2
51
52 277 pm, and 4 pm to 5 pm. During follow-up visits, tonometry will be conducted between
53
54 278 9 am and 11 am. Results from three consecutive measurements will be documented
55
56 279 during each visit, and the mean value of these measurements will be utilized for
57
58 280 assessment purposes.

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6 282 *AL measurement*

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8 283 AL measurement will be performed using the IOLMaster (IOLmaster 700, Carl Zeiss
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10 284 Meditec, Jena, Germany). Results from five consecutive measurements will be
11
12 285 documented during each visit, and the mean value of these measurements will be
13
14 286 utilized for further analysis.

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16 287

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18 288 *Central corneal thickness (CCT) measurement*

19
20 289 CCT measurement will be performed with IOLMaster (IOLmaster 700, Carl Zeiss
21
22 290 Meditec, Jena, Germany). Results from five consecutive measurements will be
23
24 291 documented during each visit, and the mean value of these measurements will be taken
25
26 292 for further analysis.

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28 293

29
30 294 *Perimetry*

31
32 295 The perimetric examination will be performed applying the Humphrey Field Analyzer
33
34 296 Mark 3 (Carl Zeiss Meditec, Dublin, CA, USA) and the Swedish Interactive Threshold
35
36 297 Algorithm Standard (SITA) 24-2 program. A reliable VF report is defined as having
37
38 298 false-positive and false-negative errors below 15%, as well as fixation losses below
39
40 299 20%.

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44 301 *Fundus photography*

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46 302 Using fundus cameras (KOWA, Nonmyd, WX3D, Nagoya, Japan; TRC-NW400,
47
48 303 TOPCON, Tokyo, Japan), two fundus images centered on the optic disc will be taken
49
50 304 for each eye under both standardized stereoscopic and non-standardized conditions.
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52 305 Additionally, a single image focused on the macula will be obtained after pupil dilation.

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56 307 *OCT examination*

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4 308 All participants will undergo a series of standardized swept-source OCT examinations
5
6 309 using the DRI-OCT Triton model (TOPCON, Tokyo, Japan), focusing on the optic disc
7
8 310 and macula. To ensure the reliability and accuracy of the results, a minimum image
9
10 311 quality score of 60 will be set. In addition to the swept-source OCT, a spectral domain
11
12 312 OCT examination will be conducted to obtain measurements of the peripapillary RNFL
13
14 313 and the macular GC-IPL.

15
16 314

17
18 315 *Pregnancy test*

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20 316 A urine pregnancy test will be performed for women of reproductive age during their
21
22 317 initial visit.

23
24 318

25
26 319 *Anthropometry and blood pressure*

27
28 320 Participants' height and weight measurements will be measured using a free-standing
29
30 321 height rod and a calibrated scale (RGZ120, Jiangsu Wujin Weighing Apparatus Factory,
31
32 322 Jiangsu, China). During the baseline visit, blood pressure readings will be obtained
33
34 323 from the participant's left arm while they are seated and have rested for a minimum of
35
36 324 five minutes with the Omron M7 Blood Pressure Monitor (Matsusaka, Mie, Japan).

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40 326 **Visit schedule**

41
42 327 **Table 1** summarizes the visit schedule for the enrolment, interventions, and
43
44 328 assessments of this trial.

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48 330 **Sample size**

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50 331 The sample size calculation for this study is determined based on the primary outcome
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52 332 and the study hypothesis, taking into account relevant findings from previous studies.

53
54 333 The objective of this study is to evaluate the potential of IOP-lowering therapy to reduce
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56 334 axial elongation during a study period of one year growth in eyes with PHM. It is
57
58 335 hypothesized that the intervention group receiving IOP-lowering therapy will exhibit a
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4 336 70% reduction in axial elongation compared to the control group. The control group is
5
6 337 estimated to experience a 0.1 mm axial elongation over 12 months, while the
7
8 338 intervention group is expected to have a mean axial elongation of 0.03 mm. The
9
10 339 common standard deviation is estimated to be 0.14 mm. To achieve a statistical power
11
12 340 of 80% with a two-sided significance level of 0.05, a total of 64 individuals per group
13
14 341 is required. Accounting for an estimated 15% loss to follow-up at the 12-months mark,
15
16 342 the final sample size is determined to be 76 individuals per group, resulting in a total
17
18 343 of 152 participants. The sample size calculation was performed using PASS 16.0
19
20 344 software (NCSS, LLC, Kaysville, UT, USA).

21
22 345

23 24 346 **Statistical analysis**

25
26 347 Statistical analysis will be conducted using Stata 16.0 software (StataCorp, College
27
28 348 Station, TX, USA). A two-sided P-value of less than 0.05 will be considered
29
30 349 statistically significant, and a 95% confidence interval will be used for parameter
31
32 350 estimation.

33
34 351 For the intention-to-treat (ITT) analysis, missing data will be addressed using the
35
36 352 multiple imputation method. No simulation will be performed for missing data in the
37
38 353 safety evaluation. Dropout rates in the two groups will be compared using chi-squared
39
40 354 tests or Fisher's exact tests. Descriptive statistics will be reported as mean and standard
41
42 355 deviation for normally distributed continuous data, and as median and interquartile
43
44 356 range for non-normally distributed continuous data. Frequency and percentage will be
45
46 357 provided for categorical data. Baseline data, including demographic and clinical
47
48 358 characteristics, will be analyzed using independent samples t-tests and Wilcoxon rank-
49
50 359 sum tests for continuous data, and chi-squared or Fisher's exact tests for categorical
51
52 360 variables.

53
54 361 The analysis of primary and secondary outcomes will follow the ITT principle,
55
56 362 including all participants. For the primary outcome, the difference in axial elongation
57
58 363 between the two groups will be analyzed using linear regression analysis. As for the
59
60

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2
3
4 364 secondary outcomes, a multifactor Poisson regression within a generalized linear model
5
6 365 will be utilized to estimate the relative risk of progression in perimetric defects and
7
8 366 myopic maculopathy. Additionally, the rate of thinning of the RNFL and the GC-IPL
9
10 367 will be assessed through log-rank tests.

11 368 Safety analysis will be performed in participants belonging to the intervention
12
13
14 369 group, comparing adverse event occurrence between the two groups using the chi-
15
16 370 squared test or Fisher's exact test.

17
18 371 The missing data will be handled using the Multiple Imputations method. With the
19
20 372 multiple imputation approach, 20 replicas of the dataset will be generated, where
21
22 373 missing values are imputed through chained equations. The final results will be
23
24 374 obtained by averaging these 20 datasets using Rubin's rules.

25
26 375

27 28 376 **Data monitoring**

29
30 377 (1) The Data Monitoring Committee (DMC) will closely monitor the data throughout
31
32 378 the trial using the EDC system to ensure the reliability and integrity of the collected
33
34 379 data. The DMC members are independent individuals who are not affiliated with the
35
36 380 researchers or sponsors, ensuring an impartial assessment. There is no conflict of
37
38 381 interest between the researchers and sponsors, further guaranteeing the transparency
39
40 382 and objectivity of the data monitoring process.

41
42 383 (2) Interim analysis: The study does not include provisions for conducting an interim
43
44 384 analysis.

45
46 385

47 48 386 **Data management**

49
50 387 The collected data will be meticulously recorded and entered into the EDC system. The
51
52 388 EDC system is securely hosted on a password-protected network server, ensuring
53
54 389 digital protection. Only the principal investigators and authorized study team members
55
56 390 will have access to the research data. To ensure confidentiality and integrity, all source
57
58 391 documents will be stored in locked file cabinets with restricted access. Prior to data
59
60

1
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3
4 392 collection, all researchers will undergo comprehensive training. The raw data will be
5
6 393 monitored by an independent data and safety monitoring committee. In the event of
7
8 394 queries or uncertainties in the case report form, the data administrator will generate a
9
10 395 data queue request (DRQ) and communicate the query to the researcher through the
11
12 396 clinical monitoring system. The researcher is expected to provide a prompt response to
13
14 397 the data administrator. If necessary, data modifications, confirmations, and entries will
15
16 398 be made, and a new DRQ will be issued.

