

# Nicotinamide and Pyruvate for Neuroenhancement in Open-Angle Glaucoma: A Phase 2 Randomized Clinical Trial

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**IMPORTANCE:** Open-angle glaucoma may continue to progress despite significant lowering of intraocular pressure (IOP) . Preclinical research has suggested that enhancing mitochondrial function and energy production may enhance retinal ganglion cell survival in animal models of glaucoma, but there is scant information on its effectiveness in a clinical setting.

**OBJECTIVE:** To test the hypothesis that a combination of nicotinamide and pyruvate can improve retinal ganglion cell function in human glaucoma as measured with standard automated perimetry.

**DESIGN, SETTING, AND PARTICIPANTS:** In this phase 2, randomized, double-blind, placebo-controlled clinical trial at a single academic institution, 197 patients were assessed for eligibility. Of these, 42 patients with treated open-angle glaucoma and moderate visual field loss in at least 1 eye were selected for inclusion and randomized. A total of 32 completed the study and were included in the final analysis. The mean (SD) age was 64.6 (9.8) years. Twenty-one participants (66%) were female. Participant race and ethnicity data were collected via self-report to ensure the distribution reflected that observed in clinical practice in the US but are not reported here to protect patient privacy. Recruitment took place in April 2019 and patients were monitored through December 2020. Data were analyzed from January to May 2021.

**INTERVENTIONS:** Ascending oral doses of nicotinamide (1000 to 3000 mg) and pyruvate (1500 to 3000 mg) vs placebo (2:1 randomization) .

**MAIN OUTCOMES AND MEASURES:** Number of visual field test locations improving beyond normal variability in the study eye. Secondary end points were the rates of change of visual field global indices (mean deviation (MD) , pattern standard deviation (PSD) , and visual field index (VFI) ) .

**RESULTS:** Twenty-two of 29 participants (76%) randomized to the intervention group and 12 of 13 participants (92%) randomized to placebo received their allocation, and 32 participants (32 eyes; ratio 21:11) completed the study (21 from the intervention group and 11 from the placebo group) . Median (IQR) follow-up time was 2.2 (2.0-2.4) months. No serious adverse events were reported during the study. The number of improving test locations was significantly higher in the treatment group than in the placebo group (median (IQR) , 15 (6-25) vs 7 (6-11) ;  $P = .005$ ) . Rates of change of PSD suggested improvement with

treatment compared with placebo (median, -0.06 vs 0.02 dB per week; 95% CI, 0.02 to 0.24; P = .02) but not MD (0.04 vs -0.002 dB per week; 95% CI, -0.27 to 0.09; P = .35) or VFI (0.09 vs -0.02% per week; 95% CI, -0.53 to 0.36; P = .71) .

**CONCLUSIONS AND RELEVANCE:** A combination of nicotinamide and pyruvate yielded significant short-term improvement in visual function, supporting prior experimental research suggesting a role for these agents in neuroprotection for individuals with glaucoma and confirming the need for long-term studies to establish their usefulness in slowing progression.

**TRIAL REGISTRATION:** ClinicalTrials.gov Identifier: NCT03797469.

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