Detailed description of the macular sensitivity changes occurring during NAC treatment in 4 subjects illustrated in Figures 6 and 7

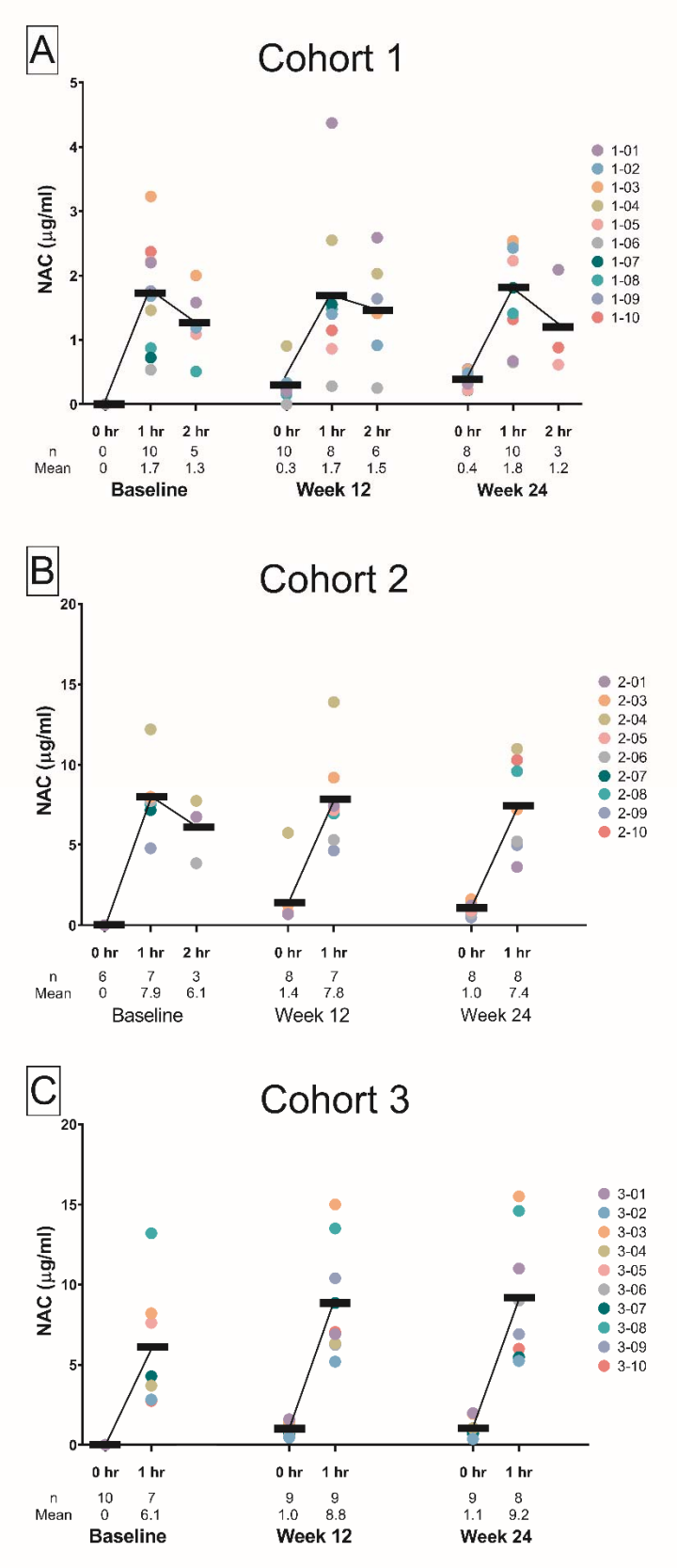
Figure 6A shows the best pretreatment sensitivity heat map of a patient in cohort 1. The arrows show regions at which improvement was subsequently detected after the start of treatment. At week 12 of NAC treatment, arrowheads show loci with improved sensitivity (Figure 6B) with additional improvement at week 24 (Figure 6C). Interestingly, most gains were maintained with some additional areas of improvement 12 weeks after cessation of NAC (Figure 6D). Figure 6E shows the pretreatment fundus image with sensitivity values corresponding to the heat map in 6A. Assessments of microperimetry test-retest variability have suggested that changes ≥ 6 dB are unlikely to be due to chance (references 18-20). In Figure 6E, loci that showed an improvement ≥ 6 dB after initiation of NAC treatment are circled in yellow. At week 12 of NAC treatment, 15 loci showed improvement from baseline ≥ 6 dB (Figure 6F, green circles). At week 24, a few loci dropped slightly so that there were 10 loci below the 6 dB threshold (Figure 6G, green circles), but these loci tended to rebound a bit during the observation period so that 14 loci were above the 6 dB threshold at week 36 (Figure 6H, green circles). For this subject, aqueous NAC levels were 117 ng/mL and 139 ng/mL at weeks 12 and 24 which is above the mean for cohort 1. Figure 6I shows the best pretreatment sensitivity heat map of a patient in cohort 2 who had visual field loss that was less advanced than the patient shown in 6A-H. Most loci showed good sensitivity, but there was an arc of reduced sensitivity superotemporal to the fovea in which there were several loci with undetectable sensitivity (arrows show loci that will show improvement after treatment initiation). After 12 weeks of NAC treatment, 2 of the absolute scotomata disappeared

(Figure 6J, arrowheads) and after 24 weeks of treatment three more scotomata were eliminated (Figure 6K, arrowheads). Aqueous NAC levels were 222 ng/mL and 405 ng/mL at weeks 12 and 24. Twelve weeks after stopping NAC, the arc of depressed sensitivity was further improved with all of the scotomata eliminated (Figure 6L, arrowheads). Figure 6M shows the pretreatment fundus image with sensitivity values corresponding to the heat map in 6I. Nine loci that will show an improvement ≥ 6 dB during NAC treatment are circled in yellow. At week 12 of NAC treatment, one of the loci showed improvement ≥ 6 dB (Figure 6N), but 8 loci had improved beyond the 6 dB threshold at week 24 (Figure 6O). All of these but one regressed during the 12 weeks after stopping NAC (Figure 6P, green circles).

Figure 7A shows the best pretreatment sensitivity heat map of a patient in cohort 3. The arrows show an absolute arcuate scotoma nasal and inferior to the fovea and two isolated scotomata temporal to the fovea that improved during the treatment period. After 12 weeks of NAC treatment one of the temporal scotomata was eliminated and the large arcuate scotoma had partially resolved (Figure 7B, arrowheads) leaving 4 isolated scotomata. There was additional improvement at week 24 and so only 2 small scotomata remained (Figure 7C). Aqueous NAC levels were 297 ng/mL and 441 ng/mL at weeks 12 and 24. Unlike the patients shown in Figures 6A-H and 6I-P, much of the benefit in macular sensitivity was lost by 12 weeks after stopping NAC and most of the arcuate scotoma nasal and inferior to the fovea had recurred (Figure 7D, arrows). Figure 7E shows the pretreatment sensitivity values corresponding to the heat map in 7A. Loci that will show an improvement ≥ 6 dB after the start of NAC treatment are circled in yellow. At week 12 of NAC treatment, 9 loci showed improvement from

baseline ≥ 6 dB (Figure 7F, green circles). At week 24 of NAC treatment, there were 15 loci that had improved from baseline ≥ 6 dB (Figure 7G, green circles). At week 36, twelve weeks after stopping NAC, much of the benefit seen during treatment had regressed and there were only 3 loci with an improvement from baseline ≥ 6 dB (Figure 7H, green circles). Figure 7I shows the best pretreatment sensitivity heat map of a patient in cohort 3 with less advanced disease than the other 3 patients shown in Figures 6 and 7. Most loci showed good sensitivity and there was excellent sensitivity in and around the fovea (Figure 7I). The arrows indicate areas of modestly reduced sensitivity that will show substantial improvement after initiation of treatment. After 12 weeks of NAC treatment, there were 2 regions at the border of the central region of excellent sensitivity that had improved (Figure 7J, arrowheads) and after 24 weeks of treatment 8 additional regions had improved resulting in expansion of the central region of excellent sensitivity (Figure 7K, yellow-green area surrounded by arrowheads). Aqueous NAC levels were 426 ng/mL and 439 ng/mL at weeks 12 and 24. Most, but not all, of the benefit was maintained 12 weeks after stopping NAC (Figure 7L). Figure 7M shows the fundus image with pretreatment sensitivity values corresponding to the heat map in 6I. Seven loci that will show an improvement ≥ 6 dB after starting NAC treatment are circled in yellow. At week 12 of NAC treatment, there was some improvement at most of the loci, but only one had improved ≥ 6 dB (Figure 7N). At week 24 of NAC treatment, 6 loci showed improvement from baseline ≥ 6 dB (Figure 7O, green circles). At week 36, four loci still showed an improvement from baseline ≥ 6 dB (Figure 7P, green circles).

