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# Longitudinal Analysis of Mesopic Microperimetry in a Phase II Trial Evaluating Minocycline for Geographic Atrophy

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***Purpose:*** To analyze mesopic microperimetry data from a recent phase II trial of minocycline for geographic atrophy (GA) for possible efficacy on the change in visual function and, in the absence of efficacy, to perform longitudinal analyses as a natural history study.

***Design:*** Phase II, prospective, single-arm, nonrandomized trial. After a 9-month run-in phase, participants began oral minocycline 100 mg twice daily for 3 years.

***Participants:*** Individuals with GA in ≥1 eye.

***Methods:*** Participants underwent mesopic microperimetry at baseline, month 3, and every 6 months thereafter, using a custom T-shaped test pattern. Rates of change in microperimetry parameters were compared between the 24-month treatment phase and 9-month run-in phase by linear spline regression.

***Main Outcome Measures:*** The mean macular and responding sensitivity; the mean perilesional and extralesional sensitivity; number of absolute and relative scotomatous loci.

***Results:*** Thirty study eyes from 30 participants (mean age 74.1 years) underwent microperimetry (mean follow-up 27.4 months). For 5 of the 6 microperimetry parameters, no significant difference in the rate of change between the treatment and run-in phases was observed. The difference between the 2 phases was −0.74 decibels (dB)/year (standard error [SE] 0.85; $P = 0.39$) for mean macular sensitivity, −0.30 dB/year (SE 0.85; $P = 0.72$) for mean responding sensitivity, 1.23 dB/year (SE 1.01; $P = 0.22$) for mean perilesional sensitivity, and −0.02 (SE 0.01; $P = 0.31$) for transformed mean extralesional sensitivity. The difference in incidence rate ratios between the 2 phases was 1.17 (SE 0.11; $P = 0.14$) for absolute scotomatous loci and 0.73 (SE 0.11; $P = 0.004$) for relative scotomatous loci.

***Conclusions:*** The results do not appear consistent with a clinically meaningful effect of minocycline on the rate of visual function decline from GA progression. This is consistent with previous analyses of the corresponding structural data. The findings demonstrate the advantages and disadvantages of different microperimetry parameters. The optimal testing patterns and parameters represent a trade-off between greater sensitivity vs. greater risk of floor/ceiling effects, with regional averages providing a useful compromise. The results may provide insights to guide the development of microperimetry end points for clinical trials.

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*Supplemental material available at www.ophthalmologyscience.org.*

Geographic atrophy (GA) represents the defining lesion of advanced atrophic age-related macular degeneration (AMD) and is characterized by the progressive loss of retinal pigment epithelium (RPE), photoreceptors, and choriocapillaris.[1] This degenerative process typically culminates in central vision impairment and can have profound impacts on quality of life.[2] Geographic atrophy affects approximately 5 million adults worldwide, and its prevalence is expected to rise due to population aging.[3] Despite this disease burden, potential treatment options remain limited. Recent clinical trials led to the United States Food and Drug Administration approval of 2 complement inhibitors for GA in AMD, on the basis of the structural outcome measure of change in GA area.[4,5] However, in both cases, no efficacy was demonstrated in prespecified analyses of a range of visual function metrics as key secondary outcome measures, at least through the time of the primary end point. It is important to identify therapeutic interventions that not only slow GA progression on structural metrics but also demonstrate



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slower decline in visual function, to ensure that their effects are clinically meaningful.[6]

A phase II clinical trial evaluating the safety and possible efficacy of oral minocycline for GA in AMD was recently completed.[7] Minocycline, a tetracycline antibiotic, is an anti-inflammatory agent and inhibitor of microglial activation. It has neuroprotective effects in cell culture models and slows photoreceptor death in animal models of several retinal diseases.[8–10] In the phase II trial, the primary outcome measure was the difference in the rate of change in GA area, as measured on fundus autofluorescence (FAF), between the 24-month treatment phase (after initiation of minocycline) and the 9-month run-in phase (before initiation of minocycline). There was no evidence that oral minocycline slowed GA progression. Similarly, there was no evidence that it slowed the rate of decline in best-corrected visual acuity (BCVA), a secondary outcome measure. However, the relationship between GA progression and visual acuity is complex, and the changes in visual acuity alone may not capture the full extent of progressive visual dysfunction.[6,11,12] Therefore, in addition to visual acuity, microperimetry testing was performed longitudinally in the trial and reserved for an exploratory analysis of functional efficacy.

Fundus guided perimetry (microperimetry) is a noninvasive visual field test that directly evaluates light sensitivity at multiple testing loci across the macula. These loci are identified on macular images obtained by scanning laser ophthalmoscopy.[13–15] Microperimetry employs live fundus-tracking technology and is especially useful in pathologies such as GA, where central vision loss affects fixation stability. The fundus tracking combined with the "follow-up function" enable testing of the same loci across sequential time points. Previous studies have demonstrated superior correlation of microperimetry parameters with GA progression, compared with traditional functional outcome measures such as BCVA, low-luminance visual acuity, and reading speed.[14] Microperimetry provides quantitative and spatial information, resulting in diverse potential approaches to analyzing raw data, including the mean sensitivity of all loci, the sensitivity of individual loci, and the number of scotomatous loci.[16] Each analysis approach has its own set of advantages and disadvantages, leading to uncertainties over the optimal approaches for evaluating macular sensitivity over time.

In this clinical trial, a novel T-shaped microperimetry testing grid was developed and employed to capture the linear enlargement of GA lesions. Its aims were to provide the greatest quantity of useful information while decreasing patient burden from lengthy testing by (1) decreasing the number of testing loci (by arranging them in a T-shape instead of a circular grid), (2) halving the distance between each locus, and (3) extending the pattern further into the peripheral macula, compared to the typical 10-2 pattern.[14,15]

The main aims of the current study were (1) to evaluate the microperimetry data for possible efficacy of oral minocycline in slowing GA progression, as a complementary approach to previous analyses of the structural outcome measures and (2) in the event of absent efficacy, to perform longitudinal analyses in the form of a natural history study of changes in macular sensitivity with GA progression. An important additional aim was to compare different approaches to analyzing longitudinal microperimetry data. Given the unmet need for standardized microperimetry outcome measures, these analyses should enhance our understanding of GA progression and help refine the development of microperimetry end points for future clinical trials.

## Methods

This was a multicenter, prospective, single-arm, phase II clinical trial assessing the safety and possible efficacy of oral minocycline in slowing GA progression in AMD.[7,17] The study was conducted at the National Institutes of Health (NIH) Clinical Center, Bethesda, MD, and the Bristol Eye Hospital, Bristol, United Kingdom. The protocol was approved by the NIH Institutional Review Board and the South Central-Oxford B Research Ethics Committee and adhered to the tenets of the Declaration of Helsinki. Written informed consent was obtained from each participant before enrollment. The study was registered at www.clinicaltrials.gov (NCT02564978; registration date, October 1, 2015). Study oversight was provided by an independent external Data and Safety Monitoring Committee that approved the protocol before trial initiation and reviewed the study data approximately every 6 months. This manuscript relating to an exploratory outcome was not reviewed by the Data and Safety Monitoring Committee, according to the Data and Safety Monitoring Committee policy on review of manuscripts for exploratory outcomes.

