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# Ophthalmology

## Relationship between intraocular pressure fluctuation and visual field progression rates in the United Kingdom Glaucoma Treatment Study --Manuscript Draft--

<b>Manuscript Number:</b>	OPHTHA-D-23-01872R3
<b>Article Type:</b>	Manuscript
<b>Keywords:</b>	visual field progression; ocular pulse amplitude; Risk factors; linear mixed models.
<b>Corresponding Author:</b>	David Garway-Heath, MD Moorfields Eye Hospital NHS Foundation Trust UNITED KINGDOM
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<b>Order of Authors:</b>	Alessandro Rabiolo, MD FEBO Giovanni Montesano, MD David P Crabb, PhD David F Garway-Heath, MD, FRCOphth
<b>Abstract:</b>	<p><b>Purpose.</b> To investigate whether intraocular pressure (IOP) fluctuation is independently associated with the rate of visual field (VF) progression in the United Kingdom Glaucoma Treatment Study.</p> <p><b>Design.</b> Randomized, double-masked, placebo-controlled multicenter trial.</p> <p><b>Participants:</b> Participants with <math>\geq 5</math> VFs (213 placebo, 217 treatment).</p> <p><b>Methods.</b> Associations between IOP metrics and the VF progression rates (mean deviation (MD) and five fastest locations) were assessed with linear mixed models. Fluctuation variables were mean ocular pulse amplitude (OPA), standard deviation (SD) of diurnal IOP (diurnal fluctuation), and SD of IOP at all visits (long-term fluctuation). Fluctuation values were normalized for mean IOP to make them independent from mean IOP. Correlated non-fluctuation IOP metrics (baseline, peak, mean, supine and peak phasing IOP) were combined with principal component analysis (PCA), and principal component 1 (PC1) was included as a covariate. Interactions between covariates and time from baseline modelled the effect of the variables on VF rates. IOP was measured with Goldmann applanation tonometry and OPA with Pascal tonometry. Analyses were conducted separately in the two treatment arms.</p> <p><b>Main Outcome Measures.</b> Associations between IOP fluctuation metrics and rates of MD and five fastest test locations.</p> <p><b>Results.</b> In the placebo arm, only PC1 was significantly associated with the MD rate (estimate [standard error (SE)]: -0.19 [0.04] dB/year, <math>p &lt; 0.001</math>), while normalized IOP fluctuation metrics were not. No variable was significantly associated with MD rates in the treatment arm. For the fastest five locations in the placebo group, PC1 (estimate [SE]: -0.58 [0.16] dB/year, <math>p &lt; 0.001</math>), CCT (estimate [standard error (SE)]: 0.26 [0.10] dB/year for 10 <math>\mu\text{m}</math> thicker, <math>p = 0.01</math>) and normalized OPA (estimate [SE]: -3.50 [1.04] dB/year, <math>p = 0.001</math>) were associated with rates of progression; normalized diurnal and long-term IOP fluctuations were not. In the treatment group, only PC1 (estimate [SE]: -0.27 [0.12] dB/year, <math>p = 0.028</math>) was associated with the rates of progression.</p> <p><b>Conclusions.</b> There is no evidence to support that either diurnal or long-term IOP fluctuation, as measured in clinical practice, are independent factors for glaucoma progression; other aspects of IOP, including mean IOP and peak IOP, may be more informative. OPA may be an independent factor for faster glaucoma progression.</p>
<b>Suggested Reviewers:</b>	
<b>Opposed Reviewers:</b>	
<b>Response to Reviewers:</b>	AE Comment: Dear authors, Congratulations on your work. I have one suggestion. In the Precis (and everywhere else where the same issue is present), please insert "either" in front of "diurnal" and replace "and" with "or" in front of "long-term". The way it now stands, one could conclude that diurnal fluctuation and long-term fluctuation are risk factors, but are not independent of one another. Does that make sense? Best

wishes, Henry Jampel

Authors' Response: We thank the Associate Editor for his positive feedback. We have now modified the precis, abstract, and discussion accordingly.

Change in the Manuscript:

Precis

"This exploratory analysis of the multicenter randomized placebo-controlled United Kingdom Glaucoma Treatment Study found no evidence to support that either diurnal or long-term IOP fluctuation are independent factors for glaucoma progression."

Abstract, page 4, lines 30-33

"Conclusions. There is no evidence to support that either diurnal or long-term IOP fluctuation, as measured in clinical practice, are independent factors for glaucoma progression; other aspects of IOP, including mean IOP and peak IOP, may be more informative."

Discussion, page 29, lines 595-597

"In conclusion, this study finds no evidence to support that either diurnal or long-term IOP fluctuation, defined in a clinically relevant manner, are independent factors for glaucoma progression."

February 3<sup>rd</sup>, 2024

Russell N. Van Gelder, MD PhD  
Chief Editor  
*Ophthalmology*

Dear Editor,

Thank you for considering our manuscript OPTHHA-D-23-01872, "**Intraocular pressure fluctuation and rates of visual field progression in primary open-angle glaucoma: an exploratory analysis from the United Kingdom Glaucoma Treatment Study (UKGTS)**" for publication in the *Ophthalmology* journal. The points raised by the Associate Editor and Editorial office have all been considered and changes incorporated into the revised manuscript where appropriate. Attached is a point-by-point response to each of these comments. Any changes to the manuscript are italicized and in quotes in the response letter.

All the authors have approved the revised manuscript for submission to the *Ophthalmology* journal. As Corresponding Author, I had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis, as well as the decision to submit it for publication.

Thank you for your consideration of our manuscripts and we look forward to your response.

Yours sincerely,

David F Garway-Heath  
Moorfields Eye Hospital  
162 City Rd, London EC1V 2PD  
United Kingdom  
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## POINT-BY-POINT RESPONSE FORM

Please list the editor's, reviewer(s)', and editorial office's comments in the left-hand column, spacing them so that you can insert the relevant response in the center column and the respective point(s) in the text (and tables or legends, if appropriate) in the right-hand column. Adding line numbers to the manuscript file and referring to specific line numbers will be useful in determining which parts of the manuscript changed.

Manuscript #: OPHTHA-D-23-01872

Manuscript title: Relationship between intraocular pressure fluctuation and visual field progression rates in the United Kingdom Glaucoma Treatment Study

Suggestion, Question, or Comment from the Editor	Author's Response	Change in the Manuscript
<p>Dear authors,</p> <p>Congratulations on your work. I have one suggestion. In the <i>Precis</i> (and everywhere else where the same issue is present), please insert "either" in front of "diurnal" and replace "and" with "or" in front of "long-term". The way it now stands, one could conclude that diurnal fluctuation and long-term fluctuation are risk factors, but are not independent of one another. Does that make sense?</p> <p>Best wishes,</p> <p>Henry Jampel</p>	<p>We thank the Associate Editor for his positive feedback. We have now modified the <i>precis</i>, abstract, and discussion accordingly.</p>	<p><u>Precis</u>  <i>"This exploratory analysis of the multicenter randomized placebo-controlled United Kingdom Glaucoma Treatment Study found no evidence to support that either diurnal or long-term IOP fluctuation are independent factors for glaucoma progression."</i></p> <p><u>Abstract, page 4, lines 30-33</u>  <b><i>Conclusions.</i></b> <i>There is no evidence to support that either diurnal or long-term IOP fluctuation, as measured in clinical practice, are independent factors for glaucoma progression; other aspects of IOP, including mean IOP and peak IOP, may be more informative."</i></p> <p><u>Discussion, page 29, lines 595-597</u>  <i>"In conclusion, this study finds no evidence to support that either diurnal or long-term IOP fluctuation, defined in a clinically relevant manner, are independent factors for glaucoma progression."</i></p>

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<b>Suggestion, Question, or Comment from the Editorial Office</b>	<b>Author's Response</b>	<b>Change in the Manuscript</b>
If your paper includes a study group/writing committee authorship, please upload the complete study group/writing committee list as a Word document "Collaborators" file to the submission.	We have now included a Word document "Collaborators" file listing the UKGTS investigators.	N/A

## PRECIS

This exploratory analysis of the multicenter randomized placebo-controlled United Kingdom Glaucoma Treatment Study found no evidence to support that either diurnal ~~and-or~~ long-term IOP fluctuation are independent factors for glaucoma progression.

- Manuscript -

**Relationship between intraocular pressure fluctuation and visual field progression rates in the United Kingdom Glaucoma Treatment Study**

**Authors:** Alessandro Rabiolo, MD, FEBO<sup>1-3</sup>; Giovanni Montesano, MD<sup>1,4</sup>; David P Crabb PhD<sup>4</sup>; David F Garway-Heath, MD, FRCOphth<sup>1</sup>, on behalf of the United Kingdom Glaucoma Treatment Study Investigators

~~United Kingdom Glaucoma Treatment Study investigators:~~

~~David F. Garway-Heath MD, David P. Crabb PhD, Catey Bunce DSc, Gerassimos Lascaratos MSc, Francesca Amalfitano BSc, Nitin Anand MD, Augusto Azuara-Blanco PhD, Rupert R. Bourne MD, David C. Broadway MD, Ian A. Cunliffe FRCOphth, Jeremy P. Diamond PhD, Scott G. Fraser MD, Tuan A. Ho MSc, Prof Keith R. Martin DM, Andrew I. McNaught MD, Anil Negi MD, Krishna Patel MSc, Richard A. Russell PhD, Ameet Shah MRCOphth, Paul G. Spry PhD, Katsuyoshi Suzuki PhD, Edward T. White BSc, Richard P. Wormald FRCOphth, Wen Xing MSc, Thierry G. Zeyen PhD~~

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**Short title:** IOP fluctuation and glaucoma progression rates in the UKGTS

**Conflict of Interest:** None of the authors has any competing interest.

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USA). DFG-H's chair at UCL is supported by funding from the nonprofit association Glaucoma UK.

Presented at: Association for Research in Vision and Ophthalmology

Annual Meeting, May 2022, Denver, Canada; 15<sup>th</sup> European Glaucoma Society

Congress, June 2022, Athens, Greece.

## ABSTRACT

1 **Purpose.** To investigate whether intraocular pressure (IOP) fluctuation is  
2 independently associated with the rate of visual field (VF) progression in the United  
3 Kingdom Glaucoma Treatment Study.

4 **Design.** Randomized, double-masked, placebo-controlled multicenter trial.

5 **Participants:** Participants with  $\geq 5$  VFs (213 placebo, 217 treatment).

6 **Methods.** Associations between IOP metrics and the VF progression rates (mean  
7 deviation (MD) and five fastest locations) were assessed with linear mixed models.  
8 Fluctuation variables were mean ocular pulse amplitude (OPA), standard deviation  
9 (SD) of diurnal IOP (diurnal fluctuation), and SD of IOP at all visits (long-term  
10 fluctuation). Fluctuation values were normalized for mean IOP to make them  
11 independent from mean IOP. Correlated non-fluctuation IOP metrics (baseline, peak,  
12 mean, supine and peak phasing IOP) were combined with principal component  
13 analysis (PCA), and principal component 1 (PC1) was included as a covariate.  
14 Interactions between covariates and time from baseline modelled the effect of the  
15 variables on VF rates. IOP was measured with Goldmann applanation tonometry and  
16 OPA with Pascal tonometry. Analyses were conducted separately in the two  
17 treatment arms.

18 **Main Outcome Measures.** Associations between IOP fluctuation metrics and rates  
19 of MD and five fastest test locations.

20 **Results.** In the placebo arm, only PC1 was significantly associated with the MD rate  
21 (estimate [standard error (SE)]: -0.19 [0.04] dB/year,  $p < 0.001$ ), while normalized IOP  
22 fluctuation metrics were not. No variable was significantly associated with MD rates  
23 in the treatment arm. For the fastest five locations in the placebo group, PC1  
24 (estimate [SE]: -0.58 [0.16] dB/year,  $p < 0.001$ ), CCT (estimate [standard error (SE)]:

25 0.26 [0.10] dB/year for 10  $\mu$ m thicker,  $p=0.01$ ) and normalized OPA (estimate [SE]: -  
26 3.50 [1.04] dB/year,  $p=0.001$ ) were associated with rates of progression; normalized  
27 diurnal and long-term IOP fluctuations were not. In the treatment group, only PC1  
28 (estimate [SE]: -0.27 [0.12] dB/year,  $p=0.028$ ) was associated with the rates of  
29 progression.

30 **Conclusions.** There is no evidence to support that either diurnal ~~and or~~ long-term  
31 IOP fluctuation, as measured in clinical practice, are independent factors for  
32 glaucoma progression; other aspects of IOP, including mean IOP and peak IOP,  
33 may be more informative. OPA may be an independent factor for faster glaucoma  
34 progression.

35

36 **Keywords:** visual field progression; ocular pulse amplitude; risk factors; linear  
37 mixed models.

## 38 INTRODUCTION

39 Intraocular pressure (IOP) is an established risk factor for glaucoma  
40 progression, and lowering IOP is currently the only available treatment to slow the  
41 disease progression.<sup>1-4</sup> Longitudinal measurement of IOP is crucial in evaluating  
42 glaucoma patients, estimating their risk of developing progressive glaucomatous  
43 damage, and assessing their response to treatment.

44 IOP is subject to fluctuations over time. Several IOP-derived parameters are  
45 commonly used in clinical practice and research to summarize the behavior of IOP,  
46 including mean IOP (average of IOP over multiple visits), peak IOP (highest IOP  
47 reading over follow-up), and IOP fluctuation (standard deviation [SD] or range IOP  
48 over time). Many studies have shown that mean IOP and peak IOP are  
49 independently associated with glaucoma progression;<sup>1, 2, 5, 6</sup> on the other hand, the  
50 exact role of IOP fluctuation is still debated, with discordant results reported in the  
51 literature.<sup>5-10</sup> Elucidating the role of IOP fluctuation is difficult for several reasons.  
52 IOP fluctuation is tightly correlated with other IOP-related metrics (e.g., mean IOP),  
53 making it difficult to isolate its role as an independent factor. IOP fluctuation may be  
54 artificially increased by escalating treatment in patients with suspect progression.  
55 The effect of IOP fluctuation may not be uniform, varying as a function of the disease  
56 stage, treatment status, mean IOP values, and definition of fluctuation.<sup>11</sup>

57 This planned secondary analysis of the United Kingdom Glaucoma Treatment  
58 Study (UKGTS) randomized controlled trial aimed to evaluate whether IOP  
59 fluctuation, as assessed by ocular pulse amplitude (OPA), diurnal variation and  
60 between-visit variation, is independently associated with the rate of visual field  
61 progression. The UKGTS is ideal for this purpose because there were no treatment

- 62 escalations artificially increasing IOP fluctuation, and the dataset allows evaluation of
- 63 IOP metrics in both untreated and treated glaucoma patients.

## 64 **METHODS**

### 65 *Study Population and Procedures*

66 This study was a planned secondary analysis of data from the UKGTS, which  
67 was a multicenter, randomized, triple-masked, placebo-controlled trial investigating  
68 the ability of Latanoprost, an IOP lowering medication, to preserve visual function in  
69 newly diagnosed open-angle glaucoma patients (trial registration number,  
70 ISRCTN96423140). The UKGTS and the subsequent analysis of anonymized data in  
71 this study complied with the tenets of the Declaration of Helsinki and were approved  
72 by local institutional review boards (Moorfields and Whittington Research Ethics  
73 Committee on June 1, 2006, ethics approval reference, 09/H0721/56). All patients  
74 provided written informed consent at the time of enrolment in the trial.

75 The UKGTS study protocol, baseline characteristics, and outcomes have  
76 been published elsewhere.<sup>3, 12, 13</sup> Participants recruited in 10 ophthalmology  
77 institutions across the United Kingdom were randomized 1:1 to receive latanoprost  
78 0.005% or placebo eye drops once in the evening in both eyes for 24 months or until  
79 meeting an endpoint. The UKGTS included patients  $\geq 18$  years of age and newly  
80 diagnosed treatment-naïve open-angle glaucoma, including primary open-angle and  
81 pseudoexfoliation glaucoma. Exclusion criteria were: advanced glaucoma, as  
82 defined by visual field mean deviation  $< -10$  dB in the better eye or  $< -16$  dB in the  
83 worse eye, mean baseline IOP  $\geq 30$  mmHg, Snellen best-corrected visual acuity  
84 (BCVA)  $< 6/12$ , and poor image quality ( $>40$   $\mu\text{m}$  mean pixel height standard  
85 deviation) with the Heidelberg retina tomograph (Heidelberg Engineering,  
86 Heidelberg, Germany).

87 Potentially eligible participants underwent two pre-randomization visits. After  
88 meeting the study criteria and signing the written informed consent, participants were

89 randomized either to receive latanoprost 0.005% or placebo eye drops. Enrolled  
90 subjects underwent IOP measurement, VF, and imaging at eleven post-  
91 randomization visits over 24 months or until meeting an endpoint. Standard  
92 automated perimetry with the Humphrey Field Analyzer (Carl Zeiss Meditec, Dublin,  
93 CA) was performed with stimulus size III, Swedish Interactive Threshold Algorithm  
94 (SITA) standard strategy, and 24-2 grid. VF testing was performed at all 11  
95 scheduled visits over 24 months, and tests were clustered (2 VFs on the same day)  
96 at baseline, 2 months, 16 months, 18 months, and 24 months. In this exploratory  
97 analysis, we included participants from the UKGTS with  $\geq 5$  reliable visual fields  
98 (VFs). Reliable VFs were defined as those with false positives less than 15%, while  
99 no limits for false negatives and fixation losses were applied. At the first post-  
100 randomization visit, the following demographic variables were collected: age, sex,  
101 ethnicity, family history of glaucoma, history of systemic diseases (i.e., systemic  
102 hypertension, cardiovascular disease, diabetes, heart attack, stroke, sleep apnea,  
103 migraine, Raynaud's phenomenon, vasospasm, angina, claudication), and smoking  
104 status. The following investigations were also performed: blood pressure  
105 measurements with the Omron M7 Blood Pressure Monitor (Matsusaka, Mie, Japan),  
106 weight, height, slit-lamp examination, refractive error measured either with an  
107 autorefractor or from spectacle focimetry (if not available, the spherical equivalent of  
108 the trial lens was used in the visual field test, based on participants' age), axial  
109 length measurement with the IOL Master (Carl Zeiss Meditec, Dublin, CA), and  
110 central corneal thickness (CCT) measured with an ultrasound pachymeter. We  
111 included one eye per patient; specifically, the eye with the worst baseline VF mean  
112 deviation (MD).

113

114 *IOP Metrics*

115           At all visits, IOP was measured with Goldmann applanation tonometry (GAT;  
116 Haag Streit, Koeniz, Switzerland), Pascal dynamic contour tonometry (Ziemer  
117 Ophthalmic Systems AG, Zurich, Switzerland), and the Ocular Response Analyzer  
118 (Reichert, Inc., Buffalo, NY). Diurnal GAT phasing with IOP measured every 2 hours  
119 from 9 am to 5 pm was performed at the first post-randomization and at the final visit.  
120 At the first post-randomization visit, supine IOP was measured with Perkins  
121 applanation tonometer.

122           The following IOP metrics were calculated and used for the analyses:

- 123     • Baseline pretreatment IOP, defined as the average of the IOP readings obtained  
124       in the two pre-randomization visits.
- 125     • Mean IOP, defined as the average of all post-randomization IOP readings.
- 126     • Peak IOP, defined as the highest IOP reading of all post-randomization IOP  
127       readings.
- 128     • Supine IOP, defined as the Perkins applanation tonometry IOP readings  
129       measured at the first post-randomization visit.
- 130     • Phasing peak IOP, defined as the highest IOP reading of the diurnal phasing  
131       performed at the first post-randomization visit.
- 132     • Diurnal IOP fluctuation, defined as the SD of IOP measurements obtained from  
133       the diurnal IOP phasing performed at the first post-randomization visit. Diurnal  
134       IOP fluctuation was also calculated using the IOP measurements from the last  
135       post-randomization visit.
- 136     • Long-term IOP fluctuation, defined as the SD of post-randomization IOP  
137       readings.

- 138 • Mean ocular pulse amplitude (OPA) from the Pascal Dynamic Contour tonometry.  
139 OPA was defined as the range of the pulse wave contour and provides a  
140 measure of how IOP fluctuates over cardiac cycle. We used the average of all  
141 post-randomization ORA values.

142

### 143 *Statistical Analysis*

144 We performed all statistical analyses with the open-source software R (R  
145 Foundation for Statistical Computing, Vienna, Austria). Variable distributions were  
146 inspected with histograms and quantile-quantile plots. We reported mean ( $\pm$   
147 Standard deviation [SD]) and median (interquartile range [IQR]) for Gaussian and  
148 non-Gaussian variables, respectively. We reported frequencies and proportions for  
149 discrete variables. Proportion and pattern of missing data were analyzed. All  
150 analyses were conducted with complete cases. All tests were 2-tailed, and p-values  
151  $<0.05$  were considered statistically significant.

152 Demographic and clinical characteristics between the two treatment groups  
153 were compared with t-test and chi-squared test for continuous and categorical  
154 variables, respectively. Agreement between diurnal IOP fluctuation calculated on the  
155 first and last post-randomization visit was investigated with Bland-Altman statistics.  
156 We also collected the timing of each IOP measurement and calculated the absolute  
157 differences from each measurement and the mean time of day for each patient's IOP  
158 measurements.

159 Linear models were used to evaluate the relationship between (i) mean IOP and  
160 long-term IOP fluctuation, (ii) mean IOP and long-term IOP fluctuation/mean IOP, (iii)  
161 mean diurnal IOP and diurnal IOP fluctuation, (iv) mean diurnal IOP and diurnal IOP

162 fluctuation/mean diurnal IOP, (v) mean OPA and mean IOP, and (vi) mean  
163 OPA/GAT IOP and mean IOP.

164 IOP fluctuation is known to be positively correlated with mean IOP. Additionally,  
165 measurement error can contribute to the variability in IOP measurements, potentially  
166 confounding true IOP fluctuation. To obtain a measure of IOP fluctuation which is  
167 independent from mean IOP, we performed a normalization of IOP fluctuation  
168 values. Specifically, we ran a linear regression of IOP fluctuation against mean IOP.  
169 We then divided the observed IOP fluctuation values by the corresponding predicted  
170 values. This process was applied distinctly for each fluctuation metric. For long-term  
171 fluctuation, we utilized the SD of all post-randomization IOP readings and their  
172 corresponding mean IOP values from all post-randomization readings. For diurnal  
173 fluctuation, we used the SD and mean IOP measurements from the diurnal IOP  
174 phasing conducted during the first post-randomization visit. For the OPA, we used  
175 the average of all post-randomization ORA values for each subject and their  
176 corresponding mean IOP across all available post-randomization visits. For OPA, we  
177 calculated the average of all post-randomization ORA values for each subject,  
178 alongside their corresponding mean IOP from all available post-randomization visits.

179 As shown in Figure S1, normalized IOP fluctuation was unrelated to mean IOP.  
180 Normalization was further performed on the two study arms separately, leading to  
181 almost identical results (data not shown). All analyses were conducted on both  
182 normalized and unnormalized IOP fluctuations values.

183 Linear mixed models with random slopes and random intercepts were used to  
184 estimate the rates of progression and investigate associations between the rate of  
185 visual field progression and variables of interest. Linear mixed models are an  
186 extension of traditional linear models, which can accommodate the repeated-

187 measure (e.g., multiple measurements from the same eye over time) and clustered  
188 (multiple test locations from the same VF) nature of data. We first look at univariable  
189 associations between the MD rate of change and each variable of interest. In all  
190 models, the MD value at each visit was the outcome variable; the follow-up time in  
191 years, the covariate of interest, and their interaction were the fixed effects; the eye  
192 identification number and follow-up time were the random intercept and random  
193 slope terms, respectively, to account for the repeated measure of data and for the  
194 fact that different eyes may have different rates of progression over time. Interactions  
195 between covariates and time from baseline modeled the variables' effect on the  
196 progression rate. We then built multiple variable linear mixed models to account for  
197 the impact of fluctuation metrics after adjusting for all other potentially confounding  
198 factors, including other IOP metrics. Correlations among candidate covariates were  
199 tested with a hierarchical cluster analysis based on the absolute value of Spearman  
200 correlations (Figure S2). Some of the variables measuring the magnitude of IOP  
201 elevation exhibited high correlations. Highly correlated variables are a source of  
202 multicollinearity, causing unstable regression coefficients and large standard errors.  
203 To address this issue, all correlated metrics measuring IOP (baseline IOP, peak IOP,  
204 mean IOP, supine IOP, peak phasing IOP) were combined using Principal  
205 Component Analysis (PCA). These variables had a |Spearman rho| of 0.50 or  
206 greater. PCA extracts uncorrelated orthogonal vectors (Principal Components [PCs])  
207 from multiple correlated variables. PCs are ranked, with the first PC (PC1) being the  
208 one containing the largest amount of combined information from the correlated  
209 variables. PCA was performed on standardized data, with zero mean and unit  
210 variance. We inspected the PCA model with biplots and scree plots (Figure S3).  
211 Scree plots were used to visualize the amount of variance explained by the various

212 Principal Components and to select the number of PCs to retain for subsequent  
213 analyses. PC1 was selected for further analyses, as it explained 81% of the overall  
214 variance in the PCA, and used as a fixed effect in the multivariable linear mixed  
215 models. The Interaction between PC1 and follow-up time modelled the effect of PC1  
216 on visual field progression rates, as previously explained. PCA was also performed  
217 on the two study arms separately, leading to similar results (data not shown).

218         Similar analyses were run in a pointwise manner, including: (i) all 52 VF test  
219 locations of the 24-2 grid (after excluding the two locations corresponding to the blind  
220 spot), and (ii) the five fastest progressing locations for each study eye (which is  
221 conceptually similar to the event-based GPA analysis which identifies the 3 or more  
222 locations most different from baseline). Models conducted on the pointwise threshold  
223 sensitivity data had a nested random intercept with eye identification number over  
224 the test location number to account for the inclusion of multiple pointwise series from  
225 the same eye. All models were run separately in the placebo and treatment arms.  
226 Regression estimates along with their 95% confidence intervals (95% CIs) and p-  
227 values were reported.

## 228 RESULTS

229 Of the 461 participants with longitudinal data included in the primary UKGTS  
230 analysis, 31 were excluded because of an insufficient number of VFs. The remaining  
231 430 (placebo arm: 213, treatment arm: 217) participants were included in this study.  
232 As shown in Figure S4, most variables had complete observations, with only a few  
233 variables having missing observations. Spherical equivalent, CCT, and supine IOP  
234 values were missing in 26 eyes (6%), 16 (3.7%), and 15 eyes (3.5%), respectively.  
235 Mean arterial pressure, body mass index, ethnicity, corneal hysteresis, peak and  
236 mean phasing IOP, and diurnal fluctuation were missing in less than 2% of patients.  
237 All other variables had no missing data.