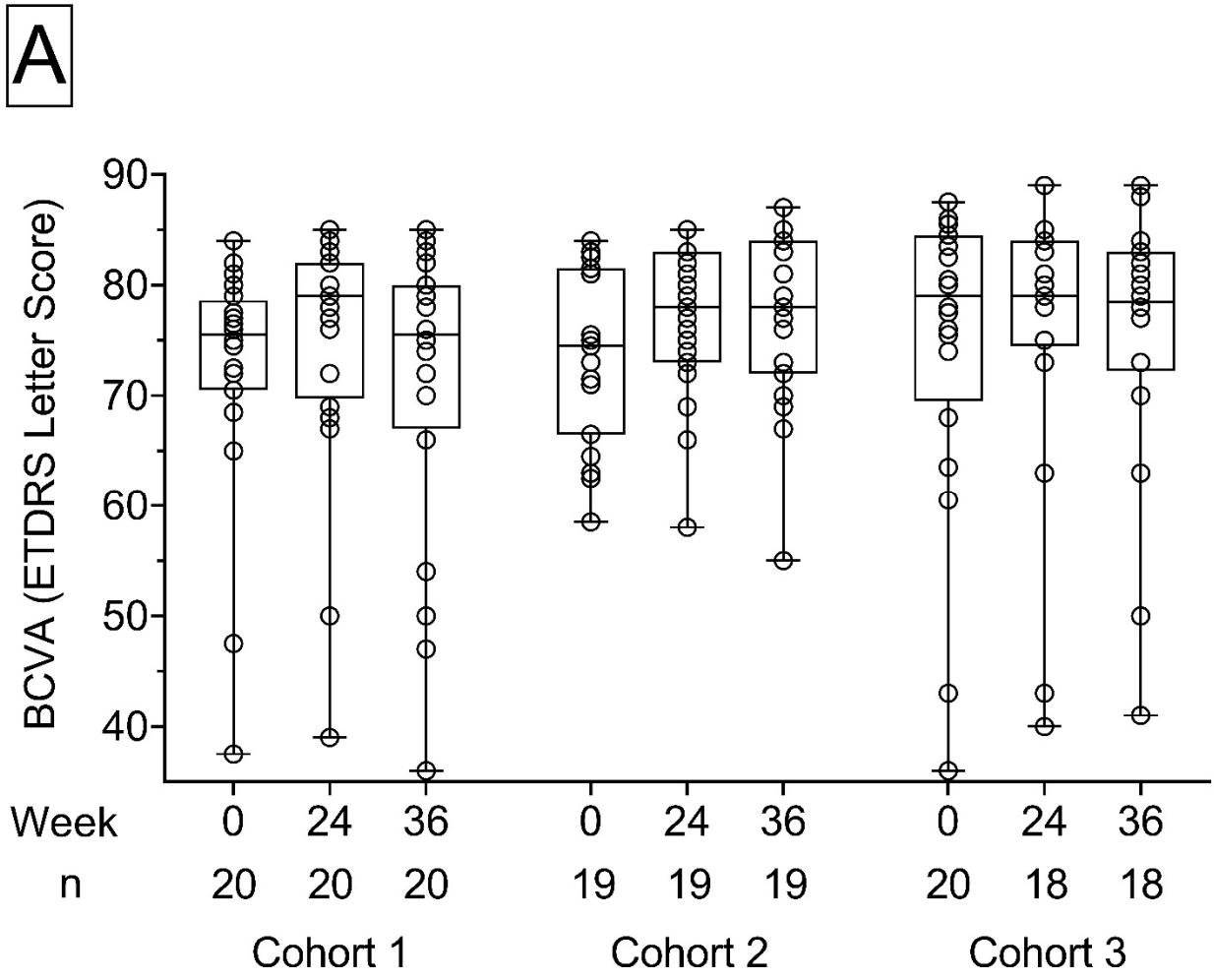
Supplemental Figure 1



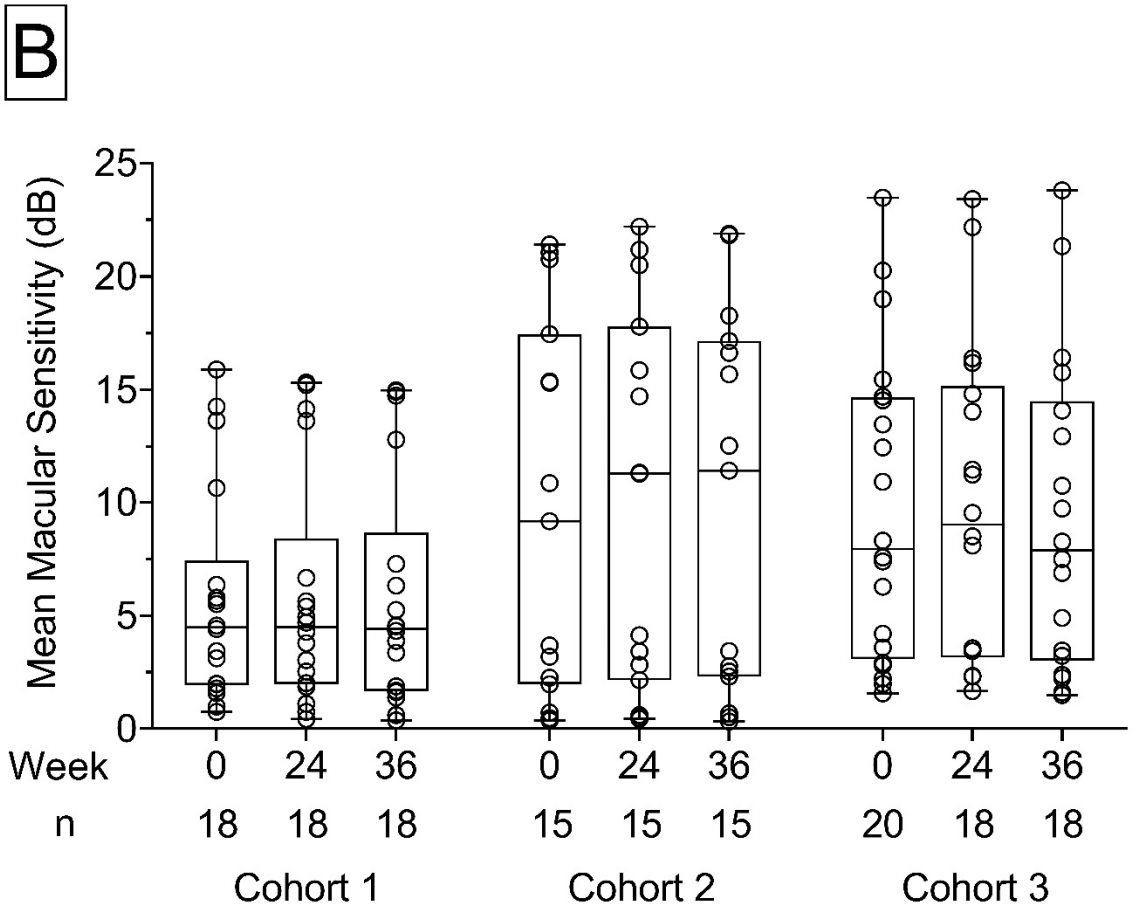
Supplemental Figure 1. N-acetylcysteine (NAC) levels in plasma

The dose of NAC was 600 mg twice a day for 12 weeks and then 600 mg three times a day for the subsequent 12 weeks in cohort 1 (A), 1200 mg twice a day for 12 weeks and then 1200 mg three times a day for the subsequent 12 weeks in cohort 2 (B), and 1800 mg twice a day for 12 weeks and then 1800 mg three times a day for the subsequent 12 weeks in cohort 3 (C). In cohort 1, patients were given their first dose of NAC at the baseline visit and a plasma sample was obtained 1 and 2 hours after the dose. For the week 12 visit, it was requested that patients not take their morning dose which was given during the study visit and plasma samples were drawn 1 and 2 hours after the dose. Patients and family members found waiting for the second plasma sample burdensome, and many refused to remain for the second sample. The protocol was amended soon after starting cohort 2 and only a 1 hour post dose sample was requested. The colored circles corresponding to patient identifiers show plasma NAC level at the designated time point. Bars shows the mean at each time point which is also listed along the X-axis. The number of eyes (n) for each time point is also shown along X-axis. The lower limit of detection was 50 ng/ml.

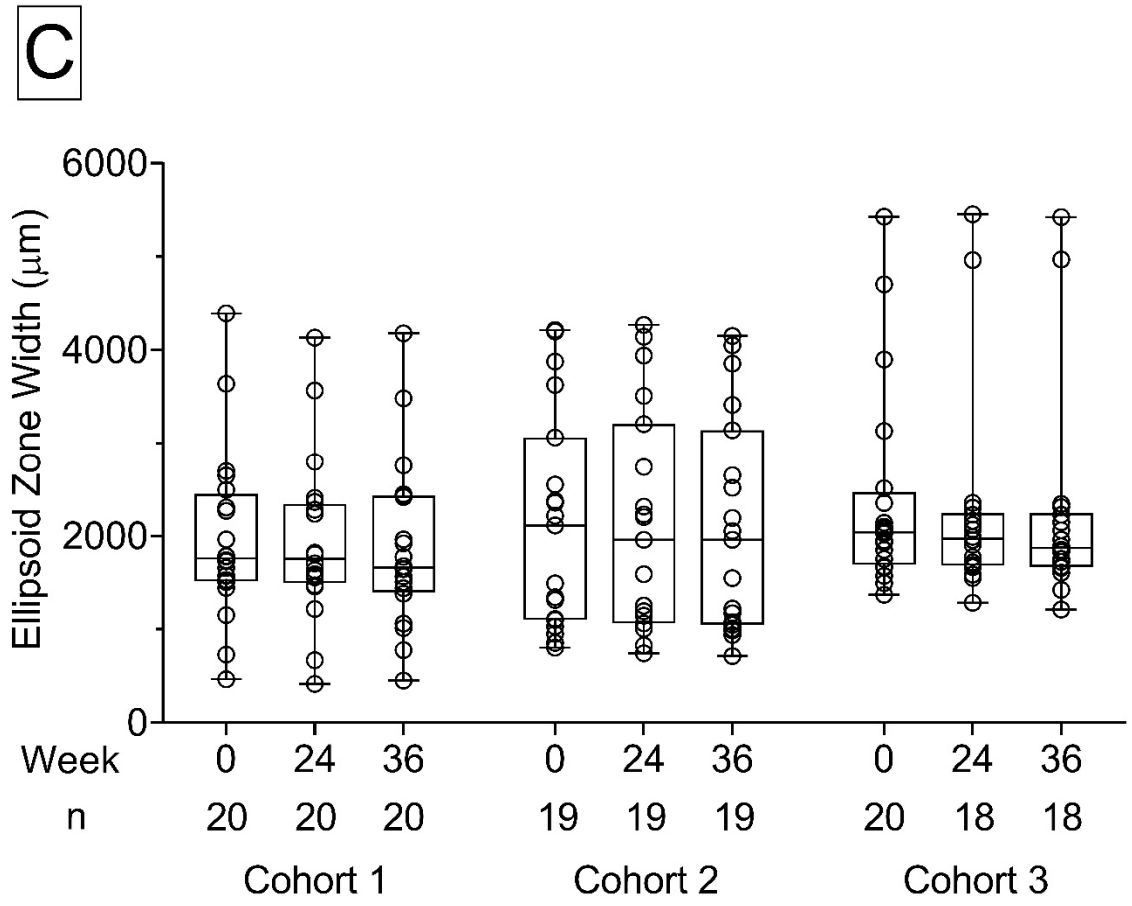
Supplemental Figure 2. Best-corrected visual acuity (A), mean macular sensitivity (B), and ellipsoid zone width (C) at baseline, week 24 and week 36



Best-corrected visual acuity (BCVA) in Early Treatment Diabetic Retinopathy Study (ETDRS) letter score was plotted for both eyes of each patient at baseline (week 0), the end of the treatment period at week 24, and the end of study at week 36. The box upper and lower borders correspond to the 25th to 75th percentile and the solid line within the box is the median.

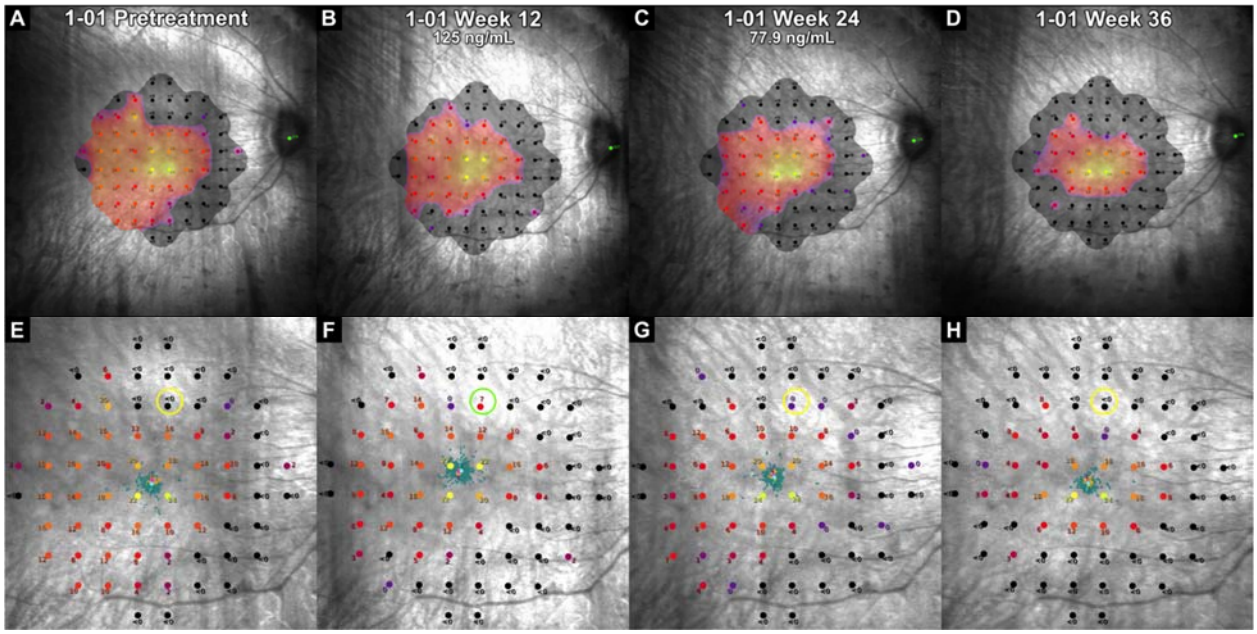


Mean macular sensitivity in decibels (dB) was plotted for both eyes of each patient at baseline (week 0), the end of the treatment period at week 24, and the end of study at week 36. The box upper and lower borders correspond to the 25th to 75th percentile and the solid line within the box is the median.



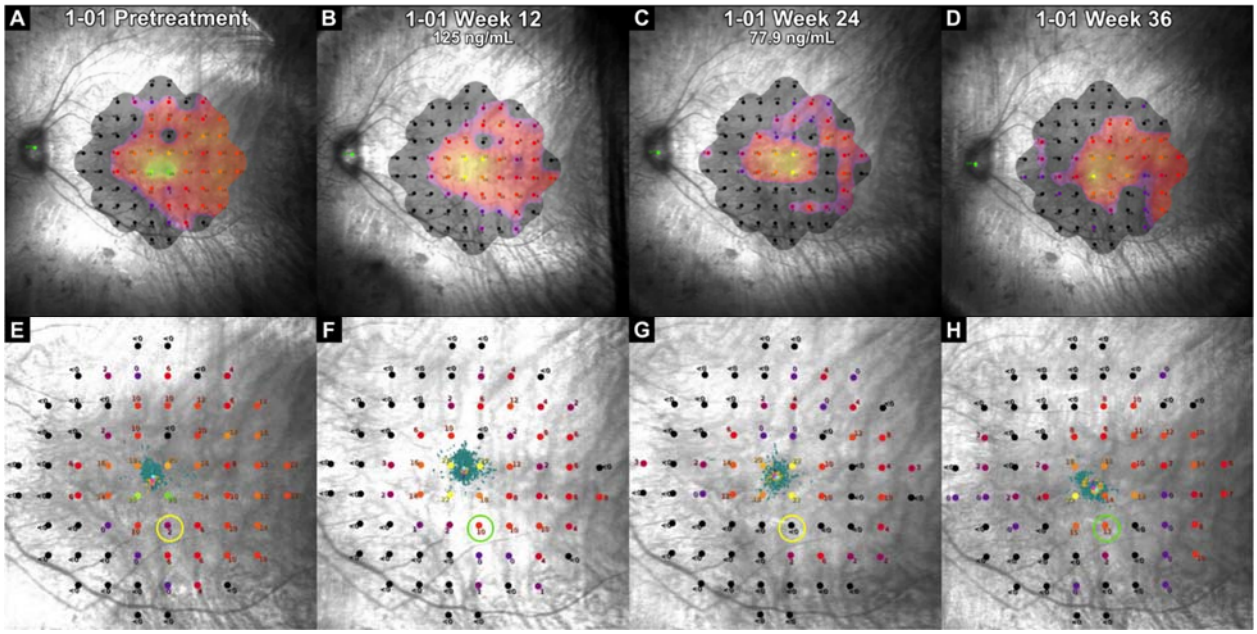
Elipsoid zone width was plotted for both eyes of each patient at baseline (week 0), the end of the treatment period at week 24, and the end of study at week 36. The box upper and lower borders correspond to the 25th to 75th percentile and the solid line within the box is the median.