The study design has been described previously.[7] In brief, eligible participants were ≥55 years old and had GA secondary to AMD in ≥1 eyes. If both eyes of an individual participant met the eligibility criteria, the eye with better BCVA was chosen as the study eye. At the eye level, the study eye eligibility criteria included: (1) GA area >0.5 and <7.0 disc areas (approximately 1.27–17.81 $mm^2$) on FAF; (2) BCVA ETDRS letter score ≥19 (Snellen 20/400); and (3) no current evidence or history of treatments for choroidal neovascularization. Eyes with or without GA foveal involvements were included.

The enrolled participants were followed during an initial 9-month run-in phase without the administration of minocycline, with in-clinic assessments at baseline and months 3, 6, and 9. At month 9, the participants began taking oral minocycline 100 mg twice daily until study termination, with in-clinic assessments at months 12, 15, and every 6 months thereafter. The primary outcome measure was assessed at month 33 (i.e., after 24 months on minocycline), and the study ended at month 45. The primary outcome measure was the difference in the rate of change in square root transformed GA area, based on FAF, between the treatment phase and the run-in phase. Hence, the rationale of the study design was to compare the GA enlargement rate under natural history, which remains relatively constant for a given eye, under the square root transformation,[18–21] and the subsequent GA enlargement rate on minocycline. Linear spline regression was used to compute GA enlargement rates during the 2 phases and test whether minocycline significantly reduced the GA enlargement rate.[22]

### Microperimetry Testing

The assessment of retinal sensitivity by mesopic microperimetry has been described previously.[23] In brief, at baseline, month 3, and every 6 months thereafter, retinal sensitivity in the study eye was assessed by mesopic microperimetry using the MP-1 microperimeter (Nidek Technologies). For each study eye, prior to the

first test, the anatomic fovea was identified using spectral-domain OCT (OCT; Spectralis HRA + OCT, Heidelberg Engineering Inc), and a horizontal line scan passing through the foveal center was uploaded into the MP-1 software. After pupillary dilation, microperimetry testing was conducted under mesopic conditions in a darkened room but without prior dark adaptation. Testing was performed using a novel custom T-shaped pattern, consisting of 40 evenly spaced testing loci with their center points 1° apart (Fig 1). The intersection of the T-shaped grid was placed at the anatomic fovea, with the 3 arms (or axes) of the T extending 15° temporally, 12° superiorly, and 12° inferiorly. A white Goldmann III stimulus (0.43° or 125 μm) was displayed for 200 ms at each testing locus. The stimulus intensities ranged from 127 to 1.27 cd/m$^2$, which corresponded to macular sensitivities of 0 to 20 decibels (dB). The starting stimulus light attenuation was set at 10 dB, and a 4-2 staircase strategy was used. A red circle with a 3° radius was set as the fixation target on a white background luminance of 4 apostilbs (1.27 cd/m$^2$). Following the first microperimetry test, all subsequent testing was performed in the instrument's "follow-up mode" to ensure spatial alignment of individual testing loci over longitudinal testing during the study. If participant cooperation was found to be unreliable or poor, the investigator had the discretion to stop testing according to the study protocol.

## Microperimetry Data Analysis

The following microperimetry parameters were used in this study: (1) mean sensitivity of all loci, (2) mean sensitivity of all non-scotomatous loci (i.e., mean responding sensitivity), (3) mean perilesional sensitivity, (4) mean extralesional sensitivity, (5) number of absolute scotomatous loci, and (6) number of relative scotomatous loci. The mean sensitivity of all loci was calculated as the arithmetic mean of all 40 loci. The mean responding sensitivity was calculated as the arithmetic mean of all loci for which a response was elicited (i.e., corresponding to sensitivities $\geq$0 dB). The responding loci were divided into perilesional and extralesional loci, based on their proximity to scotomatous loci. The mean perilesional sensitivity was calculated as the arithmetic mean of the responding loci immediately adjacent to a scotomatous locus, i.e., the first responding locus along the T axis, distally. The mean extralesional sensitivity was calculated as the arithmetic mean of all responding loci separated (distally) from a scotomatous locus by $\geq$1 testing locus. The loci averaged for mean responding sensitivity, mean perilesional sensitivity, and mean extralesional sensitivity were defined at the baseline visit. The number of absolute scotomatous loci was defined as the number at which no response was elicited, even at the highest intensity stimulus (i.e., <0 dB). The number of relative scotomatous loci was defined as the number at which a response was elicited only at a moderate high-intensity stimulus (i.e., 0−8 dB); loci that transitioned from relative scotomas to absolute scotomas during subsequent visits were included in this parameter.

In an exploratory analysis, the sensitivities of individual loci (i.e., pointwise sensitivity) were assessed. For each eye, up to 6 loci (comprising 2 loci from each of the 3 axes) were defined at the baseline visit, based on their position relative (distally) to the scotoma, and were named as follows: locus T1 was immediately adjacent to the outermost scotomatous locus on the temporal axis and locus T2 was the next locus along in the temporal direction. The positions of loci T1 and T2 were anchored at baseline and their sensitivities were monitored at all subsequent visits. Similarly, 2 loci were identified at baseline on the superior (S1 and S2) and inferior (I1 and I2) axes.

To decrease potential heterogeneity in data from differences in technician procedures during microperimetry testing at different sites, only data from the NIH site were used, while data from the Bristol Eye Hospital site (n = 7 participants) were excluded.

## Statistical Analyses for Possible Efficacy: Primary Analyses on Per-Protocol Population 2

The statistical approach to analysis of the primary and secondary outcome measures was prespecified in the statistical analysis plan and has been described in detail previously, including the sample size calculation based on the primary outcome measure.[7] The microperimetry data, as an exploratory outcome measure, were analyzed for possible efficacy of minocycline using the same statistical approach as that for the primary outcome measure, to compare the difference in the rate of change of each microperimetry parameter between the 24-month treatment phase and 9-month run-in phase in the study eye. Specifically, the data were analyzed by fitting a generalized linear spline regression model with a fixed knot at month 9 at a 1-sided type I error of 2.5% using the MIXED or GENMOD procedure in SAS, accounting for the correlation between observations from the same participant over time and with each microperimetry parameter as the outcome.

The primary analyses were based on the per-protocol population 2, as defined previously.[7] This study population comprised participants who completed $\geq$3 follow-up visits during the treatment phase and did not discontinue treatment before the completion of $\geq$3 follow-up visits; any visits after treatment discontinuation were excluded from analyses. Missing observations were considered missing completely at random. If an untransformed parameter did not meet the linearity assumptions, the parameter was square root transformed, and, if linearity assumptions were still not met, a 1/(0.01 + x) transformation was applied.[24,25] The covariate structure was selected based on the best fit model. No adjustment was made for multiple testing, as this analysis was considered exploratory in nature. The results were considered statistically significant if the estimate representing the difference in rates of change between the 2 phases was <0 for continuous parameters or <1 for discrete parameters and the *P* value was <0.025 (1-sided test).

## Statistical Analyses for Possible Efficacy: Secondary Analyses

The analyses outlined above were repeated on the enrolled population (i.e., according to intention-to-treat). Additional secondary analyses were performed with the exclusion of the baseline visit. For these analyses, the difference in the rate of change of each microperimetry parameter was compared between the 24-month treatment phase and a revised 6-month run-in phase. The statistical models were the same as those described above. These analyses were performed since 2 previous reports had observed a systematic shift in the microperimeter reference level, whereby reported sensitivity was decreased between the first and second closely spaced tests but not between the second and third tests.[26,27] In the previous report of the MP-1 device, the difference was approximately 2 dB.[26]

## Statistical Analyses as a Natural History Study

In the event of absent efficacy of oral minocycline, further analyses were performed considering the run-in phase and treatment phase as a single phase of a natural history study and assessing the rate of change in sensitivity via longitudinal analyses. These analyses were performed using similar methods to those described above but did not include a knot and were assessed at a 2-sided type I error of 5%. They were based on the per-protocol population 2.