17
18 399

400 **Drug packaging, management, dispensing and storage**

401 *Drug packaging*

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

408

409 *Drug management*

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

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

1
2
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4 419 4. Maintaining a comprehensive record of drug inventory throughout the study and
5
6 420 providing inventory logs.

7
8 421 5. Maintaining a detailed catalog of the drugs, including information on received
9
10 422 materials, dispensing dates, and records of drugs provided to participants.

11
12 423 6. Ensuring that the drug dispensing records match the usage and unused drugs and
13
14 424 providing explanations for any discrepancies. Relevant dispensing and return forms
15
16 425 must be signed by the medication administrator.

17
18 426

19
20 427 *Drug dispensing*

21
22 428 After randomisation, the medication administrator will dispense the corresponding
23
24 429 investigational drugs to the participants based on the randomized assignment and
25
26 430 document the drug dispensing.

27
28 431

29
30 432 *Drug storage*

31
32 433 Unopened medications should be stored according to the instructions provided in the
33
34 434 drug package insert. For drugs that require refrigeration between 2-8°C, the medication
35
36 435 administrator needs to monitor the temperature and humidity daily and document the
37
38 436 storage conditions. The research drugs should not be provided to anyone other than the
39
40 437 participants in the study. Access to the research drugs is limited to personnel authorized
41
42 438 by the principal investigator to dispense them. After opening, medications should be
43
44 439 stored according to the instructions provided in the drug package insert and must be
45
46 440 used within four weeks of opening the drug package.

47
48 441

49
50 442 **Safety assessments**

51
52 443 The safety assessments included in this study are as follows:

53
54 444 1. Medication-related safety assessment: The ocular hypotensive medications used in
55
56 445 this study are known to have rare occurrences of local and systemic adverse reactions,
57
58 446 such as ocular surface irritation, eyelid pigmentation, eyelash growth, and drug
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4 447 allergies. These assessments will be conducted and recorded by the investigators
5
6 448 during the study visits using slit lamp examination.

7
8 449 2. High myopia-related safety assessment: This study focuses on individuals with high
9
10 450 myopia, and during the natural course of high myopia, retinal pathologies can occur.
11
12 451 The investigators will assess and record the complications associated with high myopia
13
14 452 based on the examination results during the study visits.
15

16 453

17 18 454 **Report and management of adverse events**

19
20 455 An adverse event refers to any negative medical occurrence experienced by a
21
22 456 participant in the study, regardless of its relation to the treatment. Utmost attention will
23
24 457 be given to identifying potential adverse events or unfavorable findings. The primary
25
26 458 concern is the safety of the participant, and appropriate medical intervention will be
27
28 459 provided in case of an adverse event. All adverse events, whether reported voluntarily
29
30 460 by the participant or discovered through questioning, physical examination, or other
31
32 461 means by the study staff, will be promptly recorded on an online adverse event form
33
34 462 The Safety Supervision Committee will review each form to determine the appropriate
35
36 463 coding and reporting procedures.

37
38 464 Serious adverse events, regardless of their connection to the study drug, must be
39
40 465 reported within 24 hours to the Institutional Review Board (IRB), the DMC, and the
41
42 466 Clinical Research Center. Additionally, a faxed report must be sent to the Drug
43
44 467 Administration's drug registration office. The original and fax confirmation forms for
45
46 468 serious adverse events should be retained in the research center along with the case
47
48 469 report form.

49
50 470

51 52 471 **Discussion**

53
54 472 This trial is designed to evaluate the effect of intraocular pressure reduction on
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56 473 progressive high myopia. Due to the limited research on the use of IOP reduction
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58 474 medications in highly myopic eyes, the design of this study is based on a retrospective
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4 475 analysis of a large cohort of highly myopic individuals. It is found that the use of IOP
5
6 476 reduction medications slowed down axial elongation in approximately 70% of highly
7
8 477 myopic eyes. Therefore, we performed sample size calculations based on these findings.
9

10 478

11
12 479 **Study progress**

13
14 480 The recruitment period of this study has started in June 2023 in ZOC. As of February
15
16 481 2024, we have included 73 participants.
17

18 482

19
20 483 **Acknowledgement:** We thank all the members of the Glaucoma Suspects with High
21
22 484 Myopia Study Group (GSHM) Study Group for conducting this trial. And also, we
23
24 485 thank all staff in clinical research center of ZOC for their effort in this study.
25

26 486

27
28 487 ***GSHM study group***

29
30 488 Principal investigators:

31
32 489 Xiulan Zhang, Yizhi Liu, Lin Lv, David Friedman, Jost B. Jonas, and Tin Aung.
33

34 490 Members:

35
36 491 Shida Chen, Wei Wang, Fengbin Lin, Yunhe Song, Peiyuan Wang, Kangjie Kong,
37
38 492 Jingwen Jiang, Fei Li, Kai Gao, Bingqian Liu, Yuhong Liu, and Meiling Chen.
39

40 493 Steering committee:

41
42 494 Neil M. Bressler, Ki Ho Park, Mingguang He, Kyoko Ohno-Matsui, Dennis S.C. Lam,
43
44 495 and Robert N. Weinreb.
45

46 496 Data monitoring committee:

47
48 497 Ching-Yu Cheng, Paul Healey, and Linda M. Zangwill.
49

50 498 Safety supervision committee:

51
52 499 Xiang Chen and Guangxian Tang.
53

54 500 Biostatistics and data monitoring center:

55
56 501 Ling Jin.
57

58 502
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5
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9
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11
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15
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17

18 510

19
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21
22 512 FL wrote the primary protocol manuscript. XZ, FZ, DSL and JBJ revised the
23
24 513 manuscript. KK, PW and YS contributed to data collecting. LJ and WZ helped with
25
26 514 sample size calculation and were the statistical consultants. YL, JC and MC were
27
28 515 clinical research coordinators of the project.
29

30 516

31
32 517 **Competing interest:** Jost B. Jonas: European patent EP 3,271,392, JP 2021-
33
34 518 119187, and US 2021 0340237 A1: Agents for use in the therapeutic or
35
36 519 prophylactic treatment of myopia or hyperopia; European patent application
37
38 520 23196899.1 “EGFR Antagonists for the treatment of diseases involving unwanted
39
40 521 migration, proliferation, and metaplasia of retinal pigment epithelium (RPE)
41
42 522 cells”.
43

44 523

45
46 524 **Patient and public involvement:** Patients and/or the public were not involved in the
47
48 525 design, or conduct, or reporting, or dissemination plans of this research.
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51
52 527 **Patient consent for publication:** Not applicable
53

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56 529 **Protocol Version:** 5.0
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Figure 1 Diagram of the PHM study design.