Supplemental Figure 3



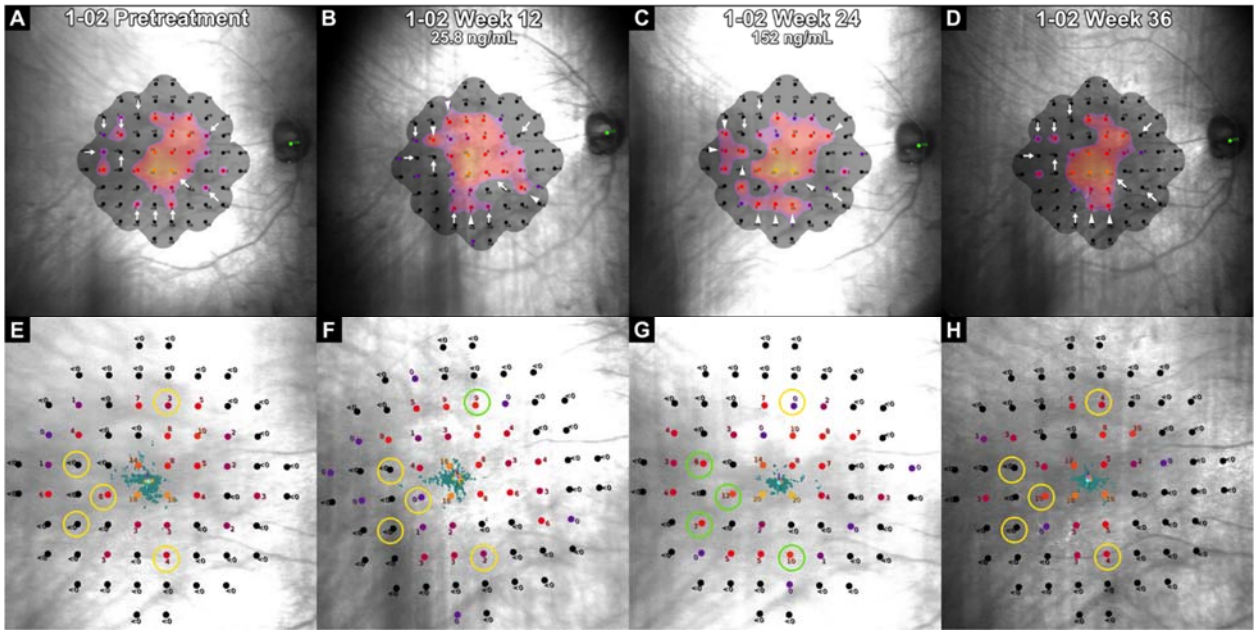
Supplemental Figure 3. Change in retinal sensitivity during treatment and post-treatment observation in the right eye of patient 1 of cohort 1.
The heat maps generated by the Macular Integrity Assessment Instrument software (A-D) and fundus images showing the sensitivity value at each retinal location (E-H) are shown for the pretreatment test with highest mean sensitivity (A and E) and the tests at weeks 12, 24, and 36. The locus circled in yellow on the pretreatment fundus images (E) has a sensitivity increased ≥ 6 dB after the onset of treatment. On subsequent fundus images, a green circle indicates that sensitivity at that location had increased ≥ 6 dB from pretreatment and a change back to yellow indicates a decline below the 6 dB threshold. There was a small decrease in sensitivity during treatment and further decrease during post-treatment observation.

Supplemental Figure 4



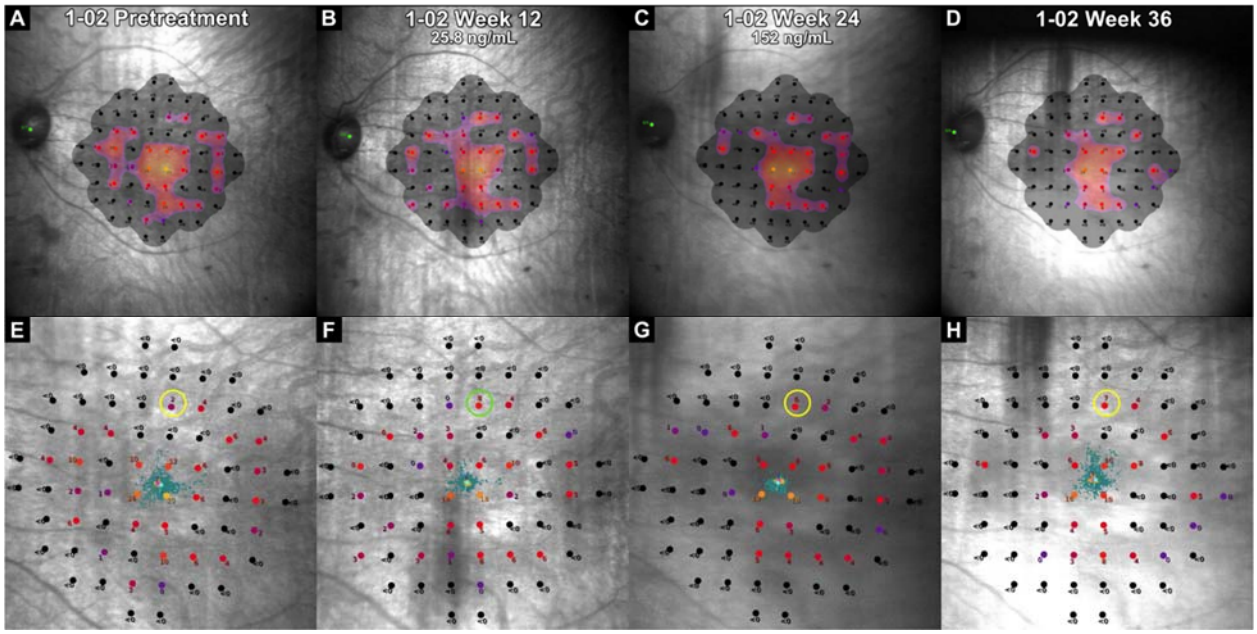
Supplemental Figure 4. Change in retinal sensitivity during treatment and post-treatment observation in the left eye of patient 1 of cohort 1.
The heat maps generated by the Macular Integrity Assessment Instrument software (A-D) and fundus images showing the sensitivity value at each retinal location (E-H) are shown for the pretreatment test with highest mean sensitivity (A and E) and the tests at weeks 12, 24, and 36. The locus circled in yellow on the pretreatment fundus images (E) has a sensitivity increased ≥ 6 dB after the onset of treatment. On subsequent fundus images, a green circle indicates that sensitivity at that location had increased ≥ 6 dB from pretreatment and a change back to yellow indicates a decline below the 6 dB threshold. There was reduction in sensitivity during treatment.

Supplemental Figure 5



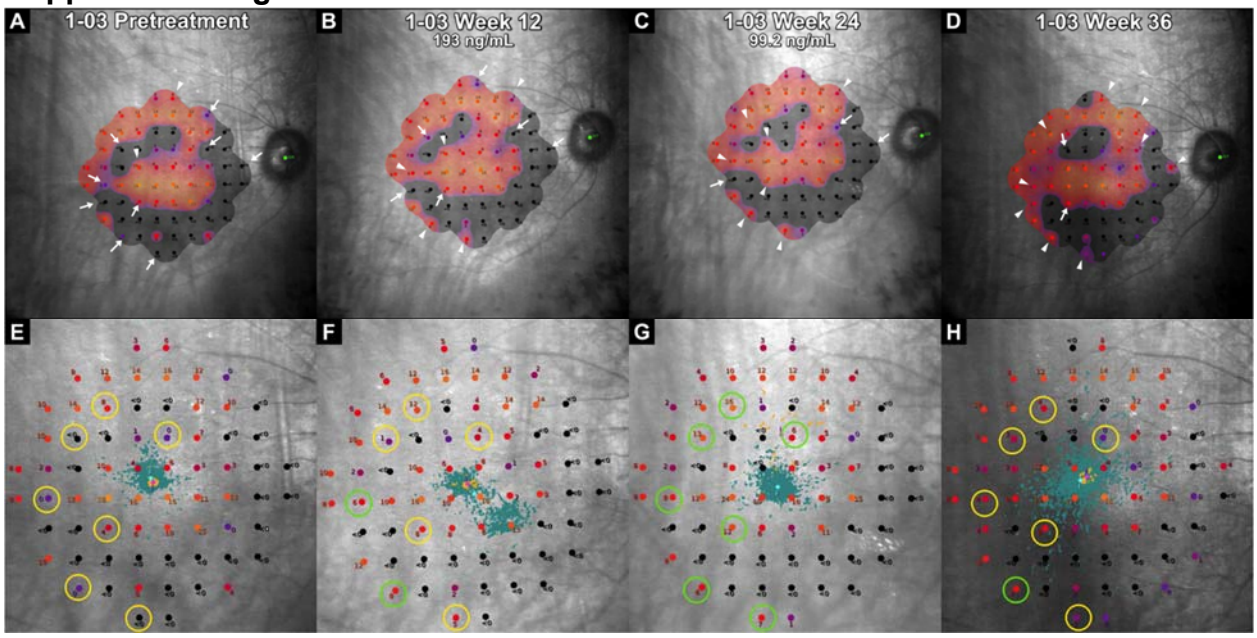
Supplemental Figure 5. Change in retinal sensitivity during treatment and post-treatment observation in the right eye of patient 2 of cohort 1.
The heat maps generated by the Macular Integrity Assessment Instrument software (A-D) and fundus images showing the sensitivity value at each retinal location (E-H) are shown for the pretreatment test with highest mean sensitivity (A and E) and the tests at weeks 12, 24, and 36. In heat maps, the arrows point to regions where the retinal sensitivity improved after the onset of treatment. A change from an arrow to an arrowhead indicated improvement had occurred, and any subsequent decline is noted by a change from arrowhead to arrow. There was expansion of the area of sensitivity during treatment with regression after treatment. The loci circled in yellow on the pretreatment fundus images (E) show loci at which sensitivity increased ≥ 6 dB after the onset of treatment. On subsequent fundus images, green circles indicate that sensitivity at that location had increased ≥ 6 dB from pretreatment and a change back to yellow indicates a decline below the 6 dB threshold. There was moderate improvement during NAC treatment that regressed after cessation of treatment.

Supplemental Figure 6



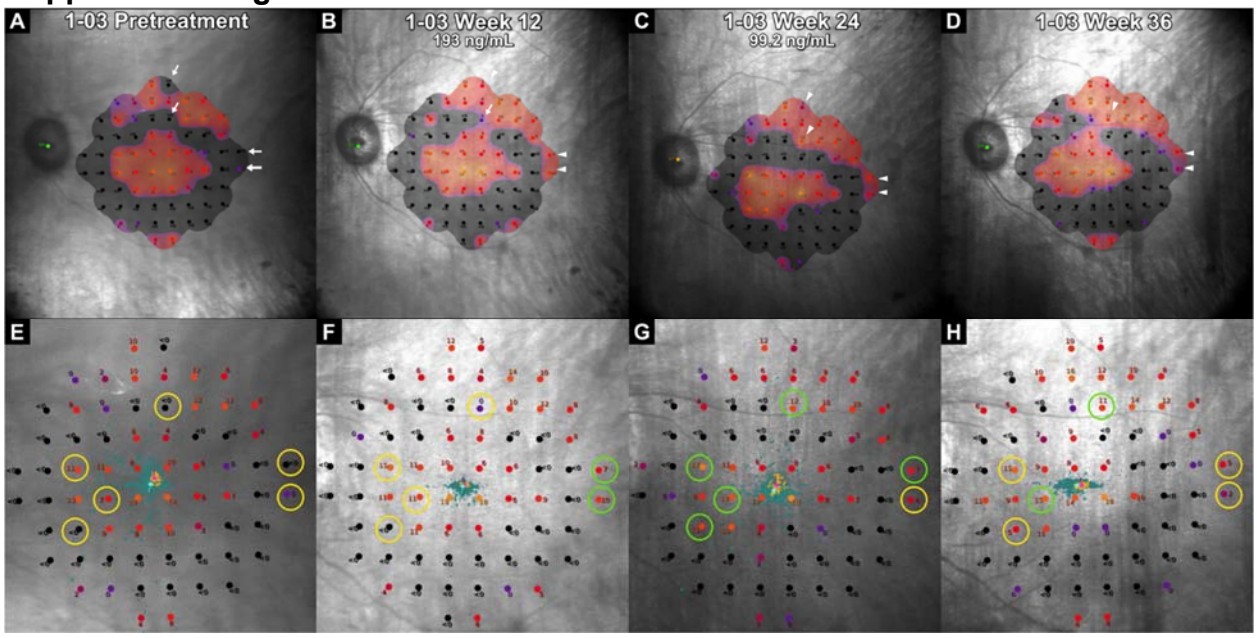
Supplemental Figure 6. Change in retinal sensitivity during treatment and post-treatment observation in the left eye of patient 2 of cohort 1.
The heat maps generated by the Macular Integrity Assessment Instrument software (A-D) and fundus images showing the sensitivity value at each retinal location (E-H) are shown for the pretreatment test with highest mean sensitivity (A and E) and the tests at weeks 12, 24, and 36. The locus circled in yellow on the pretreatment fundus images (E) has a sensitivity increased ≥ 6 dB after the onset of treatment. On subsequent fundus images, a green circle indicates that sensitivity at that location had increased ≥ 6 dB from pretreatment and a change back to yellow indicates a decline below the 6 dB threshold. There was little change in sensitivity during treatment.