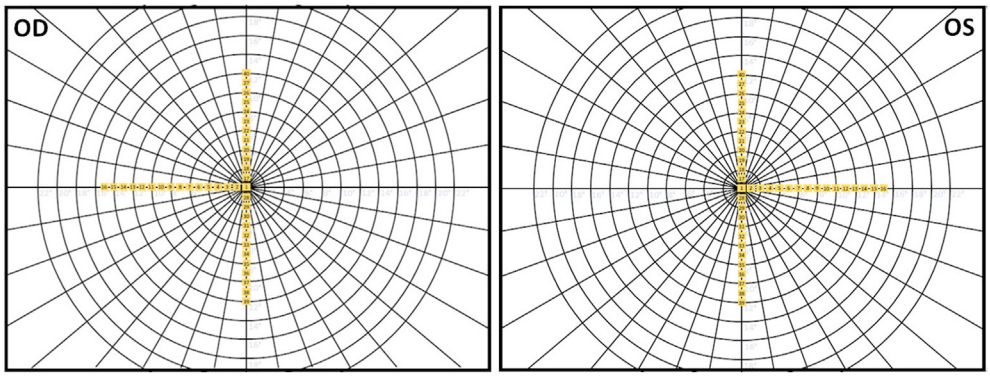


**Figure 1.** T-shaped microperimetry testing pattern, consisting of 40 evenly spaced testing loci at 1° apart, extending from the anatomic fovea in 3 directions (15° temporally, 12° superiorly, and 12° inferiorly). OD = right eye; OS = left eye.

All statistical analyses were performed using SAS version 9.4 (SAS Institute). Given the number of analyses performed and the exploratory nature of these analyses, all the results should be interpreted with caution.

## Results

### Baseline Demographics and Ocular Characteristics

A total of 30 study eyes from 30 participants underwent microperimetry testing. The demographic and ophthalmic characteristics of the enrolled population and per-protocol population 2 at the NIH are shown in Table 1. For the enrolled population, the mean participant age was 74.1 years (standard deviation [SD] 7.2 years, range 63−89 years). A total of 167 microperimetry tests were conducted between December 14, 2016, and March 8, 2023. Figure 2 displays the raw microperimetry results for a single participant during the study period. The mean participant follow-up for microperimetry testing was 27.4 months (SD 12.9 months), comprising a mean of 5.6 visits (SD 1.8 visits). Of the 30 participants, 23 (77%) formed the per-protocol population 2, having completed ≥3 follow-up visits on the study drug.

### Analyses for Possible Efficacy of Oral Minocycline: Primary Analyses

The results of the generalized linear spline regression analyses for possible efficacy of minocycline in the per-protocol population 2 are shown in Table 2. For each of the microperimetry parameters, the estimates are shown for the rate of change during the 9-month run-in phase, the rate of change during the 24-month treatment phase, and the difference between the 2. For example, the mean macular sensitivity decreased by 0.86 dB/year (standard error [SE] 0.68 dB/year) during the run-in phase and by 1.60 dB/year (SE 0.38 dB/year) during the treatment phase. The mean difference in the rate of change between the treatment and run-in phases was −0.74 dB/year (SE 0.85 dB/year; $P = 0.39$), indicating no significant difference. For 5 of the 6 microperimetry parameters, no significant difference in the rate of change between the 2 phases was observed (Table 2). The exception was the number of relative scotomatous loci; for this parameter, the incidence rate ratio (IRR) was 1.55 (SE 0.09) during the run-in phase and 1.13 (SE 0.05) during the treatment phase, with a mean difference between the 2 phases of 0.73 (SE 0.11; $P = 0.004$), i.e., corresponding to a 27% change in the direction of a beneficial effect of minocycline.

### Analyses for Possible Efficacy of Oral Minocycline: Secondary Analyses

In secondary analyses, the analyses were repeated in the enrolled population (i.e., according to intention-to-treat). The results are shown in Table S3 (available at www.ophthalmologyscience.org). In general, the results were similar to those in the per-protocol 2 population. For 4 of the 6 microperimetry parameters, no significant difference in the rate of change between the 2 phases was observed. However, for the number of absolute scotomatous loci, the mean difference in the IRR between the 2 phases was 1.33 (SE 0.11; $P = 0.01$), i.e., in the direction of a harmful effect of minocycline. For the number of relative scotomatous loci, the mean difference in the IRR was 0.61 (SE 0.11; $P < 0.001$), i.e., in the direction of a beneficial effect of minocycline.

In other secondary analyses, the analyses were repeated with the exclusion of data from the baseline visit (for the reasons described in the Methods section). These results are shown in Table 4. For all 6 microperimetry parameters, no significant difference in the rate of change between the 2 phases was observed. For the number of relative scotomatous loci, the mean difference in IRR between the 2 phases was 0.83 (SE 0.14; $P = 0.19$), corresponding to a 17% decrease in the number of relative scotomatous loci per year in the treatment phase as compared to the run-in phase. There was no evidence that the difference between the 2 phases was significant, when removing the baseline visit.

Table 1. Demographic and Ophthalmic Characteristics in the Study Eye of the National Institutes of Health Participants for the Enrolled and Per-Protocol Population 2 at Baseline

| Variable | Characteristic or Statistic | NIH Enrolled Population (N = 30) | NIH Per-Protocol Population 2 (N = 23) |
|---|---|---|---|
| Age | Mean ± SD (yrs) | 74.1 ± 7.2 | 72.8 ± 7.7 |
| | Range (min, max; yrs) | 63, 89 | 63, 89 |
| Sex | Male, N (%) | 12 (40) | 7 (30) |
| | Female, N (%) | 18 (60) | 16 (70) |
| Ethnicity | Hispanic or Latino, N (%) | 2 (7) | 2 (9) |
| | Not Hispanic or Latino, N (%) | 27 (90) | 20 (87) |
| | Unknown, N (%) | 1 (3) | 1 (4) |
| Race | Asian, N (%) | 2 (7) | 2 (9) |
| | Black, N (%) | 1 (3) | 0 |
| | White, N (%) | 27 (90) | 21 (91) |
| GA foveal involvement | Subfoveal, N (%) | 17 (57) | 14 (61) |
| | Not subfoveal, N (%) | 13 (43) | 9 (39) |
| Square root of GA area | Mean ± SD (mm) | 2.6 ± 1.0 | 2.7 ± 0.9 |
| Best-corrected visual acuity | Mean ± SD (letter score; Snellen distance*) | 70.7 ± 15.5; 57.1 ± 68.1 | 69.5 ± 17.1; 63.2 ± 76.9 |
| Low-luminance visual acuity | Mean ± SD (letter score; Snellen distance*) | 54.3 ± 15.3; 113.3 ± 100.0 | 54.7 ± 16.6; 117.2 ± 112.0 |

GA = geographic atrophy; mm = millimeters; NIH = National Institutes of Health; SD = standard deviation.
Column header counts and denominators are the number of participants in the applicable population at NIH. Percentages are rounded to the nearest whole number.
*Snellen distance represents the denominator in the 20/X Snellen notation, i.e., the size of letters read on a Snellen visual acuity chart at 20 feet.