238 Baseline characteristics of the UKGTS study population have been published  
239 elsewhere.<sup>3, 12</sup> Table 1 illustrates the main demographic and clinical characteristics  
240 of the patient cohort. Patients in the treatment cohort had significantly longer follow-  
241 up time than those in the placebo cohort, with a median (IQR) of 1.9 (1.3 to 2.0) and  
242 1.6 (1.0 to 2.0) years, respectively ( $p=0.004$ ). The number of VFs was also  
243 significantly greater ( $p=0.027$ ) in the treatment arm (median [IQR]: 15 [10-16]) than in  
244 the placebo arm (median [IQR]: 13 [10-16]). In the post-randomization study period,  
245 patients in the treatment arm showed higher mean corneal hysteresis than those in  
246 the placebo arm (mean [ $\pm$ SD]: 9.4 [ $\pm$ 1.6] vs. 8.9 [ $\pm$ 1.6] mmHg,  $p=0.003$ ). As shown in  
247 Figure 5, all post-randomization IOP metrics were significantly different between the  
248 two arms ( $p<0.045$  or below), except for normalized diurnal IOP fluctuation ( $p=0.89$ )  
249 and normalized OPA ( $p=0.93$ ). The median of the absolute differences from the  
250 mean time of day for each patient's IOP measurements was 1.1 hours, with an  
251 interquartile range (IQR) of 0.5 hours (30 minutes) to 2.0 hours.

252

253 *Global MD rate*

254 The distribution of MD rates in the two groups as estimated with linear mixed  
255 models is illustrated in Figure 6. Median (IQR) MD rates in the placebo and  
256 treatment cohort were -0.23 (-0.73 to 0.11) dB/year and 0.13 (-0.30 to 0.37) dB/year,  
257 respectively ( $p < 0.001$ ).

258 In the univariable analysis (Table S2), higher values of all non-fluctuation IOP  
259 parameters, including pretreatment baseline IOP (estimate [standard error (SE)]: -  
260 0.06 [0.02] dB/year for 1 mmHg increase,  $p < 0.001$ ), mean IOP (estimate [SE]: -0.08  
261 [0.02] dB/year for 1 mmHg increase,  $p < 0.001$ ), peak IOP (estimate [SE]: -0.07 [0.01]  
262 dB/year for 1 mmHg increase,  $p < 0.001$ ), peak phasing IOP (estimate [SE]: -0.05  
263 [0.02] dB/year for 1 mmHg increase,  $p < 0.001$ ), and supine IOP (estimate [SE]: -0.06  
264 [0.01] dB/year for 1 mmHg increase,  $p < 0.001$ ), were significantly associated with  
265 faster MD rates in the placebo group. With regards to the IOP fluctuations  
266 parameters, higher long-term IOP fluctuation (estimate [SE]: -0.27 [0.07] dB/year for  
267 1 mmHg increase,  $p < 0.001$ ) and OPA (estimate [SE]: -0.32 [0.09] dB/year for 1  
268 mmHg increase,  $p < 0.001$ ) were associated with faster MD rates of change, while  
269 diurnal IOP fluctuation was not ( $p = 0.23$ ). None of the fluctuation parameters was  
270 associated with the MD rate after normalizing for the mean IOP ( $p = 0.11$  or above). In  
271 the treatment arm, none of the variables was significantly associated with the MD  
272 rate, except for long-term IOP fluctuation (estimate [SE]: -0.12 [0.06] dB/year for 1  
273 mmHg increase,  $p = 0.047$ ).

274 Results of the multivariable model for factors associated with MD rate of  
275 progression are illustrated in Figure 7 and detailed in Table S3. In the placebo arm,  
276 PC1, which combined information from all the non-fluctuation IOP parameters, was  
277 the only factor associated with the MD rate (estimate [SE]: -0.19 [0.08] dB/year for 1

278 unit increase,  $p < 0.001$ ), while the various normalized IOP fluctuation metrics were  
279 not. Thinner CCT had an association of borderline statistical significance with faster  
280 VF progression rates (estimate [SE]: 0.05 [0.02] dB/year for 10  $\mu\text{m}$  thicker,  $p = 0.06$ ).  
281 None of the variables was significantly associated with the MD rate of progression in  
282 the treatment arm. Older age was associated with faster MD rates (estimate [SE]: -  
283 0.12 [0.06] dB/year for a 10-year increase) in the treatment arm, but this only  
284 approached nominal statistical significance ( $p = 0.06$ ). Similar results were obtained  
285 when analyzing unnormalized IOP fluctuation metrics (Table S4).

286

### 287 *Pointwise Rates*

288 Figure 6 illustrates the distribution of pointwise progression rates in the two  
289 groups. Pointwise rates were significantly faster in the placebo group than in the  
290 treatment group (median [IQR]: -0.42 [-0.59 to -0.26] dB/year vs. 0.03 [-0.14 to 0.19]  
291 dB/year,  $p < 0.001$ ). Results of the univariable analysis for factors associated with the  
292 pointwise rates of change are illustrated in Table S5. In the placebo group, all the  
293 non-fluctuation IOP parameters were significantly associated with the pointwise rates  
294 ( $p = 0.003$  or below). Higher unnormalized long-term IOP fluctuation (estimate [SE]: -  
295 0.34 [0.13] dB/year for 1 mmHg increase,  $p = 0.008$ ) and OPA (estimate [SE]: -0.65  
296 [0.15] dB/year for 1 mmHg increase,  $p < 0.001$ ) were associated with faster pointwise  
297 rates of progression. After normalizing IOP fluctuations for mean IOP, only OPA was  
298 associated with the rate of progression (estimate [SE]: -1.36 [0.48] dB/year for 1 unit  
299 increase,  $p = 0.005$ ). In the treatment arm, none of the IOP variables was associated  
300 with the pointwise rates of progression. In the multiple variable model (Figure 8 and  
301 Table S6), normalized mean OPA was associated with the pointwise rates of  
302 progression in the placebo arm (estimate [SE]: -1.23 [0.46] dB/year for 1 unit

303 increase,  $p=0.009$ ), but not in the treatment arm. None of the other fluctuation  
304 metrics was associated with the rate of progression in either group. The combined  
305 IOP metric, PC1, was associated with the pointwise rate of change in the placebo  
306 group ( $p<0.001$ ), but not in the treatment group ( $p=0.42$ ). Similarly, none of the  
307 unnormalized IOP fluctuation metrics was associated with the pointwise rate of  
308 change metrics (Table S7), except for mean OPA in the placebo group (estimate  
309 [SE]: -0.47 [0.17] dB/year for 1 mmHg increase,  $p=0.008$ ).

310 For the five fastest progressing locations, median (IQR) pointwise rates of the  
311 five in the placebo and treatment cohort were -1.00 (-1.49 to -0.80) dB/year and -  
312 0.52 (-0.93 to -0.34) dB/year, respectively ( $p<0.001$ ). Results of the univariable  
313 analysis for factors associated with the rates of the fastest five locations are  
314 illustrated in Table S8. In the placebo group, all the non-fluctuation IOP parameters  
315 were significantly associated with the pointwise rates ( $p=0.003$  or below). Higher  
316 unnormalized (estimate [SE]: -1.67 [0.34] dB/year for 1 mmHg increase,  $p<0.001$ )  
317 and normalized OPA (estimate [SE]: -3.95 [1.10] dB/year for 1 unit increase,  
318  $p<0.001$ ) were associated with faster rates of progression. In the treatment arm,  
319 higher unnormalized long-term IOP fluctuation was associated with faster rates of  
320 progression (estimate [SE]: -0.46 [0.17] dB/year for 1 mmHg increase,  $p=0.006$ ), but  
321 the association was no longer significant after normalizing IOP fluctuation (estimate  
322 [SE]: -0.81 [0.44] dB/year for 1 unit increase,  $p=0.06$ ). In the multiple variable model  
323 (Figure 9 and Table S9), CCT (estimate [SE]: 0.26 [0.10] dB/year for 10  $\mu\text{m}$  thicker,  
324  $p=0.01$ ), normalized OPA (estimate [SE]: -3.50 [1.04] dB/year for 1 unit increase,  
325  $p=0.001$ ), and PC1 (estimate [SE]: -0.58 [0.16] dB/year for 1 PC1 unit increase,  
326  $p<0.001$ ) were associated with the rates of progression of the fastest five test  
327 locations in the placebo group; while normalized diurnal and long-term IOP

328 fluctuations were not. In the treatment group, PC1 (estimate [SE]: -0.27 [0.12]  
329 dB/year for 1 PC1 unit increase,  $p=0.028$ ) was the only factor associated with  
330 progression rates. Results of the nonnormalized models are shown in Table S10.  
331 All analyses were repeated with mean IOP, peak IOP and normalized LTF fluctuation  
332 calculated from corneal compensated IOP as measured with the Ocular Response  
333 Analyzer (Reichert, Inc, Buffalo, NY) and lead to similar results (Figures S10-S14).

## 334 **DISCUSSION**

335           In this study, we evaluated whether IOP fluctuation was associated with the  
336 rate of glaucomatous visual field progression. We provided a comprehensive  
337 evaluation of clinically relevant definitions of IOP fluctuation over the course of  
338 seconds (OPA), office hours (diurnal fluctuation), and multiple visits over the entire  
339 follow-up (long-term fluctuation). We found that higher OPA was associated with  
340 faster rates of progression, while diurnal or long-term IOP fluctuations were not  
341 associated with the rate of progression. Elevated IOP metrics (e.g., mean IOP, peak  
342 IOP) were consistently associated with the rate of VF progression.

343           Establishing the relationship between IOP fluctuation and the rates of visual  
344 field progression is not an easy task for many reasons. First, IOP fluctuation may  
345 vary as a function of the time frame over which it is calculated, and there is no  
346 consensus on which type of fluctuation is most informative. Our study provided a  
347 comprehensive approach, analyzing three measures of fluctuations. Second, the  
348 definition of IOP fluctuation is not uniform across studies, with IOP range and SD  
349 IOP usually used as measures for IOP fluctuation. It has been suggested that SD  
350 IOP could be a more robust metric than range IOP as the latter may be heavily  
351 influenced by outliers and does not account for the number of IOP measurements.<sup>8</sup>  
352 In this study, we used SD IOP to calculate diurnal and long-term IOP fluctuation; on  
353 the other hand, OPA, a measure of very short-term fluctuation, was an average  
354 range of several cardiac cycles. We further mitigated the effect of potential outliers  
355 on OPA by obtaining two consecutive OPA measurements at each time point,  
356 averaging them to have a single value, and then averaging the resulting values  
357 throughout all available follow-up visits. Third, isolating the impact of fluctuation from  
358 the level of IOP may be challenging because of the intimate relationship between

359 these two variables. IOP fluctuation is known to be positively correlated with mean  
360 IOP. In a retrospective study performed on non-human primates of experimental  
361 glaucoma, Gardiner and colleagues<sup>10</sup> used the coefficient of variation (SD IOP  
362 divided by mean IOP) to remove the relationship between these two variables. In our  
363 cohort, the coefficient of variation reversed the association with mean IOP values,  
364 leading to a negative relationship between IOP fluctuation and mean IOP. The  
365 explanation for this is likely that there are two components of variability  
366 (measurement error and true IOP fluctuation), one of which (true fluctuation) is  
367 related to mean IOP and the other (measurement error) is not.<sup>14</sup> Dividing the  
368 measurement error by the mean IOP induces the negative association. The method  
369 of normalization used in our study likely respects both the increased fluctuations at  
370 higher mean IOP and constant measurement errors. Fourth, IOP-related metrics  
371 tend to be highly correlated because they are related to the same original quantity.  
372 Modeling highly correlated variables may lead to a statistical issue called  
373 multicollinearity. In the presence of multicollinearity, regression models may become  
374 inefficient with loss of statistical power, greater computation inaccuracy, unstable  
375 estimates, and high variance.<sup>15</sup> Various methods have been proposed to deal with  
376 multicollinearity. One or more highly collinear covariates may be omitted from the  
377 regression model, which may cause information loss. Ridge regression, a form of  
378 penalized linear regression, is another popular method to handle multicollinearity;  
379 however, it produces biased estimates and is better suited for predictive rather than  
380 explanatory models.<sup>16</sup> In our study, we addressed the issue of multicollinearity with  
381 PCA, which creates a new set of orthogonal linear combinations of the original  
382 variables (PCs), by definition perfectly uncorrelated to each other.<sup>17</sup> In this study, we  
383 used PCA to obtain a maximally informative combined metric of IOP control. Fifth,

384 clinicians are more likely to escalate treatment in progressing patients, inducing IOP  
385 fluctuation. This may be easily overlooked in retrospective cohort studies and even in  
386 prospective studies if countermeasures are not adopted. The findings of previous  
387 studies have been greatly questioned because of the possible bias caused by  
388 medical and surgical treatment escalation. Our study is not vulnerable to the  
389 potential confounding effect of treatment escalation as patients in the UKGTS took  
390 either latanoprost or placebo for their entire study period. In addition, our study is in  
391 the unique position to elucidate the role of IOP fluctuation on glaucomatous  
392 progression in untreated patients.

393         The relationship between IOP fluctuation and glaucomatous progression  
394 remains highly controversial, with contrasting results reported in the literature.  
395 Comparisons of results from different studies, including ours, should be done with  
396 caution because of heterogeneity in study populations, designs, definitions of  
397 fluctuation and progression, and statistical analysis. Most of the previous studies  
398 focused on long-term (intervisit) IOP fluctuation, which is the most accessible  
399 fluctuation metric to obtain as it can be estimated from single IOP measurements  
400 from multiple visits. Our study did not find any relationship between long-term IOP  
401 fluctuation and VF progression rates. Bengtsson et al.<sup>5</sup> conducted a post-hoc  
402 analysis from the Early Manifest Glaucoma Trial (EMGT); they found that mean IOP  
403 was a strong predictor of glaucoma progression, while IOP fluctuation was not.  
404 EMGT and UKGTS share many similarities, including the mild disease stage, type of  
405 treatment (i.e., nonsurgical intervention), and mean IOP values. An observational  
406 study by Medeiros et al.<sup>18</sup> investigated whether IOP fluctuations were associated  
407 with the risk of conversion from ocular hypertensive to glaucoma and found that  
408 mean IOP, but not long-term IOP fluctuation, was associated with glaucoma

409 development. Other studies found contrasting results, showing a positive association  
410 between long-term IOP fluctuation and VF progression. In a post-hoc analysis of the  
411 Advanced Glaucoma Intervention Study (AGIS), Nouri-Mahdavi and colleagues<sup>9</sup>  
412 found that long-term IOP fluctuation was an independent risk factor for glaucoma  
413 progression, while mean IOP was not. The results of this study were criticized  
414 because the authors analyzed the entire available follow-up, including time points  
415 after treatment escalation. Further intervention, either in the form of trabeculectomy  
416 or laser trabeculoplasty as per AGIS protocol, might have been itself a cause of  
417 clinician-induced increased fluctuation in patients at high risk of progression. In a  
418 subsequent post-hoc analysis of the AGIS, Caprioli and Coleman<sup>8</sup> investigated the  
419 relationship between long-term IOP fluctuation and VF progression, excluding those  
420 patients having multiple interventions; they found that long-term IOP fluctuations was  
421 significantly associated with VF progression in patients with low mean IOP, but not in  
422 those with high IOP. A post-hoc analysis from the Collaborative Initial Glaucoma  
423 Treatment Study (CIGTS)<sup>6</sup> examined the role of various IOP parameters on VF  
424 progression and found that long-term IOP fluctuation and peak IOP were associated  
425 with VF progression, while mean IOP was not.

426         The literature on the role of diurnal (or diurnal-nocturnal) IOP fluctuation is  
427 scarce, of lower quality, and with conflicting reports. In the Malmö Ocular  
428 Hypertension study,<sup>19</sup> diurnal IOP fluctuation was not an independent risk factors for  
429 the development of glaucoma; conversely, mean IOP was associated with the  
430 incidence of glaucomatous visual field loss in patients with OHT. Our study did not  
431 find an association between diurnal IOP fluctuation and the rate of glaucomatous  
432 progression in any of the models, corroborating the findings of the Malmö Ocular  
433 Hypertension study. In a secondary analysis from a Swedish clinical trial

434 randomizing patients to either pilocarpine or argon laser trabeculoplasty, Bergea et  
435 al.<sup>20</sup> investigated the relationship between visual field progression and different IOP  
436 variables, and they found that both mean IOP and diurnal IOP fluctuation were  
437 associated with visual field progression. That study, however, had several limitations,  
438 including the small sample size (76 eyes), high proportion of pseudoexfoliation  
439 glaucoma (72%), and the use of range IOP as a measure of fluctuation, which is  
440 vulnerable to outlier and highly related to peak IOP. A retrospective study by Matlach  
441 and colleagues<sup>21</sup> assessed the impact of long-term and diurnal-nocturnal IOP  
442 fluctuation on glaucoma progression in a cohort of 120 glaucoma patients randomly  
443 selected from a tertiary referral center; they found that diurnal-nocturnal IOP  
444 fluctuation was associated with glaucoma progression, while long-term IOP  
445 fluctuation and mean IOP were not. A retrospective study by Kim et al.<sup>22</sup> found  
446 similar results in a cohort of NTG patients, with higher diurnal IOP fluctuations and  
447 disc hemorrhages being associated with higher hazard of visual field progression.  
448 Both these studies are limited by their retrospective nature, making them vulnerable  
449 to potential confounders and selection bias. Also, these studies did not employ any  
450 statistical method to mitigate multicollinearity.

451 Besides including these two established measures of IOP fluctuation, we also  
452 investigated the role of very short-term fluctuation, as measured by the mean ocular  
453 pulse amplitude (OPA) over follow-up. OPA is calculated as the difference between  
454 systolic and diastolic IOP, as measured by the Pascal dynamic contour tonometer,  
455 and informs on how IOP varies across the cardiac cycle, secondary to the pulsatile  
456 influx/efflux of blood volume into the eye (mainly to choroid). Ocular pulse may be  
457 determined by various ocular and systemic factors, including ocular tissue rigidity,<sup>23-</sup>  
458 <sup>25</sup> axial length,<sup>26</sup> IOP,<sup>23, 27</sup> blood pressure pulse amplitude,<sup>28, 29</sup> left ventricular

459 ejection time,<sup>30</sup> heart rate,<sup>31, 32</sup> and conditions influencing ocular perfusion (e.g.,  
460 carotid artery stenosis, tight encircling band).<sup>33, 34</sup> To the best of our knowledge,  
461 there are currently no clinical studies investigating the role of OPA (or any metric for  
462 very short IOP fluctuation) on glaucoma progression. We found that higher OPA was  
463 significantly associated with faster pointwise rates of progression in the placebo  
464 group. Reasons for this finding are speculative. This association may result from an  
465 effect of the OPA itself or be related to one or more of its determinants. Animal  
466 studies have shown that acute IOP elevation may induce structural optic nerve head  
467 deformations and functional electrophysiological changes. Hence, multiple transient  
468 IOP spikes may cause faster glaucoma progression in vulnerable eyes. This  
469 explanation seems unlikely as these studies investigated large IOP changes, much  
470 larger than those measured with OPA. Higher OPA is associated with increased  
471 scleral rigidity and stiffer ocular tissues, which may be less compliant to IOP  
472 changes, causing larger stress within the lamina cribrosa secondary to IOP  
473 elevation.<sup>35, 36</sup> In a simulation study based on finite element analysis reconstructing a  
474 healthy eye model, Jin et al.<sup>36</sup> found that stiffer sclera was associated with higher  
475 OPA, larger ONH deformation, and increased shearing forces to neural axons of the  
476 neuroretinal rim. OPA has been proposed as a surrogate measure for  
477 hemodynamics, being influenced by the arterial pulse pressure, heart rate, and left-  
478 ventricular ejection time. Low diastolic blood pressure, vascular dysregulation and  
479 optic nerve hypoperfusion have been associated with glaucoma progression,  
480 especially in some phenotypes of open-angle glaucoma. However, one would expect  
481 an opposite association to that found in this study, as lower OPA has been  
482 associated with lower ocular blood supply. On the other hand, larger arterial pulse  
483 pressure is associated with systemic hypertension, which may lead to vascular

484 damage. So, high OPA might be a surrogate for hypertensive vascular damage, and  
485 previous studies<sup>37, 38</sup> have shown that high blood pressure may be a risk factors for  
486 primary open-angle glaucoma.

487 Our study confirms the importance of elevated IOP on glaucoma progression.  
488 PC1, which combined information from various IOP parameters (i.e., mean IOP,  
489 peak IOP, baseline IOP, peak phasing IOP, and supine IOP), was consistently  
490 associated with the rate of visual field progression in the placebo group. On the other  
491 hand, such a relationship was significant in the treatment group only for the rates of  
492 the fastest five visual field locations, but not for global rates of change. The  
493 progression rate of the treatment arm was extremely slow during the trial duration,  
494 and the signal from a few progressing locations may be obscured by the overall  
495 stability of most test locations. Comparative studies<sup>39, 40</sup> have shown that pointwise  
496 methods (especially those considering only locations with significant deterioration)  
497 have higher sensitivity and require less time to detect progression than those based  
498 on global indices or all test locations. Our study does not provide any information on  
499 which IOP metric is the most important for disease progression; this is arduous to  
500 tackle because of the intimate relationship among these variables. De Moraes and  
501 colleagues<sup>2</sup> evaluated the effect of mean IOP, peak IOP, and SD IOP in a large  
502 retrospective cohort of glaucoma patients under clinical care; they found that all  
503 these variables were associated with disease progression in the univariable analysis,  
504 but only peak IOP was significantly associated with VF progression in the  
505 multivariable model. However, mean IOP and peak IOP are highly correlated, and a  
506 multivariable model containing both variables would likely suffer from  
507 multicollinearity. Treatment modifications highly influence mean IOP and SD IOP in

508 real-world settings; although the occurrence of glaucoma surgery during follow-up  
509 was taken into consideration, medical treatment escalation was not.

510 We also investigated the impact of non-IOP and other ocular factors on  
511 glaucomatous progression rates, including age, CCT, and corneal hysteresis. The  
512 evidence for role of CCT as a risk factor for glaucoma progression is often  
513 misunderstood. A thinner cornea causes artifacts in applanation tonometry, with  
514 underestimation of the true IOP.<sup>41</sup> Alternatively, corneal thickness may serve as a  
515 biomarker of the biomechanical properties of the lamina cribrosa and peripapillary  
516 sclera, providing insights into the vulnerability of the optic nerve to increased IOP.<sup>42</sup>  
517 An experimental study by Wells and colleagues<sup>43</sup> investigated whether CCT was  
518 associated with optic disc compliance after inducing acute IOP rise and found no  
519 significant association, indicating that CCT may not reflect ocular biomechanics. In  
520 our cohort, thinner CCT was associated with faster progression rates in some  
521 multivariable models (which included IOP metrics), while it did not show significance  
522 in any of the univariable models. This suggests that CCT alone is not directly  
523 associated with glaucoma progression: rather, it becomes statistically significant  
524 when measured IOP is included in the model due to the effect of CCT on measured  
525 IOP. Other studies, including the Early Manifest Glaucoma Treatment (EMGT)<sup>44</sup> and  
526 the Los Angeles Latino Eye Study (LALES),<sup>45</sup> found similar finding, associating thin  
527 CCT with conversion to glaucoma and incident glaucoma in multivariable models,  
528 but not in univariable models. Khawaja and Jansonius<sup>46</sup> performed a simulation  
529 study that mimicked datasets similar to the LALES and Ocular Hypertensive  
530 Treatment Study so that IOP, but not CCT, was not associated with glaucoma risk.  
531 Consistent with our findings and those from other studies, they found that CCT was  
532 not associated with the risk of glaucoma in the univariable model, but a spurious

533 association between CCT and glaucoma appeared when measured IOP was added  
534 to the model.

535         Although previous studies<sup>47-49</sup> have shown a relationship between corneal  
536 hysteresis and visual field progression rates, we were not able to confirm such  
537 association in our cohort. In any given eye, corneal hysteresis is inversely related to  
538 IOP. Therefore, low corneal hysteresis may reflect high IOP, which is an established  
539 risk factors for faster glaucoma progression. Also, corneal hysteresis is directly  
540 related to corneal stiffness and thickness. Hence, IOP might have underestimated in  
541 patients with low corneal hysteresis, with consequent undertreatment leading to  
542 faster progression.

543         Many studies have reported an association between older age and faster  
544 progression rates.<sup>1, 44, 50, 51</sup> In our study, older age was associated with faster MD  
545 (but not pointwise) progression rates in the latanoprost group but not in the placebo  
546 group. Ageing causes the lamina cribrosa to become stiffer and less compliant,  
547 potentially reducing its ability and that of peripapillary sclera to comply with IOP  
548 changes. Girard and colleagues<sup>35</sup> investigated the age-related biomechanical  
549 differences in monkey posterior sclera and found that older animals had higher  
550 tensile stress secondary to IOP elevation than younger ones. As tensile stress  
551 increased non-linearly with IOP rise, the impact of ageing should theoretically be  
552 more pronounced in patients with higher mean IOP; however, we found that older  
553 age was associated with worse progression rates in the treatment arm, which had  
554 lower mean IOP than the placebo arm. This finding is in agreement with a large  
555 retrospective cohort study by De Moraes and colleagues<sup>2</sup>, reporting that older age  
556 was independently associated with glaucomatous VF progression only in patients  
557 with lower mean IOP. Similar findings were found in the JAMDIG study, a large

558 retrospective study conducted in Japanese patients with fairly low mean IOP  
559 values.<sup>50</sup> An explanation to these findings may be that the impact of non-IOP factors,  
560 including age, becomes more important only after substantially lowering the IOP.