Supplemental Figure 7



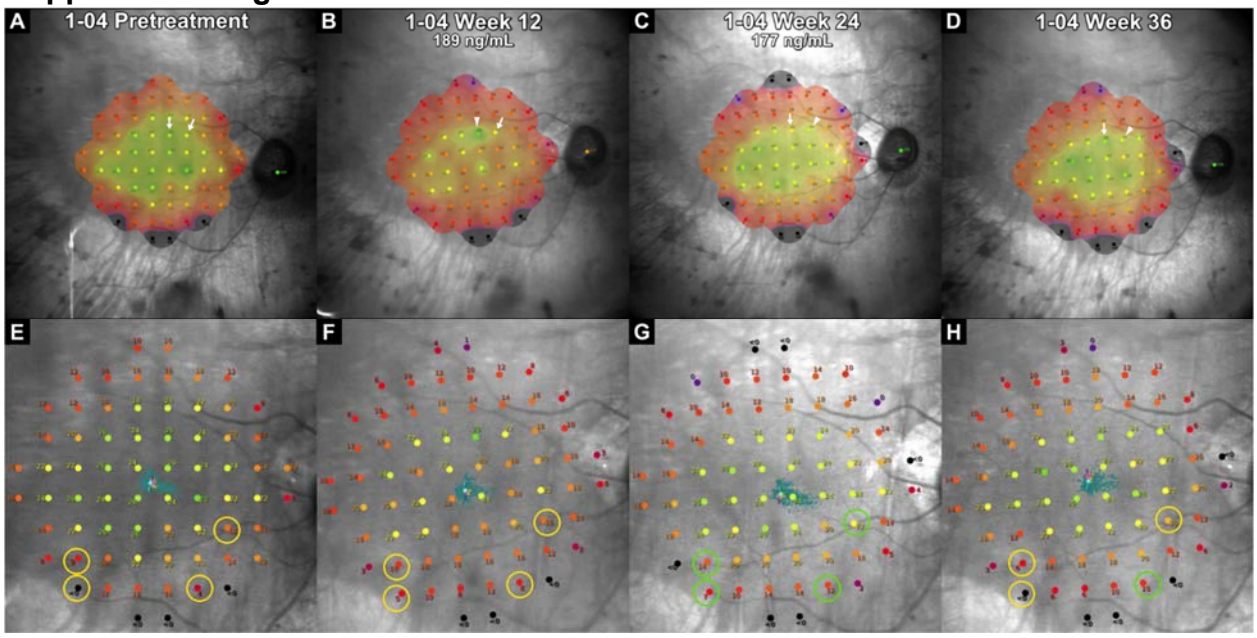
Supplemental Figure 7. Change in retinal sensitivity during treatment and post-treatment observation in the right eye of patient 3 of cohort 1.
The heat maps generated by the Macular Integrity Assessment Instrument software (A-D) and fundus images showing the sensitivity value at each retinal location (E-H) are shown for the pretreatment test with highest mean sensitivity (A and E) and the tests at weeks 12, 24, and 36. In heat maps, the arrows point to regions where the retinal sensitivity improved after the onset of treatment. A change from an arrow to an arrowhead indicates improvement had occurred, and any subsequent decline is noted by a change from arrowhead to arrow. The loci circled in yellow on the pretreatment fundus images (E) show loci at which sensitivity increased ≥ 6 dB after the onset of treatment. On subsequent fundus images, green circles indicate that sensitivity at that location was increased ≥ 6 dB from pretreatment and a change back to yellow indicates a decline below the 6 dB threshold. There was moderate improvement during treatment that regressed 3 months after treatment cessation but remained better than baseline.

Supplemental Figure 8



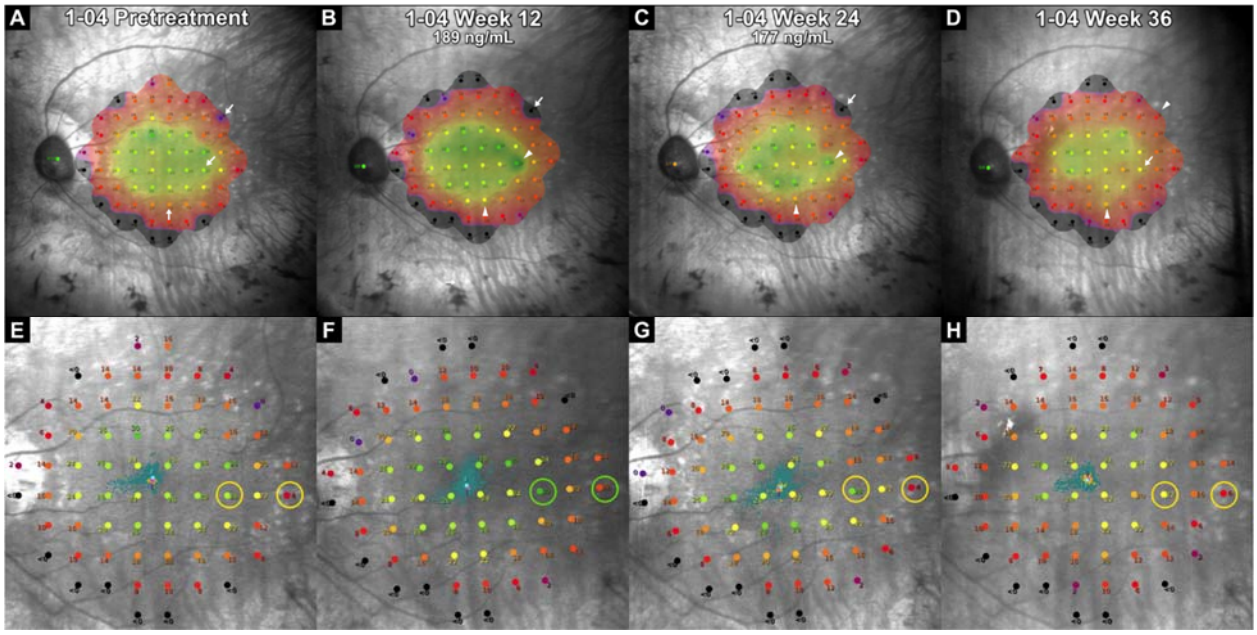
Supplemental Figure 8. Change in retinal sensitivity during treatment and post-treatment observation in the left eye of patient 3 of cohort 1.
The heat maps generated by the Macular Integrity Assessment Instrument software (A-D) and fundus images showing the sensitivity value at each retinal location (E-H) are shown for the pretreatment test with highest mean sensitivity (A and E) and the tests at weeks 12, 24, and 36. In heat maps, the arrows point to regions where the retinal sensitivity improved after the onset of treatment. A change from an arrow to an arrowhead indicates improvement had occurred, and any subsequent decline is noted by a change from arrowhead to arrow. The loci circled in yellow on the pretreatment fundus images (E) show loci at which sensitivity increases ≥ 6 dB after the onset of treatment. On subsequent fundus images, green circles indicate that sensitivity at that location was increased ≥ 6 dB from pretreatment and a change back to yellow indicates a decline below the 6 dB threshold. There was moderate improvement in sensitivity during treatment that regressed 3 months after treatment cessation but remained better than baseline.

Supplemental Figure 9



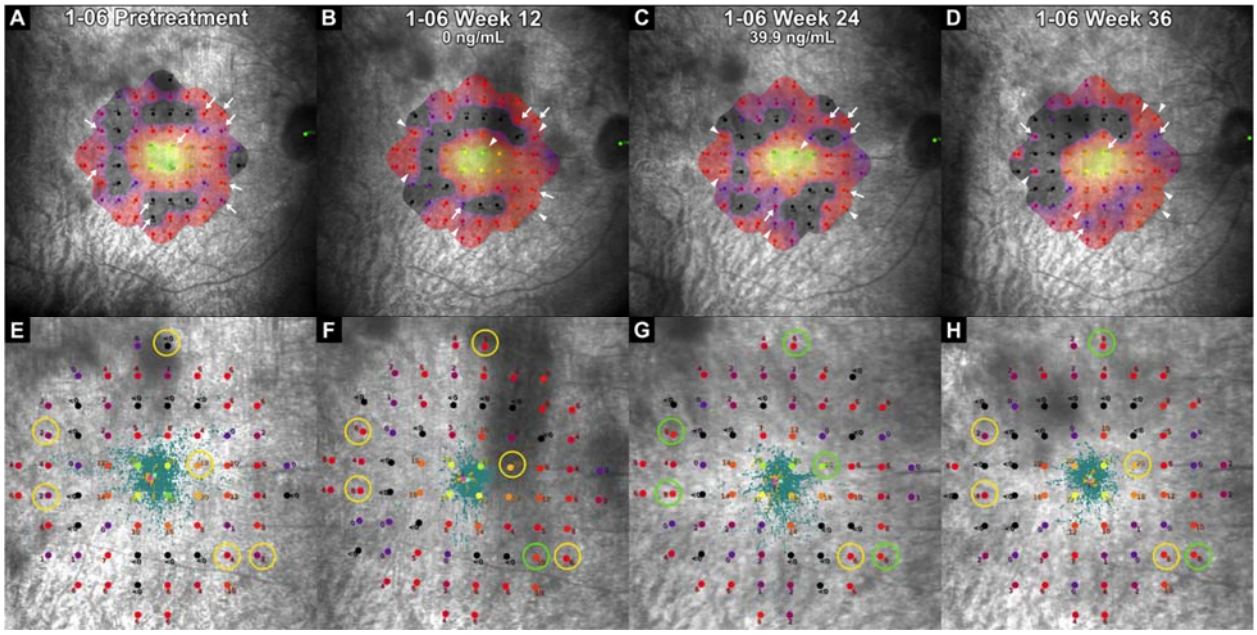
Supplemental Figure 9. Change in retinal sensitivity during treatment and post-treatment observation in the right eye of patient 4 of cohort 1.
The heat maps generated by the Macular Integrity Assessment Instrument software (A-D) and fundus images showing the sensitivity value at each retinal location (E-H) are shown for the pretreatment test with highest mean sensitivity (A and E) and the tests at weeks 12, 24, and 36. In heat maps, the arrows point to regions where the retinal sensitivity improved after the onset of treatment. A change from an arrow to an arrowhead indicates improvement had occurred, and any subsequent decline is noted by a change from arrowhead to arrow. The loci circled in yellow on the pretreatment fundus images (E) show loci at which sensitivity increased ≥ 6 dB after the onset of treatment. On subsequent fundus images, green circles indicate that sensitivity at that location was increased ≥ 6 dB from pretreatment and a change back to yellow indicates a decline below the 6 dB threshold. There was mild improvement during treatment that regressed after treatment.

Supplemental Figure 10



Supplemental Figure 10. Change in retinal sensitivity during treatment and post-treatment observation in the left eye of patient 4 of cohort 1.
The heat maps generated by the Macular Integrity Assessment Instrument software (A-D) and fundus images showing the sensitivity value at each retinal location (E-H) are shown for the pretreatment test with highest mean sensitivity (A and E) and the tests at weeks 12, 24, and 36. In heat maps, the arrows point to regions where the retinal sensitivity improved after the onset of treatment. A change from an arrow to an arrowhead indicates improvement had occurred, and any subsequent decline is noted by a change from arrowhead to arrow. The loci circled in yellow on the pretreatment fundus images (E) show loci at which sensitivity increased ≥ 6 dB after the onset of treatment. On subsequent fundus images, green circles indicate that sensitivity at that location was increased ≥ 6 dB from pretreatment and a change back to yellow indicates a decline below the 6 dB threshold. There were loci that improved and some that regressed during treatment.