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For peer review only

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665 **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
Slit 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

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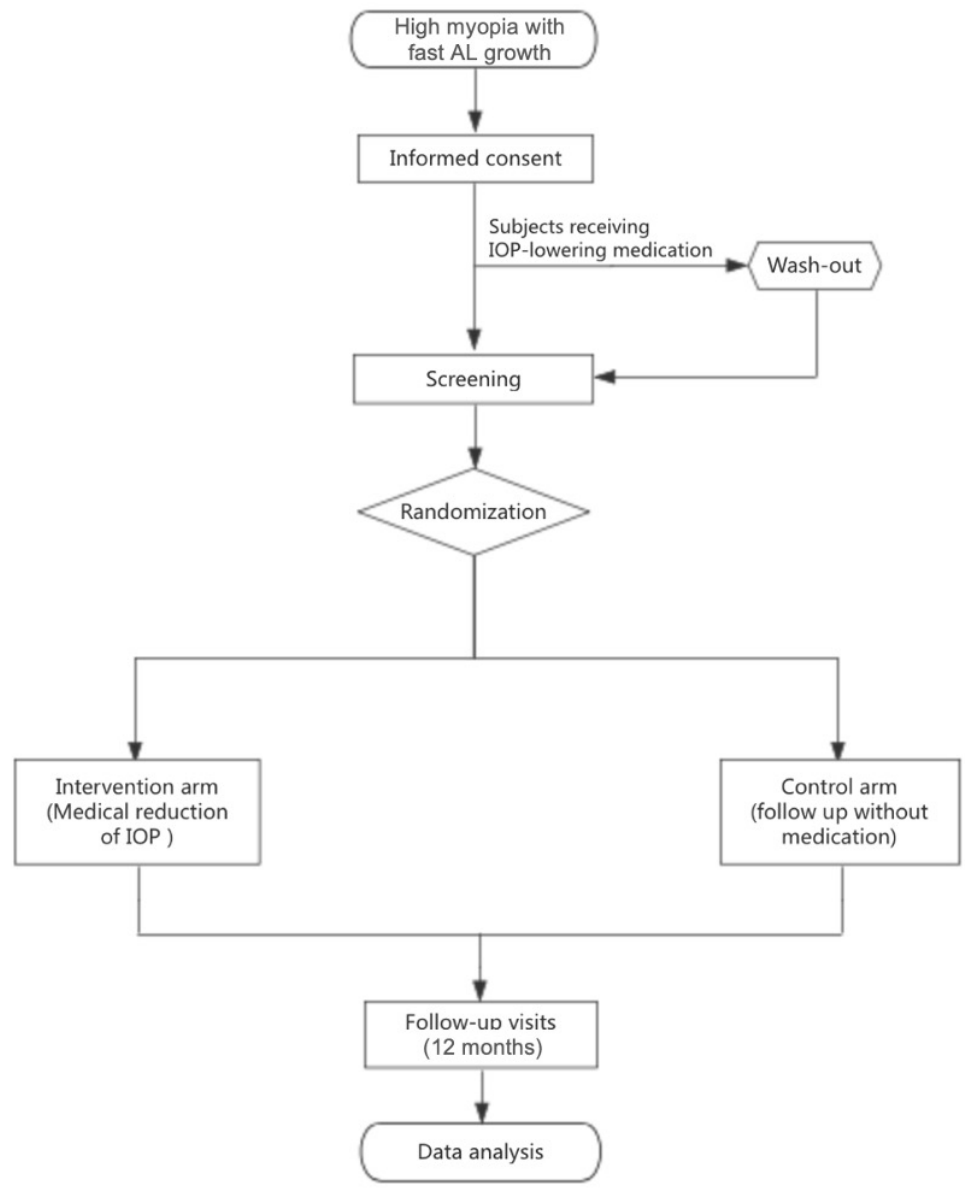


Figure 1

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)

1
2 Trial design 8 Description of trial design including type of trial (eg, parallel group,
3 crossover, factorial, single group), allocation ratio, and framework (eg,
4 superiority, equivalence, noninferiority, exploratory) (P3 L68)
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6
7

8 **Methods: Participants, interventions, and outcomes**

9
10 Study setting 9 Description of study settings (eg, community clinic, academic hospital)
11 and list of countries where data will be collected. Reference to where
12 list of study sites can be obtained (P3 L69-70)
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14 Eligibility criteria 10 Inclusion and exclusion criteria for participants. If applicable, eligibility
15 criteria for study centres and individuals who will perform the
16 interventions (eg, surgeons, psychotherapists) (P3 L69-70)
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19 Interventions 11a Interventions for each group with sufficient detail to allow replication,
20 including how and when they will be administered (P3 L70-72)
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22 11b Criteria for discontinuing or modifying allocated interventions for a
23 given trial participant (eg, drug dose change in response to harms,
24 participant request, or improving/worsening disease)
25

26 11c Strategies to improve adherence to intervention protocols, and any
27 procedures for monitoring adherence (eg, drug tablet return,
28 laboratory tests)
29
30

31 11d Relevant concomitant care and interventions that are permitted or
32 prohibited during the trial
33

34 Outcomes 12 Primary, secondary, and other outcomes, including the specific
35 measurement variable (eg, systolic blood pressure), analysis metric
36 (eg, change from baseline, final value, time to event), method of
37 aggregation (eg, median, proportion), and time point for each
38 outcome. Explanation of the clinical relevance of chosen efficacy and
39 harm outcomes is strongly recommended (P3 L73-77)
40
41

42 Participant 13 Time schedule of enrolment, interventions (including any run-ins and
43 timeline washouts), assessments, and visits for participants. A schematic
44 diagram is highly recommended (see Figure) (P25)
45

46 Sample size 14 Estimated number of participants needed to achieve study objectives
47 and how it was determined, including clinical and statistical
48 assumptions supporting any sample size calculations (P3 L69)
49
50

51 Recruitment 15 Strategies for achieving adequate participant enrolment to reach
52 target sample size (P3 L69)
53

54 **Methods: Assignment of interventions (for controlled trials)**

55 Allocation:
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1			
2	Sequence	16a	Method of generating the allocation sequence (eg, computer-
3	generation		generated random numbers), and list of any factors for stratification.
4			To reduce predictability of a random sequence, details of any planned
5			restriction (eg, blocking) should be provided in a separate document
6			that is unavailable to those who enrol participants or assign
7			interventions (P8 L198-209)
8			
9			
10	Allocation	16b	Mechanism of implementing the allocation sequence (eg, central
11	concealment		telephone; sequentially numbered, opaque, sealed envelopes),
12	mechanism		describing any steps to conceal the sequence until interventions are
13			assigned
14			
15	Implementation	16c	Who will generate the allocation sequence, who will enrol participants,
16			and who will assign participants to interventions
17			
18	Blinding	17a	Who will be blinded after assignment to interventions (eg, trial
19	(masking)		participants, care providers, outcome assessors, data analysts), and
20			how (P8 L198-209)
21			
22			
23		17b	If blinded, circumstances under which unblinding is permissible, and
24			procedure for revealing a participant's allocated intervention during
25			the trial
26			
27			

Methods: Data collection, management, and analysis

28			
29			
30	Data collection	18a	Plans for assessment and collection of outcome, baseline, and other
31	methods		trial data, including any related processes to promote data quality (eg,
32			duplicate measurements, training of assessors) and a description of
33			study instruments (eg, questionnaires, laboratory tests) along with
34			their reliability and validity, if known. Reference to where data
35			collection forms can be found, if not in the protocol (P10-P13 L271-
36			346)
37			
38			
39		18b	Plans to promote participant retention and complete follow-up,
40			including list of any outcome data to be collected for participants who
41			discontinue or deviate from intervention protocols
42			
43	Data	19	Plans for data entry, coding, security, and storage, including any
44	management		related processes to promote data quality (eg, double data entry;
45			range checks for data values). Reference to where details of data
46			management procedures can be found, if not in the protocol (P15
47			L408-240)
48			
49			
50	Statistical	20a	Statistical methods for analysing primary and secondary outcomes.
51	methods		Reference to where other details of the statistical analysis plan can be
52			found, if not in the protocol(P14 L368-396)
53			
54			
55		20b	Methods for any additional analyses (eg, subgroup and adjusted
56			analyses)
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- 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)

8 **Methods: Monitoring**

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- 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](#))

30 **Ethics and dissemination**

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- 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

1			
2	Ancillary and	30	Provisions, if any, for ancillary and post-trial care, and for
3	post-trial care		compensation to those who suffer harm from trial participation
4			
5	Dissemination	31a	Plans for investigators and sponsor to communicate trial results to
6	policy		participants, healthcare professionals, the public, and other relevant
7			groups (eg, via publication, reporting in results databases, or other
8			data sharing arrangements), including any publication restrictions(P3
9			L83-86)
10			
11		31b	Authorship eligibility guidelines and any intended use of professional
12			writers
13			
14		31c	Plans, if any, for granting public access to the full protocol, participant-
15			level dataset, and statistical code
16			
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19	Appendices		
20			
21	Informed consent	32	Model consent form and other related documentation given to
22	materials		participants and authorised surrogates(P8 L200)
23			
24	Biological	33	Plans for collection, laboratory evaluation, and storage of biological
25	specimens		specimens for genetic or molecular analysis in the current trial and for
26			future use in ancillary studies, if applicable
27			

