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Invited Commentary

Clinical Trial Design—The Best Approach Is Often the Simple One

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The well-known painter Hans Hofmann's timeless quote, "The ability to simplify means to eliminate the unnecessary so that the necessary may speak," certainly applies to randomized clinical trial design.[1(p118)] In this edition of *JAMA Ophthalmology*, Waring et al[2] report the results of their phase 3, vehicle-controlled, double-blind, randomized clinical trial of AGN-190584 in individuals with presbyopia. The authors are to be congratulated on their work on this important question, as presbyopia is estimated to affect approximately 1.8 billion individuals worldwide and can lead to a substantial decrease in quality of life and impaired productivity.[3] A new pharmacologic treatment for presbyopia could provide a convenient and reversible alternative to corrective lenses while avoiding the risks of surgery. Overall, the outcome of their study suggests that pilocarpine can be used, with minimal adverse effects, to improve near vision in patients with distance-corrected presbyopia.

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Although the results are promising, the complexity of the study design makes them less compelling than they may have been. The participants were randomized using an elaborate stratification scheme including characteristics with small effects on prognosis, such as age (inclusion criteria, narrow range for age: 40-55 years), emmetrope status (monofocal distance

correction was provided in the protocol), and eye color. It is not clear why they chose to stratify these characteristics vs others, such as pupil size or baseline accommodative amplitude, or how well this stratification was achieved. It is also not clear whether the analysis took the stratification into account with, eg, a permutation *P* value limiting to the possible permutations.

Pilocarpine can cause a myopic shift and a smaller pupil diameter and can theoretically lead to diffractive blur with loss of distance visual acuity. Therefore, the finding of improved distance-corrected near vision could have been due to myopic shift with compromise in the distance visual performance. Unfortunately, no refractions on treatment at the 30-day end point were provided, and patient-reported changes in distance visual acuity were not studied. The authors do report that no participants with 3-line or greater improvement in distance-corrected near visual acuity exhibited a greater than 5-letter loss in corrected distance visual acuity, which is somewhat vague.[4,5]

Furthermore, various light levels were tested, including photopic distance-corrected distance vision, intermediate and near visual acuity, and mesopic distance-corrected near vision, whereas scotopic conditions and traditional measures of accommodation were not tested. As acknowledged by the study authors, the effect of pilocarpine on visual performance in low-light environments needs to be evaluated. Under scotopic conditions, miosis can cause a loss in retinal illuminance, which may have an effect on visual quality. This loss in retinal illuminance may be further accentuated by greater lenticular light loss in phakic eyes in the presbyopic population. The choice of mesopic lighting levels for the primary and secondary end points may have exaggerated the positive results of AGN-190584 given the greater decrease in pupil diameter at peak efficacy in mesopic vs photopic conditions, while not finding potential adverse effects in scotopic conditions. We look forward to trials already underway addressing some of these questions.

Finally, the financial incentives driving the commercialization of a new pilocarpine reformulation are of concern. Pilocarpine, a cholinergic muscarinic receptor agonist that has been in use for decades as a therapy for glaucoma, is known to also improve depth of focus and accommodation.[6,7] AGN-190584, consisting of pilocarpine, 1.25%, with a proprietary vehicle designed to minimize ocular discomfort and blurry vision, was designed for use in individuals with presbyopia. In this study, pilocarpine, 1.25%, was compared only with vehicle. A head-to-head comparison of the study drug with pilocarpine, 1%, in both efficacy and adverse effects would have been useful given that the latter is a generic medication available to patients at a fraction of the cost. Such a comparison would also provide support as to whether the proprietary vehicle in the pilocarpine reformulation is able to minimize adverse effects, such as headache, ocular discomfort, and blurred vision, as described.

In conclusion, the prospect of being able to treat presbyopia with pharmacologic therapy is highly alluring, and this study provides encouraging evidence that we are nearing that goal with this new reformulation of pilocarpine. However, we should also keep in mind that just as a simple ophthalmic drop can be a straightforward and effective treatment, the same principle holds true for clinical trial design—the best approach is often the simple one.

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