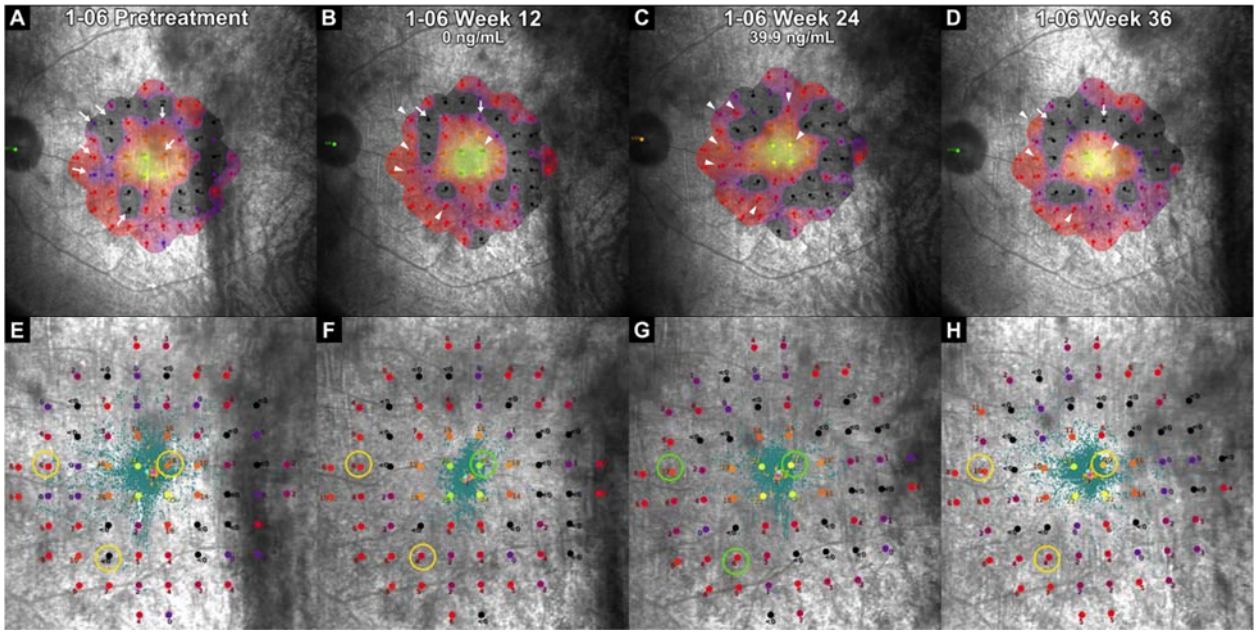
Supplemental Figure 11



Supplemental Figure 11. Change in retinal sensitivity during treatment and post-treatment observation in the right eye of patient 6 of cohort 1.

The heat maps generated by the Macular Integrity Assessment Instrument software (A-D) and fundus images showing the sensitivity value at each retinal location (E-H) are shown for the pretreatment test with highest mean sensitivity (A and E) and the tests at weeks 12, 24, and 36. In heat maps, the arrows point to regions where the retinal sensitivity improved after the onset of treatment. A change from an arrow to an arrowhead indicates improvement had occurred, and any subsequent decline is noted by a change from arrowhead to arrow. The loci circled in yellow on the pretreatment fundus images (E) show loci at which sensitivity increased ≥ 6 dB after the onset of treatment. On subsequent fundus images, green circles indicate that sensitivity at that location was increased ≥ 6 dB from pretreatment and a change back to yellow indicates a decline below the 6 dB threshold. There was moderate improvement in sensitivity during treatment that regressed after treatment, but remained better than baseline.

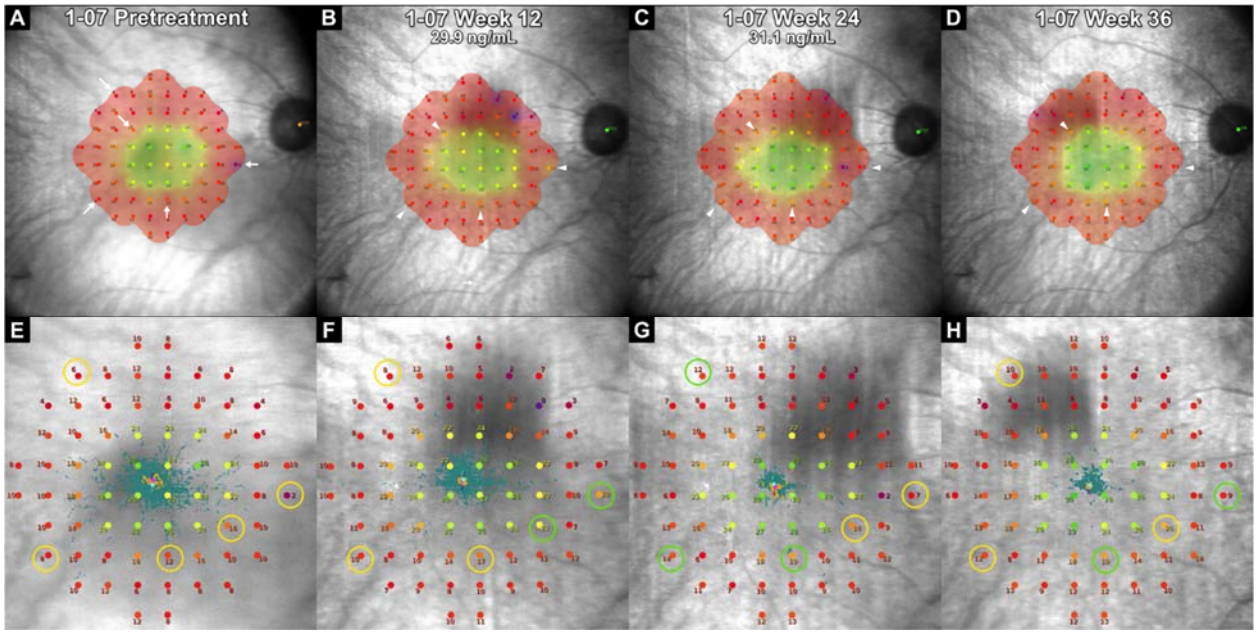
Supplemental Figure 12



Supplemental Figure 12. Change in retinal sensitivity during treatment and post-treatment observation in the left eye of patient 6 of cohort 1.

The heat maps generated by the Macular Integrity Assessment Instrument software (A-D) and fundus images showing the sensitivity value at each retinal location (E-H) are shown for the pretreatment test with highest mean sensitivity (A and E) and the tests at weeks 12, 24, and 36. In heat maps, the arrows point to regions where the retinal sensitivity improved after the onset of treatment. A change from an arrow to an arrowhead indicates improvement had occurred, and any subsequent decline is noted by a change from arrowhead to arrow. The loci circled in yellow on the pretreatment fundus images (E) show loci at which sensitivity increased ≥ 6 dB after the onset of treatment. On subsequent fundus images, green circles indicate that sensitivity at that location is increased ≥ 6 dB from pretreatment and a change back to yellow indicates a decline below the 6 dB threshold. There was mild improvement during treatment that regressed after treatment.

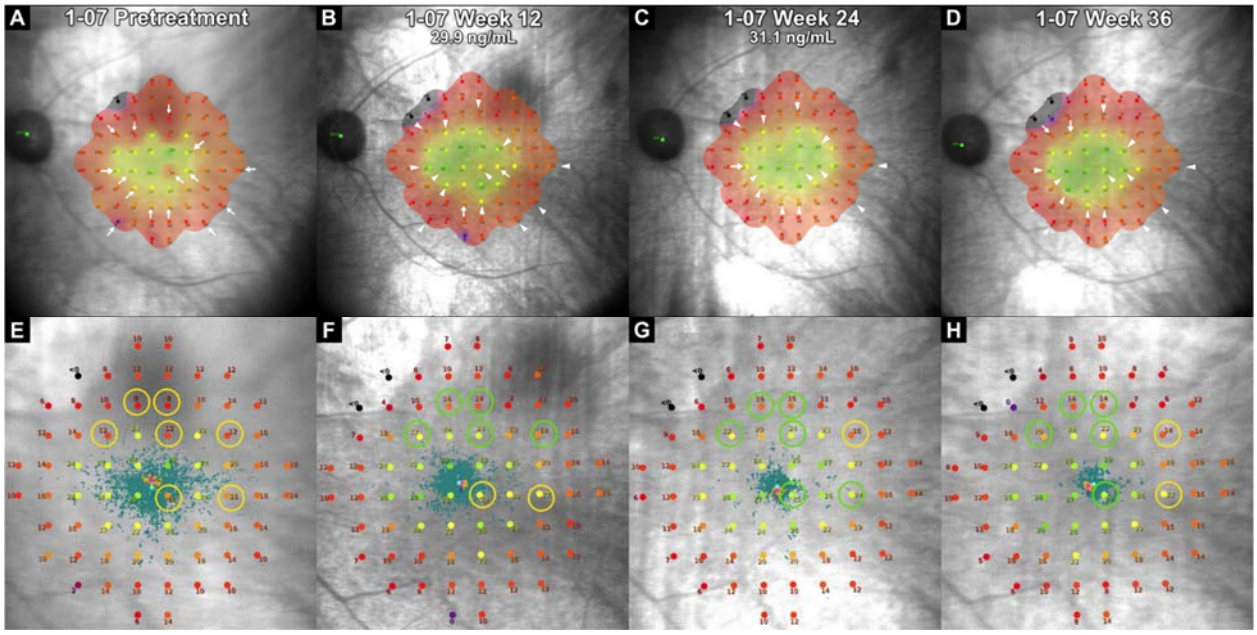
Supplemental Figure 13



Supplemental Figure 13. Change in retinal sensitivity during treatment and post-treatment observation in the right eye of patient 7 of cohort 1.

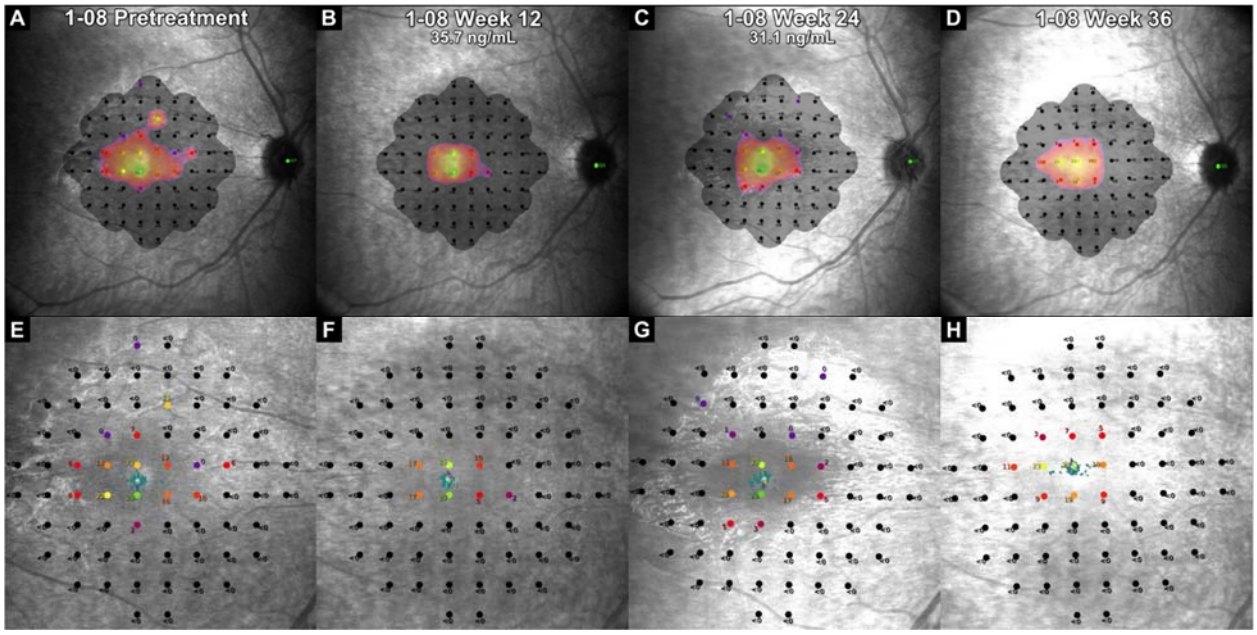
The heat maps generated by the Macular Integrity Assessment Instrument software (A-D) and fundus images showing the sensitivity value at each retinal location (E-H) are shown for the pretreatment test with highest mean sensitivity (A and E) and the tests at weeks 12, 24, and 36. In heat maps, the arrows point to regions where the retinal sensitivity improves after the onset of treatment. A change from an arrow to an arrowhead indicates improvement has occurred, and any subsequent decline is noted by a change from arrowhead to arrow. The loci circled in yellow on the pretreatment fundus images (E) show loci at which sensitivity increases ≥ 6 dB after the onset of treatment. On subsequent fundus images, green circles indicate that sensitivity at that location is increased ≥ 6 dB from pretreatment and a change back to yellow indicates a decline below the 6 dB threshold. There was moderate improvement during treatment that regressed after treatment cessation but remained better than baseline.