561 This study has limitations. This was a planned secondary analysis based on  
562 the UKGTS dataset and the number of subjects and the duration of follow-up may  
563 not provide enough statistical power to identify a meaningful relationship between  
564 IOP fluctuation and visual field progression, especially in the treatment arm, where  
565 progression rates were extremely slow over the study period. The study cohort  
566 included treatment-naïve primary open-glaucoma patients, mainly of European  
567 descent and with early glaucomatous damage. Some authors<sup>11</sup> have hypothesized  
568 that the effect of IOP fluctuation on the rates of visual progression might vary as a  
569 function of disease stage, mean IOP, glaucoma subtype, ethnicity, and treatment  
570 modality (medical vs surgical intervention); hence, the results of this study may be  
571 not entirely generalizable to other populations. Nevertheless, the results of this study  
572 are in agreement with those from the EMGT analysis.<sup>5</sup> The diurnal IOP fluctuation  
573 calculation was based on five measurements obtained during the morning and  
574 afternoon, and this study provides only IOP snapshots across the day and no  
575 information on IOP fluctuation outside office hours. Although we used clinically  
576 relevant definitions of IOP fluctuation, these measurements may not adequately  
577 characterize short-term IOP variability. Diurnal phasing has been shown to be poorly  
578 reproducible, indicating that single-day IOP measurements may not be sufficient to  
579 accurately assess short-term fluctuations.<sup>52-55</sup> Our findings are consistent with  
580 existing literature in this field. A comparison between the two available diurnal IOP  
581 curves revealed that the 95% limits of agreement were around 4 mmHg, aligning  
582 closely with the most pronounced fluctuation extremes observed in this dataset

583 (Figure S15). Differences between diurnal IOP fluctuation calculated in the first and  
584 last post-randomization visits were random and approximate a normal distribution  
585 (Figure S16). Several studies<sup>56, 57</sup> have documented a nocturnal peak in IOP,  
586 primarily attributed to an increase in episcleral venous pressure when the body is in  
587 a horizontal position. Although our study did not include night-time IOP  
588 measurements, we did record IOP in a supine position, which is recognized as a  
589 reasonable proxy for estimating nocturnal peak levels.<sup>58</sup> While devices for home IOP  
590 monitoring<sup>59, 60</sup> or continuous IOP tracking<sup>61, 62</sup> have been introduced, they were not  
591 collected in the UKGTS study and are generally reserved for research rather than  
592 routine clinical use. Although the methodology employed in this study may not  
593 capture the entire spectrum or precise patterns of IOP fluctuations, we adopted a  
594 clinically relevant approach to defining diurnal IOP fluctuation.

595 In conclusion, this study finds no evidence to support that either diurnal and-or  
596 long-term IOP fluctuation, defined in a clinically relevant manner, are independent  
597 factors for glaucoma progression. Other aspects of IOP, such as mean IOP and  
598 peak IOP, may be more informative. Higher OPA may be an independent factor for  
599 faster glaucoma progression.

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609 **Declaration of Generative AI and AI-assisted technologies in the writing**  
610 **process**

611

612 During the preparation of this work the authors used chatGPT3.5 in order to improve  
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790

791 **FIGURE LEGENDS**

792

793 **Figure 5.** Boxplots comparing the various IOP metrics in the placebo and treatment  
794 groups. IOP: intraocular pressure; MD: mean deviation; OPA: ocular pulse  
795 amplitude; SD: standard deviation.

796

797 **Figure 6.** Density plots for the distribution of MD (**left panel**) and pointwise (**right**  
798 **panel**) rates of progression in the placebo and latanoprost groups. MD: mean  
799 deviation. PLR: pointwise linear rates.

800

801 **Figure 7.** Forest plots for factors associated with the MD rates of progression in the  
802 placebo (**left panel**) and treatment (**right panel**) group. Dots and bars indicate point  
803 estimates and 95% confidence intervals, respectively. Estimates are intended for 1-  
804 unit increase, unless specified otherwise. Combined IOP metrics PC1 is an unitless  
805 variable, which combines fluctuation unrelated IOP metrics (baseline IOP, peak IOP,  
806 mean IOP, supine IOP, peak phasing IOP) through Principal Component Analysis.  
807 CCT: central corneal thickness; CH: corneal hysteresis; IOP: intraocular pressure;  
808 MD: mean deviation; OPA: ocular pulse amplitude; PC1: principal component 1.

809

810 **Figure 8.** Forest plots for factors associated with the pointwise rates of progression  
811 in the placebo (**left panel**) and treatment (**right panel**) group. Dots and bars indicate  
812 point estimates and 95% confidence intervals, respectively. Estimates are intended  
813 for 1-unit increase, unless specified otherwise. Combined IOP metrics PC1 is an  
814 unitless variable, which combines fluctuation unrelated IOP metrics (baseline IOP,  
815 peak IOP, mean IOP, supine IOP, peak phasing IOP) through Principal Component

816 Analysis. CCT: central corneal thickness; CH: corneal hysteresis; IOP: intraocular  
817 pressure; OPA: ocular pulse amplitude; PC1: principal component 1; PLR: pointwise  
818 linear rates.

819

820 **Figure 9.** Forest plots for factors associated with the pointwise rates of progression  
821 of the five fastest locations in the placebo (**left panel**) and treatment (**right panel**)  
822 group. Dots and bars indicate point estimates and 95% confidence intervals,  
823 respectively. Estimates are intended for 1-unit increase, unless specified otherwise.  
824 Combined IOP metrics PC1 is an unitless variable, which combines fluctuation  
825 unrelated IOP metrics (baseline IOP, peak IOP, mean IOP, supine IOP, peak  
826 phasing IOP) through Principal Component Analysis. CCT: central corneal thickness;  
827 CH: corneal hysteresis; IOP: intraocular pressure; OPA: ocular pulse amplitude;  
828 PC1: principal component 1; PLR: pointwise linear rates.

**- Manuscript -**

**Relationship between intraocular pressure fluctuation and visual field progression rates in the United Kingdom Glaucoma Treatment Study**

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**Short title:** IOP fluctuation and glaucoma progression rates in the UKGTS

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## ABSTRACT

1 **Purpose.** To investigate whether intraocular pressure (IOP) fluctuation is  
2 independently associated with the rate of visual field (VF) progression in the United  
3 Kingdom Glaucoma Treatment Study.

4 **Design.** Randomized, double-masked, placebo-controlled multicenter trial.

5 **Participants:** Participants with  $\geq 5$  VFs (213 placebo, 217 treatment).

6 **Methods.** Associations between IOP metrics and the VF progression rates (mean  
7 deviation (MD) and five fastest locations) were assessed with linear mixed models.  
8 Fluctuation variables were mean ocular pulse amplitude (OPA), standard deviation  
9 (SD) of diurnal IOP (diurnal fluctuation), and SD of IOP at all visits (long-term  
10 fluctuation). Fluctuation values were normalized for mean IOP to make them  
11 independent from mean IOP. Correlated non-fluctuation IOP metrics (baseline, peak,  
12 mean, supine and peak phasing IOP) were combined with principal component  
13 analysis (PCA), and principal component 1 (PC1) was included as a covariate.  
14 Interactions between covariates and time from baseline modelled the effect of the  
15 variables on VF rates. IOP was measured with Goldmann applanation tonometry and  
16 OPA with Pascal tonometry. Analyses were conducted separately in the two  
17 treatment arms.

18 **Main Outcome Measures.** Associations between IOP fluctuation metrics and rates  
19 of MD and five fastest test locations.

20 **Results.** In the placebo arm, only PC1 was significantly associated with the MD rate  
21 (estimate [standard error (SE)]: -0.19 [0.04] dB/year,  $p < 0.001$ ), while normalized IOP  
22 fluctuation metrics were not. No variable was significantly associated with MD rates  
23 in the treatment arm. For the fastest five locations in the placebo group, PC1  
24 (estimate [SE]: -0.58 [0.16] dB/year,  $p < 0.001$ ), CCT (estimate [standard error (SE)]:

25 0.26 [0.10] dB/year for 10  $\mu$ m thicker,  $p=0.01$ ) and normalized OPA (estimate [SE]: -  
26 3.50 [1.04] dB/year,  $p=0.001$ ) were associated with rates of progression; normalized  
27 diurnal and long-term IOP fluctuations were not. In the treatment group, only PC1  
28 (estimate [SE]: -0.27 [0.12] dB/year,  $p=0.028$ ) was associated with the rates of  
29 progression.

30 **Conclusions.** There is no evidence to support that either diurnal or long-term IOP  
31 fluctuation, as measured in clinical practice, are independent factors for glaucoma  
32 progression; other aspects of IOP, including mean IOP and peak IOP, may be more  
33 informative. OPA may be an independent factor for faster glaucoma progression.

34

35 **Keywords:** visual field progression; ocular pulse amplitude; risk factors; linear  
36 mixed models.

## 37 INTRODUCTION

38 Intraocular pressure (IOP) is an established risk factor for glaucoma  
39 progression, and lowering IOP is currently the only available treatment to slow the  
40 disease progression.<sup>1-4</sup> Longitudinal measurement of IOP is crucial in evaluating  
41 glaucoma patients, estimating their risk of developing progressive glaucomatous  
42 damage, and assessing their response to treatment.

43 IOP is subject to fluctuations over time. Several IOP-derived parameters are  
44 commonly used in clinical practice and research to summarize the behavior of IOP,  
45 including mean IOP (average of IOP over multiple visits), peak IOP (highest IOP  
46 reading over follow-up), and IOP fluctuation (standard deviation [SD] or range IOP  
47 over time). Many studies have shown that mean IOP and peak IOP are  
48 independently associated with glaucoma progression;<sup>1, 2, 5, 6</sup> on the other hand, the  
49 exact role of IOP fluctuation is still debated, with discordant results reported in the  
50 literature.<sup>5-10</sup> Elucidating the role of IOP fluctuation is difficult for several reasons.  
51 IOP fluctuation is tightly correlated with other IOP-related metrics (e.g., mean IOP),  
52 making it difficult to isolate its role as an independent factor. IOP fluctuation may be  
53 artificially increased by escalating treatment in patients with suspect progression.  
54 The effect of IOP fluctuation may not be uniform, varying as a function of the disease  
55 stage, treatment status, mean IOP values, and definition of fluctuation.<sup>11</sup>

56 This planned secondary analysis of the United Kingdom Glaucoma Treatment  
57 Study (UKGTS) randomized controlled trial aimed to evaluate whether IOP  
58 fluctuation, as assessed by ocular pulse amplitude (OPA), diurnal variation and  
59 between-visit variation, is independently associated with the rate of visual field  
60 progression. The UKGTS is ideal for this purpose because there were no treatment

- 61 escalations artificially increasing IOP fluctuation, and the dataset allows evaluation of
- 62 IOP metrics in both untreated and treated glaucoma patients.

## 63 **METHODS**

### 64 *Study Population and Procedures*

65         This study was a planned secondary analysis of data from the UKGTS, which  
66 was a multicenter, randomized, triple-masked, placebo-controlled trial investigating  
67 the ability of Latanoprost, an IOP lowering medication, to preserve visual function in  
68 newly diagnosed open-angle glaucoma patients (trial registration number,  
69 ISRCTN96423140). The UKGTS and the subsequent analysis of anonymized data in  
70 this study complied with the tenets of the Declaration of Helsinki and were approved  
71 by local institutional review boards (Moorfields and Whittington Research Ethics  
72 Committee on June 1, 2006, ethics approval reference, 09/H0721/56). All patients  
73 provided written informed consent at the time of enrolment in the trial.

74         The UKGTS study protocol, baseline characteristics, and outcomes have  
75 been published elsewhere.<sup>3, 12, 13</sup> Participants recruited in 10 ophthalmology  
76 institutions across the United Kingdom were randomized 1:1 to receive latanoprost  
77 0.005% or placebo eye drops once in the evening in both eyes for 24 months or until  
78 meeting an endpoint. The UKGTS included patients  $\geq 18$  years of age and newly  
79 diagnosed treatment-naïve open-angle glaucoma, including primary open-angle and  
80 pseudoexfoliation glaucoma. Exclusion criteria were: advanced glaucoma, as  
81 defined by visual field mean deviation  $< -10$  dB in the better eye or  $< -16$  dB in the  
82 worse eye, mean baseline IOP  $\geq 30$  mmHg, Snellen best-corrected visual acuity  
83 (BCVA)  $< 6/12$ , and poor image quality ( $>40$   $\mu\text{m}$  mean pixel height standard  
84 deviation) with the Heidelberg retina tomograph (Heidelberg Engineering,  
85 Heidelberg, Germany).

86         Potentially eligible participants underwent two pre-randomization visits. After  
87 meeting the study criteria and signing the written informed consent, participants were

88 randomized either to receive latanoprost 0.005% or placebo eye drops. Enrolled  
89 subjects underwent IOP measurement, VF, and imaging at eleven post-  
90 randomization visits over 24 months or until meeting an endpoint. Standard  
91 automated perimetry with the Humphrey Field Analyzer (Carl Zeiss Meditec, Dublin,  
92 CA) was performed with stimulus size III, Swedish Interactive Threshold Algorithm  
93 (SITA) standard strategy, and 24-2 grid. VF testing was performed at all 11  
94 scheduled visits over 24 months, and tests were clustered (2 VFs on the same day)  
95 at baseline, 2 months, 16 months, 18 months, and 24 months. In this exploratory  
96 analysis, we included participants from the UKGTS with  $\geq 5$  reliable visual fields  
97 (VFs). Reliable VFs were defined as those with false positives less than 15%, while  
98 no limits for false negatives and fixation losses were applied. At the first post-  
99 randomization visit, the following demographic variables were collected: age, sex,  
100 ethnicity, family history of glaucoma, history of systemic diseases (i.e., systemic  
101 hypertension, cardiovascular disease, diabetes, heart attack, stroke, sleep apnea,  
102 migraine, Raynaud's phenomenon, vasospasm, angina, claudication), and smoking  
103 status. The following investigations were also performed: blood pressure  
104 measurements with the Omron M7 Blood Pressure Monitor (Matsusaka, Mie, Japan),  
105 weight, height, slit-lamp examination, refractive error measured either with an  
106 autorefractor or from spectacle focimetry (if not available, the spherical equivalent of  
107 the trial lens was used in the visual field test, based on participants' age), axial  
108 length measurement with the IOL Master (Carl Zeiss Meditec, Dublin, CA), and  
109 central corneal thickness (CCT) measured with an ultrasound pachymeter. We  
110 included one eye per patient; specifically, the eye with the worst baseline VF mean  
111 deviation (MD).

112

113 *IOP Metrics*

114           At all visits, IOP was measured with Goldmann applanation tonometry (GAT;  
115 Haag Streit, Koeniz, Switzerland), Pascal dynamic contour tonometry (Ziemer  
116 Ophthalmic Systems AG, Zurich, Switzerland), and the Ocular Response Analyzer  
117 (Reichert, Inc., Buffalo, NY). Diurnal GAT phasing with IOP measured every 2 hours  
118 from 9 am to 5 pm was performed at the first post-randomization and at the final visit.  
119 At the first post-randomization visit, supine IOP was measured with Perkins  
120 applanation tonometer.

121           The following IOP metrics were calculated and used for the analyses:

- 122     • Baseline pretreatment IOP, defined as the average of the IOP readings obtained  
123       in the two pre-randomization visits.
- 124     • Mean IOP, defined as the average of all post-randomization IOP readings.
- 125     • Peak IOP, defined as the highest IOP reading of all post-randomization IOP  
126       readings.
- 127     • Supine IOP, defined as the Perkins applanation tonometry IOP readings  
128       measured at the first post-randomization visit.
- 129     • Phasing peak IOP, defined as the highest IOP reading of the diurnal phasing  
130       performed at the first post-randomization visit.
- 131     • Diurnal IOP fluctuation, defined as the SD of IOP measurements obtained from  
132       the diurnal IOP phasing performed at the first post-randomization visit. Diurnal  
133       IOP fluctuation was also calculated using the IOP measurements from the last  
134       post-randomization visit.
- 135     • Long-term IOP fluctuation, defined as the SD of post-randomization IOP  
136       readings.

- 137 • Mean ocular pulse amplitude (OPA) from the Pascal Dynamic Contour tonometry.  
138 OPA was defined as the range of the pulse wave contour and provides a  
139 measure of how IOP fluctuates over cardiac cycle. We used the average of all  
140 post-randomization ORA values.

141

### 142 *Statistical Analysis*

143 We performed all statistical analyses with the open-source software R (R  
144 Foundation for Statistical Computing, Vienna, Austria). Variable distributions were  
145 inspected with histograms and quantile-quantile plots. We reported mean ( $\pm$   
146 Standard deviation [SD]) and median (interquartile range [IQR]) for Gaussian and  
147 non-Gaussian variables, respectively. We reported frequencies and proportions for  
148 discrete variables. Proportion and pattern of missing data were analyzed. All  
149 analyses were conducted with complete cases. All tests were 2-tailed, and p-values  
150  $<0.05$  were considered statistically significant.

151 Demographic and clinical characteristics between the two treatment groups  
152 were compared with t-test and chi-squared test for continuous and categorical  
153 variables, respectively. Agreement between diurnal IOP fluctuation calculated on the  
154 first and last post-randomization visit was investigated with Bland-Altman statistics.  
155 We also collected the timing of each IOP measurement and calculated the absolute  
156 differences from each measurement and the mean time of day for each patient's IOP  
157 measurements.

158 Linear models were used to evaluate the relationship between (i) mean IOP and  
159 long-term IOP fluctuation, (ii) mean IOP and long-term IOP fluctuation/mean IOP, (iii)  
160 mean diurnal IOP and diurnal IOP fluctuation, (iv) mean diurnal IOP and diurnal IOP

161 fluctuation/mean diurnal IOP, (v) mean OPA and mean IOP, and (vi) mean  
162 OPA/GAT IOP and mean IOP.

163 IOP fluctuation is known to be positively correlated with mean IOP. Additionally,  
164 measurement error can contribute to the variability in IOP measurements, potentially  
165 confounding true IOP fluctuation. To obtain a measure of IOP fluctuation which is  
166 independent from mean IOP, we performed a normalization of IOP fluctuation  
167 values. Specifically, we ran a linear regression of IOP fluctuation against mean IOP.  
168 We then divided the observed IOP fluctuation values by the corresponding predicted  
169 values. This process was applied distinctly for each fluctuation metric. For long-term  
170 fluctuation, we utilized the SD of all post-randomization IOP readings and their  
171 corresponding mean IOP values from all post-randomization readings. For diurnal  
172 fluctuation, we used the SD and mean IOP measurements from the diurnal IOP  
173 phasing conducted during the first post-randomization visit. For the OPA, we used  
174 the average of all post-randomization ORA values for each subject and their  
175 corresponding mean IOP across all available post-randomization visits. For OPA, we  
176 calculated the average of all post-randomization ORA values for each subject,  
177 alongside their corresponding mean IOP from all available post-randomization visits.

178 As shown in Figure S1, normalized IOP fluctuation was unrelated to mean IOP.  
179 Normalization was further performed on the two study arms separately, leading to  
180 almost identical results (data not shown). All analyses were conducted on both  
181 normalized and unnormalized IOP fluctuations values.

182 Linear mixed models with random slopes and random intercepts were used to  
183 estimate the rates of progression and investigate associations between the rate of  
184 visual field progression and variables of interest. Linear mixed models are an  
185 extension of traditional linear models, which can accommodate the repeated-

186 measure (e.g., multiple measurements from the same eye over time) and clustered  
187 (multiple test locations from the same VF) nature of data. We first look at univariable  
188 associations between the MD rate of change and each variable of interest. In all  
189 models, the MD value at each visit was the outcome variable; the follow-up time in  
190 years, the covariate of interest, and their interaction were the fixed effects; the eye  
191 identification number and follow-up time were the random intercept and random  
192 slope terms, respectively, to account for the repeated measure of data and for the  
193 fact that different eyes may have different rates of progression over time. Interactions  
194 between covariates and time from baseline modeled the variables' effect on the  
195 progression rate. We then built multiple variable linear mixed models to account for  
196 the impact of fluctuation metrics after adjusting for all other potentially confounding  
197 factors, including other IOP metrics. Correlations among candidate covariates were  
198 tested with a hierarchical cluster analysis based on the absolute value of Spearman  
199 correlations (Figure S2). Some of the variables measuring the magnitude of IOP  
200 elevation exhibited high correlations. Highly correlated variables are a source of  
201 multicollinearity, causing unstable regression coefficients and large standard errors.  
202 To address this issue, all correlated metrics measuring IOP (baseline IOP, peak IOP,  
203 mean IOP, supine IOP, peak phasing IOP) were combined using Principal  
204 Component Analysis (PCA). These variables had a |Spearman rho| of 0.50 or  
205 greater. PCA extracts uncorrelated orthogonal vectors (Principal Components [PCs])  
206 from multiple correlated variables. PCs are ranked, with the first PC (PC1) being the  
207 one containing the largest amount of combined information from the correlated  
208 variables. PCA was performed on standardized data, with zero mean and unit  
209 variance. We inspected the PCA model with biplots and scree plots (Figure S3).  
210 Scree plots were used to visualize the amount of variance explained by the various

211 Principal Components and to select the number of PCs to retain for subsequent  
212 analyses. PC1 was selected for further analyses, as it explained 81% of the overall  
213 variance in the PCA, and used as a fixed effect in the multivariable linear mixed  
214 models. The Interaction between PC1 and follow-up time modelled the effect of PC1  
215 on visual field progression rates, as previously explained. PCA was also performed  
216 on the two study arms separately, leading to similar results (data not shown).

217         Similar analyses were run in a pointwise manner, including: (i) all 52 VF test  
218 locations of the 24-2 grid (after excluding the two locations corresponding to the blind  
219 spot), and (ii) the five fastest progressing locations for each study eye (which is  
220 conceptually similar to the event-based GPA analysis which identifies the 3 or more  
221 locations most different from baseline). Models conducted on the pointwise threshold  
222 sensitivity data had a nested random intercept with eye identification number over  
223 the test location number to account for the inclusion of multiple pointwise series from  
224 the same eye. All models were run separately in the placebo and treatment arms.  
225 Regression estimates along with their 95% confidence intervals (95% CIs) and p-  
226 values were reported.

## 227 RESULTS

228 Of the 461 participants with longitudinal data included in the primary UKGTS  
229 analysis, 31 were excluded because of an insufficient number of VFs. The remaining  
230 430 (placebo arm: 213, treatment arm: 217) participants were included in this study.  
231 As shown in Figure S4, most variables had complete observations, with only a few  
232 variables having missing observations. Spherical equivalent, CCT, and supine IOP  
233 values were missing in 26 eyes (6%), 16 (3.7%), and 15 eyes (3.5%), respectively.  
234 Mean arterial pressure, body mass index, ethnicity, corneal hysteresis, peak and  
235 mean phasing IOP, and diurnal fluctuation were missing in less than 2% of patients.  
236 All other variables had no missing data.

237 Baseline characteristics of the UKGTS study population have been published  
238 elsewhere.<sup>3, 12</sup> Table 1 illustrates the main demographic and clinical characteristics  
239 of the patient cohort. Patients in the treatment cohort had significantly longer follow-  
240 up time than those in the placebo cohort, with a median (IQR) of 1.9 (1.3 to 2.0) and  
241 1.6 (1.0 to 2.0) years, respectively ( $p=0.004$ ). The number of VFs was also  
242 significantly greater ( $p=0.027$ ) in the treatment arm (median [IQR]: 15 [10-16]) than in  
243 the placebo arm (median [IQR]: 13 [10-16]). In the post-randomization study period,  
244 patients in the treatment arm showed higher mean corneal hysteresis than those in  
245 the placebo arm (mean [ $\pm$ SD]: 9.4 [ $\pm$ 1.6] vs. 8.9 [ $\pm$ 1.6] mmHg,  $p=0.003$ ). As shown in  
246 Figure 5, all post-randomization IOP metrics were significantly different between the  
247 two arms ( $p<0.045$  or below), except for normalized diurnal IOP fluctuation ( $p=0.89$ )  
248 and normalized OPA ( $p=0.93$ ). The median of the absolute differences from the  
249 mean time of day for each patient's IOP measurements was 1.1 hours, with an  
250 interquartile range (IQR) of 0.5 hours (30 minutes) to 2.0 hours.

251

252 *Global MD rate*

253           The distribution of MD rates in the two groups as estimated with linear mixed  
254 models is illustrated in Figure 6. Median (IQR) MD rates in the placebo and  
255 treatment cohort were -0.23 (-0.73 to 0.11) dB/year and 0.13 (-0.30 to 0.37) dB/year,  
256 respectively ( $p < 0.001$ ).

257           In the univariable analysis (Table S2), higher values of all non-fluctuation IOP  
258 parameters, including pretreatment baseline IOP (estimate [standard error (SE)]: -  
259 0.06 [0.02] dB/year for 1 mmHg increase,  $p < 0.001$ ), mean IOP (estimate [SE]: -0.08  
260 [0.02] dB/year for 1 mmHg increase,  $p < 0.001$ ), peak IOP (estimate [SE]: -0.07 [0.01]  
261 dB/year for 1 mmHg increase,  $p < 0.001$ ), peak phasing IOP (estimate [SE]: -0.05  
262 [0.02] dB/year for 1 mmHg increase,  $p < 0.001$ ), and supine IOP (estimate [SE]: -0.06  
263 [0.01] dB/year for 1 mmHg increase,  $p < 0.001$ ), were significantly associated with  
264 faster MD rates in the placebo group. With regards to the IOP fluctuations  
265 parameters, higher long-term IOP fluctuation (estimate [SE]: -0.27 [0.07] dB/year for  
266 1 mmHg increase,  $p < 0.001$ ) and OPA (estimate [SE]: -0.32 [0.09] dB/year for 1  
267 mmHg increase,  $p < 0.001$ ) were associated with faster MD rates of change, while  
268 diurnal IOP fluctuation was not ( $p = 0.23$ ). None of the fluctuation parameters was  
269 associated with the MD rate after normalizing for the mean IOP ( $p = 0.11$  or above). In  
270 the treatment arm, none of the variables was significantly associated with the MD  
271 rate, except for long-term IOP fluctuation (estimate [SE]: -0.12 [0.06] dB/year for 1  
272 mmHg increase,  $p = 0.047$ ).

273           Results of the multivariable model for factors associated with MD rate of  
274 progression are illustrated in Figure 7 and detailed in Table S3. In the placebo arm,  
275 PC1, which combined information from all the non-fluctuation IOP parameters, was  
276 the only factor associated with the MD rate (estimate [SE]: -0.19 [0.08] dB/year for 1

277 unit increase,  $p < 0.001$ ), while the various normalized IOP fluctuation metrics were  
278 not. Thinner CCT had an association of borderline statistical significance with faster  
279 VF progression rates (estimate [SE]: 0.05 [0.02] dB/year for 10  $\mu\text{m}$  thicker,  $p = 0.06$ ).  
280 None of the variables was significantly associated with the MD rate of progression in  
281 the treatment arm. Older age was associated with faster MD rates (estimate [SE]: -  
282 0.12 [0.06] dB/year for a 10-year increase) in the treatment arm, but this only  
283 approached nominal statistical significance ( $p = 0.06$ ). Similar results were obtained  
284 when analyzing unnormalized IOP fluctuation metrics (Table S4).

