PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Effect of Intraocular Pressure Reduction on Progressive High Myopia (PHM study): Study Protocol of a Randomized Controlled Trial
AUTHORS	Jiang, Jingwen; Lin, Tingting; Lin, Fengbin; Kong, Kangjie; Wang, Peiyuan; Song, Yunhe; Zhou, Fengqi; Wang, Zhenyu; Jin, Ling; Liu, Yuhong; Gao, Xinbo; Chen, Jinmei; Chen, Meiling; Lam, Dennis SC; Jonas, Jost; Chen, Shida; Zhang, Xiulan

VERSION 1 – REVIEW

REVIEWER	Karasu, Bugra Tuzla State Hospital, Ophtalmology
REVIEW RETURNED	11-Jan-2024

GENERAL COMMENTS	In myopia, growth depends on UV rays falling on the retina and it has been proven that. Eye development continues until the age of 14, and usually stops progression at the age of 25.It is impossible for such a thing to be true because myopes have open painful glaucoma, so there should be no progression in them.For this hypothesis to be true, there must be proven similar studies.

REVIEWER	Han, Xiaotong State Key Laboratory of Ophthalmology, Zhongshan Ophthalmic Center, Sun Yat-sen University
REVIEW RETURNED	12-Jan-2024

GENERAL COMMENTS	The authors have addressed my comments appropriately and updated the manuscript accordingly, I do not have any additional comments.

REVIEWER	Li, Fen-Fen Wenzhou Medical University Eye Hospital
REVIEW RETURNED	31-Jan-2024

GENERAL COMMENTS	This study has the potential to contribute valuable insights into the efficacy of medical IOP reduction in managing progressive high myopia, and I look forward to seeing the results in the future publications. Overall, the protocol is well-structured and addresses key elements of a clinical trial. However, a little issue should be addressed to enhance clarity and completeness. 1. Randomization and Allocation Concealment: The randomization ratio (1:1) is appropriate. However, provide details on the method of randomization and allocation concealment to ensure transparency and reduce bias, such as age, gender, and IOP level at baseline. 2. Study Design: Clarify if blinding participants and investigators to the intervention was considered, and if not, provide justification for

	the open-label design. 3. The control group is not receiving medication; why was a placebo group not considered? This is important to assess whether there is a placebo effect, and how this design addresses blinding. Please provide justification for the choice of not including a placebo group in the trial. 4. Considering the daily fluctuations in intraocular pressure, have you considered standardizing the time for patients to measure their eye pressure? For instance, could all measurements be taken either in the morning or afternoon? This would help control for variations in eye pressure due to circadian rhythm.

REVIEWER	Hansen, Niklas Rigshospitalet Glostrup, Neurological Clinic
REVIEW RETURNED	12-Feb-2024

GENERAL COMMENTS	"Patients who have been using IOP-lowering medications prior to enrollment need to undergo a drug washout period." - why not exclude these individuals? Too many excluded that way? Different drugs with different mechanisms of action will be used to achieve target IOP. In my opinion, that's a bit of a confounder, for who is to say that it might not be ex. latanoprost having a direct effect on scleral remodelling affecting the AL elongation and not latanoprosts effect on IOP? In other words, perhaps one or two of the drugs have an effect on AL elongation irrespective of IOP reduction, but you wouldn't necessarily know which based on the study design. "It is hypothesized that the intervention group receiving IOP-lowering therapy will exhibit a 70% reduction in axial elongation compared to the control group." Sounds rather optimistic for the power-calculation, but what do I know?

VERSION 1 – AUTHOR RESPONSE

Reviewer 1:

Comment 1: In myopia, growth depends on UV rays falling on the retina and it has been proven that. Eye development continues until the age of 14, and usually stops progression at the age of 25. It is impossible for such a thing to be true because myopes have open painful glaucoma, so there should be no progression in them. For this hypothesis to be true, there must be proven similar studies.
Response 1: We acknowledge that the progression of myopia may be influenced by various complex factors, and that in most myopic patients, the axial length tends to stabilize in adulthood. However, previous studies have also indicated the presence of individuals with continuous axial elongation among highly myopic patients, and the application of IOP-lowering medications might delay the progression (JAMA Ophthalmol. 2021;139(10):1096-1103; Am J Ophthalmol. 2021;225:76-85). So, in this study, we focus on highly myopic eyes with continuous fast axial elongation (progressive high myopia, PHM). Meanwhile, animal experiments have confirmed that IOP-lowering medications in guinea pig models can delay the growth of axial length and refractive diopters (Invest Ophthalmol Vis Sci. 2018;59(6):2644-2651, Basic Clin Pharmacol Toxicol. 2018;123(3):263-270). Building upon these findings, we firstly performed thoroughly literature review and proposed a perspective that IOP-lowering medications may be a potential approach for controlling high myopia progression (Invest Ophthalmol Vis Sci. 2021;62(14):17). This RCT is designed to explore possible clinical treatment options for progressive myopic patients.

Reviewer 2:

Comment 1: The authors have addressed my comments appropriately and updated the manuscript accordingly, I do not have any additional comments.
Response 1: Thank you for your effort in reviewing this manuscript and we are honored that this manuscript met your requirement.