Supplemental Figure 14



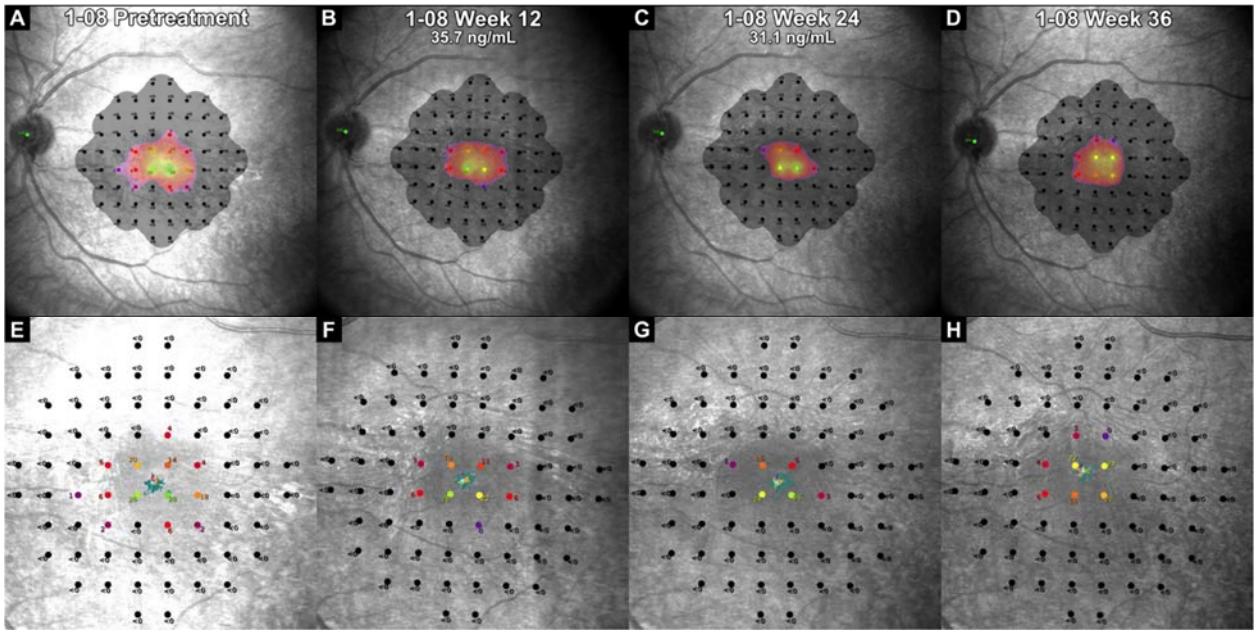
Supplemental Figure 14. Change in retinal sensitivity during treatment and post-treatment observation in the left eye of patient 7 of cohort 1.
The heat maps generated by the Macular Integrity Assessment Instrument software (A-D) and fundus images showing the sensitivity value at each retinal location (E-H) are shown for the pretreatment test with highest mean sensitivity (A and E) and the tests at weeks 12, 24, and 36. In heat maps, the arrows point to regions where the retinal sensitivity improved after the onset of treatment. A change from an arrow to an arrowhead indicates improvement had occurred, and any subsequent decline is noted by a change from arrowhead to arrow. The loci circled in yellow on the pretreatment fundus images (E) show loci at which sensitivity increased ≥ 6 dB after the onset of treatment. On subsequent fundus images, green circles indicate that sensitivity at that location was increased ≥ 6 dB from pretreatment and a change back to yellow indicates a decline below the 6 dB threshold. There was moderate improvement during treatment that regressed after treatment cessation, but remained better than baseline.

Supplemental Figure 15



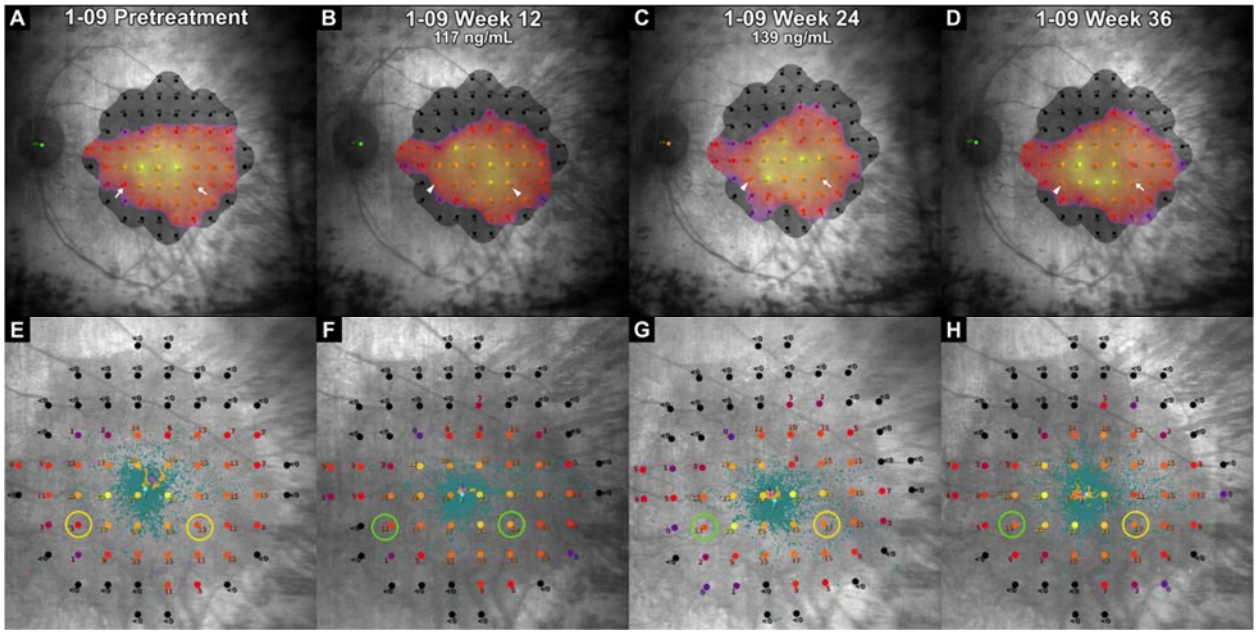
Supplemental Figure 15. Change in retinal sensitivity during treatment and post-treatment observation in the right eye of patient 8 of cohort 1.
The heat maps generated by the Macular Integrity Assessment Instrument software (A-D) and fundus images showing the sensitivity value at each retinal location (E-H) are shown for the pretreatment test with the highest mean sensitivity (A and E) and the tests at weeks 12, 24, and 36. There was severe loss of sensitivity at baseline that worsened during treatment.

Supplemental Figure 16



Supplemental Figure 16. Change in retinal sensitivity during treatment and post-treatment observation in the left eye of patient 8 of cohort 1.
The heat maps generated by the Macular Integrity Assessment Instrument software (A-D) and fundus images showing the sensitivity value at each retinal location (E-H) are shown for the pretreatment test with the highest mean sensitivity (A and E) and the tests at weeks 12, 24, and 36. There was severe loss of sensitivity at baseline that worsened during treatment.

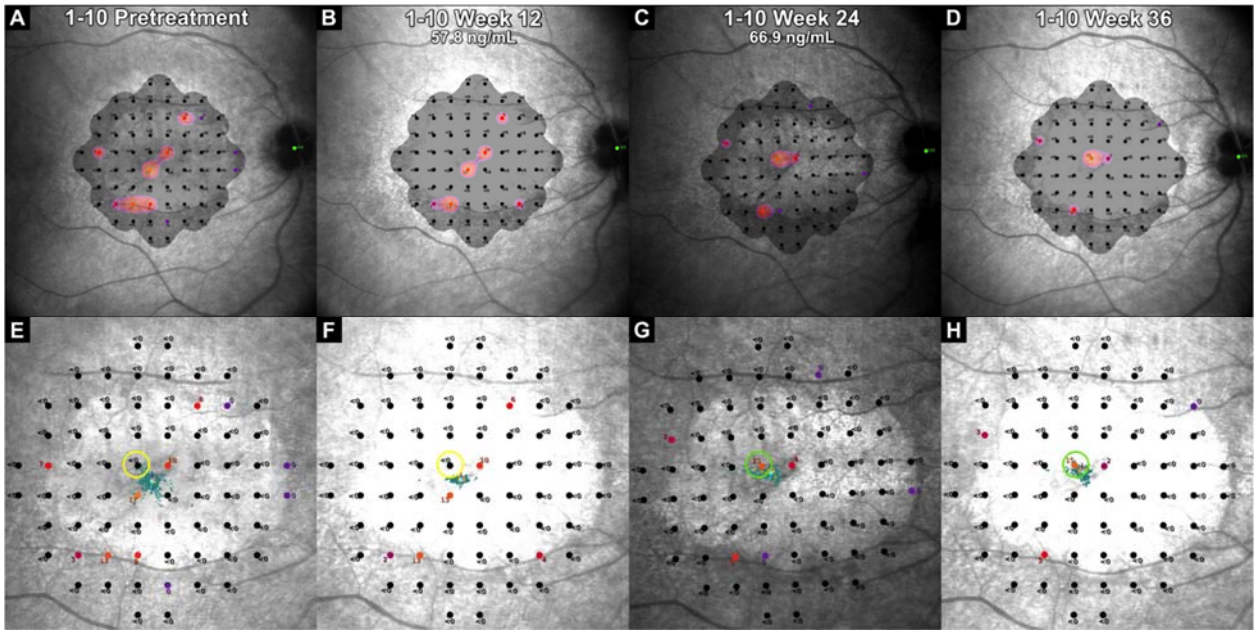
Supplemental Figure 17



Supplemental Figure 17. Change in retinal sensitivity during treatment and post-treatment observation in the left eye of patient 9 of cohort 1.
The heat maps generated by the Macular Integrity Assessment Instrument software (A-D) and fundus images showing the sensitivity value at each retinal location (E-H) are shown for the pretreatment test with highest mean sensitivity (A and E) and the tests at weeks 12, 24, and 36. In heat maps, the arrows point to regions where the retinal sensitivity improves after the onset of treatment. A change from an arrow to an arrowhead indicates improvement had occurred, and any subsequent decline is noted by a change from arrowhead to arrow. The loci circled in yellow on the pretreatment fundus images (E) show loci at which sensitivity increased ≥ 6 dB after the onset of treatment. On subsequent fundus images, green circles indicate that sensitivity at that location was increased ≥ 6 dB from pretreatment and a change back to yellow indicates a decline below the 6 dB threshold. A few loci improved and a few worsened during treatment.

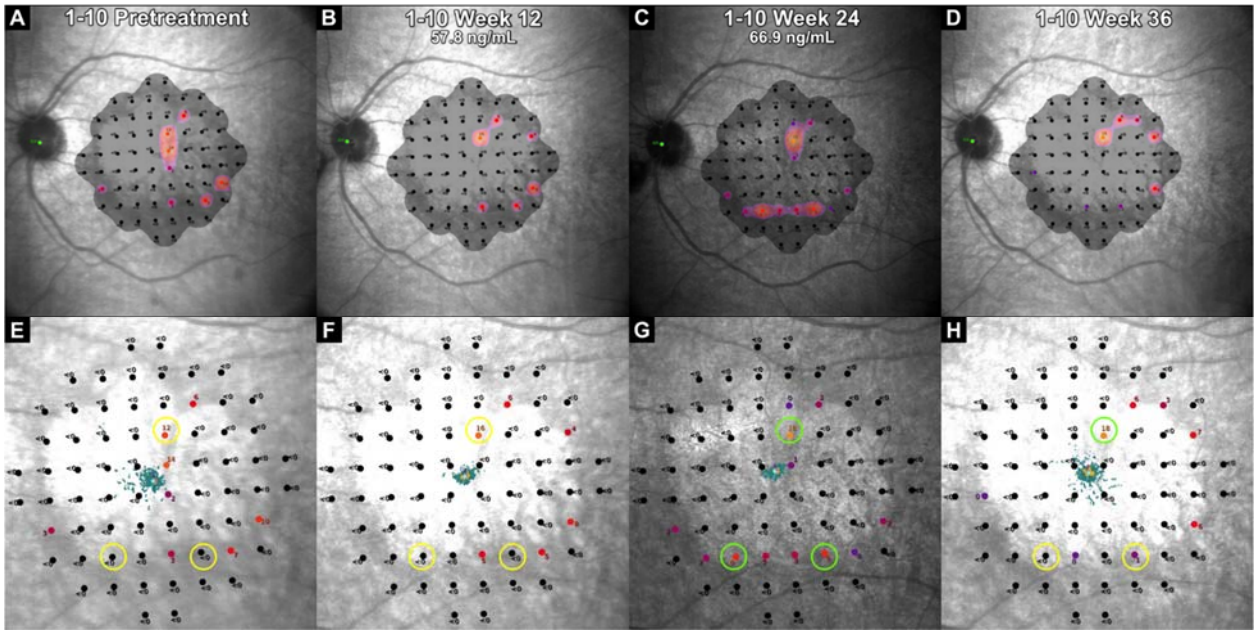
The RE for patient 9 is shown in Figure 6A-H.