285

### 286 *Pointwise Rates*

287 Figure 6 illustrates the distribution of pointwise progression rates in the two  
288 groups. Pointwise rates were significantly faster in the placebo group than in the  
289 treatment group (median [IQR]: -0.42 [-0.59 to -0.26] dB/year vs. 0.03 [-0.14 to 0.19]  
290 dB/year,  $p < 0.001$ ). Results of the univariable analysis for factors associated with the  
291 pointwise rates of change are illustrated in Table S5. In the placebo group, all the  
292 non-fluctuation IOP parameters were significantly associated with the pointwise rates  
293 ( $p = 0.003$  or below). Higher unnormalized long-term IOP fluctuation (estimate [SE]: -  
294 0.34 [0.13] dB/year for 1 mmHg increase,  $p = 0.008$ ) and OPA (estimate [SE]: -0.65  
295 [0.15] dB/year for 1 mmHg increase,  $p < 0.001$ ) were associated with faster pointwise  
296 rates of progression. After normalizing IOP fluctuations for mean IOP, only OPA was  
297 associated with the rate of progression (estimate [SE]: -1.36 [0.48] dB/year for 1 unit  
298 increase,  $p = 0.005$ ). In the treatment arm, none of the IOP variables was associated  
299 with the pointwise rates of progression. In the multiple variable model (Figure 8 and  
300 Table S6), normalized mean OPA was associated with the pointwise rates of  
301 progression in the placebo arm (estimate [SE]: -1.23 [0.46] dB/year for 1 unit

302 increase,  $p=0.009$ ), but not in the treatment arm. None of the other fluctuation  
303 metrics was associated with the rate of progression in either group. The combined  
304 IOP metric, PC1, was associated with the pointwise rate of change in the placebo  
305 group ( $p<0.001$ ), but not in the treatment group ( $p=0.42$ ). Similarly, none of the  
306 unnormalized IOP fluctuation metrics was associated with the pointwise rate of  
307 change metrics (Table S7), except for mean OPA in the placebo group (estimate  
308 [SE]: -0.47 [0.17] dB/year for 1 mmHg increase,  $p=0.008$ ).

309         For the five fastest progressing locations, median (IQR) pointwise rates of the  
310 five in the placebo and treatment cohort were -1.00 (-1.49 to -0.80) dB/year and -  
311 0.52 (-0.93 to -0.34) dB/year, respectively ( $p<0.001$ ). Results of the univariable  
312 analysis for factors associated with the rates of the fastest five locations are  
313 illustrated in Table S8. In the placebo group, all the non-fluctuation IOP parameters  
314 were significantly associated with the pointwise rates ( $p=0.003$  or below). Higher  
315 unnormalized (estimate [SE]: -1.67 [0.34] dB/year for 1 mmHg increase,  $p<0.001$ )  
316 and normalized OPA (estimate [SE]: -3.95 [1.10] dB/year for 1 unit increase,  
317  $p<0.001$ ) were associated with faster rates of progression. In the treatment arm,  
318 higher unnormalized long-term IOP fluctuation was associated with faster rates of  
319 progression (estimate [SE]: -0.46 [0.17] dB/year for 1 mmHg increase,  $p=0.006$ ), but  
320 the association was no longer significant after normalizing IOP fluctuation (estimate  
321 [SE]: -0.81 [0.44] dB/year for 1 unit increase,  $p=0.06$ ). In the multiple variable model  
322 (Figure 9 and Table S9), CCT (estimate [SE]: 0.26 [0.10] dB/year for 10  $\mu\text{m}$  thicker,  
323  $p=0.01$ ), normalized OPA (estimate [SE]: -3.50 [1.04] dB/year for 1 unit increase,  
324  $p=0.001$ ), and PC1 (estimate [SE]: -0.58 [0.16] dB/year for 1 PC1 unit increase,  
325  $p<0.001$ ) were associated with the rates of progression of the fastest five test  
326 locations in the placebo group; while normalized diurnal and long-term IOP

327 fluctuations were not. In the treatment group, PC1 (estimate [SE]: -0.27 [0.12]  
328 dB/year for 1 PC1 unit increase,  $p=0.028$ ) was the only factor associated with  
329 progression rates. Results of the nonnormalized models are shown in Table S10.  
330 All analyses were repeated with mean IOP, peak IOP and normalized LTF fluctuation  
331 calculated from corneal compensated IOP as measured with the Ocular Response  
332 Analyzer (Reichert, Inc, Buffalo, NY) and lead to similar results (Figures S10-S14).

## 333 **DISCUSSION**

334           In this study, we evaluated whether IOP fluctuation was associated with the  
335 rate of glaucomatous visual field progression. We provided a comprehensive  
336 evaluation of clinically relevant definitions of IOP fluctuation over the course of  
337 seconds (OPA), office hours (diurnal fluctuation), and multiple visits over the entire  
338 follow-up (long-term fluctuation). We found that higher OPA was associated with  
339 faster rates of progression, while diurnal or long-term IOP fluctuations were not  
340 associated with the rate of progression. Elevated IOP metrics (e.g., mean IOP, peak  
341 IOP) were consistently associated with the rate of VF progression.

342           Establishing the relationship between IOP fluctuation and the rates of visual  
343 field progression is not an easy task for many reasons. First, IOP fluctuation may  
344 vary as a function of the time frame over which it is calculated, and there is no  
345 consensus on which type of fluctuation is most informative. Our study provided a  
346 comprehensive approach, analyzing three measures of fluctuations. Second, the  
347 definition of IOP fluctuation is not uniform across studies, with IOP range and SD  
348 IOP usually used as measures for IOP fluctuation. It has been suggested that SD  
349 IOP could be a more robust metric than range IOP as the latter may be heavily  
350 influenced by outliers and does not account for the number of IOP measurements.<sup>8</sup>  
351 In this study, we used SD IOP to calculate diurnal and long-term IOP fluctuation; on  
352 the other hand, OPA, a measure of very short-term fluctuation, was an average  
353 range of several cardiac cycles. We further mitigated the effect of potential outliers  
354 on OPA by obtaining two consecutive OPA measurements at each time point,  
355 averaging them to have a single value, and then averaging the resulting values  
356 throughout all available follow-up visits. Third, isolating the impact of fluctuation from  
357 the level of IOP may be challenging because of the intimate relationship between

358 these two variables. IOP fluctuation is known to be positively correlated with mean  
359 IOP. In a retrospective study performed on non-human primates of experimental  
360 glaucoma, Gardiner and colleagues<sup>10</sup> used the coefficient of variation (SD IOP  
361 divided by mean IOP) to remove the relationship between these two variables. In our  
362 cohort, the coefficient of variation reversed the association with mean IOP values,  
363 leading to a negative relationship between IOP fluctuation and mean IOP. The  
364 explanation for this is likely that there are two components of variability  
365 (measurement error and true IOP fluctuation), one of which (true fluctuation) is  
366 related to mean IOP and the other (measurement error) is not.<sup>14</sup> Dividing the  
367 measurement error by the mean IOP induces the negative association. The method  
368 of normalization used in our study likely respects both the increased fluctuations at  
369 higher mean IOP and constant measurement errors. Fourth, IOP-related metrics  
370 tend to be highly correlated because they are related to the same original quantity.  
371 Modeling highly correlated variables may lead to a statistical issue called  
372 multicollinearity. In the presence of multicollinearity, regression models may become  
373 inefficient with loss of statistical power, greater computation inaccuracy, unstable  
374 estimates, and high variance.<sup>15</sup> Various methods have been proposed to deal with  
375 multicollinearity. One or more highly collinear covariates may be omitted from the  
376 regression model, which may cause information loss. Ridge regression, a form of  
377 penalized linear regression, is another popular method to handle multicollinearity;  
378 however, it produces biased estimates and is better suited for predictive rather than  
379 explanatory models.<sup>16</sup> In our study, we addressed the issue of multicollinearity with  
380 PCA, which creates a new set of orthogonal linear combinations of the original  
381 variables (PCs), by definition perfectly uncorrelated to each other.<sup>17</sup> In this study, we  
382 used PCA to obtain a maximally informative combined metric of IOP control. Fifth,

383 clinicians are more likely to escalate treatment in progressing patients, inducing IOP  
384 fluctuation. This may be easily overlooked in retrospective cohort studies and even in  
385 prospective studies if countermeasures are not adopted. The findings of previous  
386 studies have been greatly questioned because of the possible bias caused by  
387 medical and surgical treatment escalation. Our study is not vulnerable to the  
388 potential confounding effect of treatment escalation as patients in the UKGTS took  
389 either latanoprost or placebo for their entire study period. In addition, our study is in  
390 the unique position to elucidate the role of IOP fluctuation on glaucomatous  
391 progression in untreated patients.

392         The relationship between IOP fluctuation and glaucomatous progression  
393 remains highly controversial, with contrasting results reported in the literature.  
394 Comparisons of results from different studies, including ours, should be done with  
395 caution because of heterogeneity in study populations, designs, definitions of  
396 fluctuation and progression, and statistical analysis. Most of the previous studies  
397 focused on long-term (intervisit) IOP fluctuation, which is the most accessible  
398 fluctuation metric to obtain as it can be estimated from single IOP measurements  
399 from multiple visits. Our study did not find any relationship between long-term IOP  
400 fluctuation and VF progression rates. Bengtsson et al.<sup>5</sup> conducted a post-hoc  
401 analysis from the Early Manifest Glaucoma Trial (EMGT); they found that mean IOP  
402 was a strong predictor of glaucoma progression, while IOP fluctuation was not.  
403 EMGT and UKGTS share many similarities, including the mild disease stage, type of  
404 treatment (i.e., nonsurgical intervention), and mean IOP values. An observational  
405 study by Medeiros et al.<sup>18</sup> investigated whether IOP fluctuations were associated  
406 with the risk of conversion from ocular hypertensive to glaucoma and found that  
407 mean IOP, but not long-term IOP fluctuation, was associated with glaucoma

408 development. Other studies found contrasting results, showing a positive association  
409 between long-term IOP fluctuation and VF progression. In a post-hoc analysis of the  
410 Advanced Glaucoma Intervention Study (AGIS), Nouri-Mahdavi and colleagues<sup>9</sup>  
411 found that long-term IOP fluctuation was an independent risk factor for glaucoma  
412 progression, while mean IOP was not. The results of this study were criticized  
413 because the authors analyzed the entire available follow-up, including time points  
414 after treatment escalation. Further intervention, either in the form of trabeculectomy  
415 or laser trabeculoplasty as per AGIS protocol, might have been itself a cause of  
416 clinician-induced increased fluctuation in patients at high risk of progression. In a  
417 subsequent post-hoc analysis of the AGIS, Caprioli and Coleman<sup>8</sup> investigated the  
418 relationship between long-term IOP fluctuation and VF progression, excluding those  
419 patients having multiple interventions; they found that long-term IOP fluctuations was  
420 significantly associated with VF progression in patients with low mean IOP, but not in  
421 those with high IOP. A post-hoc analysis from the Collaborative Initial Glaucoma  
422 Treatment Study (CIGTS)<sup>6</sup> examined the role of various IOP parameters on VF  
423 progression and found that long-term IOP fluctuation and peak IOP were associated  
424 with VF progression, while mean IOP was not.

425         The literature on the role of diurnal (or diurnal-nocturnal) IOP fluctuation is  
426 scarce, of lower quality, and with conflicting reports. In the Malmö Ocular  
427 Hypertension study,<sup>19</sup> diurnal IOP fluctuation was not an independent risk factors for  
428 the development of glaucoma; conversely, mean IOP was associated with the  
429 incidence of glaucomatous visual field loss in patients with OHT. Our study did not  
430 find an association between diurnal IOP fluctuation and the rate of glaucomatous  
431 progression in any of the models, corroborating the findings of the Malmö Ocular  
432 Hypertension study. In a secondary analysis from a Swedish clinical trial

433 randomizing patients to either pilocarpine or argon laser trabeculoplasty, Bergea et  
434 al.<sup>20</sup> investigated the relationship between visual field progression and different IOP  
435 variables, and they found that both mean IOP and diurnal IOP fluctuation were  
436 associated with visual field progression. That study, however, had several limitations,  
437 including the small sample size (76 eyes), high proportion of pseudoexfoliation  
438 glaucoma (72%), and the use of range IOP as a measure of fluctuation, which is  
439 vulnerable to outlier and highly related to peak IOP. A retrospective study by Matlach  
440 and colleagues<sup>21</sup> assessed the impact of long-term and diurnal-nocturnal IOP  
441 fluctuation on glaucoma progression in a cohort of 120 glaucoma patients randomly  
442 selected from a tertiary referral center; they found that diurnal-nocturnal IOP  
443 fluctuation was associated with glaucoma progression, while long-term IOP  
444 fluctuation and mean IOP were not. A retrospective study by Kim et al.<sup>22</sup> found  
445 similar results in a cohort of NTG patients, with higher diurnal IOP fluctuations and  
446 disc hemorrhages being associated with higher hazard of visual field progression.  
447 Both these studies are limited by their retrospective nature, making them vulnerable  
448 to potential confounders and selection bias. Also, these studies did not employ any  
449 statistical method to mitigate multicollinearity.

450 Besides including these two established measures of IOP fluctuation, we also  
451 investigated the role of very short-term fluctuation, as measured by the mean ocular  
452 pulse amplitude (OPA) over follow-up. OPA is calculated as the difference between  
453 systolic and diastolic IOP, as measured by the Pascal dynamic contour tonometer,  
454 and informs on how IOP varies across the cardiac cycle, secondary to the pulsatile  
455 influx/efflux of blood volume into the eye (mainly to choroid). Ocular pulse may be  
456 determined by various ocular and systemic factors, including ocular tissue rigidity,<sup>23-</sup>  
457 <sup>25</sup> axial length,<sup>26</sup> IOP,<sup>23, 27</sup> blood pressure pulse amplitude,<sup>28, 29</sup> left ventricular

458 ejection time,<sup>30</sup> heart rate,<sup>31, 32</sup> and conditions influencing ocular perfusion (e.g.,  
459 carotid artery stenosis, tight encircling band).<sup>33, 34</sup> To the best of our knowledge,  
460 there are currently no clinical studies investigating the role of OPA (or any metric for  
461 very short IOP fluctuation) on glaucoma progression. We found that higher OPA was  
462 significantly associated with faster pointwise rates of progression in the placebo  
463 group. Reasons for this finding are speculative. This association may result from an  
464 effect of the OPA itself or be related to one or more of its determinants. Animal  
465 studies have shown that acute IOP elevation may induce structural optic nerve head  
466 deformations and functional electrophysiological changes. Hence, multiple transient  
467 IOP spikes may cause faster glaucoma progression in vulnerable eyes. This  
468 explanation seems unlikely as these studies investigated large IOP changes, much  
469 larger than those measured with OPA. Higher OPA is associated with increased  
470 scleral rigidity and stiffer ocular tissues, which may be less compliant to IOP  
471 changes, causing larger stress within the lamina cribrosa secondary to IOP  
472 elevation.<sup>35, 36</sup> In a simulation study based on finite element analysis reconstructing a  
473 healthy eye model, Jin et al.<sup>36</sup> found that stiffer sclera was associated with higher  
474 OPA, larger ONH deformation, and increased shearing forces to neural axons of the  
475 neuroretinal rim. OPA has been proposed as a surrogate measure for  
476 hemodynamics, being influenced by the arterial pulse pressure, heart rate, and left-  
477 ventricular ejection time. Low diastolic blood pressure, vascular dysregulation and  
478 optic nerve hypoperfusion have been associated with glaucoma progression,  
479 especially in some phenotypes of open-angle glaucoma. However, one would expect  
480 an opposite association to that found in this study, as lower OPA has been  
481 associated with lower ocular blood supply. On the other hand, larger arterial pulse  
482 pressure is associated with systemic hypertension, which may lead to vascular

483 damage. So, high OPA might be a surrogate for hypertensive vascular damage, and  
484 previous studies<sup>37, 38</sup> have shown that high blood pressure may be a risk factors for  
485 primary open-angle glaucoma.

486 Our study confirms the importance of elevated IOP on glaucoma progression.  
487 PC1, which combined information from various IOP parameters (i.e., mean IOP,  
488 peak IOP, baseline IOP, peak phasing IOP, and supine IOP), was consistently  
489 associated with the rate of visual field progression in the placebo group. On the other  
490 hand, such a relationship was significant in the treatment group only for the rates of  
491 the fastest five visual field locations, but not for global rates of change. The  
492 progression rate of the treatment arm was extremely slow during the trial duration,  
493 and the signal from a few progressing locations may be obscured by the overall  
494 stability of most test locations. Comparative studies<sup>39, 40</sup> have shown that pointwise  
495 methods (especially those considering only locations with significant deterioration)  
496 have higher sensitivity and require less time to detect progression than those based  
497 on global indices or all test locations. Our study does not provide any information on  
498 which IOP metric is the most important for disease progression; this is arduous to  
499 tackle because of the intimate relationship among these variables. De Moraes and  
500 colleagues<sup>2</sup> evaluated the effect of mean IOP, peak IOP, and SD IOP in a large  
501 retrospective cohort of glaucoma patients under clinical care; they found that all  
502 these variables were associated with disease progression in the univariable analysis,  
503 but only peak IOP was significantly associated with VF progression in the  
504 multivariable model. However, mean IOP and peak IOP are highly correlated, and a  
505 multivariable model containing both variables would likely suffer from  
506 multicollinearity. Treatment modifications highly influence mean IOP and SD IOP in

507 real-world settings; although the occurrence of glaucoma surgery during follow-up  
508 was taken into consideration, medical treatment escalation was not.

509 We also investigated the impact of non-IOP and other ocular factors on  
510 glaucomatous progression rates, including age, CCT, and corneal hysteresis. The  
511 evidence for role of CCT as a risk factor for glaucoma progression is often  
512 misunderstood. A thinner cornea causes artifacts in applanation tonometry, with  
513 underestimation of the true IOP.<sup>41</sup> Alternatively, corneal thickness may serve as a  
514 biomarker of the biomechanical properties of the lamina cribrosa and peripapillary  
515 sclera, providing insights into the vulnerability of the optic nerve to increased IOP.<sup>42</sup>  
516 An experimental study by Wells and colleagues<sup>43</sup> investigated whether CCT was  
517 associated with optic disc compliance after inducing acute IOP rise and found no  
518 significant association, indicating that CCT may not reflect ocular biomechanics. In  
519 our cohort, thinner CCT was associated with faster progression rates in some  
520 multivariable models (which included IOP metrics), while it did not show significance  
521 in any of the univariable models. This suggests that CCT alone is not directly  
522 associated with glaucoma progression: rather, it becomes statistically significant  
523 when measured IOP is included in the model due to the effect of CCT on measured  
524 IOP. Other studies, including the Early Manifest Glaucoma Treatment (EMGT)<sup>44</sup> and  
525 the Los Angeles Latino Eye Study (LALES),<sup>45</sup> found similar finding, associating thin  
526 CCT with conversion to glaucoma and incident glaucoma in multivariable models,  
527 but not in univariable models. Khawaja and Jansonius<sup>46</sup> performed a simulation  
528 study that mimicked datasets similar to the LALES and Ocular Hypertensive  
529 Treatment Study so that IOP, but not CCT, was not associated with glaucoma risk.  
530 Consistent with our findings and those from other studies, they found that CCT was  
531 not associated with the risk of glaucoma in the univariable model, but a spurious

532 association between CCT and glaucoma appeared when measured IOP was added  
533 to the model.

534 Although previous studies<sup>47-49</sup> have shown a relationship between corneal  
535 hysteresis and visual field progression rates, we were not able to confirm such  
536 association in our cohort. In any given eye, corneal hysteresis is inversely related to  
537 IOP. Therefore, low corneal hysteresis may reflect high IOP, which is an established  
538 risk factors for faster glaucoma progression. Also, corneal hysteresis is directly  
539 related to corneal stiffness and thickness. Hence, IOP might have underestimated in  
540 patients with low corneal hysteresis, with consequent undertreatment leading to  
541 faster progression.

542 Many studies have reported an association between older age and faster  
543 progression rates.<sup>1, 44, 50, 51</sup> In our study, older age was associated with faster MD  
544 (but not pointwise) progression rates in the latanoprost group but not in the placebo  
545 group. Ageing causes the lamina cribrosa to become stiffer and less compliant,  
546 potentially reducing its ability and that of peripapillary sclera to comply with IOP  
547 changes. Girard and colleagues<sup>35</sup> investigated the age-related biomechanical  
548 differences in monkey posterior sclera and found that older animals had higher  
549 tensile stress secondary to IOP elevation than younger ones. As tensile stress  
550 increased non-linearly with IOP rise, the impact of ageing should theoretically be  
551 more pronounced in patients with higher mean IOP; however, we found that older  
552 age was associated with worse progression rates in the treatment arm, which had  
553 lower mean IOP than the placebo arm. This finding is in agreement with a large  
554 retrospective cohort study by De Moraes and colleagues<sup>2</sup>, reporting that older age  
555 was independently associated with glaucomatous VF progression only in patients  
556 with lower mean IOP. Similar findings were found in the JAMDIG study, a large

557 retrospective study conducted in Japanese patients with fairly low mean IOP  
558 values.<sup>50</sup> An explanation to these findings may be that the impact of non-IOP factors,  
559 including age, becomes more important only after substantially lowering the IOP.

560 This study has limitations. This was a planned secondary analysis based on  
561 the UKGTS dataset and the number of subjects and the duration of follow-up may  
562 not provide enough statistical power to identify a meaningful relationship between  
563 IOP fluctuation and visual field progression, especially in the treatment arm, where  
564 progression rates were extremely slow over the study period. The study cohort  
565 included treatment-naïve primary open-glaucoma patients, mainly of European  
566 descent and with early glaucomatous damage. Some authors<sup>11</sup> have hypothesized  
567 that the effect of IOP fluctuation on the rates of visual progression might vary as a  
568 function of disease stage, mean IOP, glaucoma subtype, ethnicity, and treatment  
569 modality (medical vs surgical intervention); hence, the results of this study may be  
570 not entirely generalizable to other populations. Nevertheless, the results of this study  
571 are in agreement with those from the EMGT analysis.<sup>5</sup> The diurnal IOP fluctuation  
572 calculation was based on five measurements obtained during the morning and  
573 afternoon, and this study provides only IOP snapshots across the day and no  
574 information on IOP fluctuation outside office hours. Although we used clinically  
575 relevant definitions of IOP fluctuation, these measurements may not adequately  
576 characterize short-term IOP variability. Diurnal phasing has been shown to be poorly  
577 reproducible, indicating that single-day IOP measurements may not be sufficient to  
578 accurately assess short-term fluctuations.<sup>52-55</sup> Our findings are consistent with  
579 existing literature in this field. A comparison between the two available diurnal IOP  
580 curves revealed that the 95% limits of agreement were around 4 mmHg, aligning  
581 closely with the most pronounced fluctuation extremes observed in this dataset

582 (Figure S15). Differences between diurnal IOP fluctuation calculated in the first and  
583 last post-randomization visits were random and approximate a normal distribution  
584 (Figure S16). Several studies<sup>56, 57</sup> have documented a nocturnal peak in IOP,  
585 primarily attributed to an increase in episcleral venous pressure when the body is in  
586 a horizontal position. Although our study did not include night-time IOP  
587 measurements, we did record IOP in a supine position, which is recognized as a  
588 reasonable proxy for estimating nocturnal peak levels.<sup>58</sup> While devices for home IOP  
589 monitoring<sup>59, 60</sup> or continuous IOP tracking<sup>61, 62</sup> have been introduced, they were not  
590 collected in the UKGTS study and are generally reserved for research rather than  
591 routine clinical use. Although the methodology employed in this study may not  
592 capture the entire spectrum or precise patterns of IOP fluctuations, we adopted a  
593 clinically relevant approach to defining diurnal IOP fluctuation.

594 In conclusion, this study finds no evidence to support that either diurnal or  
595 long-term IOP fluctuation, defined in a clinically relevant manner, are independent  
596 factors for glaucoma progression. Other aspects of IOP, such as mean IOP and  
597 peak IOP, may be more informative. Higher OPA may be an independent factor for  
598 faster glaucoma progression.

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608 **Declaration of Generative AI and AI-assisted technologies in the writing**  
609 **process**

610

611 During the preparation of this work the authors used chatGPT3.5 in order to improve  
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613 reviewed and edited the content as needed and take full responsibility for the content  
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789

790 **FIGURE LEGENDS**

791

792 **Figure 5.** Boxplots comparing the various IOP metrics in the placebo and treatment  
793 groups. IOP: intraocular pressure; MD: mean deviation; OPA: ocular pulse  
794 amplitude; SD: standard deviation.

795

796 **Figure 6.** Density plots for the distribution of MD (**left panel**) and pointwise (**right**  
797 **panel**) rates of progression in the placebo and latanoprost groups. MD: mean  
798 deviation. PLR: pointwise linear rates.

799

800 **Figure 7.** Forest plots for factors associated with the MD rates of progression in the  
801 placebo (**left panel**) and treatment (**right panel**) group. Dots and bars indicate point  
802 estimates and 95% confidence intervals, respectively. Estimates are intended for 1-  
803 unit increase, unless specified otherwise. Combined IOP metrics PC1 is an unitless  
804 variable, which combines fluctuation unrelated IOP metrics (baseline IOP, peak IOP,  
805 mean IOP, supine IOP, peak phasing IOP) through Principal Component Analysis.  
806 CCT: central corneal thickness; CH: corneal hysteresis; IOP: intraocular pressure;  
807 MD: mean deviation; OPA: ocular pulse amplitude; PC1: principal component 1.