Reviewer 3:

Comment 1: Randomization and Allocation Concealment: The randomization ratio (1:1) is appropriate. However, provide details on the method of randomization and allocation concealment to ensure transparency and reduce bias, such as age, gender, and IOP level at baseline.
Response 1: We fully agree that implementing a more refined stratified randomization would result in more balanced outcomes. Considering the large sample size and minimal impact factors, it was suggested not to implement stratified randomization. The random sequence will be generated using an electronic data collection (EDC) system to ensure unbiased allocation. Once again, we appreciate your valuable suggestion.

Comment 2: Study Design: Clarify if blinding participants and investigators to the intervention was considered, and if not, provide justification for the open-label design.
Response 2: We fully acknowledge the importance of conducting a double-blind and placebo-controlled RCT, and we have made prior attempts in this regard. However, there are differences in the appearance of the commercially available sodium hyaluronate eye drops and the study medication's vials. Additionally, no certified manufacturer provides placebo vials for this study. As a result, we have designed this RCT as an open-label study. We have added the corresponding description in P6 L151-152 as “This study does not permit blinding and is therefore designed as an open-label trial”.

Comment 3: The control group is not receiving medication; why was a placebo group not considered? This is important to assess whether there is a placebo effect, and how this design addresses blinding. Please provide justification for the choice of not including a placebo group in the trial.
Response 3: Thank you for your valuable comment. As discussed above, participants are not blinded in this study and we have designed it as an open-label study. Additionally, the primary outcome measure of this study is the objective measurement of axial length, which may help mitigate the limitations of an open-label design.

Comment 4: Considering the daily fluctuations in intraocular pressure, have you considered standardizing the time for patients to measure their eye pressure? For instance, could all measurements be taken either in the morning or afternoon? This would help control for variations in eye pressure due to circadian rhythm.
Response 4: Thank you for your insightful comment. We fully acknowledge the presence of fluctuations in intraocular pressure at different times. Therefore, we have modified accordingly as “During follow-up visits, tonometry will be conducted between 9 am and 11 am” in P11 L299-300.

Reviewer 4:

Comment 1: Patients who have been using IOP-lowering medications prior to enrollment need to undergo a drug washout period." - why not exclude these individuals? Too many excluded that way?
Response 1: We fully agree that the inclusion of such patients may introduce bias, and have accordingly modified the exclusion criteria as “Patients who have been using IOP-lowering medications within the last year” in P7 L177 and removed the washout paragraph in P8 L212-220.

Comment 2: Different drugs with different mechanisms of action will be used to achieve target IOP. In my opinion, that's a bit of a confounder, for who is to say that it might not be ex. latanoprost having a direct effect on scleral remodeling affecting the AL elongation and not latanoprosts effect on IOP? In other words, perhaps one or two of the drugs have an effect on AL elongation irrespective of IOP reduction, but you wouldn't necessarily know which based on the study design.
Response 2: Thank you for your valuable comment. We fully acknowledge that latanoprost eye drops may affect the biomechanics of the cornea and sclera, thereby influencing IOP measurements. Additionally, different medications may impact the results.

After analyzing our cohort data, we found that compared with those without IOP-lowering medications

(0.04 mm/y), eyes using prostaglandin analogues showed slower axial elongation (0.01 mm/y, P = 0.04); and compared with those with monotherapy (0.02 mm/y), eyes with fixed-combination therapy showed slower axial elongation (0.01 mm/y, P = 0.22) (Am J Ophthalmol. 2024 (submitted)). Meanwhile, among highly myopic eyes using Xalacom, 89.9% achieved a 10% IOP reduction from baseline. Considering the clinical evidence above, we have chosen Xalacom as the preferred medication (P9 L226-234& L237-238& L242-246). And we decided to remove the target IOP and the process for adding medications if target IOP not achieved from the protocol.

Comment 3: It is hypothesized that the intervention group receiving IOP-lowering therapy will exhibit a 70% reduction in axial elongation compared to the control group." Sounds rather optimistic for the power-calculation, but what do I know?
Response 3: Thank you for your insightful comment. Due to the limited availability of relevant clinical studies, the parameters used for sample size calculation in this study relies on unpublished data from a retrospective analysis of a high myopia cohort. We found that using anti-glaucoma medications (OR, 0.46; 95% CI, 0.27-0.79; P = 0.005) was more likely to protect against axial elongation, and after adjusting for confounding factors including sex, age and baseline axial length, using IOP-lowering medications slowed down axial elongation by 75% (from 0.04 [0.06] to 0.01 [0.06] mm/y, P < 0.001) (Am J Ophthalmol. 2024 (submitted)). Additionally, our preceding animal experiment data lend further support to this hypothesis (J Transl Med.2024 (under review), Exp Eye Res. 2024 (under review)). These details had been added into the manuscript in the Discussion in P18 L496-497 to facilitate reader understanding. Thank you once again for your support of the manuscript. We hope that these revisions meet your satisfaction.

VERSION 2 – REVIEW

REVIEWER	Li, Fen-Fen Wenzhou Medical University Eye Hospital
REVIEW RETURNED	01-Apr-2024

GENERAL COMMENTS	It is a creative study design.