## Analyses for Possible Efficacy of Oral Minocycline: Exploratory Analyses of Pointwise Sensitivity

The results of analyses of pointwise sensitivity are shown in Table S5 (available at www.ophthalmologyscience.org). For 7 of the 9 loci or loci pairs, no significant difference in the rate of change between the 2 phases was observed. However, for T1, the estimate for difference in rate of change was 4.11 dB/year (SE 1.43 dB/year; $P = 0.005$), i.e., in the direction of a beneficial effect of minocycline. Similarly, for I1, the estimate for difference in rate of change was 1.17 $\sqrt{}$dB/year (SE 0.47 $\sqrt{}$dB/year; $P = 0.02$), i.e., also in the direction of a beneficial effect. However, visual inspection of the raw data for T1 and I1, as well as for the other pointwise sensitivity loci, demonstrated that for most study eyes, the sensitivity at these loci had decreased to 0 dB well before the end of the 24-month treatment phase, so the sensitivity was unable to decrease further at subsequent time points. This floor effect would tend to generate a slower rate of decline in sensitivity in the regression analyses during the treatment phase so would tend artifactually to suggest a beneficial effect of minocycline.

These analyses were repeated with the exclusion of data from the baseline visit. The results are shown in Table S6 (available at www.ophthalmologyscience.org). In all cases, including T1 and I1, no significant difference in the rate of change between the 2 phases was observed.

## Longitudinal Analysis of Microperimetry Parameters as a Natural History Study

Given the absence of consistent evidence for efficacy of minocycline on retinal sensitivity loss between the run-in and treatment phases, all data were subsequently considered as a single phase in a natural history study. Natural history analyses were not performed for the number of relative scotomatous loci, given the significant difference observed between the 2 phases for this parameter in the analyses described above.

Plots of changes over time for all the microperimetry parameters are shown in Figures 3 to 5. A summary of these results is shown in Table 7. For all parameters, a monotonic worsening was observed from baseline to month 27 (Figs 3–5). The trend diverged slightly at month 33, where fewer participants had data available.

A significant decrease between baseline and month 33 was observed for sensitivity of all loci, responding sensitivity, perilesional sensitivity, and extralesional sensitivity (Table 7). The mean sensitivity of all loci changed at a rate of −1.39 dB/year (SE = 0.30 dB/year, $P < 0.001$), while the mean responding sensitivity changed at a rate of −1.64 dB/year (SE = 0.17 dB/year, $P < 0.001$). Hence, the mean responding sensitivity started at a higher level (as expected, given the exclusion of absolute scotomatous loci, Fig 3) and declined at a numerically faster rate. Compared to extralesional sensitivity, perilesional loci tended to exhibit lower mean values at baseline, due to their closer proximity to GA, but the mean perilesional and mean extralesional sensitivity appeared to decline at approximately similar rates (Fig 4, Table 7). Similarly, in the regression analyses, the number of absolute scotomatous loci increased significantly over time (Table 7). The IRR was 1.23 (SE = 0.04, $P < 0.001$), corresponding to a 23% increase in the number of absolute scotomatous loci per year. The mean number of relative scotomatous loci was numerically

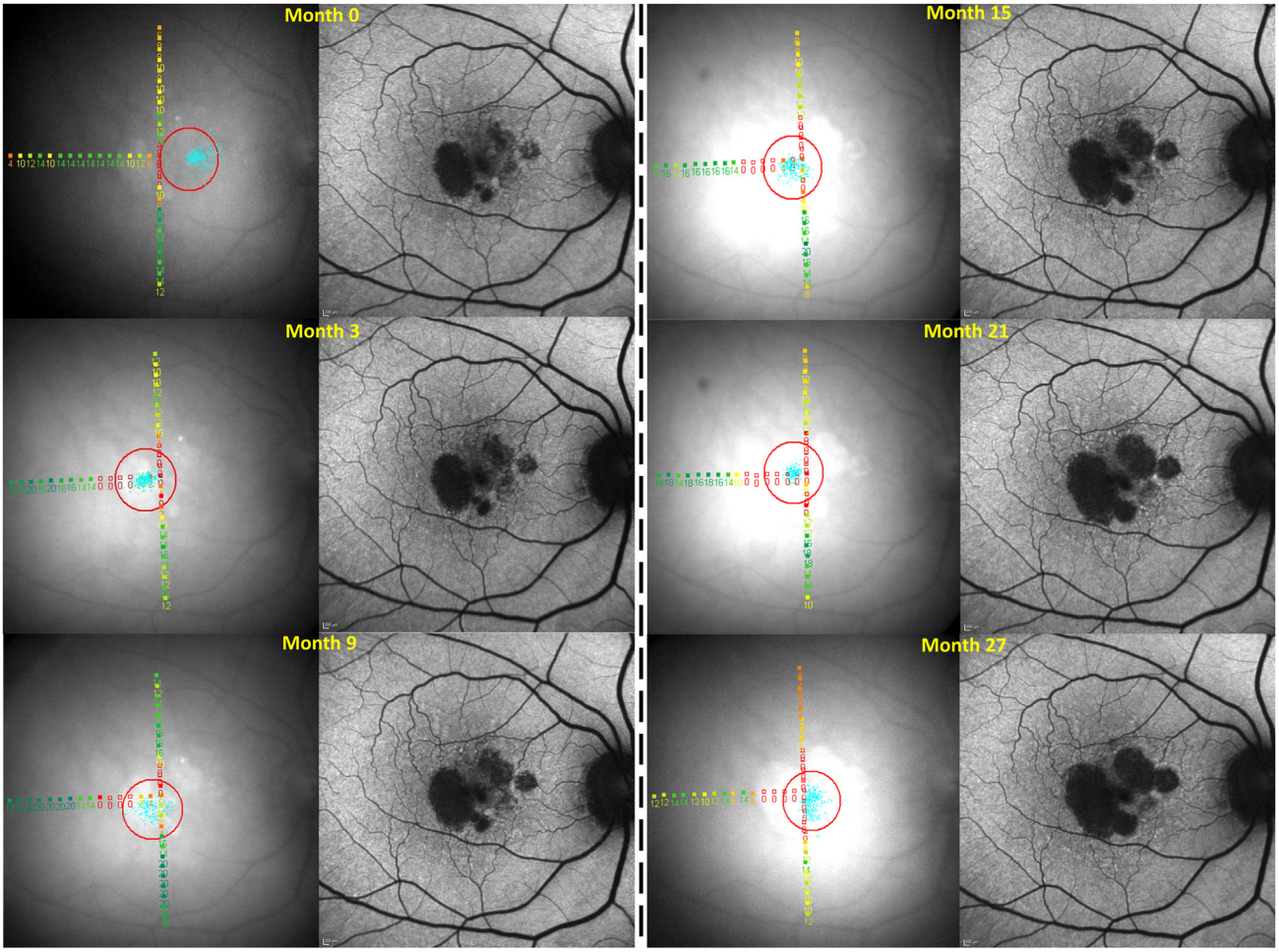


**Figure 2.** Longitudinal microperimetry data from a single study eye over the study period. For each time point, the microperimetry image is shown on the left, the accompanying fundus autofluorescence image (registered to the microperimetry image) is shown on the right, and the study month is shown at the top. The sensitivity results are shown numerically in dB, with color-coding ranging from red (0 dB) to green (20 dB), and absolute scotomas shown as empty red squares. The results of fixation testing are also shown (blue dots, with surrounding red circle). dB = decibels.

higher than the mean number of absolute scotomatous loci, except at baseline, with a qualitatively larger increase in the number of relative scotomatous loci over time (Fig 5).