808

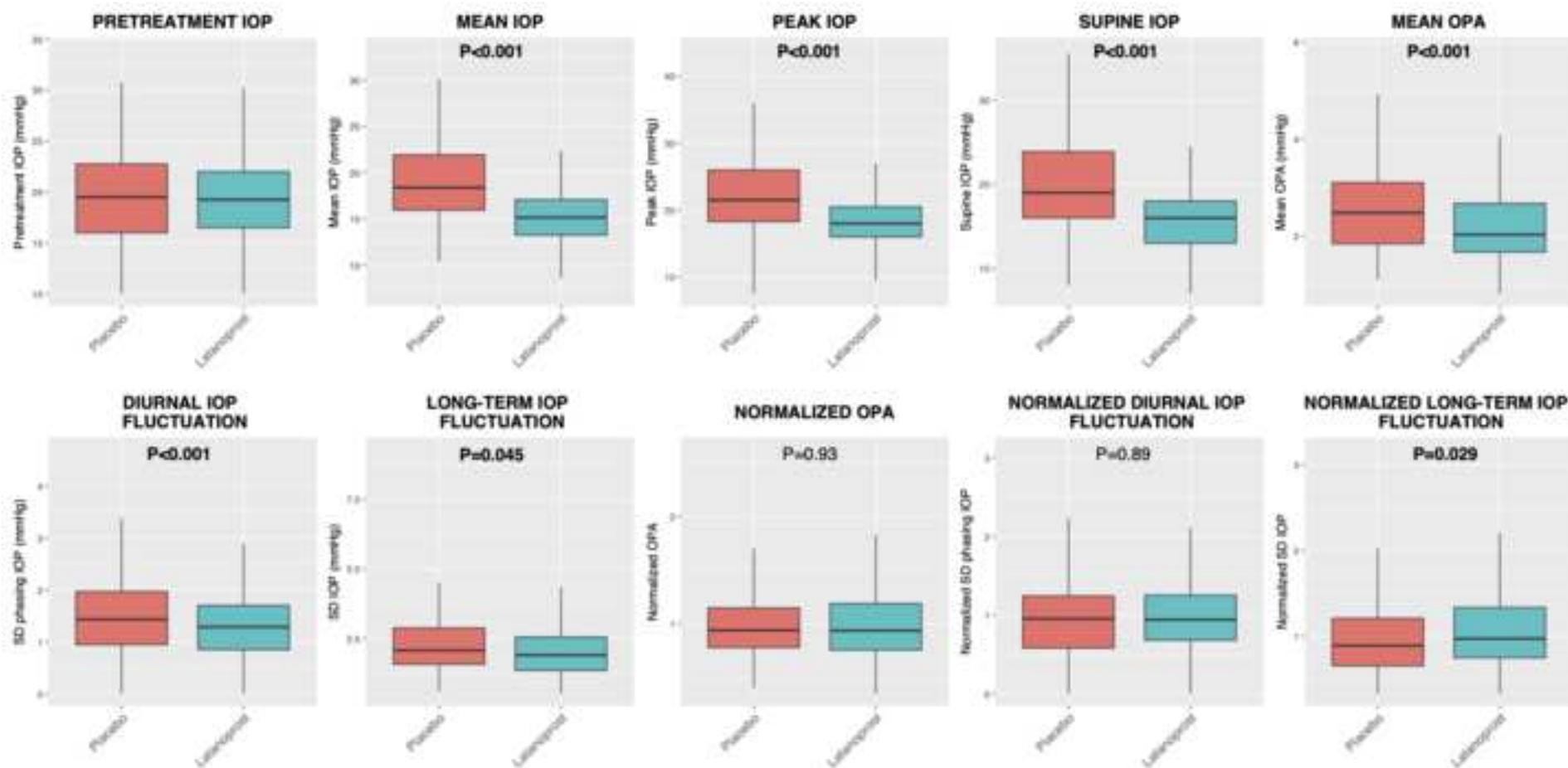
809 **Figure 8.** Forest plots for factors associated with the pointwise rates of progression  
810 in the placebo (**left panel**) and treatment (**right panel**) group. Dots and bars indicate  
811 point estimates and 95% confidence intervals, respectively. Estimates are intended  
812 for 1-unit increase, unless specified otherwise. Combined IOP metrics PC1 is an  
813 unitless variable, which combines fluctuation unrelated IOP metrics (baseline IOP,  
814 peak IOP, mean IOP, supine IOP, peak phasing IOP) through Principal Component

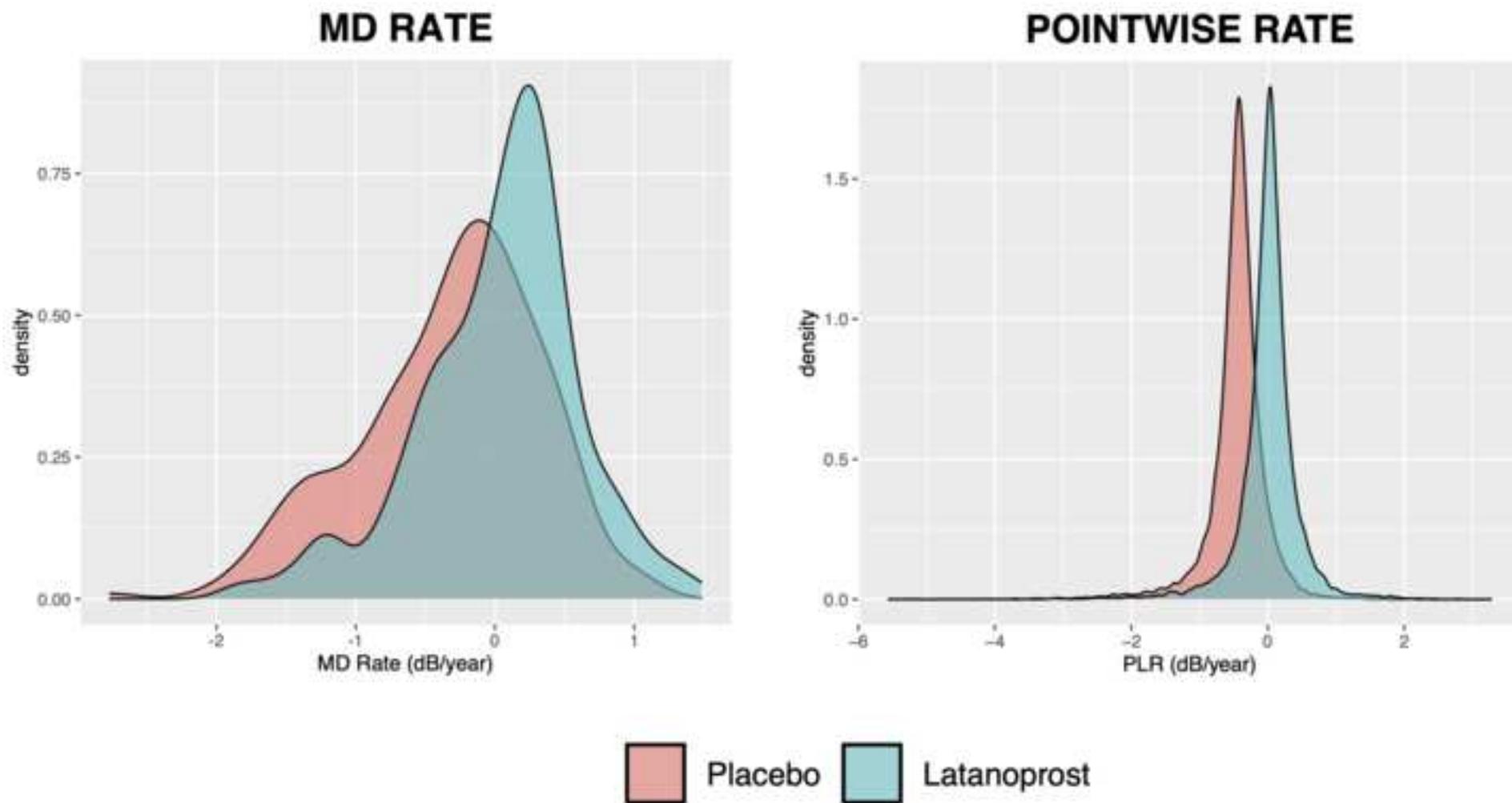
815 Analysis. CCT: central corneal thickness; CH: corneal hysteresis; IOP: intraocular  
816 pressure; OPA: ocular pulse amplitude; PC1: principal component 1; PLR: pointwise  
817 linear rates.

818

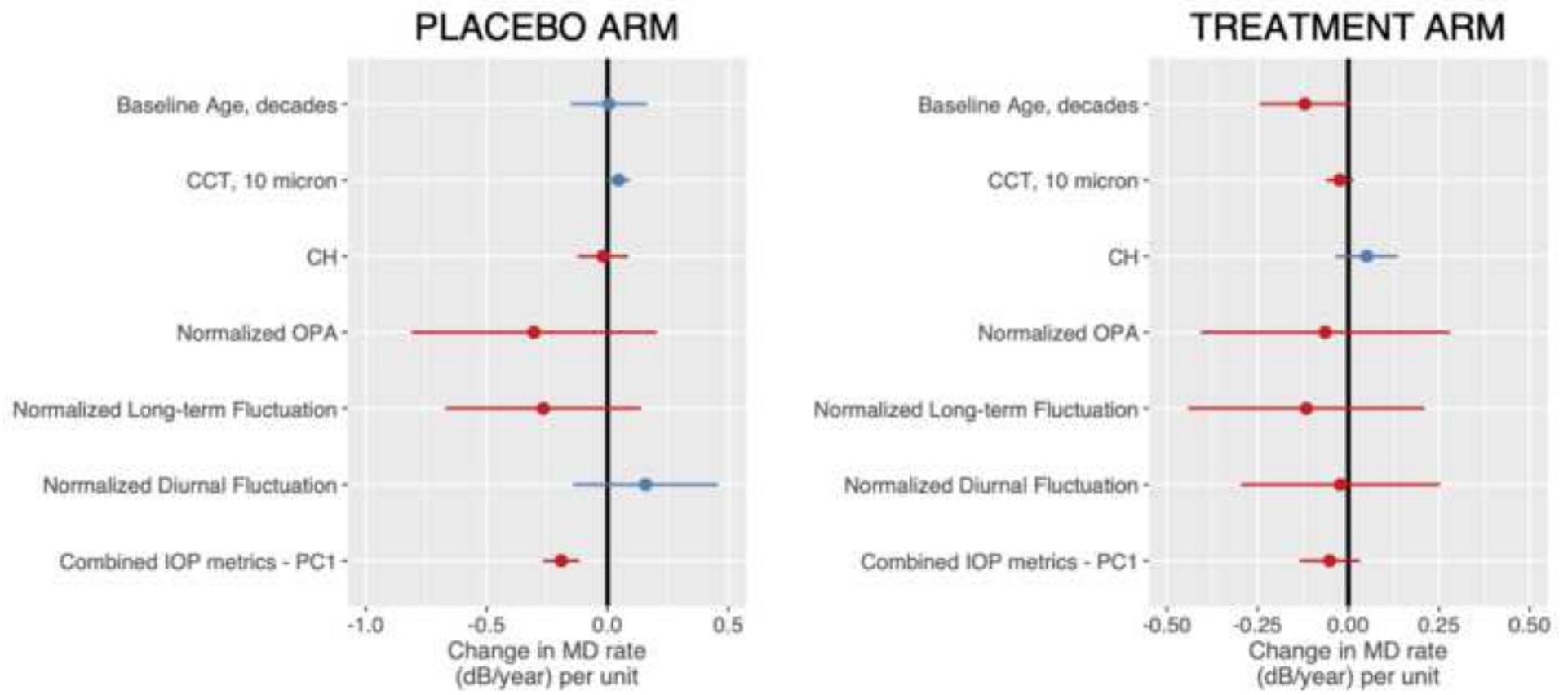
819 **Figure 9.** Forest plots for factors associated with the pointwise rates of progression  
820 of the five fastest locations in the placebo (**left panel**) and treatment (**right panel**)  
821 group. Dots and bars indicate point estimates and 95% confidence intervals,  
822 respectively. Estimates are intended for 1-unit increase, unless specified otherwise.  
823 Combined IOP metrics PC1 is an unitless variable, which combines fluctuation  
824 unrelated IOP metrics (baseline IOP, peak IOP, mean IOP, supine IOP, peak  
825 phasing IOP) through Principal Component Analysis. CCT: central corneal thickness;  
826 CH: corneal hysteresis; IOP: intraocular pressure; OPA: ocular pulse amplitude;  
827 PC1: principal component 1; PLR: pointwise linear rates.

Figure 5

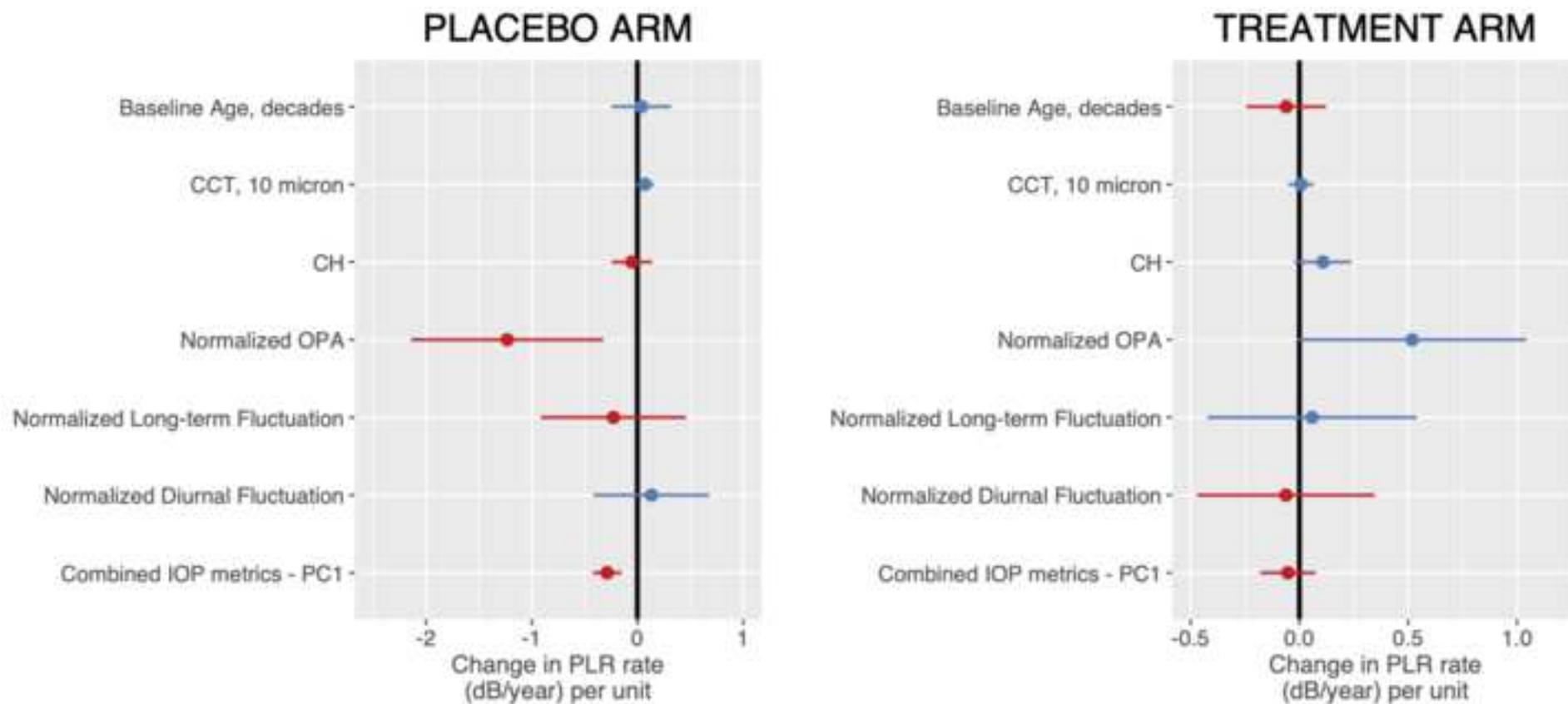




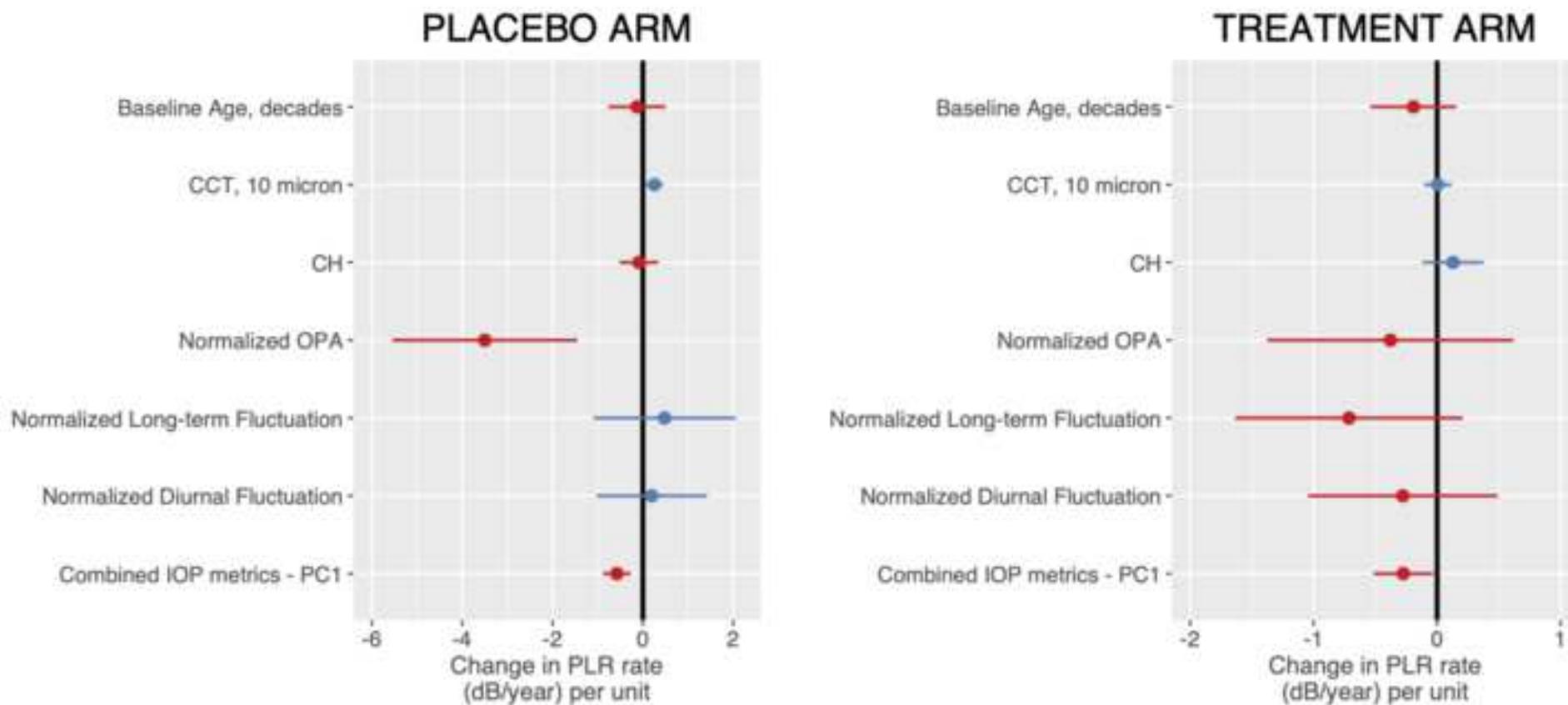
# MD RATE



# PLR – ALL LOCATIONS

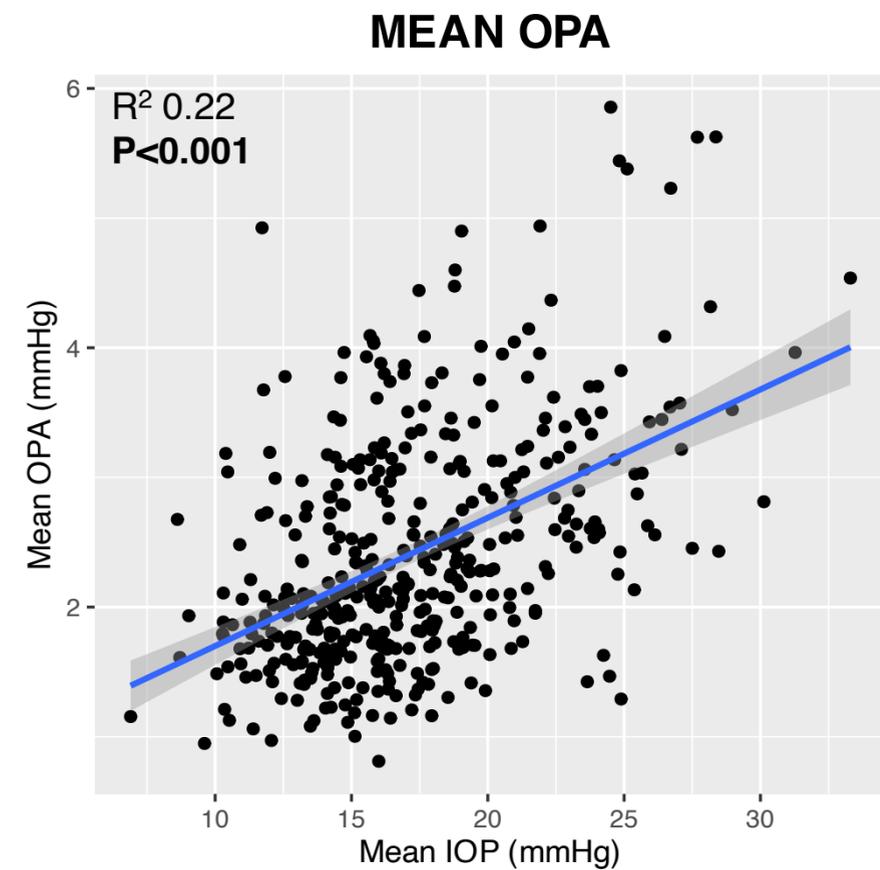
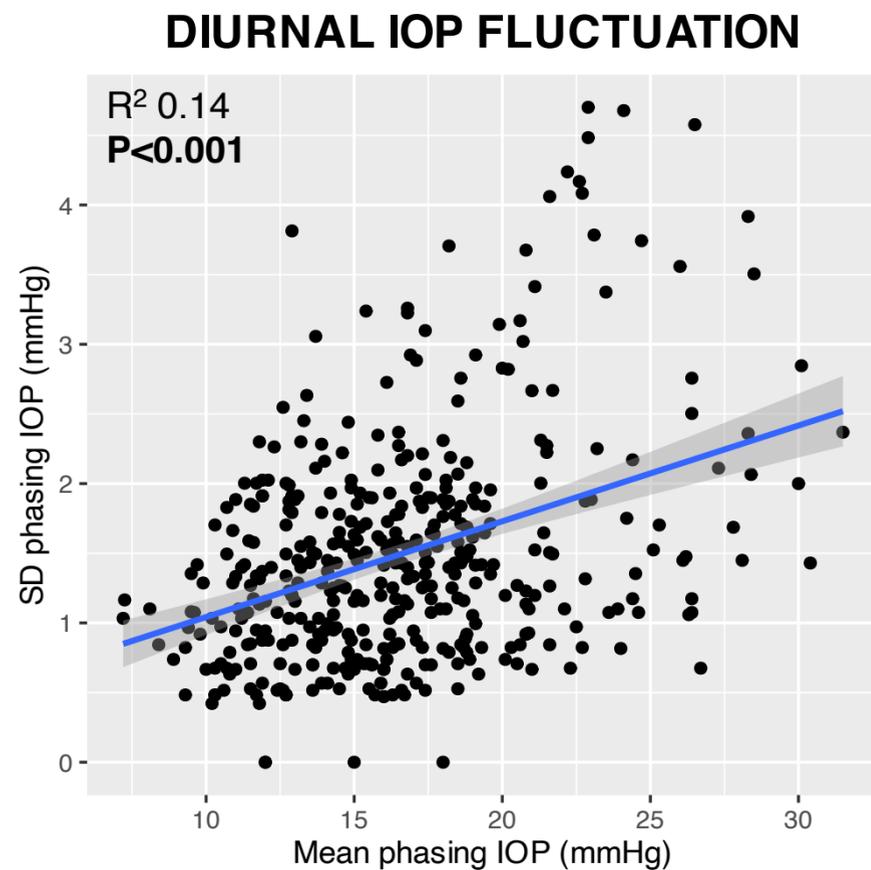
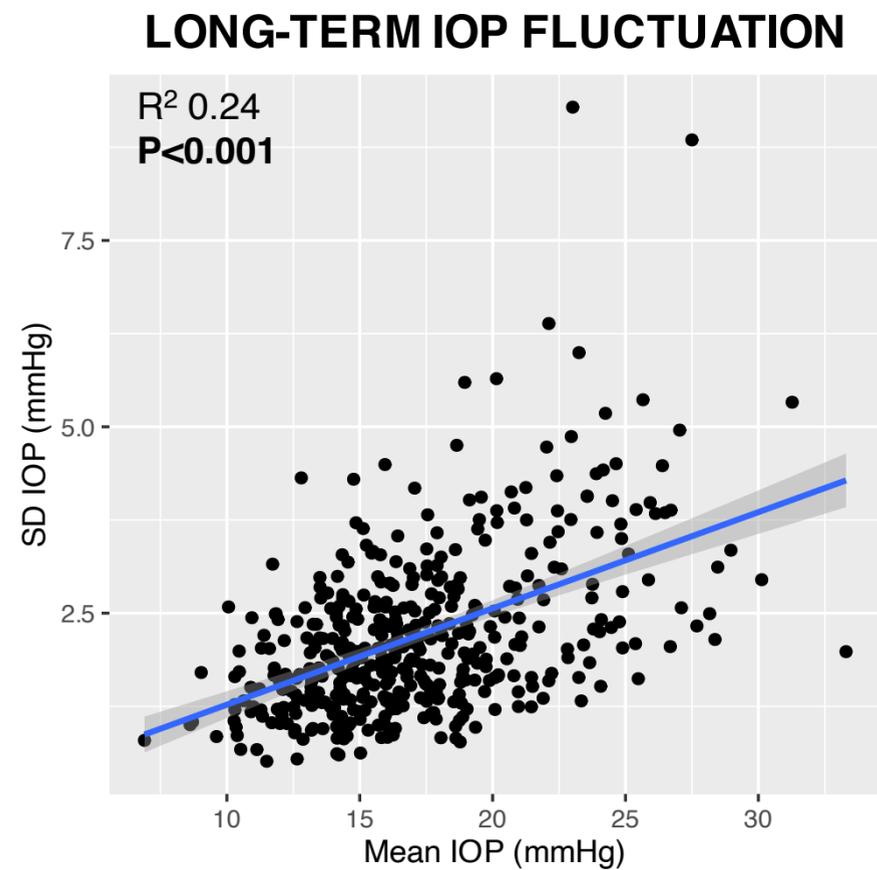