Supplemental Figure 18



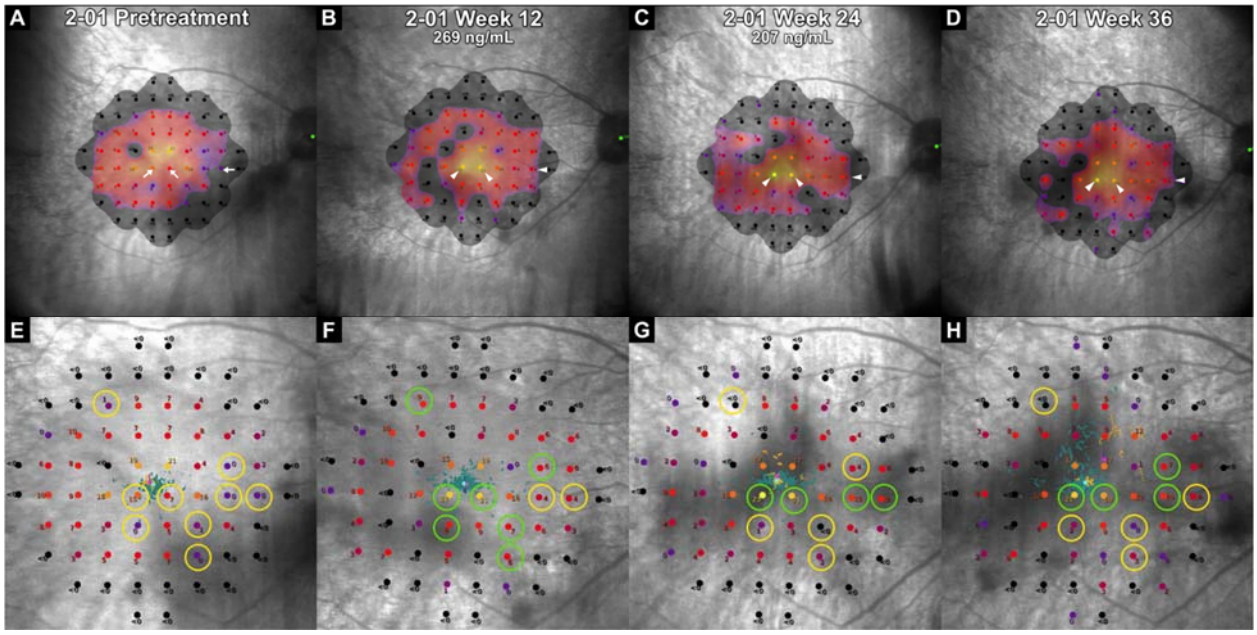
Supplemental Figure 18. Change in retinal sensitivity during treatment and post-treatment observation in the right eye of patient 10 of cohort 1.
The heat maps generated by the Macular Integrity Assessment Instrument software (A-D) and fundus images showing the sensitivity value at each retinal location (E-H) are shown for the pretreatment test with highest mean sensitivity (A and E) and the tests at weeks 12, 24, and 36. The locus circled in yellow on the pretreatment fundus images (E) has a sensitivity increased ≥ 6 dB after the onset of treatment. On subsequent fundus images, a green circle indicates that sensitivity at that location had increased ≥ 6 dB from pretreatment and a change back to yellow indicates a decline below the 6 dB threshold. There was advanced loss of sensitivity with little change during treatment.

Supplemental Figure 19



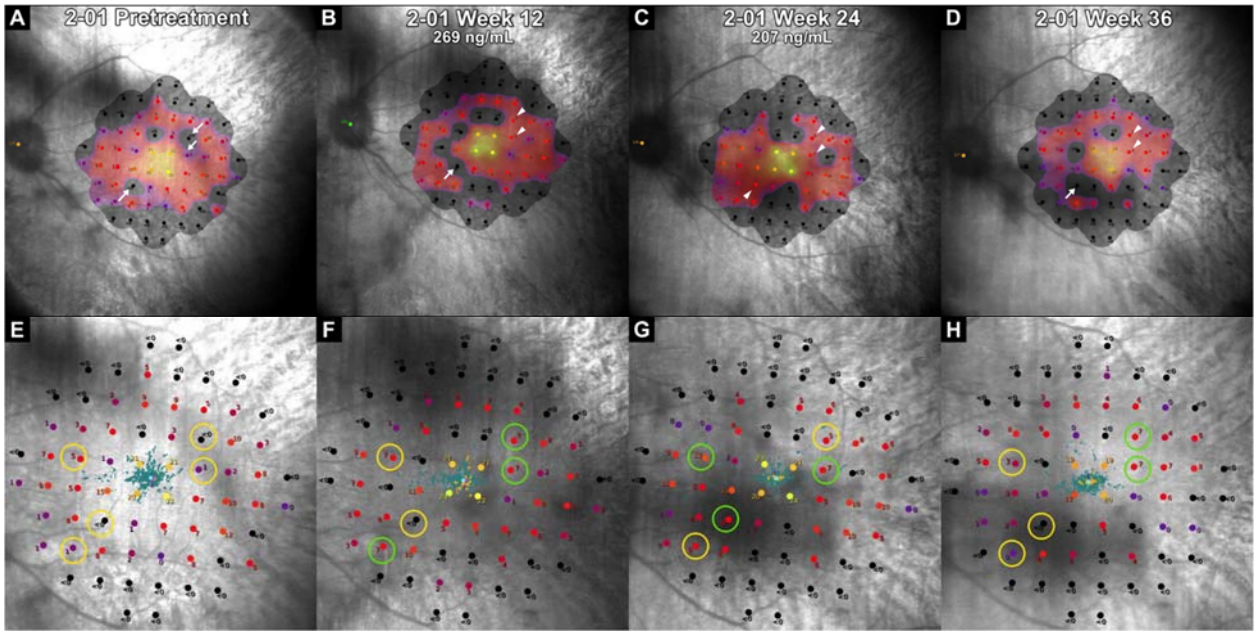
Supplemental Figure 19. Change in retinal sensitivity during treatment and post-treatment observation in the left eye of patient 10 of cohort 1.
The heat maps generated by the Macular Integrity Assessment Instrument software (A-D) and fundus images showing the sensitivity value at each retinal location (E-H) are shown for the pretreatment test with highest mean sensitivity (A and E) and the tests at weeks 12, 24, and 36. The loci circled in yellow on the pretreatment fundus images (E) show loci at which sensitivity increased ≥ 6 dB after the onset of treatment. On subsequent fundus images, green circles indicate that sensitivity at that location is increased ≥ 6 dB from pretreatment and a change back to yellow indicates a decline below the 6 dB threshold. Despite severe loss of sensitivity at baseline there was mild improvement 24 weeks after starting treatment.

Supplemental Figure 20



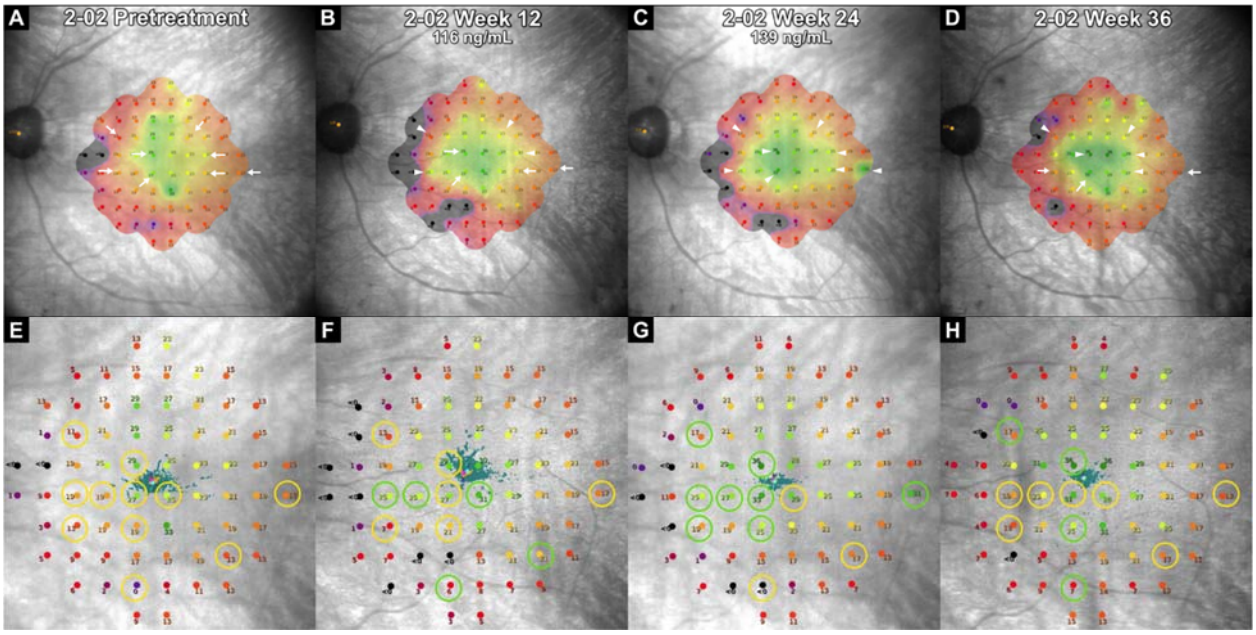
Supplemental Figure 20. Change in retinal sensitivity during treatment and post-treatment observation in the right eye of patient 1 of cohort 2.
The heat maps generated by the Macular Integrity Assessment Instrument software (A-D) and fundus images showing the sensitivity value at each retinal location (E-H) are shown for the pretreatment test with highest mean sensitivity (A and E) and the tests at weeks 12, 24, and 36. In heat maps, the arrows point to regions where the retinal sensitivity improved after the onset of treatment. A change from an arrow to an arrowhead indicates improvement had occurred, and any subsequent decline is noted by a change from arrowhead to arrow. The loci circled in yellow on the pretreatment fundus images (E) show loci at which sensitivity increased ≥ 6 dB after the onset of treatment. On subsequent fundus images, green circles indicate that sensitivity at that location is increased ≥ 6 dB from pretreatment and a change back to yellow indicates a decline below the 6 dB threshold. There was moderate improvement during treatment that was partially sustained after treatment.

Supplemental Figure 21



Supplemental Figure 21. Change in retinal sensitivity during treatment and post-treatment observation in the left eye of patient 1 of cohort 2.
The heat maps generated by the Macular Integrity Assessment Instrument software (A-D) and fundus images showing the sensitivity value at each retinal location (E-H) are shown for the pretreatment test with highest mean sensitivity (A and E) and the tests at weeks 12, 24, and 36. In heat maps, the arrows point to regions where the retinal sensitivity improved after the onset of treatment. A change from an arrow to an arrowhead indicates improvement had occurred, and any subsequent decline is noted by a change from arrowhead to arrow. The loci circled in yellow on the pretreatment fundus images (E) show loci at which sensitivity increased ≥ 6 dB after the onset of treatment. On subsequent fundus images, green circles indicate that sensitivity at that location is increased ≥ 6 dB from pretreatment and a change back to yellow indicates a decline below the 6 dB threshold. There was mild improvement during treatment that was partially sustained after treatment.

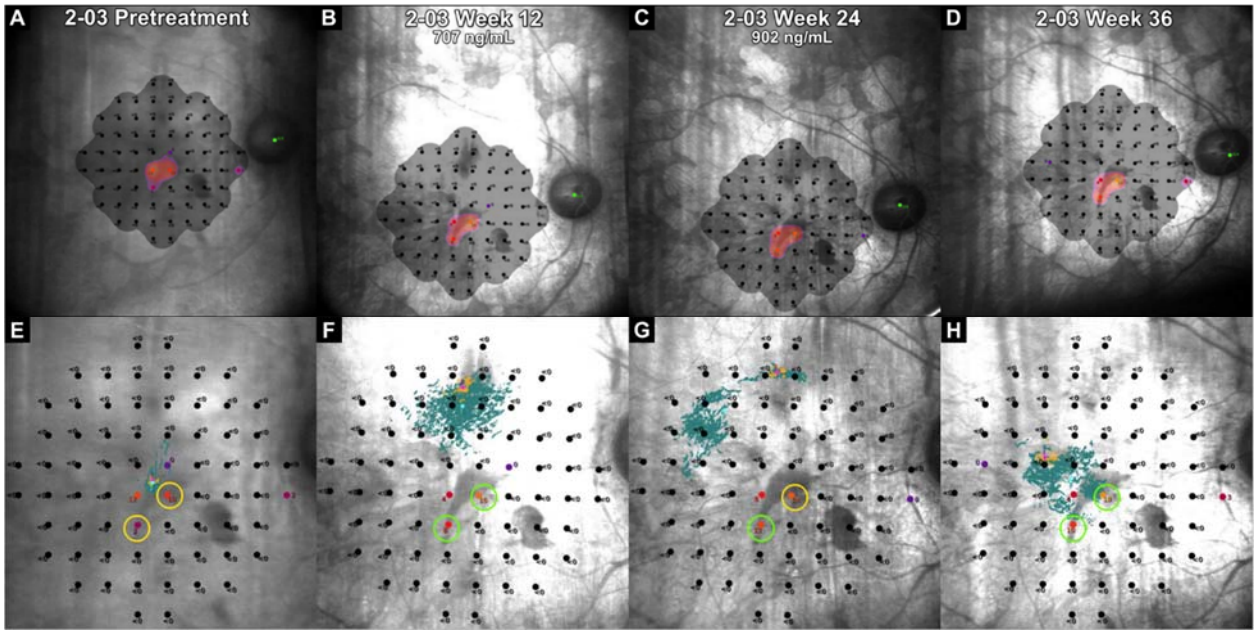
Supplemental Figure 22



Supplemental Figure 22. Change in retinal sensitivity during treatment and post-treatment observation in the left eye of patient 2 of cohort 2.
The heat maps generated by the Macular Integrity Assessment Instrument software (A-D) and fundus images showing the sensitivity value at each retinal location (E-H) are shown for the pretreatment test with highest mean sensitivity (A and E) and the tests at weeks 12, 24, and 36. In heat maps, the arrows point to regions where the retinal sensitivity improved after the onset of treatment. A change from an arrow to an arrowhead indicates improvement had occurred, and any subsequent decline is noted by a change from arrowhead to arrow. The loci circled in yellow on the pretreatment fundus images (E) show loci at which sensitivity increased ≥ 6 dB after the onset of treatment. On subsequent fundus images, green circles indicate that sensitivity at that location is increased ≥ 6 dB from pretreatment and a change back to yellow indicates a decline below the 6 dB threshold. There was a large improvement during treatment that regressed 3 months after treatment ended but remained better than baseline.