The results were generally similar in secondary analyses of the enrolled population and in secondary analyses that excluded data from the baseline visit (data not shown).

## Discussion

In this phase II clinical trial, we performed detailed exploratory analyses of the rate of change in retinal sensitivity according to mesopic microperimetry, using multiple different microperimetry parameters, to evaluate for possible efficacy of oral minocycline in slowing GA progression. For the majority of the microperimetry parameters analyzed, the study drug was not associated with a decrease in the rate of decline in retinal sensitivity over 24 months of treatment compared with the preceding 9-month run-in phase. These observations were relatively similar in both the main and sensitivity analyses. Overall, the findings do not appear consistent with a clinically meaningful beneficial treatment effect of oral minocycline on the rate of visual function decline associated with GA progression.

These results are in keeping with our previous analyses of the corresponding structural data, including the prespecified primary outcome analysis of GA enlargement rate from FAF imaging, in which no significant difference in the GA enlargement rate was observed between the 2 phases.[7] They are also consistent with our previous analyses of BCVA and low-luminance visual acuity, as secondary outcome measures; in both cases, no significant difference in the rate of change was observed between the 2 phases.[7] However, analyses of microperimetry data are expected to be more sensitive in detecting the functional consequences of slower GA enlargement than those of visual acuity, given the higher degree of spatial information possible with microperimetry together with the complex relationship between visual acuity and GA enlargement.[6,11,12]

For only 1 of the 6 main microperimetry parameters studied (i.e., number of relative scotomatous loci), the

Table 2. Results of Generalized Linear Spline Regression Analyses for Potential Efficacy of Minocycline Based on Multiple Microperimetry Parameters (Per-Protocol Population 2)

| Microperimetry Parameter* (Covariance Structure†) | Estimate | SE | *P* Value‡ |
|---|---|---|---|
| Mean sensitivity of all loci (AR [1]) | | N = 23 | |
| Run-in phase | −0.86 | 0.68 | 0.21 |
| Treatment phase | −1.60 | 0.38 | <0.001 |
| Difference between treatment and run-in phases | −0.74 | 0.85 | 0.39 |
| Mean responding sensitivity (CS) | | N = 23 | |
| Run-in phase | −1.42 | 0.64 | 0.03 |
| Treatment phase | −1.72 | 0.29 | <0.001 |
| Difference between treatment and run-in phases | −0.30 | 0.85 | 0.72 |
| Mean perilesional sensitivity (CS) | | N = 22 | |
| Run-in phase | −2.45 | 0.77 | 0.002 |
| Treatment phase | −1.22 | 0.34 | <0.001 |
| Difference between treatment and run-in phases | 1.23 | 1.01 | 0.22 |
| Mean extralesional sensitivity§ (UN) | | N = 23 | |
| Run-in phase | 0.03 | 0.01 | 0.01 |
| Treatment phase | 0.01 | 0.01 | 0.12 |
| Difference between treatment and run-in phases | −0.02 | 0.01 | 0.31 |
| Absolute scotomatous loci‖ (AR [1]) | | N = 23 | |
| Run-in phase | 1.10 | 0.08 | 0.27 |
| Treatment phase | 1.28 | 0.05 | <0.001 |
| Difference between treatment and run-in phases | 1.17 | 0.11 | 0.14 |
| Relative scotomatous loci‖ (UN) | | N = 23 | |
| Run-in phase | 1.55 | 0.09 | <0.001 |
| Treatment phase | 1.13 | 0.05 | 0.02 |
| Difference between treatment and run-in phases | 0.73 | 0.11 | 0.004 |

AR(1) = autoregressive model of order 1; CS = compound symmetry; dB = decibels; SE = standard error; UN = unstructured.
Results are based on a repeated measures linear spline regression model with a knot at month 9, unless otherwise specified.
*Rate of change (dB/year), unless otherwise specified.
†Covariance structure that provided the best model fit.
‡*P* values for the run-in phase and treatment phase relate to the change over time being significantly different to zero, whereas *P* values for the difference between the phases relate to the change over time being significantly different between the 2 phases.
§Results are based on a repeated measures linear spline regression model with a knot at month 9 and a 1/(0.01 + x) transformation.
‖Rate of change (incidence rate ratio). Results are based on a repeated measures negative binomial spline regression model with a knot at month 9.

Table 4. Results of Generalized Linear Spline Regression Analyses for Potential Efficacy of Minocycline Based on Multiple Microperimetry Parameters with Exclusion of Data from Baseline Visits (Per-Protocol Population 2)

| Microperimetry Parameter* (Covariance Structure†) | Estimate | SE | *P* Value‡ |
|---|---|---|---|
| Mean sensitivity of all loci (AR [1]) | | N = 23 | |
| Run-in phase | −0.26 | 0.80 | 0.74 |
| Treatment phase | −1.58 | 0.38 | <0.001 |
| Difference between treatment and run-in phases | −1.32 | 0.95 | 0.17 |
| Mean responding sensitivity (CS) | | N = 23 | |
| Run-in phase | 0.12 | 0.97 | 0.90 |
| Treatment phase | −1.90 | 0.28 | <0.001 |
| Difference between treatment and run-in phases | −2.02 | 1.14 | 0.08 |
| Mean perilesional sensitivity (CS) | | N = 22 | |
| Run-in phase | −1.00 | 1.05 | 0.34 |
| Treatment phase | −1.39 | 0.31 | <0.001 |
| Difference between treatment and run-in phases | −0.38 | 1.24 | 0.76 |
| Mean extralesional sensitivity§ (CSH) | | N = 23 | |
| Run-in phase | −0.01 | 0.02 | 0.75 |
| Treatment phase | 0.04 | 0.01 | <0.001 |
| Difference between treatment and run-in phases | 0.04 | 0.02 | 0.08 |
| Absolute scotomatous loci‖ (AR [1]) | | N = 23 | |
| Run-in phase | 1.16 | 0.15 | 0.31 |
| Treatment phase | 1.28 | 0.05 | <0.001 |
| Difference between treatment and run-in phases | 1.11 | 0.17 | 0.54 |
| Relative scotomatous loci‖ (UN) | | N = 23 | |
| Run-in phase | 1.43 | 0.14 | 0.01 |
| Treatment phase | 1.18 | 0.08 | 0.03 |
| Difference between treatment and run-in phases | 0.83 | 0.14 | 0.19 |

AR = autoregressive; CS = compound symmetry; CSH = heterogeneous compound symmetry; dB = decibels; SE = standard error; UN = unstructured.
Results are based on a repeated measures linear spline regression model with a knot at month 9, unless otherwise specified.
*Rate of change (dB/year), unless otherwise specified.
†Covariance structure that provided the best model fit.
‡*P* values for the run-in phase and treatment phase relate to the change over time being significantly different to zero, whereas *P* values for the difference between the phases relate to the change over time being significantly different between the 2 phases.
§Results are based on a repeated measures linear spline regression model with a knot at month 9 and a 1/(0.01 + x) transformation.
‖Rate of change (incidence rate ratio). Results are based on a repeated measures negative binomial spline regression model with a knot at month 9.

results were consistent with a possible beneficial effect of minocycline. A similar result was observed in sensitivity analyses in the enrolled population, but not in sensitivity analyses excluding data from the study baseline. However, these results should be interpreted with caution, in light of a high degree of multiple testing. In addition, importantly, this outcome measure may be more prone to a potential ceiling effect than some other outcome measures (such as the number of absolute scotomatous loci), since decreased retinal sensitivity is known to extend well beyond GA borders.[28,29] Hence, during the later stages of GA progression occurring during the 24-month treatment phase, in some cases, the advancing boundary of relative scotomatous loci might pass beyond the end of the microperimetry testing grid, leading to a decrease in the number of assessed loci capable of conversion to relative scotomas. This ceiling effect would tend to suggest a slower rate of incident relative scotomatous loci during the treatment phase and thus would tend artifactually to suggest a beneficial effect of minocycline. Notably, no similar potential beneficial result was observed for the closely related outcome measure of number of absolute scotomatous loci.