## PLR – 5 FASTEST LOCATIONS

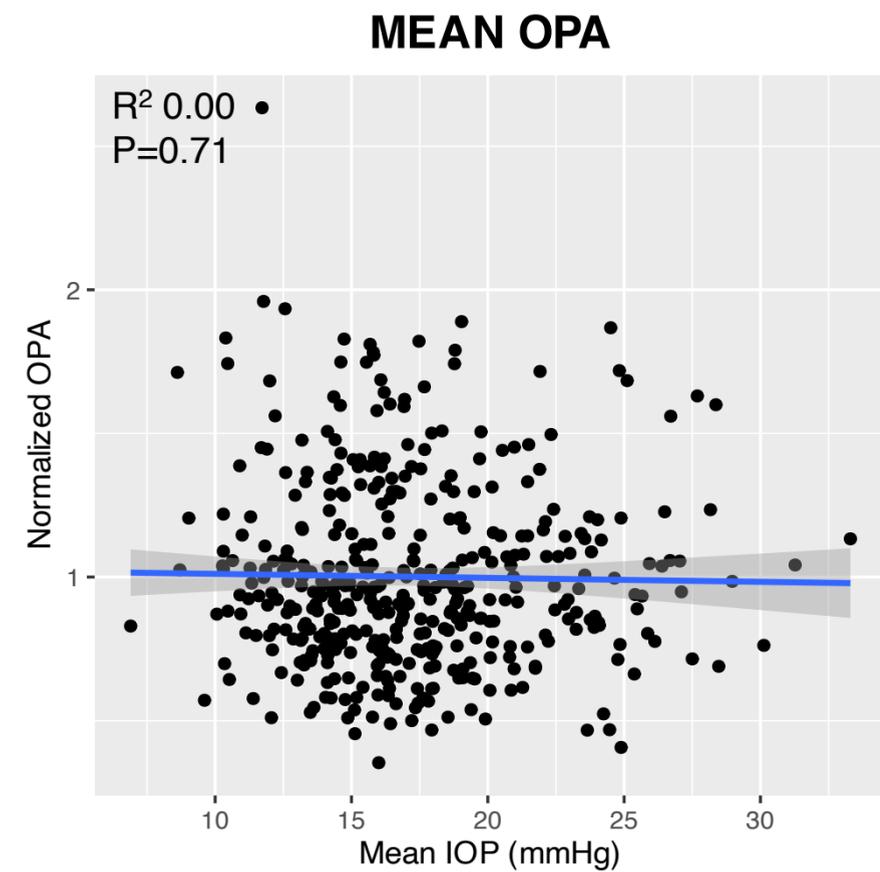
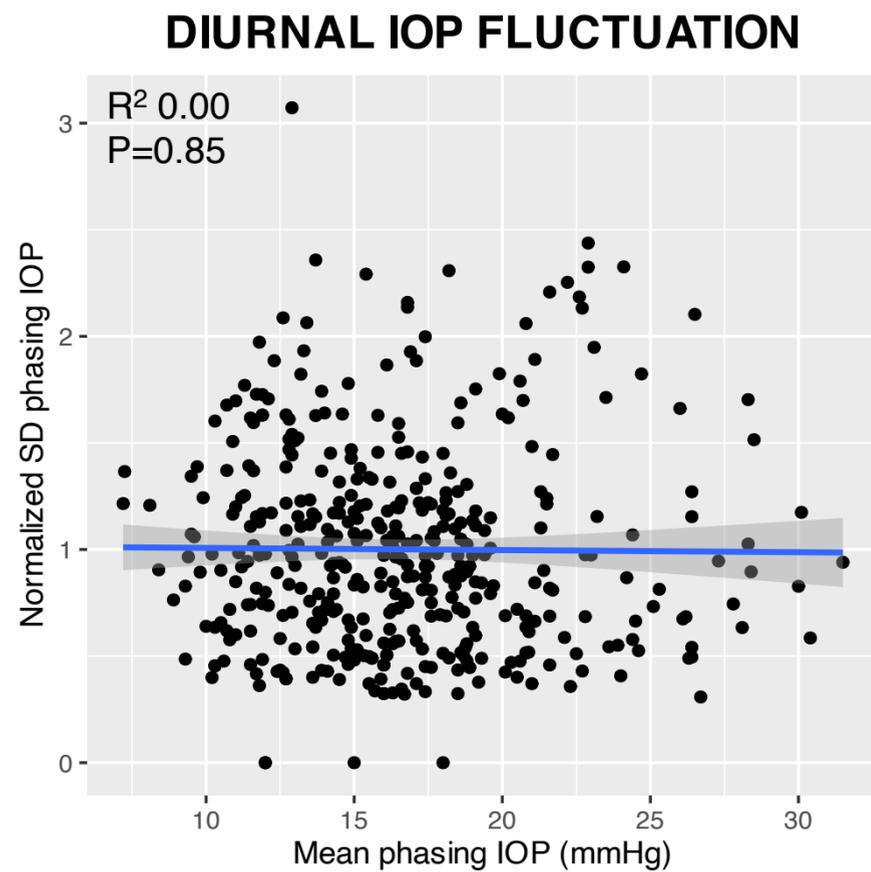
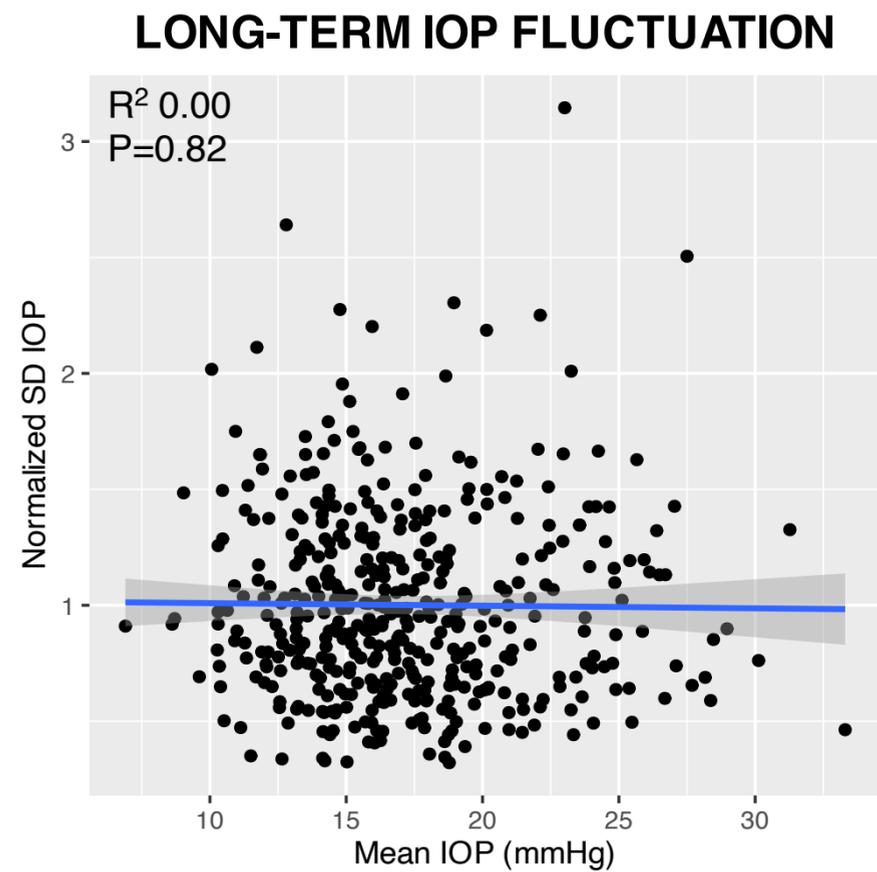


<b>Table 1.</b> Baseline demographic and clinical characteristics of the study population		
<b>Variable</b>	<b>Placebo Cohort</b>	<b>Treatment Cohort</b>
No. Eyes/Patients	213/213	217/217
Age, years, mean ( $\pm$ SD)	66.5 ( $\pm$ 10.3)	65.1 ( $\pm$ 10.4)
Sex, male/female	105/108	119/98
Eye, right / left	92/121	80/137
Ethnicity		
White	193 (90.6%)	197 (90.8%)
Black	11 (5.2%)	7 (3.2%)
Asian	5 (2.3%)	9 (4.2%)
Other	1 (0.5%)	2 (0.9%)
Unknown	3 (1.4%)	2 (0.9%)
Baseline IOP, mmHg, mean ( $\pm$ SD)	19.5 (16.0 to 22.8)	19.3 (16.5 to 22.0)
Baseline MD, dB, median (IQR)	-3.4 (-2.0 to -5.6)	-3.4 (-2.1 to -5.4)
CCT, micron, mean ( $\pm$ SD)	544 ( $\pm$ 34)	539 ( $\pm$ 34)
CCT: central corneal thickness, IOP: intraocular pressure; IQR: interquartile range; MD: mean deviation; SD: standard deviation.		

UNNORMALIZED

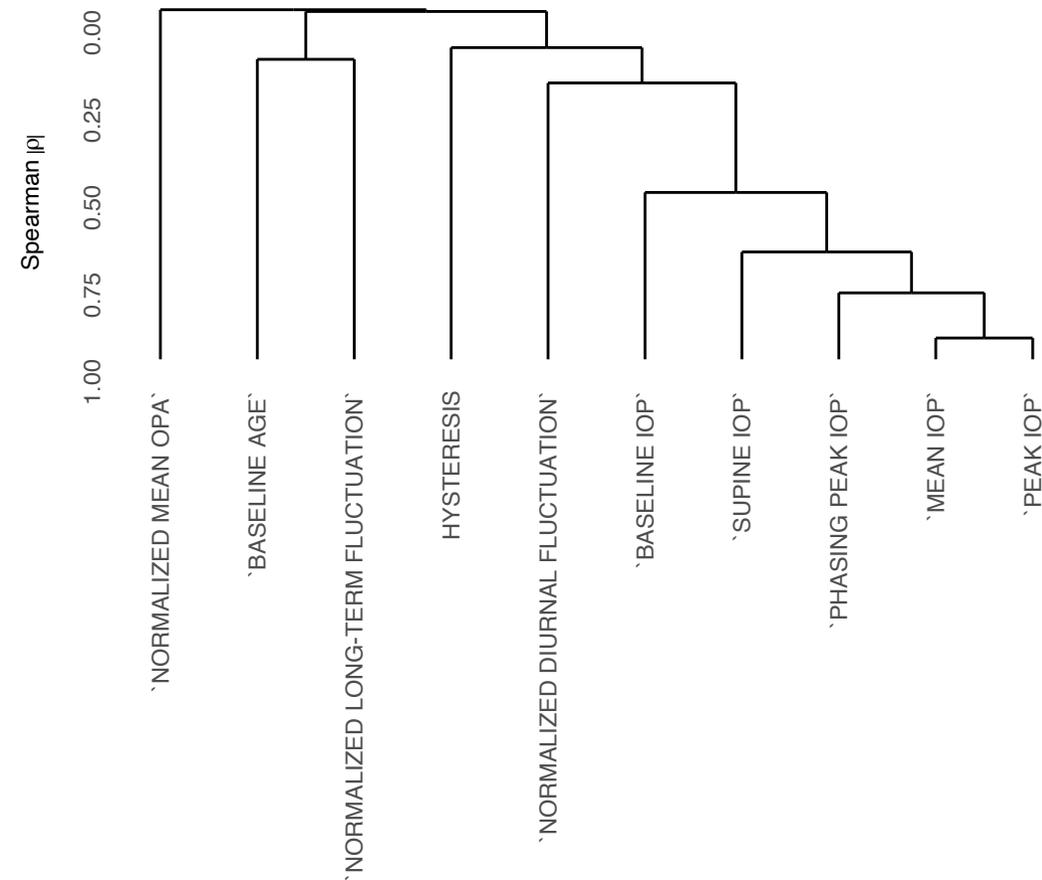


NORMALIZED

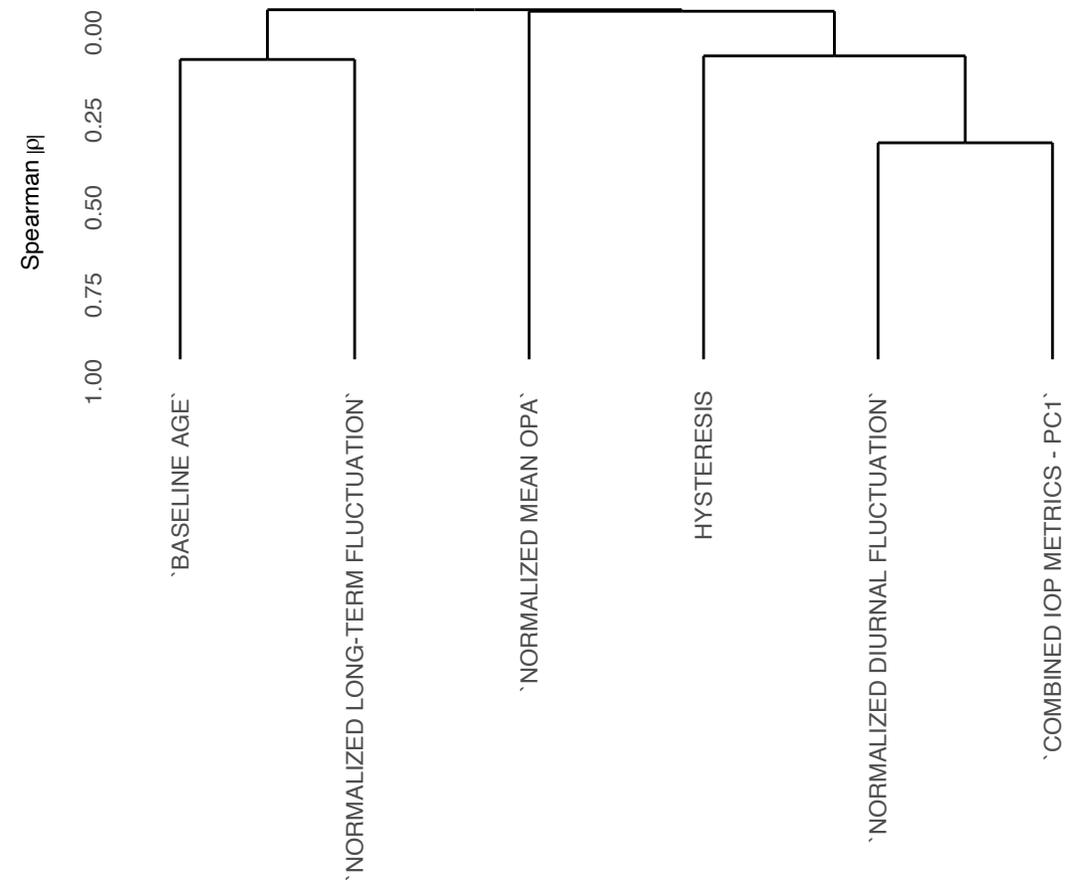


**Figure S1.** Bivariate plots showing the relationship between mean IOPs and the various unnormalized (**top row**) and normalized (**bottom row**) IOP fluctuation metrics. Blue lines and grey shadow represent regression lines and 95% confidence intervals, respectively. IOP: intraocular pressure; OPA: ocular pulse amplitude; SD: standard deviation.

## COVARIATES CORRELATIONS ORIGINAL VARIABLES

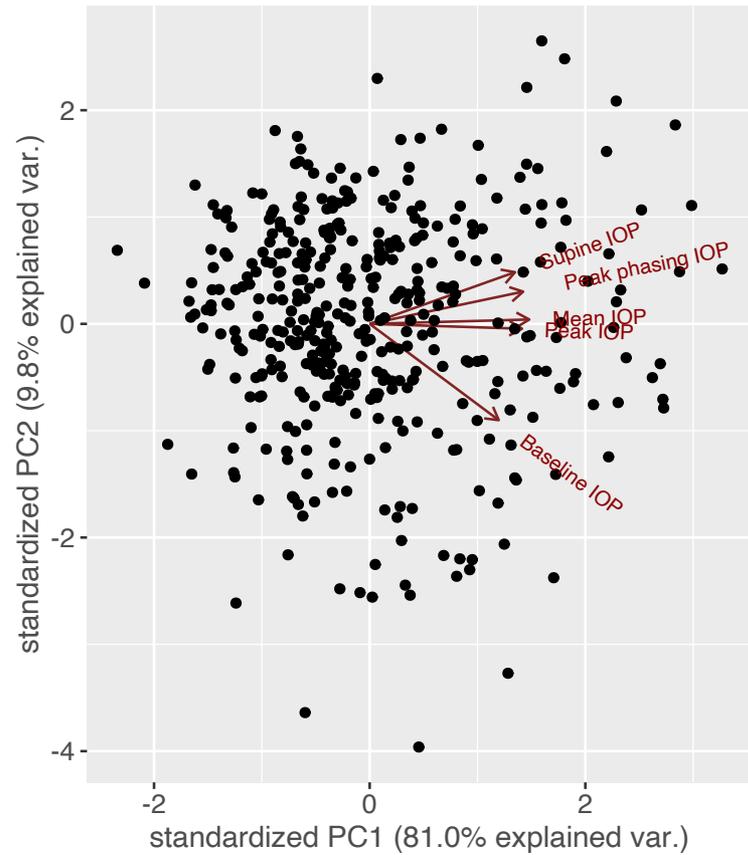


## COVARIATES CORRELATIONS PCA

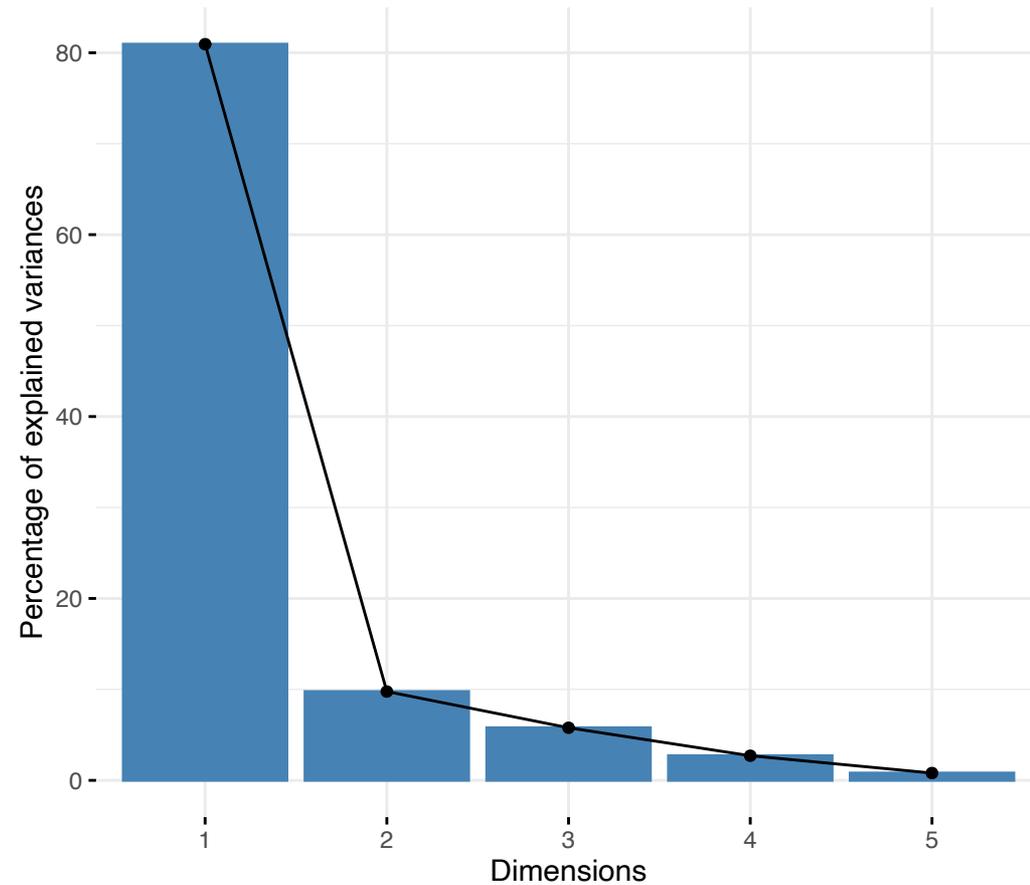


**Figure S2.** Hierarchical cluster analysis of covariates based on the absolute value of Spearman's correlation coefficient for original variables (**left panel**) and after combining baseline IOP, peak IOP, mean IOP, supine IOP, peak phasing IOP into a combined IOP metric through PCA (**right panel**). IOP: intraocular pressure; OPA: ocular pulse amplitude; PCA: principal component analysis; PC1: principal component 1.

## PCA BIPLLOT



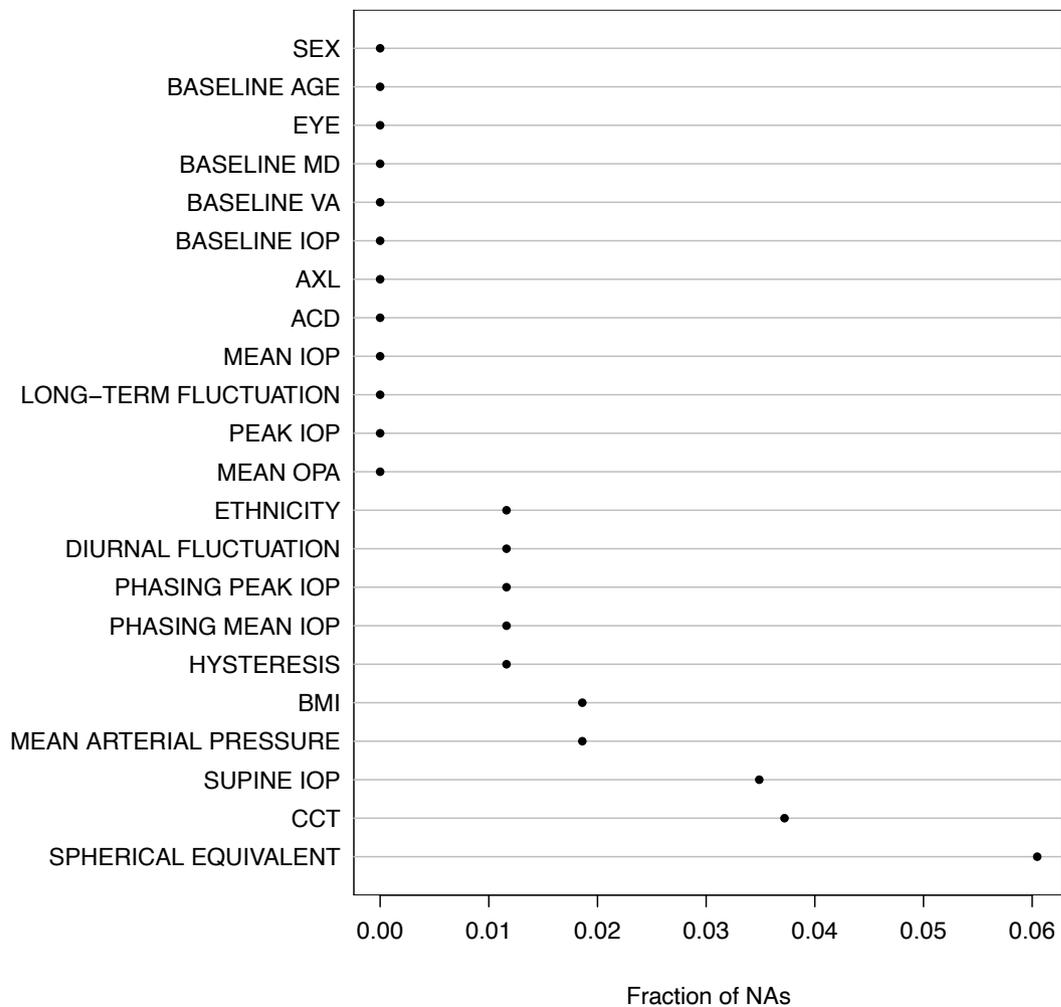
## PCA SCREE PLOT



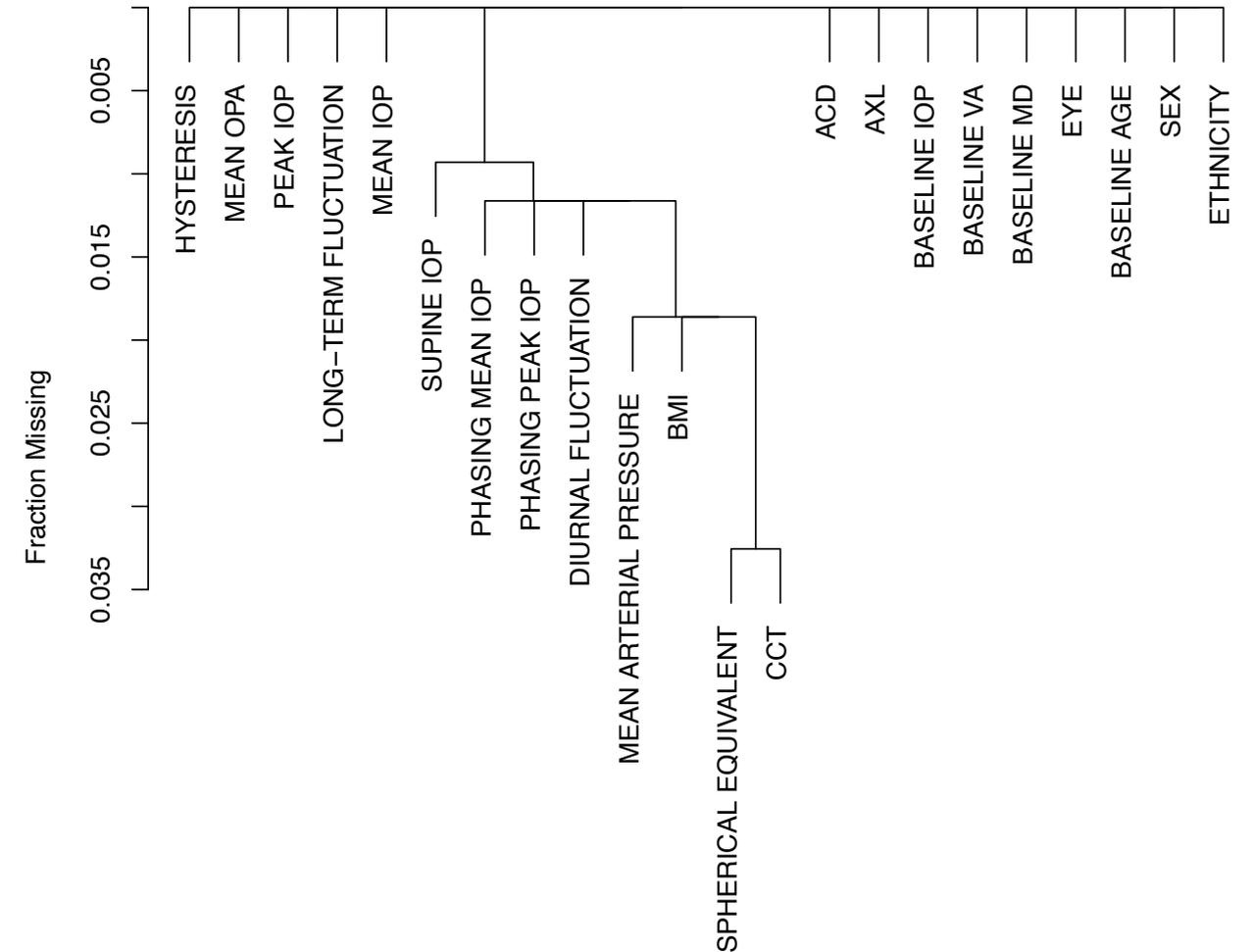
**Figure S3.** Principal component analysis (PCA) Biplot (**left panel**) and scree plot (**right panel**). IOP: intraocular pressure; PC1: principal component 1; PC2: principal component 2.

Figure S4

## Proportion of Missing Data



## Patterns of Missing Data



**Figure S4.** Fraction of missing data for each variable (**left panel**) and hierarchical cluster analysis of missingness combinations (**right panel**). ACD: anterior chamber depth; AXL: axial length; BMI: body mass index; CCT: central corneal thickness; IOP: intraocular pressure; MD: mean deviation; OPA: ocular pulse amplitude; VA: visual acuity.