*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

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Primary Subject Heading:	Ophthalmology
Secondary Subject Heading:	Ophthalmology

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Keywords:	Randomized Controlled Trial, OPHTHALMOLOGY, Glaucoma < OPHTHALMOLOGY

SCHOLARONE™
Manuscripts

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4 1 **Effect of Intraocular Pressure Reduction on Progressive High**
5 **Myopia (PHM study): Study Protocol of a Randomized**
6 **Controlled Trial**
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12 5 Jingwen Jiang, MD^{1, *}, Tingting Lin, MD^{1, *}, Fengbin Lin, MD, PhD¹, Kangjie
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15 37

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18 38 **Competing Interest Statement and Financial Disclosure:**

19
20 39 Jost B. Jonas: European patent EP 3,271,392, JP 2021-119187, and US 2021
21 0340237 A1: Agents for use in the therapeutic or prophylactic treatment of myopia
22 or hyperopia; European patent application 23196899.1 “EGFR Antagonists for the
23 treatment of diseases involving unwanted migration, proliferation, and metaplasia
24 of retinal pigment epithelium (RPE) cells”.

25
26 44

27 45 **Ethics Statement:** The study was approved by the ethical committee of the
28 Zhongshan Ophthalmic Center and adhered to the tenets of the Declaration of
29 Helsinki. Written informed consent was obtained from all subjects.

30
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32 49 **Key Words:** High myopia, Axial length, Intraocular pressure, Randomized
33 controlled trial

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4 59 **ABSTRACT**

5
6 60 **Background** In adult patients with high myopia (HM), progressive axial elongation
7
8 61 poses a significant risk for the development of subsequent ocular complications that
9
10 62 may lead to visual impairment. Effective strategies to reduce or prevent further axial
11
12 63 elongation in highly myopic adult patients have not been available so far. Recent studies
13
14 64 suggested that medically lowering intraocular pressure (IOP) may reduce axial
15
16 65 elongation.

17
18 66 **Objective** This clinical randomized controlled trial (RCT) aims to evaluate the efficacy
19
20 67 of medical IOP reduction in adult patients with progressive HM (PHM).

21
22 68 **Trial Design** Single-center, open-label, prospective RCT.

23
24 69 **Methods** This RCT will recruit 152 participants with PHM at the Zhongshan
25
26 70 Ophthalmic Center (ZOC). Randomized in a ratio of 1:1, participants will receive IOP-
27
28 71 lowering eyedrops (intervention group) or will be followed without treatment (control
29
30 72 group) for 12 months. Follow-up visits will be conducted at 1, 6, and 12 months after
31
32 73 baseline. Only one eye per eligible participant will be included for analysis. The
33
34 74 primary outcome is the change in axial length (AL) within the study period of 12
35
36 75 months. Secondary outcomes include the incidence and progression of visual field (VF)
37
38 76 defects, changes in optic disc morphology and incidence and progression of myopic
39
40 77 maculopathy. Difference in AL changes between the two groups will be analyzed using
41
42 78 linear regression analysis. For the secondary outcomes, a multifactor Poisson
43
44 79 regression within a generalized linear model will be utilized to estimate the relative risk
45
46 80 of progression in VF defects and myopic maculopathy, and the rate of thinning in retinal
47
48 81 nerve fiber layer and ganglion cell-inner plexiform will be assessed through Kaplan-
49
50 82 Meier curves and log-rank tests.

51
52 83 **Ethics and dissemination** Full ethics approval for this trial has been obtained from the
53
54 84 Ethics Committee of ZOC, Sun Yat-sen University, China (ID: 2023KYPJ110). Results
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56 85 of this trial will be disseminated through peer-reviewed journals and conference
57
58 86 presentations.

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4 87 **Trial registration number** NCT05850936 *clinicaltrials.gov*

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8 89 **Strengths and limitations of this study**

9
10 90 1. Prospective, interventional, randomized controlled trial to evaluate the effect of
11
12 91 intraocular pressure-lowering medications for controlling axial elongation in adult
13
14 92 patients.

15
16 93 2. Designing and performing this randomized controlled trial based on an on-going
17
18 94 large-scale highly myopic cohort.

19
20 95 3. Study does not include a placebo group and blinding is not applied.

21
22 96 4. Participants are recruited from a single center.

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115 **Introduction**

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

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

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

136 Building upon these findings, we hypothesize that medically IOP-lowering may
137 slow axial elongation by potentially three pathways related to the sclera and choroid
138 [19]. We therefore aim to conduct a randomized controlled trial (RCT) to assess the
139 efficacy of medical IOP-lowering in managing axial elongation in patients with
140 progressive HM (PHM). Additionally, this study should generate data on the effects of
141 IOP-lowering treatment on the incidence and changes in the visual field (VF), changes
142 in the optic nerve head morphology and myopic maculopathy. The outcomes of the

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4 143 study may establish a basis for treatment recommendations for preventing axial
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6 144 elongation of highly myopic eyes.

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10 146 **Methods and Analysis**

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12 147 **Study design**

13
14 148 The PHM study is an open-label, single-center RCT. The study will be conducted at
15
16 149 the Zhongshan Ophthalmic Center (ZOC), Sun Yat-Sen University, a tertiary
17
18 150 specialized hospital in Guangzhou, China. All examinations and interventions will be
19
20 151 carried out in the Clinical Research Center at ZOC. This study does not permit blinding
21
22 152 and is therefore designed as an open-label trial. **Figure 1** summarizes the design of the
23
24 153 PHM study.

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28 155 **Objective**

29
30 156 The primary aim of this trial is to evaluate the effectiveness of medically IOP-lowering
31
32 157 therapy in managing axial elongation in patients with PHM over a 12-month
33
34 158 observation period. Additionally, the trial will assess alterations in VF, optic disc
35
36 159 morphology, thickness of the retinal nerve fiber layer (RNFL) and retinal ganglion cell-
37
38 160 inner plexiform layer (GC-IPL), and the occurrence or advancement of myopic
39
40 161 maculopathy.

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44 163 **Recruitment**

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46 164 *Inclusion criteria*

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48 165 1. Age ≥ 18 years and ≤ 65 years.
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50 166 2. Diagnosed with HM [20-21]: spherical equivalent ≤ -6.00 diopters or AL ≥ 26.5 mm.
51
52 167 3. Diagnosed with PHM: axial elongation ≥ 0.05 mm in the past 6 months or ≥ 0.1 mm
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54 168 in the past 12 months.
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4 169 4. IOP: ≥ 10 mmHg and ≤ 21 mmHg on at least 2 visits using Goldmann applanation
5
6 170 tonometry with correction for the dependence of the IOP-reading on corneal thickness
7
8 171 [22].

9
10 172 5. Best corrected visual acuity (BCVA) $\geq 6/12$, ability to undergo AL measurement,
11
12 173 fundus photography, optical coherence tomography (OCT), and complete VF
13
14 174 examination.

15
16 175

17
18 176 *Exclusion criteria*

19
20 177 1. Patients who have been using IOP-lowering medications within the last year.

21
22 178 2. Allergy to any kind of IOP-lowering eyedrops.

23
24 179 3. Presence of serious fundus pathologies like proliferative diabetic retinopathy, retinal
25
26 180 detachment, central retinal artery occlusion, etc.

27
28 181 4. Presence of chronic, recurrent, or severe ocular inflammatory lesions such as chronic
29
30 182 or recurrent uveitis.

31
32 183 5. Significant corneal or iris lesions, severe cataract affecting fundus examination, or
33
34 184 patients with only one eye.

35
36 185 6. Intraocular surgery or laser treatment within the last year, such as cataract surgery.