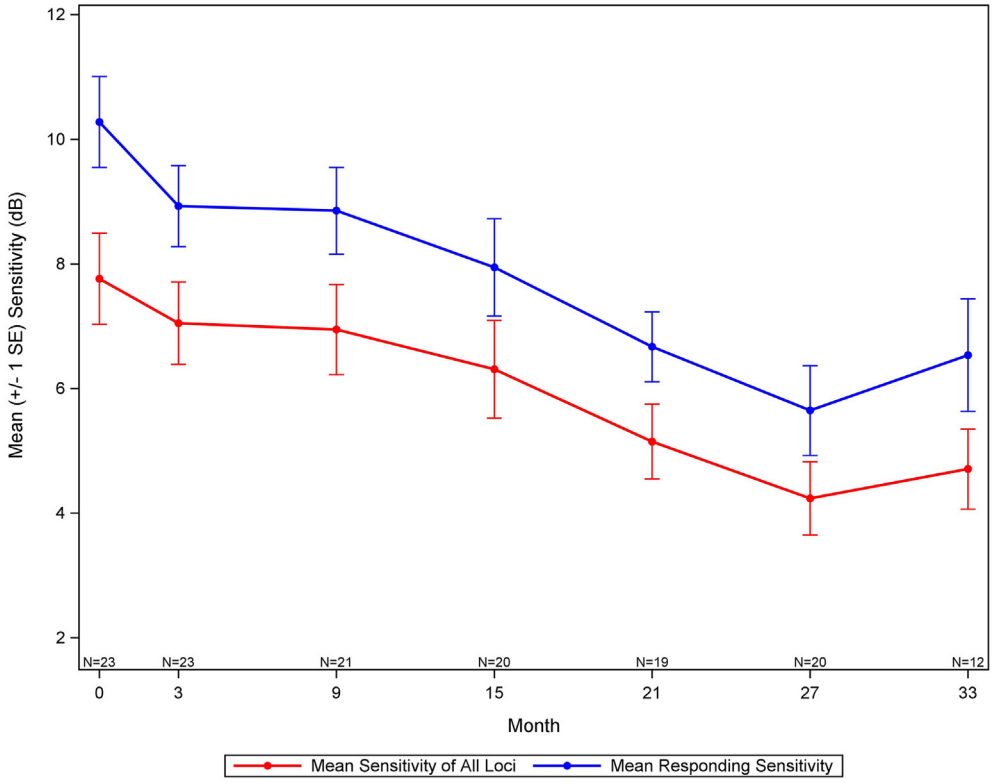


**Figure 3.** Longitudinal analysis of microperimetry parameters as a natural history study: mean sensitivity of all loci and mean sensitivity of all responding loci (per-protocol population 2). Error bars indicate ±1 SE. dB = decibels; SE = standard error.

The analyses of pointwise sensitivity were highly exploratory. We have included these results more for illustrative purposes than for a meaningful determination of potential study drug efficacy. These demonstrate powerfully the phenomenon of a floor effect in some microperimetry analyses, particularly for the study design of comparing rates of change during a run-in phase and a subsequent treatment phase. Superficial analyses of the pointwise sensitivity data would suggest a beneficial treatment effect of the study drug. However, inspection of the raw data revealed that sensitivity often decreased to 0 dB well before the end of the treatment phase, creating a floor effect that would tend artifactually to suggest a beneficial effect of minocycline. Statistical approaches that may be able to address this phenomenon to some extent, such as the use of a tobit model, were explored (results not shown). The tobit model accommodates a continuous variable below a censoring threshold and therefore, permits estimation of the rate of change beyond this threshold (i.e., below 0 dB).[30,31] However, we are not aware of their previous use in analyzing microperimetry data. Overall, the dynamic ranges of individual testing loci must be considered carefully at both the study design and data analysis stages. Loci that are too close to GA borders are unlikely to provide meaningful data to discriminate progression rates in longer trials; however, loci that are too far from GA borders are unlikely to be informative in shorter trials. For these reasons, global measures based on information from many loci will generally provide more meaningful information in a wider range of scenarios than pointwise measures.

After the results suggesting no clinically meaningful effect of oral minocycline in slowing visual function decline from GA progression, the microperimetry analyses were repeated in the form of a natural history study. Specifically, the regression analyses were repeated with the removal of the fixed knot at 9 months. The aim was to provide useful data to characterize the functional decline associated with GA progression from a prospective study of GA with long follow-up time and prespecified microperimetry testing repeated frequently, employing a wide range of microperimetry parameters.

## Novel T-Shaped Microperimetry Testing Pattern

For this clinical trial, we developed a novel T-shaped microperimetry testing pattern to capture the linear enlargement of GA.[23] This design offers several advantages. It aims to provide the greatest quantity of useful information while decreasing patient burden from lengthy testing. The standard 10-2 pattern commonly used in AMD clinical trials comprises 68 loci arranged in a circular grid centered on the fovea, with 2° spacing between the center points of each locus and a radius of 10°.[14,15] By contrast, the testing pattern used in this study comprises 40 loci arranged in a T-shape, with 1° spacing between the center points of each locus and a radius extending 15° temporally, 12° superiorly, and 12° inferiorly. Hence, the loci of the 10-2 pattern are twice as widely spaced as those of the T-shaped pattern, thus providing less granular