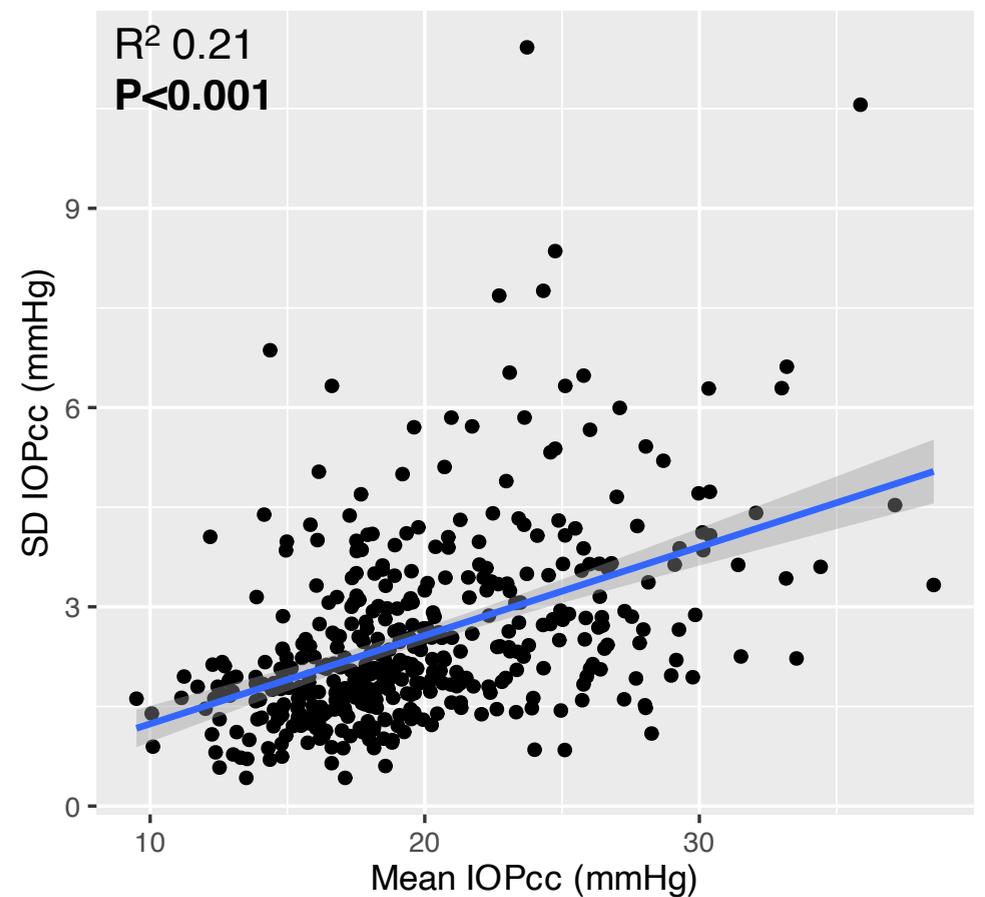
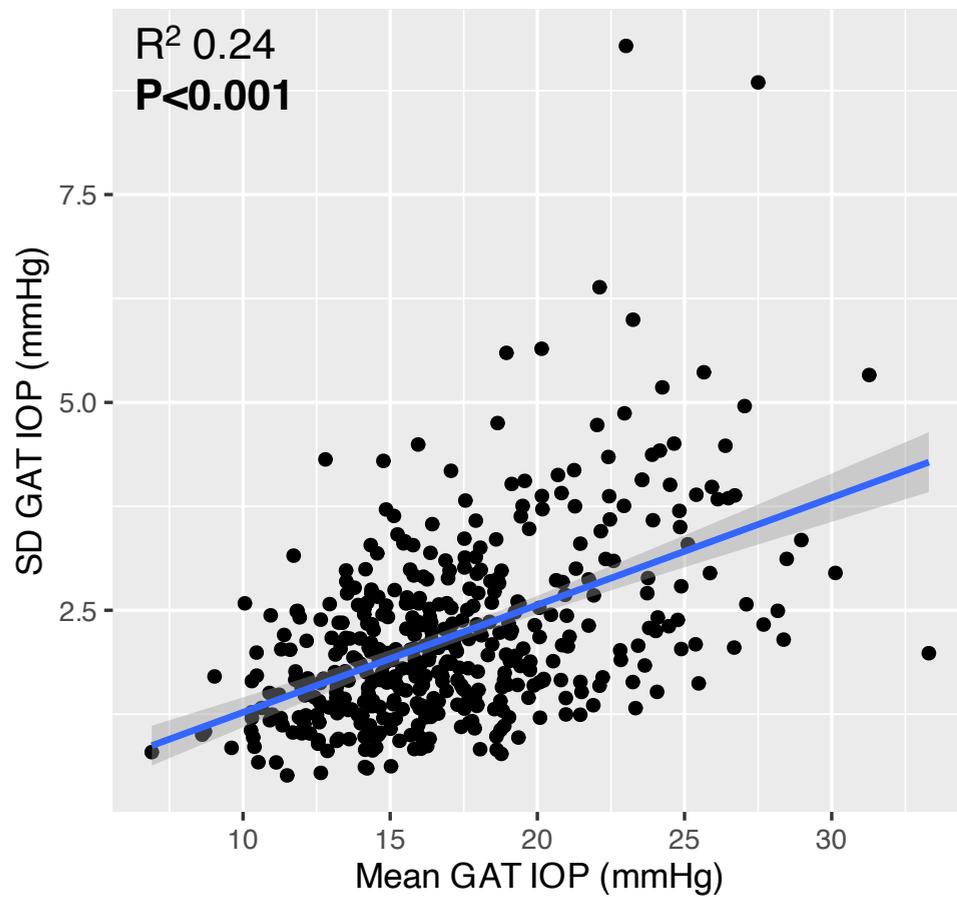
## GAT IOP

ORA IOP<sub>cc</sub>

LONG-TERM GAT IOP FLUCTUATION

LONG-TERM IOP<sub>cc</sub> FLUCTUATION

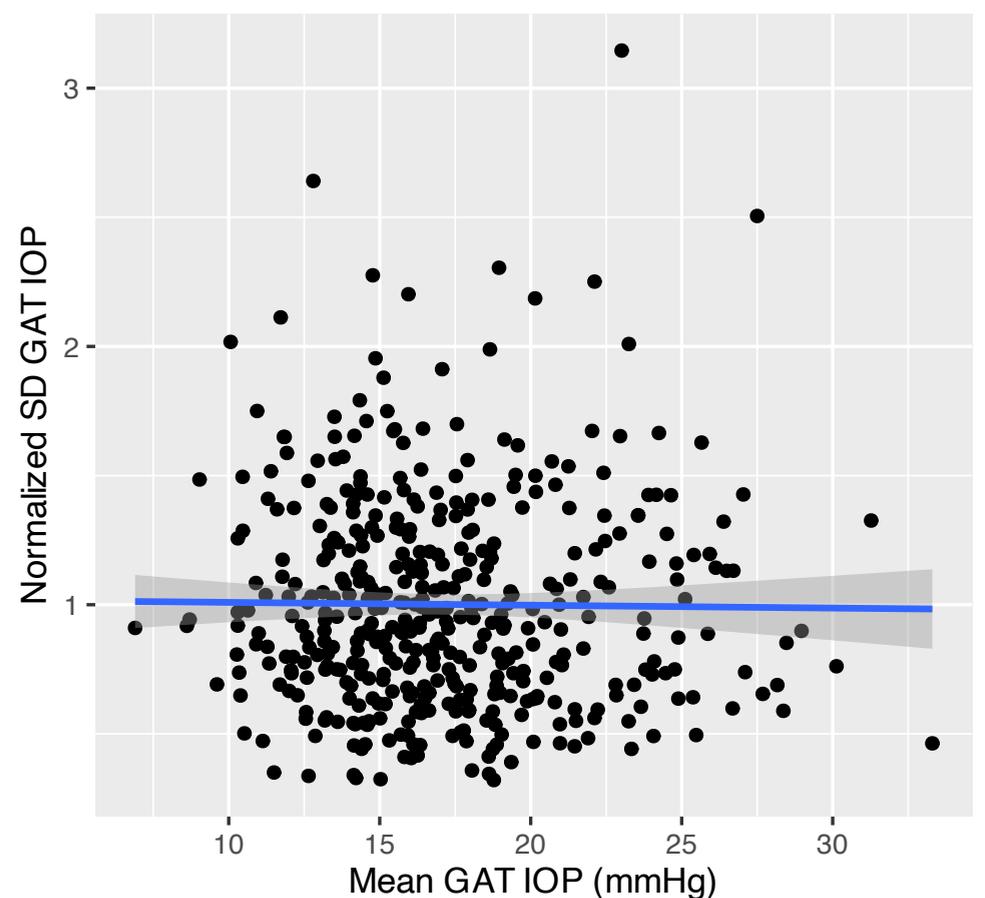
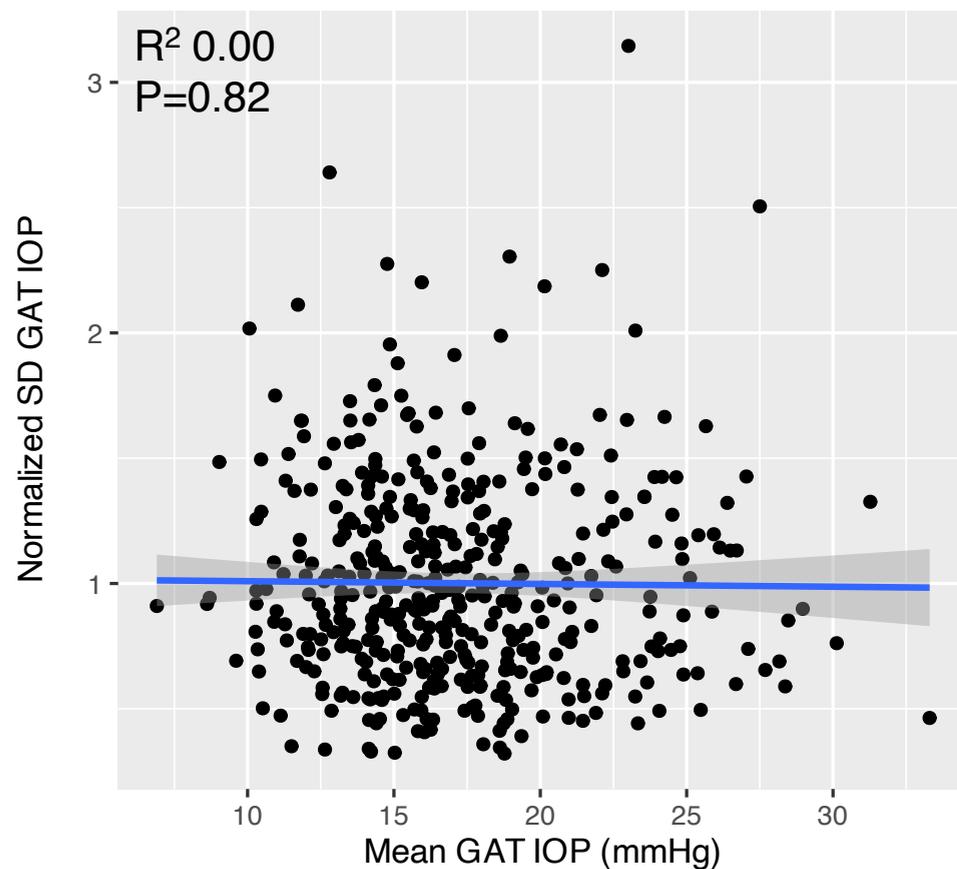
UNNORMALIZED



LONG-TERM GAT IOP FLUCTUATION

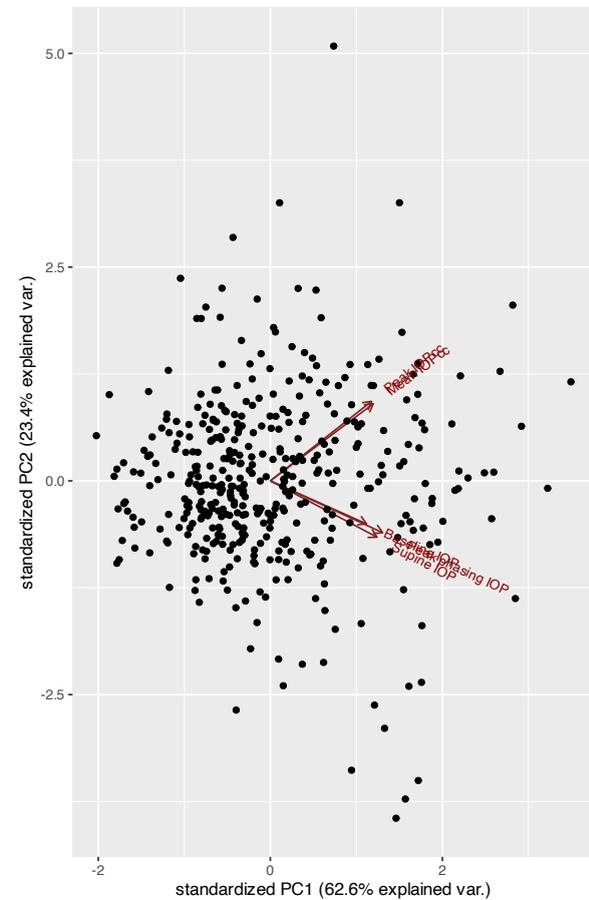
LONG-TERM IOP<sub>cc</sub> FLUCTUATION

NORMALIZED

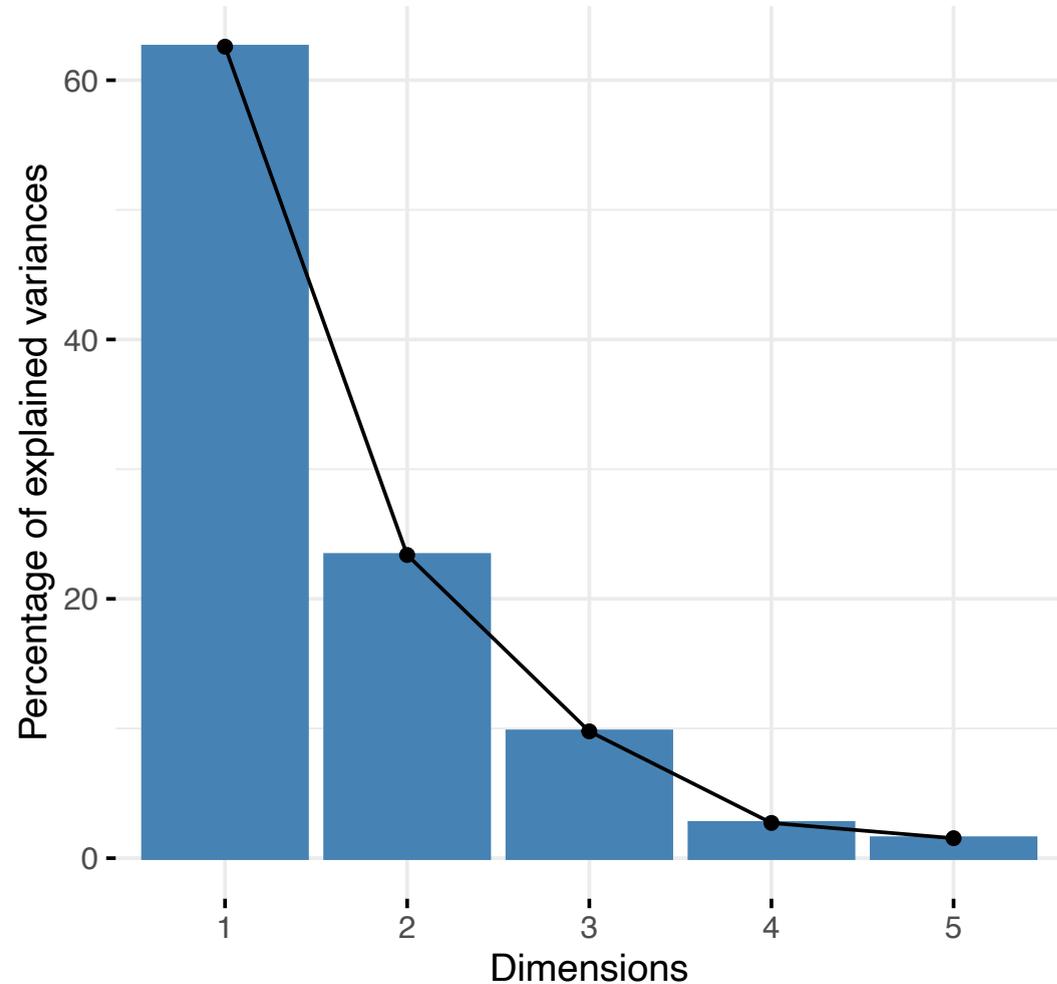


**Figure S10.** Bivariate plots showing the relationship between mean IOP and long-term IOP fluctuation as measured with GAT (**left column**) and ORA (**right column**). Blue lines and grey shadow represent regression lines and 95% confidence intervals, respectively. GAT: Goldmann applanation tonometer; IOP: intraocular pressure; IOP<sub>cc</sub>: corneal-compensated IOP; ORA: ocular response analyzer; SD: standard deviation.

## PCA BIPLLOT

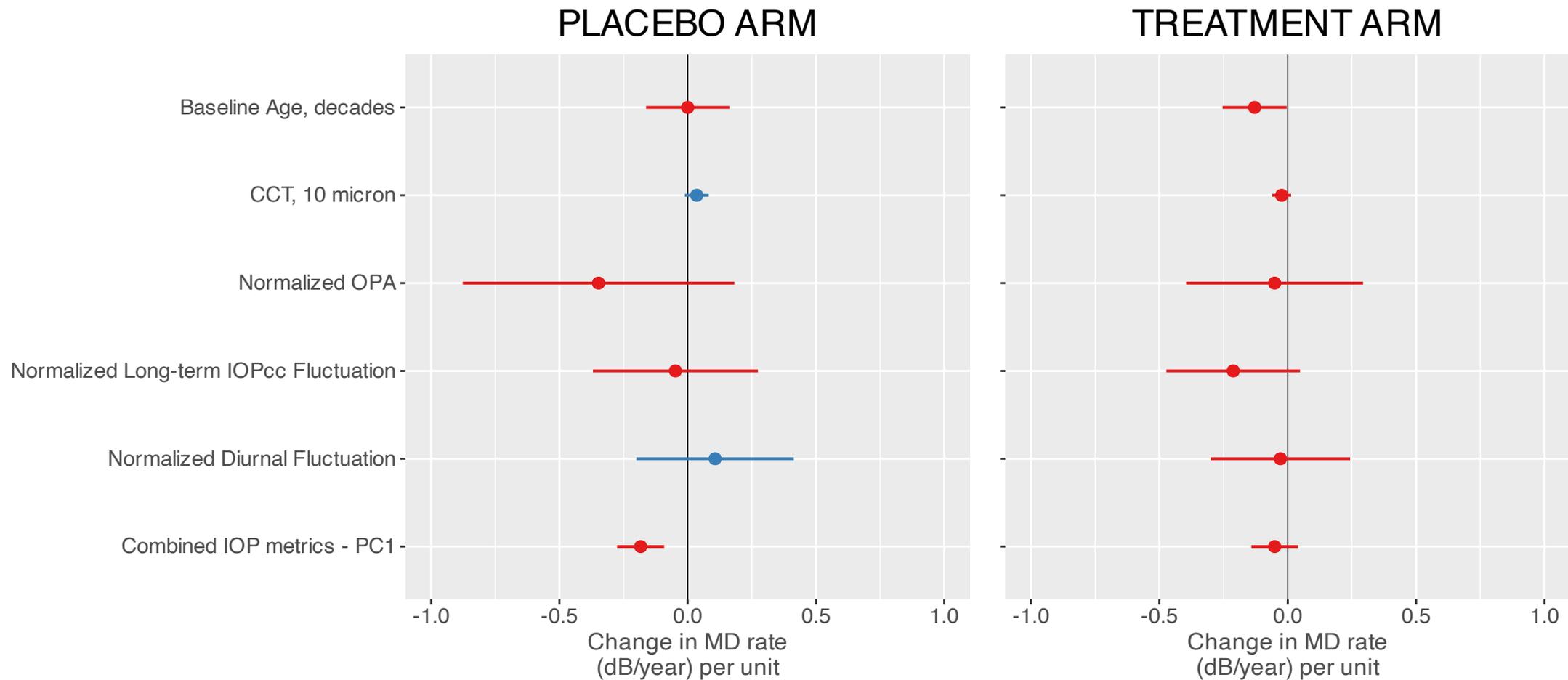


## PCA SCREE PLOT



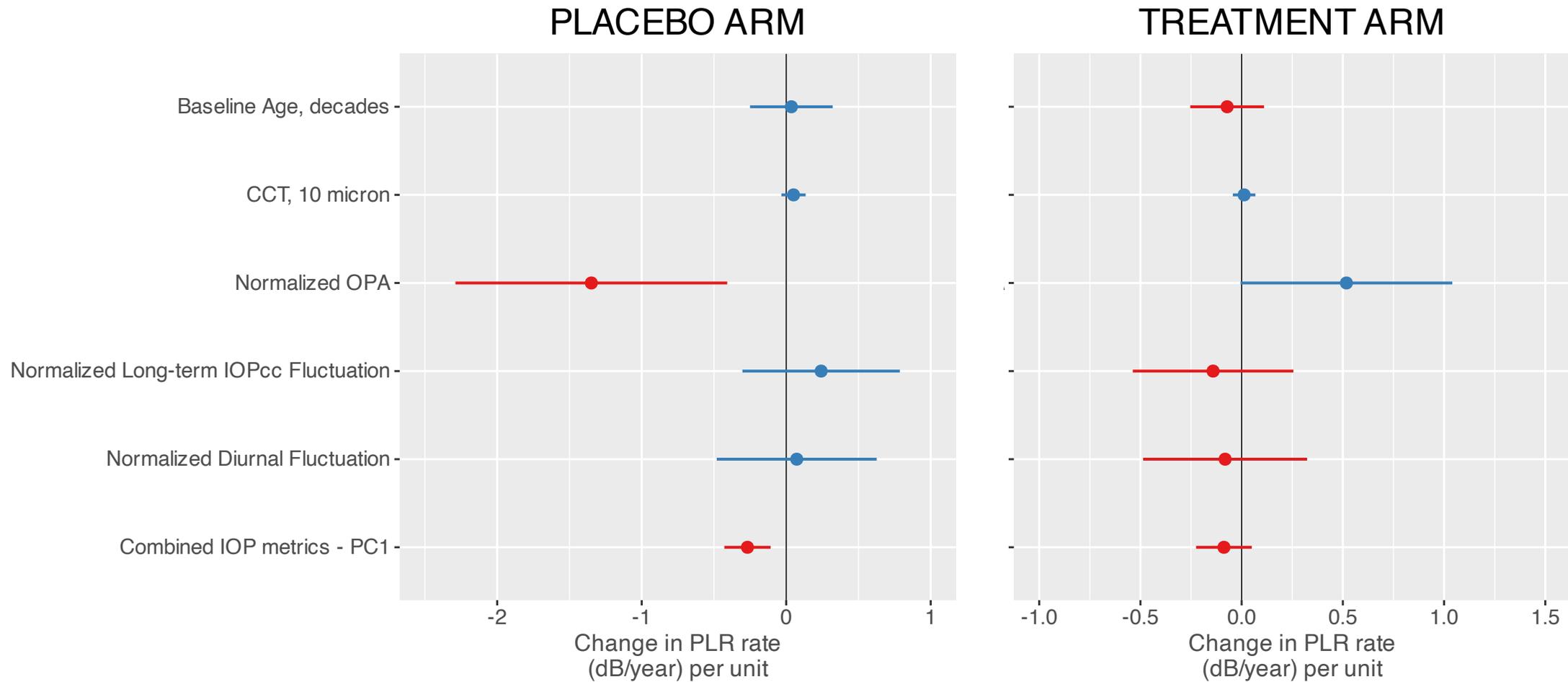
**Figure S11.** Principal component analysis (PCA) biplot (**left panel**) and scree plot (**right panel**) using IOPcc values to estimate mean and peak IOP. IOP: intraocular pressure; IOPcc: corneal-compensated IOP; PC1: principal component 1; PC2: principal component 2.