37
38 186 7. With a history of previous refractive surgery or prior treatment for myopia-related
39
40 187 conditions (e.g., orthokeratology lens wear, low-intensity red light therapy, or low-
41
42 188 concentration atropine treatment).

43
44 189 8. Presence of other serious systemic diseases (e.g., hypertension, heart disease,
45
46 190 diabetes, rheumatic immune system disease) that hinder long-term follow-up and eye
47
48 191 treatment.

49
50 192 9. Pregnancy, lactation, or plans to have children during the follow-up period.

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54 194 In this study, only one eye per eligible participant will be included. If both eyes meet
55
56 195 the inclusion criteria, the eye with a higher rate of axial elongation, a worse mean
57
58 196 perimetric deviation (MD) value, and a worse BCVA will be selected.

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4 1975 198 **Randomisation and blinding**

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8 199 In this trial, randomisation will be employed to mitigate distribution bias. After
9
10 200 confirming all inclusion and exclusion criteria and obtaining signed written informed
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12 201 consent forms (see supplemental material), qualified individuals within each block,
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14 202 with a block size of 4, will be assigned in an even (1:1) manner to either the intervention
15
16 203 group or the control group. The random sequence will be generated using an electronic
17
18 204 data collection (EDC) system to ensure unbiased allocation.

19
20 205 In this trial, the participants and physicians will not be blinded to the intervention
21
22 206 assignment. The technicians conducting the examinations and interpreting the images
23
24 207 will be unaware of the participants' group assignments during the screening and follow-
25
26 208 up stages. The researchers analyzing the data will also be unaware of the information
27
28 209 regarding randomisation.

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30 21031
32 211 **Interventions**33
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36 213 *Intervention group*

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38 214 Participants assigned to the intervention group will receive medical IOP-lowering
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40 215 therapy for a duration of 12 months or until they reach the endpoint. Only the study
41
42 216 eye will receive medication in the enrolled participants. The preferred medication for
43
44 217 reducing IOP is Xalacom[®] eye drop (Pfizer Inc., New York, NY, USA), a fixed
45
46 218 latanoprost and timolol combination.

47
48 219 The treatment protocol will involve the instillation of a single drop of
49
50 220 prostaglandin ophthalmic solution in the study eye once daily in the evening for
51
52 221 medications such as Xalacom. To ensure the standardisation of medication usage
53
54 222 among participants, subjects will be provided with medication logbooks, which will
55
56 223 be collected and recorded by the investigators during the study visits.

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4 225 *Control group*

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6 226 Participants assigned to the control group will be followed up for 12 months or until
7
8 227 they reach the endpoint without medical IOP-lowering therapy.
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12 229 **Outcome measures**

13
14 230 *Primary outcome*

15
16 231 The primary outcome is the change of AL at 12-month from baseline measured by
17
18 232 IOLMaster.
19

20 233

21
22 234 *Secondary outcomes*

23
24 235 1. Incidence and progression of VF defects at 12 months from baseline based on
25
26 236 Humphrey 24-2 standard VF. Under the premise of reliable VF examination,
27
28 237 compared to the baseline, two consecutive perimetric examinations reveal the
29
30 238 incidence of VF defects or significant perimetric progression in at least three points at
31
32 239 a significance level of $p < 0.05$. Furthermore, two subsequent diagnostic VF
33
34 240 examinations conducted within one month also confirm the progression at the
35
36 241 locations. The time of progression is defined as the time of the initial diagnostic VF
37
38 242 examination [23-24].
39

40 243 2. Changes in optic disc morphology (including thinning of RNFL and GC-IPL) at
41
42 244 12-month from baseline based on fundus photography and OCT [25-27].
43

44 245 3. Incidence and progression of myopic maculopathy at 12 months from baseline based
45
46 246 on fundus photography and OCT. The determination of incidence and progression of
47
48 247 myopic maculopathy is based on the META-PM classification system [28-29].
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52 249 **Study assessments**

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54 250 *Visual acuity*

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56 251 Visual acuity assessment will be conducted prior to any procedures that may potentially
57
58 252 impact vision, such as pupil dilation or VF examination. The measurement of visual
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4 253 acuity will be performed using an ETDRS (Early Treatment of Diabetic Retinopathy
5
6 254 Study) LogMAR chart (Precision Vision, Villa Park, Illinois, USA) under standard
7
8 255 illumination conditions at 4 meters [30]. For BCVA, a trial frame will be positioned
9
10 256 and adjusted on the participant's face based on auto refractometric readings and
11
12 257 subsequent subjective refinement.

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15
16 259 *Refractometry*

17
18 260 Following pupil dilation using 0.25% compound tropicamide (Zhuobian®; Sinqi,
19
20 261 China), three measurements will be taken for each eye using an auto refractometer
21
22 262 (KR800, TOPCON, Tokyo, Japan). The average values for spherical refractive error,
23
24 263 cylindrical refractive error, and astigmatic axis will be recorded for further analysis and
25
26 264 documentation.

27
28 265

29
30 266 *Slit-lamp biomicroscopy*

31
32 267 The evaluation of the anterior segment with the pupil undilated will be performed using
33
34 268 a slit lamp (BQ-900, Haag Streit, Koeniz, Switzerland). After medical pupillary dilation,
35
36 269 a slit lamp-based grading of lens opacities is conducted and using a 90D indirect
37
38 270 ophthalmoscopic lens (Ocular 90D Slit Lamp Lenses, Ocular, Washington, DC, USA),
39
40 271 the optic disc, macula, and peripheral retina will be examined.

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44 273 *Tonometry*

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46 274 IOP measurements will be performed by Goldmann applanation tonometry (AT900,
47
48 275 Haag Streit, Koeniz, Switzerland). Prior to enrollment, all participants will undergo
49
50 276 three baseline IOP readings during specific time intervals: 9 am to 10 am, 1 pm to 2
51
52 277 pm, and 4 pm to 5 pm. During follow-up visits, tonometry will be conducted between
53
54 278 9 am and 11 am. Results from three consecutive measurements will be documented
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56 279 during each visit, and the mean value of these measurements will be utilized for
57
58 280 assessment purposes.

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6 282 *AL measurement*

7
8 283 AL measurement will be performed using the IOLMaster (IOLmaster 700, Carl Zeiss
9
10 284 Meditec, Jena, Germany). Results from five consecutive measurements will be
11
12 285 documented during each visit, and the mean value of these measurements will be
13
14 286 utilized for further analysis.

15
16 287

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18 288 *Central corneal thickness (CCT) measurement*

19
20 289 CCT measurement will be performed with IOLMaster (IOLmaster 700, Carl Zeiss
21
22 290 Meditec, Jena, Germany). Results from five consecutive measurements will be
23
24 291 documented during each visit, and the mean value of these measurements will be taken
25
26 292 for further analysis.

27
28 293

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30 294 *Perimetry*

31
32 295 The perimetric examination will be performed applying the Humphrey Field Analyzer
33
34 296 Mark 3 (Carl Zeiss Meditec, Dublin, CA, USA) and the Swedish Interactive Threshold
35
36 297 Algorithm Standard (SITA) 24-2 program. A reliable VF report is defined as having
37
38 298 false-positive and false-negative errors below 15%, as well as fixation losses below
39
40 299 20%.

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42 300

43
44 301 *Fundus photography*

45
46 302 Using fundus cameras (KOWA, Nonmyd, WX3D, Nagoya, Japan; TRC-NW400,
47
48 303 TOPCON, Tokyo, Japan), two fundus images centered on the optic disc will be taken
49
50 304 for each eye under both standardized stereoscopic and non-standardized conditions.
51
52 305 Additionally, a single image focused on the macula will be obtained after pupil dilation.