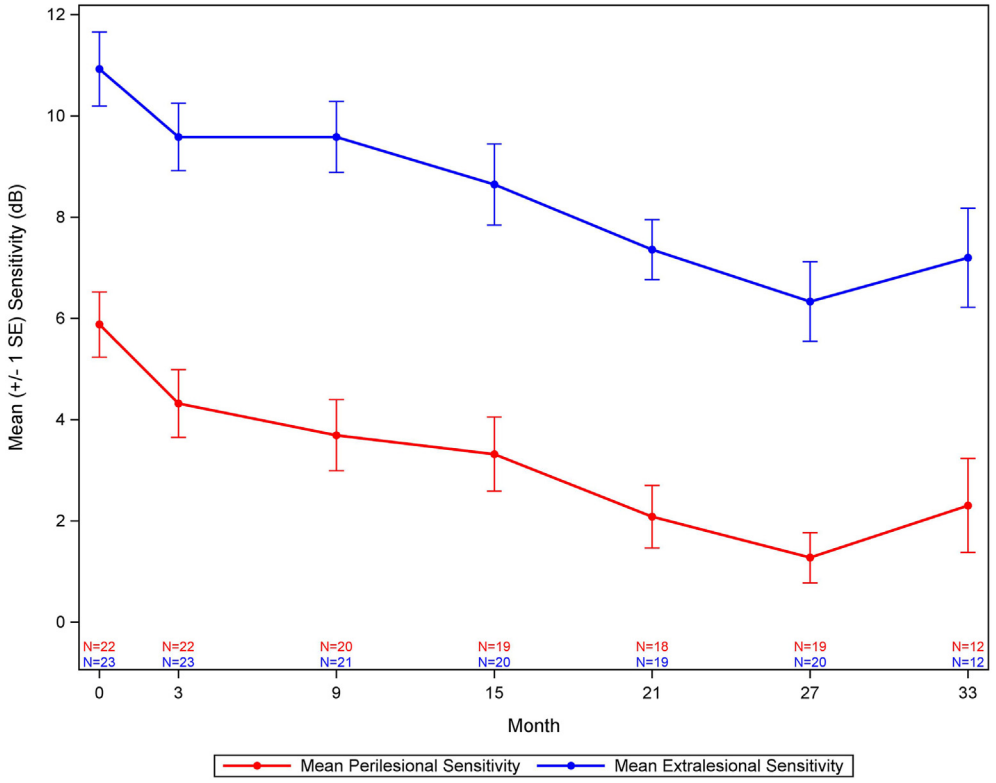


**Figure 4.** Longitudinal analysis of microperimetry parameters as a natural history study: mean perilesional sensitivity and mean extralesional sensitivity (per-protocol population 2). Error bars indicate ±1 SE. dB = decibels; SE = standard error.

information, particularly over shorter follow-up periods. In addition, the 10-2 pattern extends less far into the more peripheral macula, thus providing less information on GA progression at these locations and less information on the advancing ring of partially decreased retinal sensitivity extending beyond the GA borders.[28,29] The T-shaped pattern overcomes these disadvantages, while avoiding excessive testing time by limiting its loci to 3 linear axes rather than a full grid. The nasal axis was considered lower priority, so it was omitted from the testing pattern, since fewer loci would be available for meaningful information (given the location of the optic disc and the possibility of peripapillary atrophy). Although this leads to some loss of information (particularly in rare cases of eyes with no or minimal overlap between GA and the T-shaped pattern, e.g., with GA confined to the nasal macula), it may still capture GA progression well, which is increasingly considered in terms of linear enlargement at GA borders.[19,32] Overall, it is likely to provide a wide dynamic range for capturing the functional consequences of GA progression, despite heterogeneity in baseline GA size, for studies of both short and long follow-up times.

## Advantages and Disadvantages of Different Microperimetry Parameters

We explored various approaches to analyzing the microperimetry data, such as global and regional averages, as well as approaches intended to focus either within or beyond GA lesions. Global sensitivity approaches involve averaging loci across the entire grid, as exemplified by mean macular sensitivity and mean responding sensitivity. Although the mean macular sensitivity is the simplest and most widely used microperimetry parameter in the literature,[14,15] it has some disadvantages. By including points that are already absolute scotomatous loci at baseline so that they cannot decline further, meaningful information is diluted so that the rate of change is shallower and the sensitivity of the measure to detect change over time is decreased. The mean responding sensitivity helps address that limitation. Indeed, our analyses demonstrated that mean responding sensitivity starts higher and appears to decline more quickly than mean macular sensitivity, i.e., with a greater dynamic range owing to fewer redundant loci. However, neither of those approaches takes full advantage of the rich spatial information enabled by microperimetry. Even with the mean responding sensitivity, the inclusion of loci that are highly distant from the GA border at baseline (and so are less likely to decline at any time point) means that, again, meaningful information is diluted.

By contrast, the mean perilesional sensitivity seeks to use this spatial information to concentrate on the loci at greatest risk of imminent decline, i.e., essentially those in the GA junctional zone.[28] In this way, it may provide a highly sensitive measure for clinical trials of shorter duration. On the other hand, it is susceptible to floor effects with clinical trials of longer duration. In addition, since this measure is based on fewer testing loci, its limitations

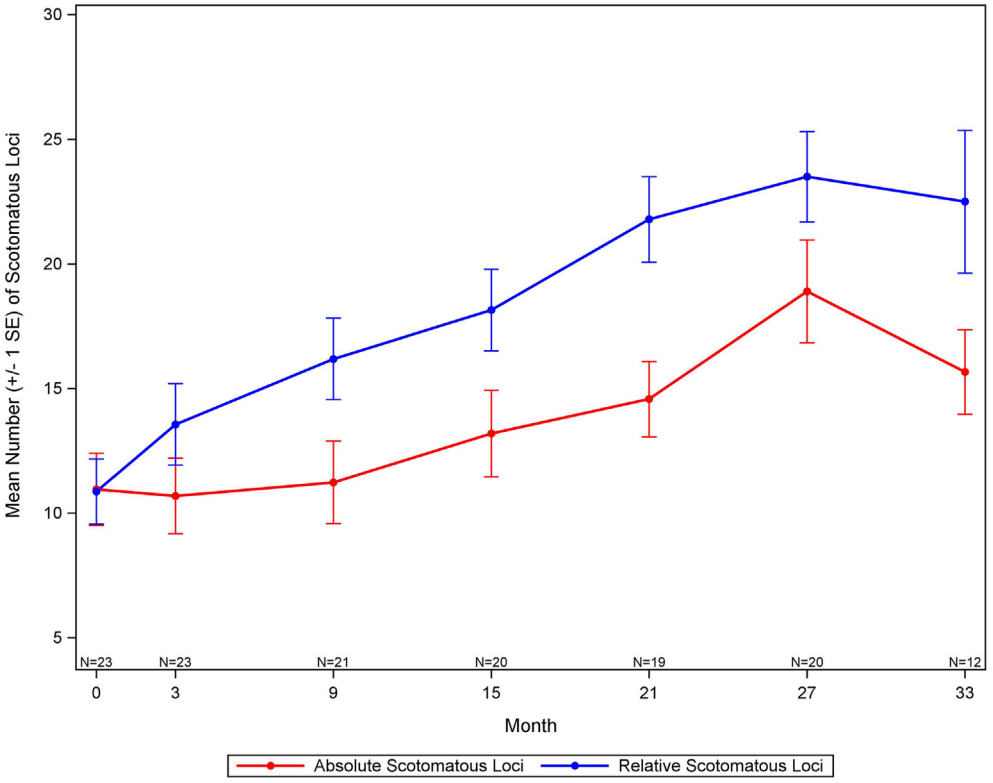


**Figure 5.** Longitudinal analysis of microperimetry parameters as a natural history study: mean number of absolute scotomatous loci and mean number of relative scotomatous loci (per-protocol population 2). Error bars indicate ±1 SE. SE = standard error.

Table 7. Results of Generalized Linear Regression Analyses of Microperimetry Parameters from Baseline to Month 33 as a Natural History Study (Per-Protocol Population 2)

| Microperimetry Parameter* (Covariance Structure†) | Estimate | SE | *P* Value‡ |
|---|---|---|---|
| Mean sensitivity of all loci (AR [1]) | | N = 23 | |
| Baseline to month 33 | −1.39 | 0.30 | <0.001 |
| Mean responding sensitivity (CS) | | N = 23 | |
| Baseline to month 33 | −1.64 | 0.17 | <0.001 |
| Mean perilesional sensitivity (CS) | | N = 22 | |
| Baseline to month 33 | −1.55 | 0.21 | <0.001 |
| Mean extralesional sensitivity§ (UN) | | N = 23 | |
| Baseline to month 33 | 0.02 | 0.01 | 0.02 |
| Absolute scotomatous loci‖ (AR [1]) | | N = 23 | |
| Baseline to month 33 | 1.23 | 0.04 | <0.001 |

AR = autoregressive; CS = compound symmetry; dB = decibels; SE = standard error; UN = unstructured.
Results are based on a repeated measures linear regression model, unless otherwise specified.
*Rate of change (dB/year), unless otherwise specified.
†Covariance structure that provided the best model fit.
‡*P* values relate to the change over time being significantly different to zero.
§Results are based on a repeated measures linear regression model with a 1/(0.01 + x) transformation.
‖Rate of change (incidence rate ratio). Results are based on a repeated measures negative binomial regression model.

include increased noise. The mean extralesional sensitivity overcomes those limitations since it is based on many more loci. However, similar to the mean responding sensitivity, it may be less sensitive (particularly in clinical trials with shorter duration) since many loci furthest from the GA border at baseline may not contribute useful information over the course of a trial.