# MD RATE



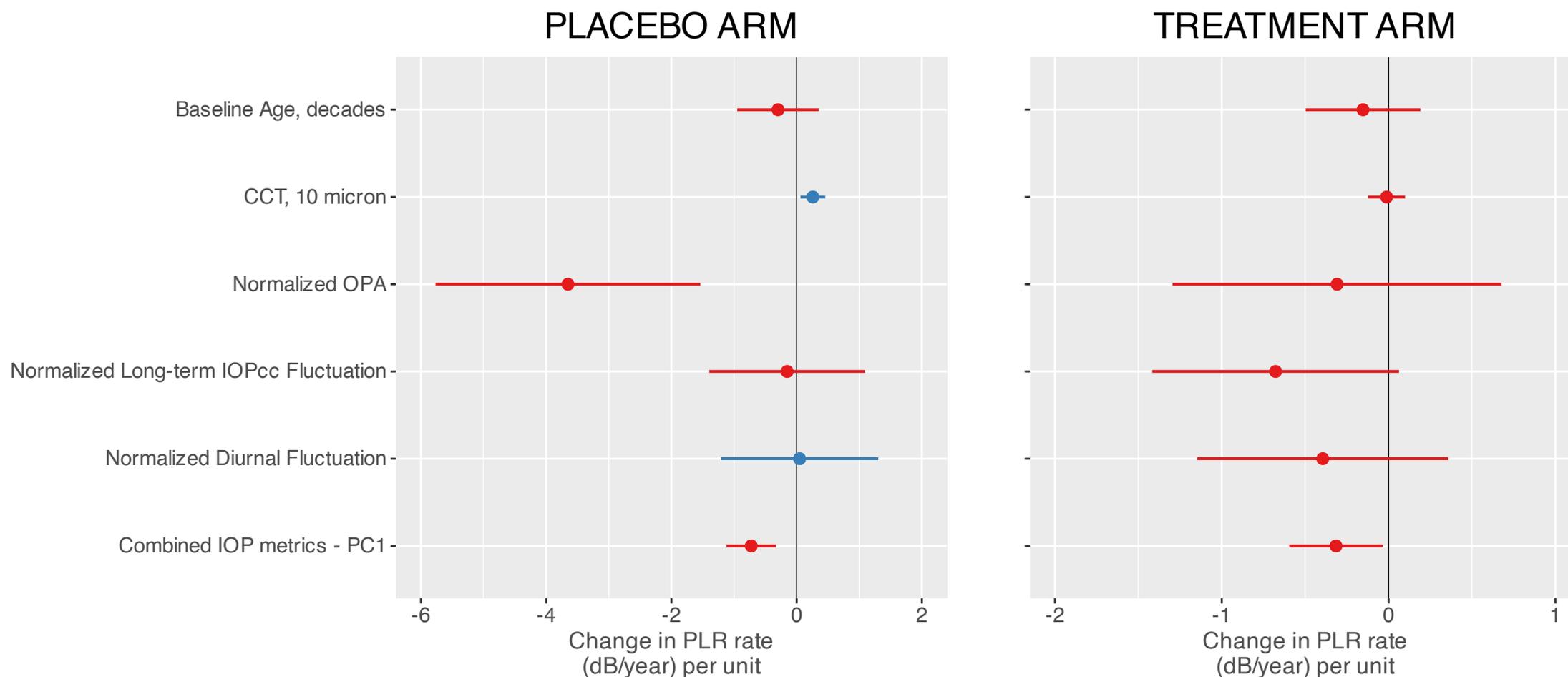
**Figure S12.** Forest plots for factors associated with the MD rates of progression in the placebo (**left panel**) and treatment (**right panel**) group. Mean IOP, peak IOP and normalized LTF fluctuation were calculated from corneal compensated IOP as measured with the Ocular Response Analyzer (Reichert, Inc, Buffalo, NY). Dots and bars indicate point estimates and 95% confidence intervals, respectively. Estimates are intended for 1-unit increase, unless specified otherwise. CCT: central corneal thickness; IOP: intraocular pressure; IOPcc: corneal-compensated IOP; MD: mean deviation; OPA: ocular pulse amplitude; PC1: principal component 1

# PLR – ALL LOCATIONS



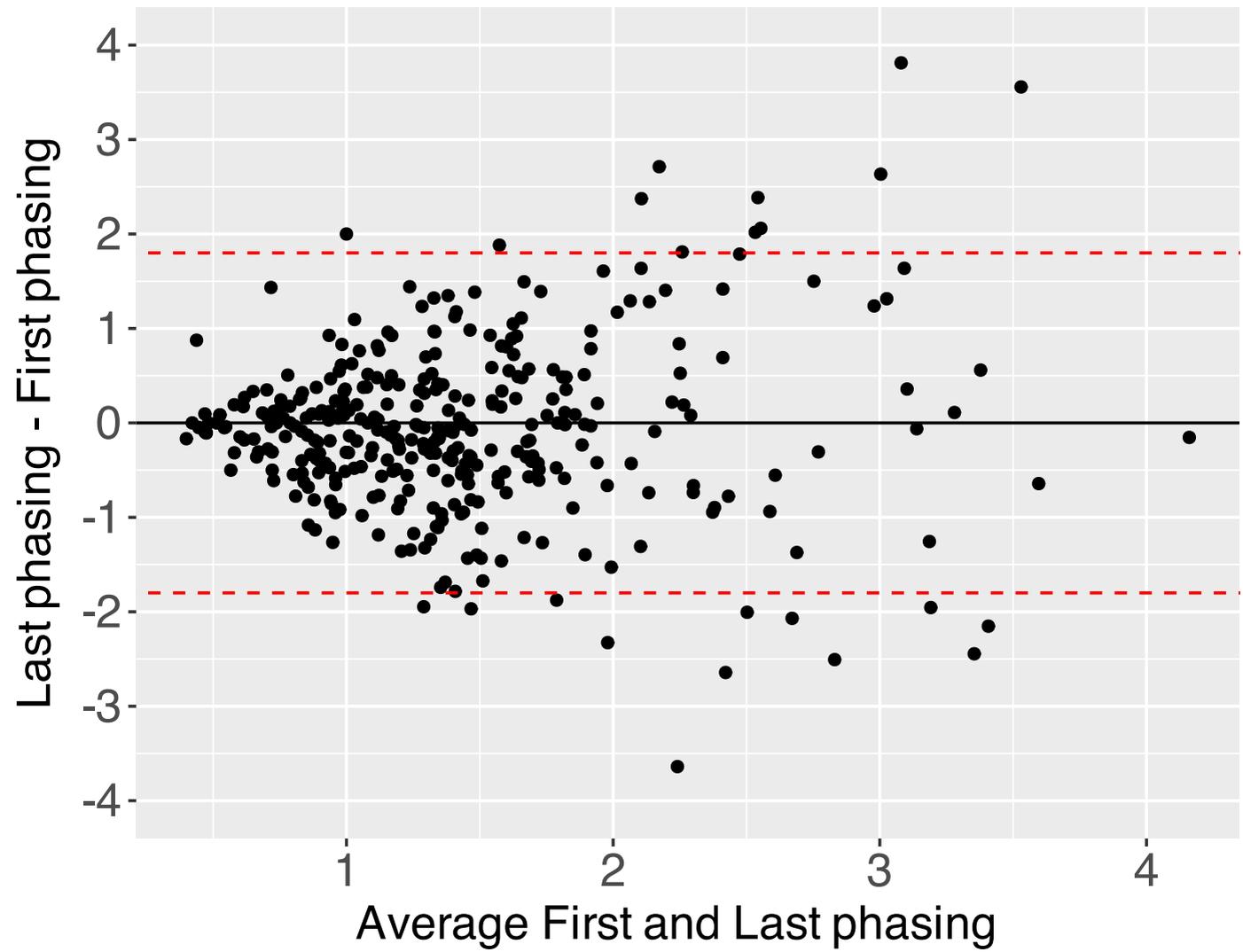
**Figure S13.** Forest plots for factors associated with the pointwise rates of progression in the placebo (**left panel**) and treatment (**right panel**) group. Mean IOP, peak IOP and normalized LTF fluctuation were calculated from corneal compensated IOP as measured with the Ocular Response Analyzer (Reichert, Inc, Buffalo, NY). Dots and bars indicate point estimates and 95% confidence intervals, respectively. Estimates are intended for 1-unit increase, unless specified otherwise. CCT: central corneal thickness; IOP: intraocular pressure; IOPcc: corneal-compensated IOP; MD: mean deviation; OPA: ocular pulse amplitude; PC1: principal component 1

# PLR – 5 FASTEST LOCATIONS



**Figure S14.** Forest plots for factors associated with the pointwise rates of progression of the fastest five locations in the placebo (**left panel**) and treatment (**right panel**) group. Mean IOP, peak IOP and normalized LTF fluctuation were calculated from corneal compensated IOP as measured with the Ocular Response Analyzer (Reichert, Inc, Buffalo, NY). Dots and bars indicate point estimates and 95% confidence intervals, respectively. Estimates are intended for 1-unit increase, unless specified otherwise. CCT: central corneal thickness; IOP: intraocular pressure; IOPcc: corneal-compensated IOP; MD: mean deviation; OPA: ocular pulse amplitude; PC1: principal component 1

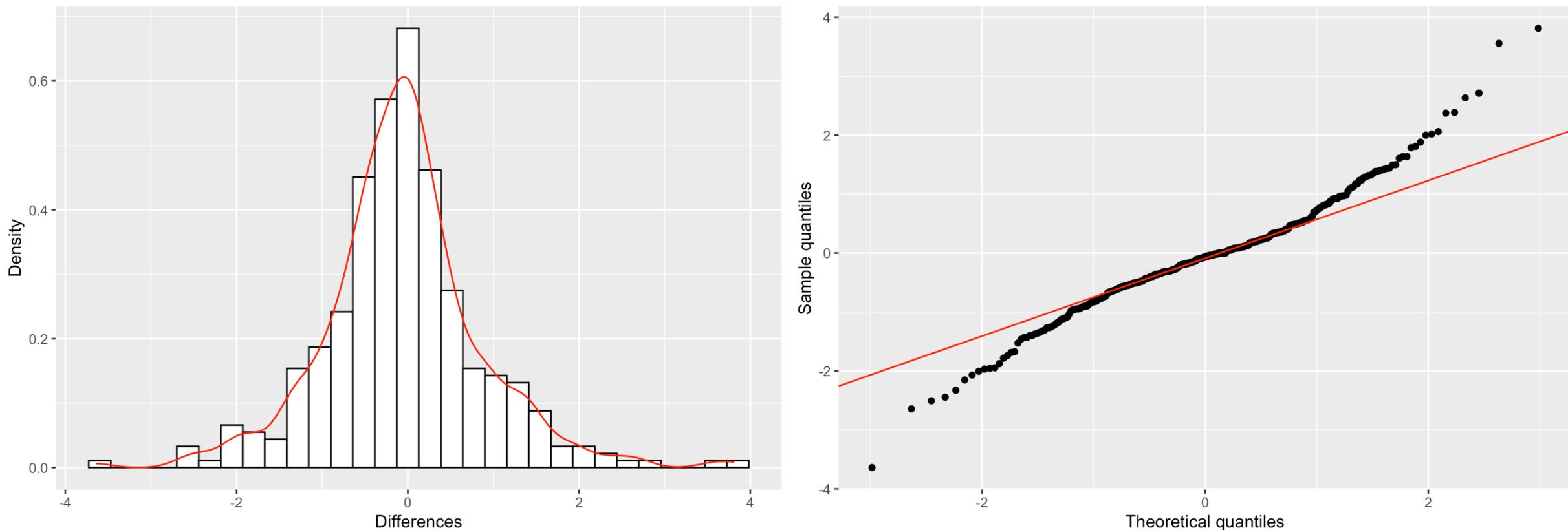
# DIURNAL IOP FLUCTUATION



**Figure S15.** Bland-Altman plots of agreement for diurnal IOP fluctuation calculated from the IOP phasing performed at the first and last post-randomization visits. Black solid line and red dashed lines indicate the no difference lines. and 95% limits of agreements, respectively.

Figure S16

# DIURNAL SD IOP DIFFERENCES BETWEEN LAST AND FIRST PHASING



**Figure S16.** Frequency histogram (**left panel**) and quantile-quantile plot (**right panel**) for the difference in IOP fluctuation values calculated from IOP phasings performed at the last and first post-randomization visits.

<b>Table S2.</b> Univariable analysis for factors associated with the MD rate of progression				
<b>Variable</b>	<b>PLACEBO</b>		<b>TREATMENT</b>	
	Est (SE)	p-value	Est (SE)	p-value
Baseline Age, decades	-0.01 (0.08)	0.89	-0.08 (0.06)	0.18
CCT, per 10 $\mu\text{m}$	0.02 (0.02)	0.34	-0.02 (0.02)	0.35
CH	0.05 (0.05)	0.34	0.05 (0.04)	0.25
Baseline IOP	-0.06 (0.02)	<b>&lt;0.001</b>	0.00 (0.01)	0.77
Mean IOP	-0.08 (0.02)	<b>&lt;0.001</b>	-0.03 (0.02)	0.18
Peak IOP	-0.07 (0.01)	<b>&lt;0.001</b>	-0.02 (0.01)	0.10
Peak Phasing IOP	-0.05 (0.02)	<b>&lt;0.001</b>	-0.02 (0.02)	0.14
Supine IOP	-0.06 (0.01)	<b>&lt;0.001</b>	-0.01 (0.02)	0.49
OPA	-0.32 (0.09)	<b>&lt;0.001</b>	-0.04 (0.08)	0.62
Long-term Fluctuation	-0.27 (0.07)	<b>&lt;0.001</b>	-0.12 (0.06)	<b>0.047</b>
Diurnal Fluctuation	-0.11 (0.09)	0.23	-0.09 (0.09)	0.35
Normalized OPA	-0.42 (0.26)	0.11	0.02 (0.18)	0.90
Normalized long-term Fluctuation	-0.28 (0.20)	0.17	-0.16 (0.15)	0.30
Normalized diurnal Fluctuation	0.05 (0.15)	0.77	-0.01 (0.13)	0.91

Estimates are intended for 1-unit increase unless specified otherwise.  
CCT: central corneal thickness; CH: corneal hysteresis; IOP: intraocular pressure; OPA: ocular pulse amplitude; SE: standard error.

<b>Table S3.</b> Multivariable analysis for factors associated with the MD rate of progression				
	<b>PLACEBO</b>		<b>TREATMENT</b>	
<b>Variable</b>	Est (SE)	p-value	Est (SE)	p-value
Baseline Age, decades	0.01 (0.08)	0.95	-0.12 (0.06)	0.06
CCT, per 10 $\mu\text{m}$	0.05 (0.02)	0.06	-0.02 (0.02)	0.23
CH	-0.02 (0.05)	0.73	0.05 (0.04)	0.25
Normalized OPA	-0.30 (0.26)	0.24	-0.06 (0.18)	0.72
Normalized long-term Fluctuation	-0.27 (0.21)	0.20	-0.12 (0.17)	0.49
Normalized diurnal Fluctuation	0.16 (0.15)	0.31	-0.02 (0.14)	0.88
Combined IOP metrics – PC1	-0.19 (0.04)	<b>&lt;0.001</b>	-0.05 (0.04)	0.23
<p>Estimates are intended for 1-unit increase. Combined IOP metrics PC1 is an unitless variables, combining fluctuation unrelated IOP metrics (baseline IOP, peak IOP, mean IOP, supine IOP, peak phasing IOP) through Principal Component Analysis.  CCT: central corneal thickness; CH: corneal hysteresis; IOP: intraocular pressure; PC1: principal component 1; SE: standard error.</p>				

<b>Table S4.</b> Multivariable analysis for factors associated with the MD rate of progression				
	<b>PLACEBO</b>		<b>TREATMENT</b>	
<b>Variable</b>	Est (SE)	p-value	Est (SE)	p-value
Baseline Age, decades	0.02 (0.08)	0.85	-0.13 (0.06)	<b>0.037</b>
CCT, per 10 $\mu\text{m}$	0.05 (0.02)	0.056	-0.03 (0.02)	0.19
CH	-0.02 (0.05)	0.73	0.04 (0.04)	0.32
OPA	-0.15 (0.10)	0.11	-0.05 (0.08)	0.54
Long-term Fluctuation	-0.12 (0.09)	0.17	-0.12 (0.08)	0.11
Diurnal Fluctuation	0.09 (0.10)	0.35	-0.06 (0.11)	0.61
Combined IOP metrics – PC1	-0.14 (0.05)	<b>0.005</b>	0.00 (0.05)	0.95
<p>Estimates are intended for 1-unit increase. Combined IOP metrics PC1 is a unitless variable, combining fluctuation unrelated IOP metrics (baseline IOP, peak IOP, mean IOP, supine IOP, peak phasing IOP) through Principal Component Analysis.</p> <p>CCT: central corneal thickness; CH: corneal hysteresis; IOP: intraocular pressure; OPA: ocular pulse amplitude; PC1: principal component 1; SE: standard error.</p>				

<b>Table S5.</b> Univariable analysis for factors associated with the pointwise rate of progression				
	<b>PLACEBO</b>		<b>TREATMENT</b>	
<b>Variable</b>	Est (SE)	p-value	Est (SE)	p-value
Baseline Age, decades	-0.04 (0.14)	0.78	-0.04 (0.09)	0.67
CCT, per 10 $\mu\text{m}$	0.03 (0.04)	0.50	0.01 (0.03)	0.84
CH	0.07 (0.09)	0.49	0.10 (0.06)	0.12
Baseline IOP	-0.09 (0.03)	<b>0.003</b>	0.00 (0.02)	0.87
Mean IOP	-0.13 (0.03)	<b>&lt;0.001</b>	-0.03 (0.03)	0.36
Peak IOP	-0.11 (0.03)	<b>&lt;0.001</b>	-0.02 (0.02)	0.30
Peak IOP Phasing	-0.09 (0.03)	<b>&lt;0.001</b>	-0.02 (0.03)	0.32
Supine IOP	-0.10 (0.03)	<b>&lt;0.001</b>	0.00 (0.02)	0.86
OPA	-0.65 (0.15)	<b>&lt;0.001</b>	0.11 (0.11)	0.32
Long-term Fluctuation	-0.34 (0.13)	<b>0.008</b>	-0.12 (0.08)	0.16
Diurnal Fluctuation	-0.22 (0.15)	0.14	-0.08 (0.13)	0.53
Normalized OPA	-1.36 (0.48)	<b>0.005</b>	0.48 (0.26)	0.07
Normalized Long-term Fluctuation	-0.36 (0.35)	0.32	-0.12 (0.22)	0.58
Normalized Diurnal Fluctuation	-0.02 (0.29)	0.93	-0.01 (0.20)	0.97
Estimates are intended for 1-unit increase, unless specified otherwise. CCT: central corneal thickness; CH: corneal hysteresis; IOP: intraocular pressure; OPA: Ocular Pulse Amplitude; SE: standard error.				

<b>Table S6.</b> Multivariable analysis for factors associated with the pointwise rate of progression				
	<b>PLACEBO</b>		<b>TREATMENT</b>	
<b>Variable</b>	Est (SE)	p-value	Est (SE)	p-value
Baseline Age, decades	0.04 (0.14)	0.79	-0.06 (0.09)	0.52
CCT, per 10 $\mu\text{m}$	0.07 (0.04)	0.11	0.01 (0.03)	0.81
CH	-0.05 (0.10)	0.59	0.11 (0.07)	0.11
Normalized OPA	-1.23 (0.46)	<b>0.009</b>	0.52 (0.27)	0.055
Normalized Long-term Fluctuation	-0.23 (0.35)	0.52	0.06 (0.25)	0.81
Normalized Diurnal Fluctuation	0.13 (0.28)	0.63	-0.06 (0.21)	0.77
Combined IOP metrics – PC1	-0.29 (0.07)	<b>&lt;0.001</b>	-0.05 (0.06)	0.42

Estimates are intended for 1-unit increase unless specified otherwise. Combined IOP metrics PC1 is an unitless variable, combining fluctuation unrelated IOP metrics (baseline IOP, peak IOP, mean IOP, supine IOP, peak phasing IOP) through Principal Component Analysis.

CCT: central corneal thickness; CH: corneal hysteresis; IOP: intraocular pressure; OPA: ocular pulse amplitude; PC1: principal component 1; SE: standard error.

<b>Table S7.</b> Multivariable analysis for factors associated with the pointwise rate of progression				
	<b>PLACEBO</b>		<b>TREATMENT</b>	
<b>Variable</b>	Est (SE)	p-value	Est (SE)	p-value
Baseline Age, decades	0.05 (0.14)	0.74	-0.07 (0.09)	0.44
CCT, per 10 $\mu\text{m}$	0.07 (0.04)	0.13	0.01 (0.03)	0.84
CH	-0.05 (0.10)	0.60	0.10 (0.07)	0.15
OPA	-0.47 (0.17)	<b>0.008</b>	0.18 (0.12)	0.14
Long-term Fluctuation	-0.09 (0.14)	0.54	-0.06 (0.11)	0.60
Diurnal Fluctuation	0.03 (0.16)	0.87	-0.09 (0.14)	0.55
Combined IOP metrics – PC1	-0.17 (0.09)	0.06	-0.05 (0.08)	0.50

Estimates are intended for 1-unit increase unless specified otherwise. Combined IOP metrics PC1 is an unitless variable, combining fluctuation unrelated IOP metrics (baseline IOP, peak IOP, mean IOP, supine IOP, peak phasing IOP) through Principal Component Analysis.

CCT: central corneal thickness; CH: corneal hysteresis; IOP: intraocular pressure; OPA: ocular pulse amplitude; PC1: principal component 1; SE: standard error.

<b>Table S8.</b> Univariable analysis for factors associated with the rate of fastest five locations				
<b>Variable</b>	<b>PLACEBO</b>		<b>TREATMENT</b>	
	Est (SE)	p-value	Est (SE)	p-value
Baseline Age, decades	-0.42 (0.33)	0.19	-0.16 (0.17)	0.37
CCT, per 10 $\mu\text{m}$	0.15 (0.10)	0.11	0.01 (0.05)	0.88
CH	0.25 (0.22)	0.26	0.15 (0.12)	0.24
Baseline IOP	-0.21 (0.07)	<b>0.003</b>	-0.07 (0.04)	0.06
Mean IOP	-0.27 (0.07)	<b>&lt;0.001</b>	-0.09 (0.05)	0.09
Peak IOP	-0.19 (0.06)	<b>0.002</b>	-0.07 (0.04)	0.07
Peak IOP Phasing	-0.20 (0.06)	<b>0.002</b>	-0.08 (0.05)	0.12
Supine IOP	-0.21 (0.06)	<b>&lt;0.001</b>	-0.01 (0.05)	0.80
OPA	-1.67 (0.34)	<b>&lt;0.001</b>	-0.24 (0.28)	0.28
Long-term Fluctuation	-0.49 (0.30)	0.11	-0.46 (0.17)	<b>0.006</b>
Diurnal Fluctuation	-0.56 (0.34)	0.10	-0.33 (0.26)	0.20
Normalized OPA	-3.95 (1.10)	<b>&lt;0.001</b>	-0.19 (0.52)	0.71
Normalized Long-term Fluctuation	0.23 (0.83)	0.79	-0.81 (0.44)	0.06
Normalized Diurnal Fluctuation	-0.15 (0.65)	0.82	-0.19 (0.40)	0.63

Estimates are intended for 1-unit increase, unless specified otherwise.  
CCT: central corneal thickness; CH: corneal hysteresis; IOP: intraocular pressure; OPA: Ocular Pulse Amplitude; SE: standard error.

<b>Table S9.</b> Multivariable analysis for factors associated with the rate of fastest five locations				
	<b>PLACEBO</b>		<b>TREATMENT</b>	
<b>Variable</b>	Est (SE)	p-value	Est (SE)	p-value
Baseline Age, decades	-0.13 (0.33)	0.69	-0.19 (0.18)	0.28
CCT, per 10 $\mu\text{m}$	0.26 (0.10)	<b>0.010</b>	0.01 (0.06)	0.93
CH	-0.09 (0.22)	0.69	0.13 (0.13)	0.31
Normalized OPA	-3.50 (1.04)	<b>0.001</b>	-0.38 (0.51)	0.46
Normalized Long-term Fluctuation	0.48 (0.80)	0.55	-0.71 (0.47)	0.13
Normalized Diurnal Fluctuation	0.20 (0.62)	0.75	-0.28 (0.39)	0.48
Combined IOP metrics – PC1	-0.58 (0.16)	<b>&lt;0.001</b>	-0.27 (0.12)	<b>0.028</b>
<p>Estimates are intended for 1-unit increase unless specified otherwise. Combined IOP metrics PC1 is an unitless variable, combining fluctuation unrelated IOP metrics (baseline IOP, peak IOP, mean IOP, supine IOP, peak phasing IOP) through Principal Component Analysis.</p> <p>CCT: central corneal thickness; CH: corneal hysteresis; IOP: intraocular pressure; OPA: ocular pulse amplitude; PC1: principal component 1; SE: standard error.</p>				

<b>Table S10.</b> Multivariable analysis for factors associated with the rate of fastest five locations				
	<b>PLACEBO</b>		<b>TREATMENT</b>	
<b>Variable</b>	Est (SE)	p-value	Est (SE)	p-value
Baseline Age, decades	-0.14 (0.32)	0.66	-0.24 (0.18)	0.18
CCT, per 10 $\mu\text{m}$	0.24 (0.10)	<b>0.016</b>	0.01 (0.06)	0.91
CH	-0.09 (0.22)	0.66	0.11 (0.13)	0.40
OPA	-1.36 (0.39)	<b>&lt;0.001</b>	-0.19 (0.23)	0.40
Long-term Fluctuation	0.12 (0.33)	0.73	-0.47 (0.22)	<b>0.032</b>
Diurnal Fluctuation	-0.06 (0.36)	0.87	-0.33 (0.27)	0.22
Combined IOP metrics – PC1	-0.32 (0.21)	0.13	-0.06 (0.15)	0.71
<p>Estimates are intended for 1-unit increase unless specified otherwise. Combined IOP metrics PC1 is an unitless variable, combining fluctuation unrelated IOP metrics (baseline IOP, peak IOP, mean IOP, supine IOP, peak phasing IOP) through Principal Component Analysis.</p> <p>CCT: central corneal thickness; CH: corneal hysteresis; IOP: intraocular pressure; OPA: ocular pulse amplitude; PC1: principal component 1; SE: standard error.</p>				

## ICMJE FORM

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**Manuscript Title:** Intraocular pressure fluctuation and rates of visual field progression in primary open-angle glaucoma: an exploratory analysis from the United Kingdom Glaucoma Treatment Study (UKGTS)

**US-based Author (if yes, you must fill out Open Payment section below):** NO

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CenterVue-Icare	Financial support											

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10	Leadership or fiduciary role in	<input checked="" type="checkbox"/> <b>None</b>											

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	other board, society, committee or advocacy group, paid or unpaid	<input type="checkbox"/>	
<b>11</b>	Stock or stock options	<input checked="" type="checkbox"/> <b>None</b>	
<b>12</b>	Receipt of equipment, materials, drugs, medical writing, gifts or other services	<input checked="" type="checkbox"/> <b>None</b>	
<b>13</b>	Other financial or non-financial interests	<input type="checkbox"/> <b>None</b>	
		Santen	Non-remunerative
		Medisoft	Non-remunerative

Please place an "X" next to the following statement to indicate your agreement:

I certify that I have answered every question and have not altered the wording of any of the questions on this form.

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Open Payments URL:

Match Disclosure Form?

YES/NO

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## ICMJE FORM

**Date:** 10/4/2023

**Your Name:** David F Garway-Heath

**Manuscript Title:** Intraocular pressure fluctuation and rates of visual field progression in primary open-angle glaucoma: an exploratory analysis from the United Kingdom Glaucoma Treatment Study (UKGTS)

**US-based Author (if yes, you must fill out Open Payment section below):** NO

**Manuscript Number (if known):** [Click or tap here to enter text.](#)

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**Match Disclosure Form?**

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**If no, please briefly explain discrepancy:**



## ICMJE FORM

**Date:** 9/22/2023

**Your Name:** Giovanni Montesano

**Manuscript Title:** Intraocular pressure fluctuation and rates of visual field progression in primary open-angle glaucoma: an exploratory analysis from the United Kingdom Glaucoma Treatment Study (UKGTS)

**US-based Author (if yes, you must fill out Open Payment section below):** NO

**Manuscript Number (if known):** [Click or tap here to enter text.](#)

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Open Payments URL:

Match Disclosure Form?

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## ICMJE FORM

**Date:** 9/23/2023

**Your Name:** Alessandro Rabiolo

**Manuscript Title:** Intraocular pressure fluctuation and rates of visual field progression in primary open-angle glaucoma: an exploratory analysis from the United Kingdom Glaucoma Treatment Study (UKGTS)

**US-based Author (if yes, you must fill out Open Payment section below):** NO

**Manuscript Number (if known):** [Click or tap here to enter text.](#)

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		Bausch + Lomb	Flight, hotel reservation, and congress fee for ARVO 2023 meeting
		Thea farma spa	Flight and hotel reservation for the 2023 Moorfields International Glaucoma Symposium
		Visufarma spa	Hotel reservation and congress fee for the the Associazione per lo Studio del Glaucoma (AISG) 2023 annual meeting
<b>8</b>	Patents planned, issued or pending	<input checked="" type="checkbox"/> <b>None</b>	
<b>9</b>	Participation on a Data Safety Monitoring Board or Advisory Board	<input checked="" type="checkbox"/> <b>None</b>	

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TITLE OF ARTICLE: **Intraocular pressure fluctuation and rates of visual field progression in primary open-angle**

**glaucoma: an exploratory analysis from the United Kingdom Glaucoma Treatment Study (UKGTS)**

AUTHORS: Alessandro Rabiolo, Giovanni Montesano, David P Crabb, David F Garway-Heath

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