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56 307 *OCT examination*

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4 308 All participants will undergo a series of standardized swept-source OCT examinations
5
6 309 using the DRI-OCT Triton model (TOPCON, Tokyo, Japan), focusing on the optic disc
7
8 310 and macula. To ensure the reliability and accuracy of the results, a minimum image
9
10 311 quality score of 60 will be set. In addition to the swept-source OCT, a spectral domain
11
12 312 OCT examination will be conducted to obtain measurements of the peripapillary RNFL
13
14 313 and the macular GC-IPL.

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16 314

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18 315 *Pregnancy test*

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20 316 A urine pregnancy test will be performed for women of reproductive age during their
21
22 317 initial visit.

23
24 318

25
26 319 *Anthropometry and blood pressure*

27
28 320 Participants' height and weight measurements will be measured using a free-standing
29
30 321 height rod and a calibrated scale (RGZ120, Jiangsu Wujin Weighing Apparatus Factory,
31
32 322 Jiangsu, China). During the baseline visit, blood pressure readings will be obtained
33
34 323 from the participant's left arm while they are seated and have rested for a minimum of
35
36 324 five minutes with the Omron M7 Blood Pressure Monitor (Matsusaka, Mie, Japan).

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40 326 **Visit schedule**

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42 327 **Table 1** summarizes the visit schedule for the enrolment, interventions, and
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44 328 assessments of this trial.

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48 330 **Sample size**

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50 331 The sample size calculation for this study is determined based on the primary outcome
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52 332 and the study hypothesis, taking into account relevant findings from previous studies.

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54 333 The objective of this study is to evaluate the potential of IOP-lowering therapy to reduce
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56 334 axial elongation during a study period of one year growth in eyes with PHM. It is
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58 335 hypothesized that the intervention group receiving IOP-lowering therapy will exhibit a
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4 336 70% reduction in axial elongation compared to the control group. The control group is
5
6 337 estimated to experience a 0.1 mm axial elongation over 12 months, while the
7
8 338 intervention group is expected to have a mean axial elongation of 0.03 mm. The
9
10 339 common standard deviation is estimated to be 0.14 mm. To achieve a statistical power
11
12 340 of 80% with a two-sided significance level of 0.05, a total of 64 individuals per group
13
14 341 is required. Accounting for an estimated 15% loss to follow-up at the 12-months mark,
15
16 342 the final sample size is determined to be 76 individuals per group, resulting in a total
17
18 343 of 152 participants. The sample size calculation was performed using PASS 16.0
19
20 344 software (NCSS, LLC, Kaysville, UT, USA).

21
22 345

23 24 346 **Statistical analysis**

25
26 347 Statistical analysis will be conducted using Stata 16.0 software (StataCorp, College
27
28 348 Station, TX, USA). A two-sided P-value of less than 0.05 will be considered
29
30 349 statistically significant, and a 95% confidence interval will be used for parameter
31
32 350 estimation.

33
34 351 For the intention-to-treat (ITT) analysis, missing data will be addressed using the
35
36 352 multiple imputation method. No simulation will be performed for missing data in the
37
38 353 safety evaluation. Dropout rates in the two groups will be compared using chi-squared
39
40 354 tests or Fisher's exact tests. Descriptive statistics will be reported as mean and standard
41
42 355 deviation for normally distributed continuous data, and as median and interquartile
43
44 356 range for non-normally distributed continuous data. Frequency and percentage will be
45
46 357 provided for categorical data. Baseline data, including demographic and clinical
47
48 358 characteristics, will be analyzed using independent samples t-tests and Wilcoxon rank-
49
50 359 sum tests for continuous data, and chi-squared or Fisher's exact tests for categorical
51
52 360 variables.

53
54 361 The analysis of primary and secondary outcomes will follow the ITT principle,
55
56 362 including all participants. For the primary outcome, the difference in axial elongation
57
58 363 between the two groups will be analyzed using linear regression analysis. As for the
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4 364 secondary outcomes, a multifactor Poisson regression within a generalized linear model
5
6 365 will be utilized to estimate the relative risk of progression in perimetric defects and
7
8 366 myopic maculopathy. Additionally, the rate of thinning of the RNFL and the GC-IPL
9
10 367 will be assessed through log-rank tests.

11
12 368 Safety analysis will be performed in participants belonging to the intervention
13
14 369 group, comparing adverse event occurrence between the two groups using the chi-
15
16 370 squared test or Fisher's exact test.

17
18 371 The missing data will be handled using the Multiple Imputations method. With the
19
20 372 multiple imputation approach, 20 replicas of the dataset will be generated, where
21
22 373 missing values are imputed through chained equations. The final results will be
23
24 374 obtained by averaging these 20 datasets using Rubin's rules.

25
26 375

27 28 376 **Data monitoring**

29
30 377 (1) The Data Monitoring Committee (DMC) will closely monitor the data throughout
31
32 378 the trial using the EDC system to ensure the reliability and integrity of the collected
33
34 379 data. The DMC members are independent individuals who are not affiliated with the
35
36 380 researchers or sponsors, ensuring an impartial assessment. There is no conflict of
37
38 381 interest between the researchers and sponsors, further guaranteeing the transparency
39
40 382 and objectivity of the data monitoring process.

41
42 383 (2) Interim analysis: The study does not include provisions for conducting an interim
43
44 384 analysis.

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46 385

47 48 386 **Data management**

49
50 387 The collected data will be meticulously recorded and entered into the EDC system. The
51
52 388 EDC system is securely hosted on a password-protected network server, ensuring
53
54 389 digital protection. Only the principal investigators and authorized study team members
55
56 390 will have access to the research data. To ensure confidentiality and integrity, all source
57
58 391 documents will be stored in locked file cabinets with restricted access. Prior to data
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4 392 collection, all researchers will undergo comprehensive training. The raw data will be
5
6 393 monitored by an independent data and safety monitoring committee. In the event of
7
8 394 queries or uncertainties in the case report form, the data administrator will generate a
9
10 395 data queue request (DRQ) and communicate the query to the researcher through the
11
12 396 clinical monitoring system. The researcher is expected to provide a prompt response to
13
14 397 the data administrator. If necessary, data modifications, confirmations, and entries will
15
16 398 be made, and a new DRQ will be issued.

17
18 399

400 **Drug packaging, management, dispensing and storage**

401 *Drug packaging*

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

408

409 *Drug management*

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

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

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4 419 4. Maintaining a comprehensive record of drug inventory throughout the study and
5
6 420 providing inventory logs.

7
8 421 5. Maintaining a detailed catalog of the drugs, including information on received
9
10 422 materials, dispensing dates, and records of drugs provided to participants.

11
12 423 6. Ensuring that the drug dispensing records match the usage and unused drugs and
13
14 424 providing explanations for any discrepancies. Relevant dispensing and return forms
15
16 425 must be signed by the medication administrator.

17
18 426

19
20 427 *Drug dispensing*

21
22 428 After randomisation, the medication administrator will dispense the corresponding
23
24 429 investigational drugs to the participants based on the randomized assignment and
25
26 430 document the drug dispensing.

27
28 431

29
30 432 *Drug storage*

31
32 433 Unopened medications should be stored according to the instructions provided in the
33
34 434 drug package insert. For drugs that require refrigeration between 2-8°C, the medication
35
36 435 administrator needs to monitor the temperature and humidity daily and document the
37
38 436 storage conditions. The research drugs should not be provided to anyone other than the
39
40 437 participants in the study. Access to the research drugs is limited to personnel authorized
41
42 438 by the principal investigator to dispense them. After opening, medications should be
43
44 439 stored according to the instructions provided in the drug package insert and must be
45
46 440 used within four weeks of opening the drug package.

47
48 441

49
50 442 **Safety assessments**

51
52 443 The safety assessments included in this study are as follows:

53
54 444 1. Medication-related safety assessment: The ocular hypotensive medications used in
55
56 445 this study are known to have rare occurrences of local and systemic adverse reactions,
57
58 446 such as ocular surface irritation, eyelid pigmentation, eyelash growth, and drug
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4 447 allergies. These assessments will be conducted and recorded by the investigators
5
6 448 during the study visits using slit lamp examination.