We also analyzed the expansion of the absolute scotoma associated with GA progression, by using the number of absolute scotomatous loci as an outcome measure. This parameter may be considered the closest functional equivalent to the commonly used structural outcome measure of GA area.[14] Indeed, our recent structure-function comparisons in this same dataset demonstrated high spatial concordance between zones with FAF-defined GA and zones with absolute scotomatous loci.[23] By contrast, the number of relative scotomatous loci may represent a more sensitive measure for detecting disease progression with its lower threshold. However, importantly, it may also reflect a partially different disease phenomenon. Subnormal retinal sensitivity (i.e., short of an absolute scotoma) is thought to extend beyond GA borders, such that an advancing wave of partially decreased sensitivity presumably progresses concentrically in parallel with the expansion of GA borders themselves.[28,29] However, the degree and extent of this phenomenon might vary between different eyes.[33,34] In

addition, it is possible that the treatment effect of a particular drug might slow absolute or relative scotomatous loci progression preferentially, perhaps related to preferential targeting of RPE vs. photoreceptor cells. For these reasons, we recommend the use of both these outcome measures as providing complementary information. However, as mentioned above, the relative scotomatous loci measure is more prone to a potential ceiling effect, particularly with GA lesions closer to the peripheral macula or smaller microperimetry testing patterns like the 10-2 grid. In addition, for both absolute and relative scotomatous loci, the binarization involved in generating these outcome measures involves a substantial loss of the highly quantitative information enabled by microperimetry. Hence, for example, the mean extralesional sensitivity may provide a more granular and meaningful outcome measure than the number of relative scotomatous loci, as observed in the results of the current study.

Overall, the optimal approaches for analyzing microperimetry data depend heavily on the study design, particularly the intended time course of the study. They can be viewed in terms of an important trade-off between greater sensitivity to detect change vs. greater risk of floor effects. Global averages tend to have lower risk of floor effects but lower sensitivity to detect change, while local measures (like mean perilesional sensitivity and pointwise sensitivity) tend to have higher sensitivity to detect change but higher risk of floor effects. Therefore, an appropriate compromise may be regional averages, such as mean responding sensitivity or mean extralesional sensitivity, though several outcome measures might be required to provide a fuller picture. In addition, for many of these parameters, a study design with randomization may be preferable to one without randomization, as in the current study, to minimize the risk of floor or ceiling effects, artifactually suggesting efficacy of the study drug. Similarly, the choice of testing grid (including the spacing of loci and their lateral extent) represents a trade-off between greater sensitivity to detect change (particularly for shorter studies) and lower risk of running out of loci (particularly for longer studies) vs. testing burden. Importantly, the most appropriate microperimetry outcome measures should be tailored carefully to both the study design (including baseline GA size eligibility criteria and study duration) and the microperimetry testing grid.

## Strengths and Limitations

The strengths of this study include its prospective clinical trial setting, with microperimetry testing performed at regular intervals using prespecified methods and a novel testing grid and with a relatively long follow-up time. We sought to analyze the microperimetry data using multiple different outcome measures, both with and without a fixed knot in the regression analyses. First, this enabled us to investigate the potential efficacy of minocycline as comprehensively as possible and explore the strengths and weaknesses of the various outcome measures in different settings. Second, this permitted us to report detailed natural history data for the different parameters.

Potential limitations of the study include the small sample size and absence of randomization in the study design; the analyses of potential efficacy of minocycline rely on participants serving as their own controls. Other potential limitations include the premature discontinuation of the drug or study in some participants, though this was mitigated by aspects of the study design and analyses; for example, exclusion of participants from analysis populations if there was an insufficient amount of time on study or time on study drug. Finally, the microperimetry analyses were not prespecified in the statistical analysis plan, though we used the same statistical approach that had been prespecified for analysis of the primary outcome measure. As mentioned above, the study was not powered for these analyses, and no adjustments were made for multiple testing; as such, the results of these exploratory analyses should be interpreted with caution and should be considered hypothesis generating.

## Conclusions

In these exploratory longitudinal analyses of the mesopic microperimetry data from a phase II trial, the results do not appear consistent with a clinically meaningful beneficial treatment effect of oral minocycline on the rate of visual function decline associated with GA progression. These results are in keeping with previous analyses of the corresponding structural data. For the majority of the microperimetry parameters analyzed, the study drug was not associated with a decrease in the rate of decline in retinal sensitivity between the 2 phases. Of the 6 main parameters analyzed, only 1 suggested a possible beneficial effect. However, this result should be interpreted with caution, given the degree of multiple testing, the possibility of artifact from ceiling effects, and some lack of consistency in sensitivity analyses.

The longitudinal analyses considering the whole study duration may provide useful information as a natural history study. They also demonstrate potential advantages and disadvantages of the different microperimetry parameters. Overall, the optimal microperimetry testing patterns and parameters depend heavily on the study design and participant baseline characteristics. They represent a trade-off between greater sensitivity to detect change vs. greater risk of floor or ceiling effects. In this respect, regional averages (such as mean responding sensitivity or mean extralesional sensitivity) may offer a useful compromise, though several parameters may be required to provide a comprehensive picture. If designed and applied appropriately to clinical trials, microperimetry has the ability to provide a rich plethora of quantitative information on the decline in visual function associated with GA progression. Given the importance of visual function data to regulatory agencies, the results of this study may provide useful insights to guide the development of microperimetry end points for future clinical trials.

## Footnotes and Disclosures

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HUMAN SUBJECTS: Human subjects were included in this study. The protocol was approved by the National Institutes of Health Institutional Review Board and the South Central-Oxford B Research Ethics Committee and adhered to the tenets of the Declaration of Helsinki. Written informed consent was obtained from each participant before enrollment. The study was registered at www.clinicaltrials.gov (NCT02564978; registration date, October 1, 2015). Study oversight was provided by an independent external Data and Safety Monitoring Committee (DSMC) that approved the protocol prior to trial initiation and reviewed study data approximately every 6 months. This manuscript relating to an exploratory outcome was not reviewed by the DSMC, according to the DSMC policy on review of manuscripts for exploratory outcomes.

No animal subjects were included in this study.

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Obtained funding: Keenan

Overall responsibility: Arunachalam, Abraham, Orndahl, Menezes, Mukherjee, Duic, Prasad, Siddig, Bellur, Thavikulwat, Bailey, Sadda, Chew, Wong, Jeffrey, Keenan

Abbreviations and Acronyms:
**AMD** = age-related macular degeneration; **BCVA** = best-corrected visual acuity; **dB** = decibels; **FAF** = fundus autofluorescence; **GA** = geographic atrophy; **IRR** = incidence rate ratio; **NIH** = National Institutes of Health; **SD** = standard deviation; **SE** = standard error; **RPE** = retinal pigment epithelium.

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