7
8 449 2. High myopia-related safety assessment: This study focuses on individuals with high
9
10 450 myopia, and during the natural course of high myopia, retinal pathologies can occur.
11
12 451 The investigators will assess and record the complications associated with high myopia
13
14 452 based on the examination results during the study visits.
15

16 453

17 18 454 **Report and management of adverse events**

19
20 455 An adverse event refers to any negative medical occurrence experienced by a
21
22 456 participant in the study, regardless of its relation to the treatment. Utmost attention will
23
24 457 be given to identifying potential adverse events or unfavorable findings. The primary
25
26 458 concern is the safety of the participant, and appropriate medical intervention will be
27
28 459 provided in case of an adverse event. All adverse events, whether reported voluntarily
29
30 460 by the participant or discovered through questioning, physical examination, or other
31
32 461 means by the study staff, will be promptly recorded on an online adverse event form
33
34 462 The Safety Supervision Committee will review each form to determine the appropriate
35
36 463 coding and reporting procedures.

37
38 464 Serious adverse events, regardless of their connection to the study drug, must be
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40 465 reported within 24 hours to the Institutional Review Board (IRB), the DMC, and the
41
42 466 Clinical Research Center. Additionally, a faxed report must be sent to the Drug
43
44 467 Administration's drug registration office. The original and fax confirmation forms for
45
46 468 serious adverse events should be retained in the research center along with the case
47
48 469 report form.

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50 470

51 52 471 **Discussion**

53
54 472 This trial is designed to evaluate the effect of intraocular pressure reduction on
55
56 473 progressive high myopia. Due to the limited research on the use of IOP reduction
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58 474 medications in highly myopic eyes, the design of this study is based on a retrospective
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4 475 analysis of a large cohort of highly myopic individuals. It is found that the use of IOP
5
6 476 reduction medications slowed down axial elongation in approximately 70% of highly
7
8 477 myopic eyes. Therefore, we performed sample size calculations based on these findings.
9

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11
12 479 **Study progress**

13
14 480 The recruitment period of this study has started in June 2023 in ZOC. As of February
15
16 481 2024, we have included 73 participants.
17

18 482

19
20 483 **Acknowledgement:** We thank all the members of the Glaucoma Suspects with High
21
22 484 Myopia Study Group (GSHM) Study Group for conducting this trial. And also, we
23
24 485 thank all staff in clinical research center of ZOC for their effort in this study.
25

26 486

27
28 487 ***GSHM study group***

29
30 488 Principal investigators:

31
32 489 Xiulan Zhang, Yizhi Liu, Lin Lv, David Friedman, Jost B. Jonas, and Tin Aung.
33

34 490 Members:

35
36 491 Shida Chen, Wei Wang, Fengbin Lin, Yunhe Song, Peiyuan Wang, Kangjie Kong,
37

38 492 Jingwen Jiang, Fei Li, Kai Gao, Bingqian Liu, Yuhong Liu, and Meiling Chen.
39

40 493 Steering committee:

41
42 494 Neil M. Bressler, Ki Ho Park, Mingguang He, Kyoko Ohno-Matsui, Dennis S.C. Lam,
43

44 495 and Robert N. Weinreb.
45

46 496 Data monitoring committee:

47
48 497 Ching-Yu Cheng, Paul Healey, and Linda M. Zangwill.
49

50 498 Safety supervision committee:

51
52 499 Xiang Chen and Guangxian Tang.
53

54 500 Biostatistics and data monitoring center:

55
56 501 Ling Jin.
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5
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9
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17

18 510

19
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21
22 512 FL wrote the primary protocol manuscript. XZ, FZ, DSL and JBJ revised the
23
24 513 manuscript. KK, PW and YS contributed to data collecting. LJ and WZ helped with
25
26 514 sample size calculation and were the statistical consultants. YL, JC and MC were
27
28 515 clinical research coordinators of the project.
29

30 516

31
32 517 **Competing interest:** Jost B. Jonas: European patent EP 3,271,392, JP 2021-
33
34 518 119187, and US 2021 0340237 A1: Agents for use in the therapeutic or
35
36 519 prophylactic treatment of myopia or hyperopia; European patent application
37
38 520 23196899.1 “EGFR Antagonists for the treatment of diseases involving unwanted
39
40 521 migration, proliferation, and metaplasia of retinal pigment epithelium (RPE)
41
42 522 cells”.
43

44 523

45
46 524 **Patient and public involvement:** Patients and/or the public were not involved in the
47
48 525 design, or conduct, or reporting, or dissemination plans of this research.
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50 526

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52 527 **Patient consent for publication:** Not applicable
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56 529 **Protocol Version:** 5.0
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Figure 1 Diagram of the PHM study design.

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For peer review only

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665 **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
Slit 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

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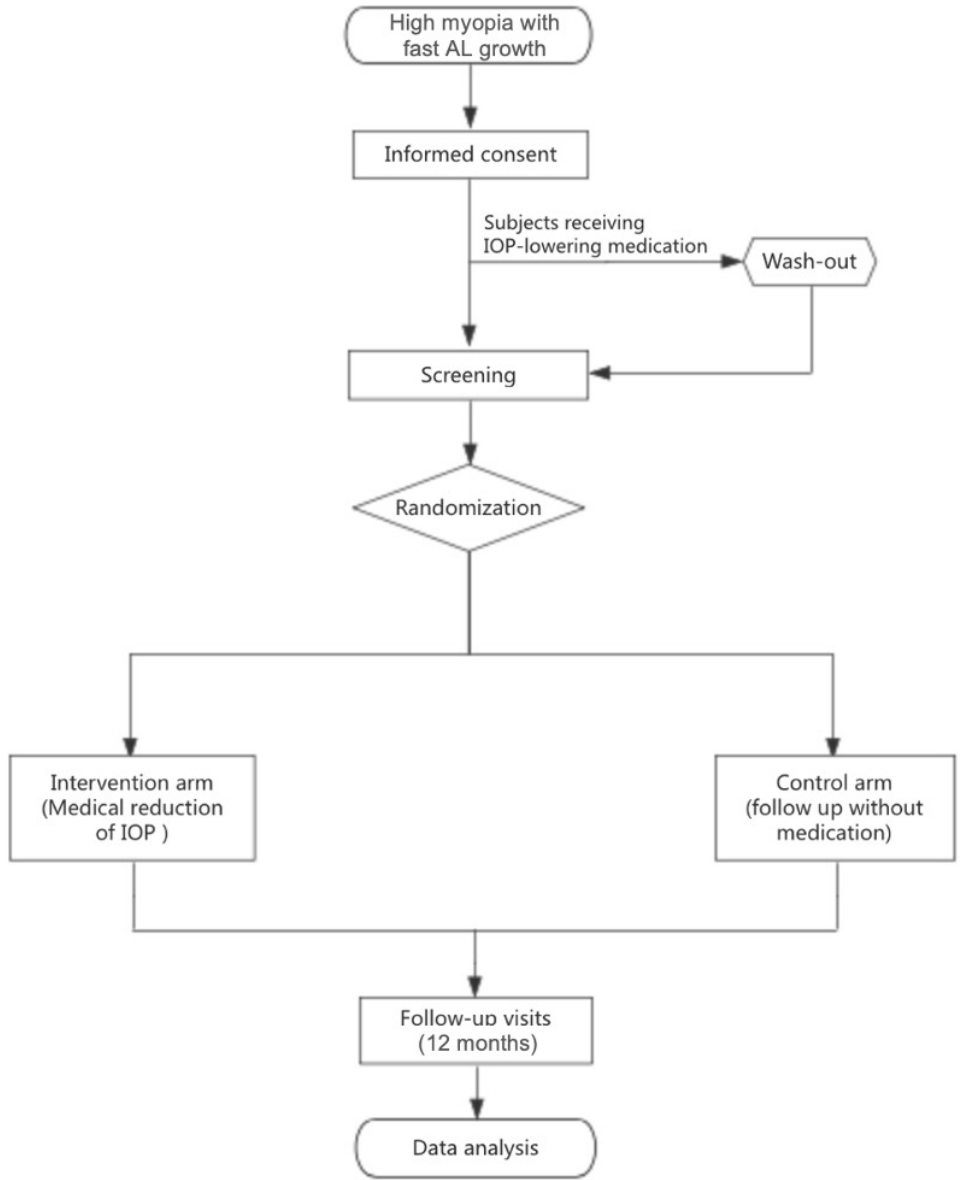


Figure 1

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 ≥ 0.05 mm in the past 6 months or ≥ 0.1 mm in the past 12 months.
4. IOP: ≥ 10 mmHg and ≤ 21 mmHg 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) $\geq 6/12$, ability to undergo axial length measurement, fundus

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3 photography, optical coherence tomography (OCT), and complete visual field examination.
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7 *Exclusion criteria*

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9 1. Patients who have been using IOP-lowering medications within the last year.
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11 2. Allergy to any kind of IOP-lowering eyedrops.
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13 3. Presence of serious fundus pathologies like proliferative diabetic retinopathy, retinal detachment, central
14 retinal artery occlusion, etc.
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16 4. Presence of chronic, recurrent, or severe ocular inflammatory lesions such as chronic or recurrent uveitis.
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18 5. Significant corneal or iris lesions, severe cataract affecting fundus examination, or patients with only one
19 eye.
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21 6. Intraocular surgery or laser treatment within the last year, such as cataract surgery.
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23 7. With a history of previous refractive surgery or prior treatment for myopia-related conditions (e.g.,
24 orthokeratology lens wear, low-intensity red light therapy, or low-concentration atropine treatment).
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26 8. Presence of other serious systemic diseases (e.g., hypertension, heart disease, diabetes, rheumatic immune
27 system disease) that hinder long-term follow-up and eye treatment.
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29 9. Pregnancy, lactation, or plans to have children during the follow-up period.
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36 In this study, only one eye per eligible participant will be included. If both eyes meet the inclusion criteria, the
37 eye with a higher rate of axial elongation, a worse mean perimetric deviation (MD) value, and a worse BCVA
38 will be selected.
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44 **3. How is the study conducted?**

45 Once you are diagnosed with PHM, we will provide you with the above explanation. If you agree to participate
46 in this study, we will proceed with the following research procedures after you have signed this informed
47 consent form. These procedures involve collecting your research data and relevant examination results as
48 specified in the research protocol. The study process is as follows:
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55 1) Informed consent and screening for eligibility, with medication washout if necessary.
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57 2) The study physician will select the appropriate eye for research observation based on the requirements of
58 the research protocol and the patient's individual circumstances.
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3 3) Randomization: Participants will be randomly assigned in a 1:1 ratio to either the intraocular pressure-
4 lowering medication group or the control group (no medication).
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9 Participants assigned to the intervention group will receive medical IOP-lowering therapy for a duration of 12
10 months or until they reach the endpoint. Only the study eye will receive medication in the enrolled participants.
11 The preferred medication for reducing IOP is Xalacom[®] eye drop (Pfizer Inc., New York, NY, USA), a fixed
12 latanoprost and timolol combination.
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16 The treatment protocol will involve the instillation of a single drop of prostaglandin ophthalmic solution
17 in the study eye once daily in the evening for medications such as Xalacom. To ensure the standardisation of
18 medication usage among participants, subjects will be provided with medication logbooks, which will be
19 collected and recorded by the investigators during the study visits.
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26 *Control group*

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28 Participants assigned to the control group will be followed up for 12 months or until they reach the endpoint
29 without medical IOP-lowering therapy.
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34 ● Medication Administration:

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36 Xalacom: One drop once daily at 22:00 (± 1 hour), with lacrimal sac compression for one minute after
37 administration.
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40 ● Medication Follow-up Duration: 1 year (Participants are required to complete three visits within one year,
41 scheduled at approximately 1 month (± 1 week), 6 months (± 2 weeks), and 12 months (± 4 weeks)
42 respectively).
43
44

45 ● Follow-up Examinations: Visual acuity (uncorrected visual acuity, BCVA), computerized auto-refraction,
46 Goldmann tonometry, central corneal thickness, axial length, visual field, fundus photography, OCT
47 examination, quality of life questionnaire, etc.
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53 Throughout the study, we will closely monitor any changes in your condition and make necessary adjustments
54 to the follow-up plan in order to ensure your rights and safety.
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59 **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. Thank 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: _____



STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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)

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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)
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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)
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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)
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Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered (P3 L70-72)
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	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)
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	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)
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	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial
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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)
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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)
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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)
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Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size (P3 L69)
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Methods: Assignment of interventions (for controlled trials)

Allocation:

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2	Sequence	16a	Method of generating the allocation sequence (eg, computer-
3	generation		generated random numbers), and list of any factors for stratification.
4			To reduce predictability of a random sequence, details of any planned
5			restriction (eg, blocking) should be provided in a separate document
6			that is unavailable to those who enrol participants or assign
7			interventions (P8 L198-209)
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9			
10	Allocation	16b	Mechanism of implementing the allocation sequence (eg, central
11	concealment		telephone; sequentially numbered, opaque, sealed envelopes),
12	mechanism		describing any steps to conceal the sequence until interventions are
13			assigned
14			
15	Implementation	16c	Who will generate the allocation sequence, who will enrol participants,
16			and who will assign participants to interventions
17			
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19	Blinding	17a	Who will be blinded after assignment to interventions (eg, trial
20	(masking)		participants, care providers, outcome assessors, data analysts), and
21			how (P8 L198-209)
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23		17b	If blinded, circumstances under which unblinding is permissible, and
24			procedure for revealing a participant's allocated intervention during
25			the trial
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Methods: Data collection, management, and analysis

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30	Data collection	18a	Plans for assessment and collection of outcome, baseline, and other
31	methods		trial data, including any related processes to promote data quality (eg,
32			duplicate measurements, training of assessors) and a description of
33			study instruments (eg, questionnaires, laboratory tests) along with
34			their reliability and validity, if known. Reference to where data
35			collection forms can be found, if not in the protocol (P10-P13 L271-
36			346)
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39		18b	Plans to promote participant retention and complete follow-up,
40			including list of any outcome data to be collected for participants who
41			discontinue or deviate from intervention protocols
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44	Data	19	Plans for data entry, coding, security, and storage, including any
45	management		related processes to promote data quality (eg, double data entry;
46			range checks for data values). Reference to where details of data
47			management procedures can be found, if not in the protocol (P15
48			L408-240)
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51	Statistical	20a	Statistical methods for analysing primary and secondary outcomes.
52	methods		Reference to where other details of the statistical analysis plan can be
53			found, if not in the protocol(P14 L368-396)
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55		20b	Methods for any additional analyses (eg, subgroup and adjusted
56			analyses)
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- 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)

8 **Methods: Monitoring**

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- 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](#))

30 **Ethics and dissemination**

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- 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

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2	Ancillary and	30	Provisions, if any, for ancillary and post-trial care, and for
3	post-trial care		compensation to those who suffer harm from trial participation
4			
5	Dissemination	31a	Plans for investigators and sponsor to communicate trial results to
6	policy		participants, healthcare professionals, the public, and other relevant
7			groups (eg, via publication, reporting in results databases, or other
8			data sharing arrangements), including any publication restrictions(P3
9			L83-86)
10			
11		31b	Authorship eligibility guidelines and any intended use of professional
12			writers
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14		31c	Plans, if any, for granting public access to the full protocol, participant-
15			level dataset, and statistical code
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19	Appendices		
20			
21	Informed consent	32	Model consent form and other related documentation given to
22	materials		participants and authorised surrogates(P8 L200)
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24	Biological	33	Plans for collection, laboratory evaluation, and storage of biological
25	specimens		specimens for genetic or molecular analysis in the current trial and for
26			future use in ancillary studies, if applicable
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*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.