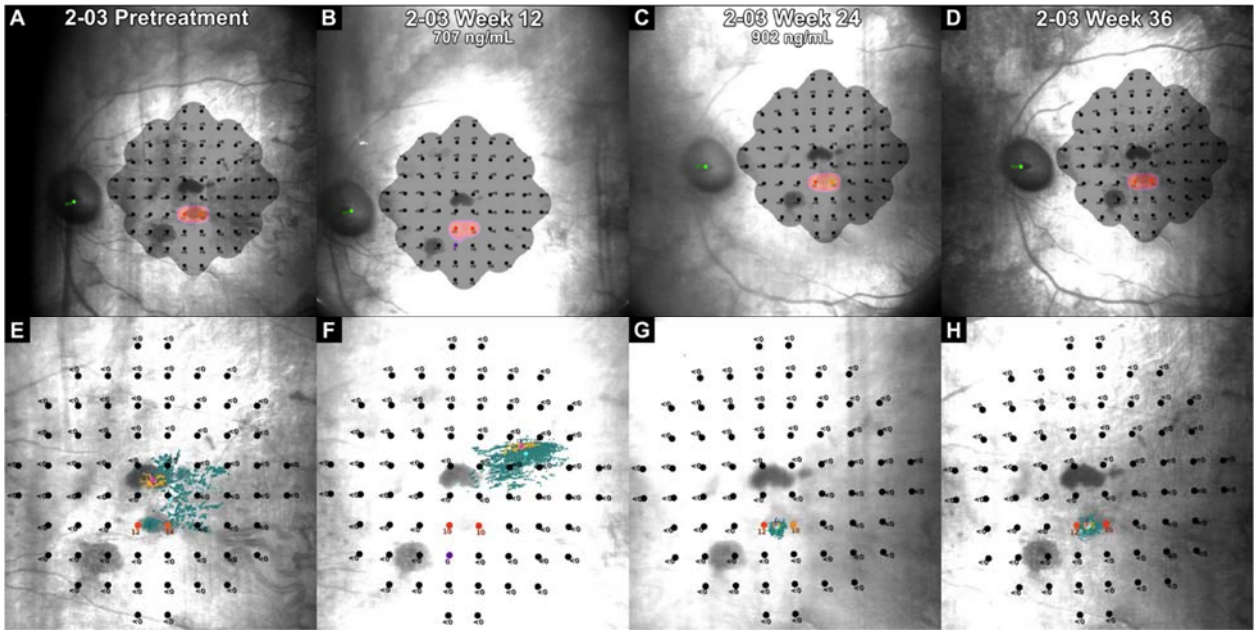
Right eye of patient 2-02 was ineligible due to a central retinal vein occlusion.

Supplemental Figure 23



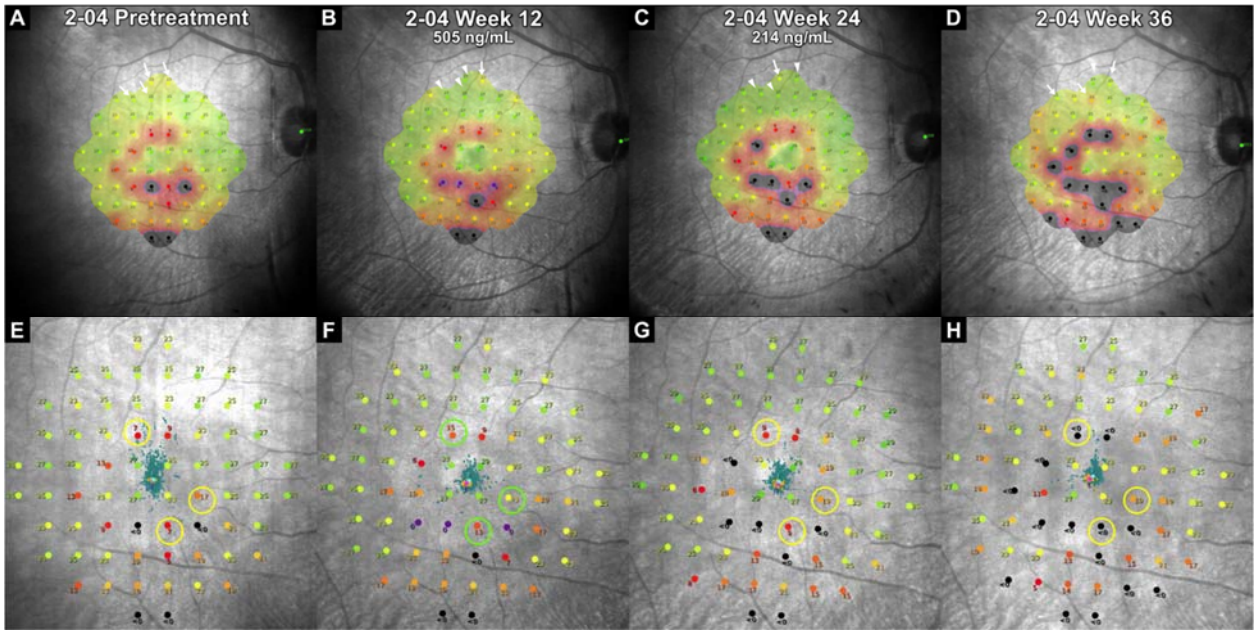
Supplemental Figure 23. Change in retinal sensitivity during treatment and post-treatment observation in the right eye of patient 3 of cohort 2.
The heat maps generated by the Macular Integrity Assessment Instrument software (A-D) and fundus images containing the sensitivity value at each retinal location (E-H) are shown for the pretreatment test with highest mean sensitivity (A and E) and the tests at weeks 12, 24, and 36. The loci circled in yellow on the pretreatment fundus images (E) show loci at which sensitivity increased ≥ 6 dB after the onset of treatment. On subsequent fundus images, green circles indicate that sensitivity at that location is increased ≥ 6 dB from pretreatment and a change back to yellow indicates a decline below the 6 dB threshold. There was severe loss of sensitivity with only a small central region remaining at baseline, but there were two loci that showed improvement ≥ 6 dB.

Supplemental Figure 24



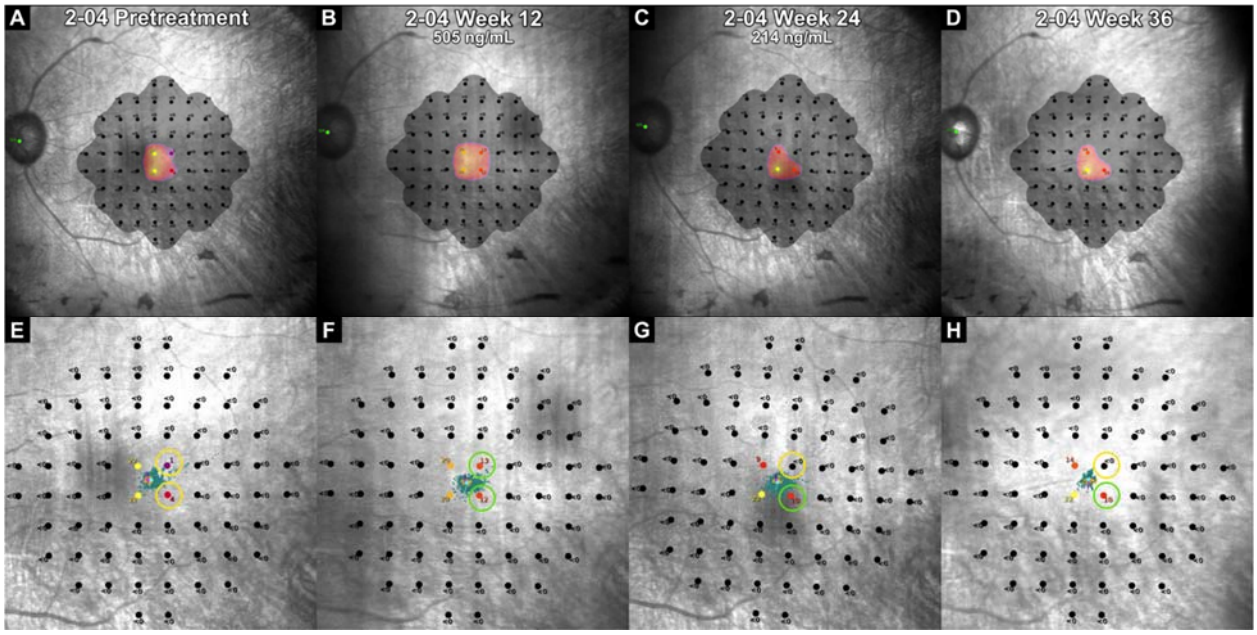
Supplemental Figure 24. Change in retinal sensitivity during treatment and post-treatment observation in the left eye of patient 3 of cohort 2.
The heat maps generated by the Macular Integrity Assessment Instrument software (A-D) and fundus images showing the sensitivity value at each retinal location (E-H) are shown for the pretreatment test with highest mean sensitivity (A and E) and the tests at weeks 12, 24, and 36. There was severe loss of sensitivity with only a small central area remaining at baseline that did not change during treatment.

Supplemental Figure 25



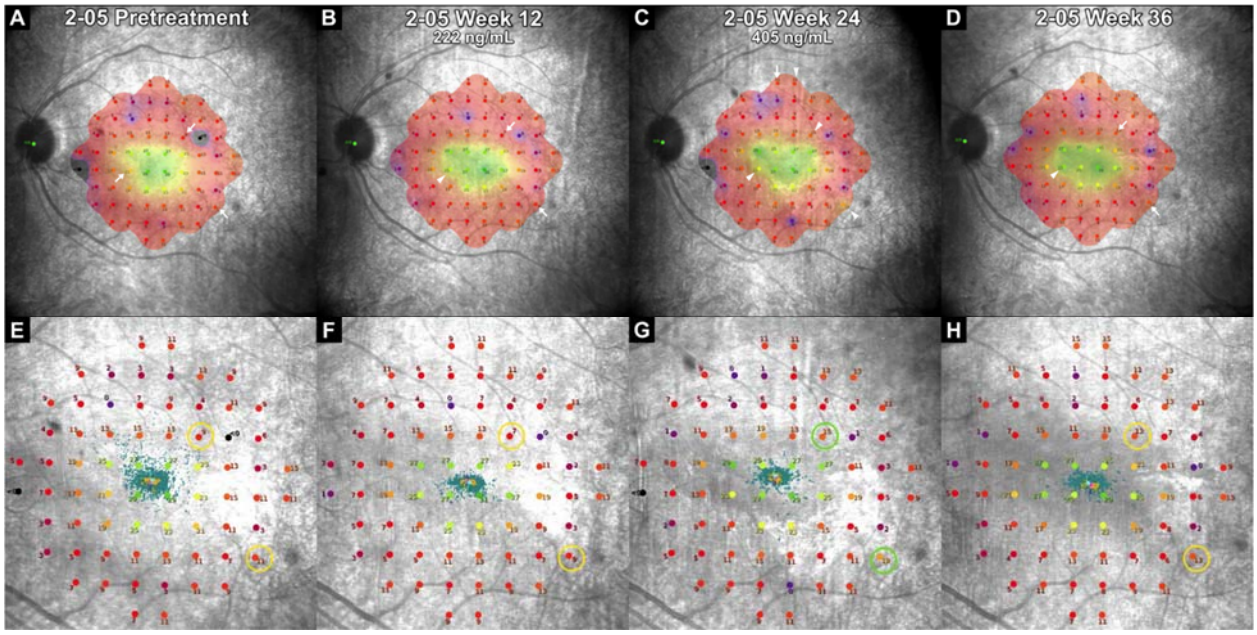
Supplemental Figure 25. Change in retinal sensitivity during treatment and post-treatment observation in the right eye of patient 4 of cohort 2.
The heat maps generated by the Macular Integrity Assessment Instrument software (A-D) and fundus images showing the sensitivity value at each retinal location (E-H) are shown for the pretreatment test with highest mean sensitivity (A and E) and the tests at weeks 12, 24, and 36. In heat maps, the arrows point to regions where the retinal sensitivity improved after the onset of treatment. A change from an arrow to an arrowhead indicates improvement had occurred, and any subsequent decline is noted by a change from arrowhead to arrow. The loci circled in yellow on the pretreatment fundus images (E) show loci at which sensitivity increased ≥ 6 dB after the onset of treatment. On subsequent fundus images, green circles indicate that sensitivity at that location is increased ≥ 6 dB from pretreatment and a change back to yellow indicates a decline below the 6 dB threshold. There was some improvement at week 12 which regressed by week 24 and then worsened after cessation of treatment.

Supplemental Figure 26



Supplemental Figure 26. Change in retinal sensitivity during treatment and post-treatment observation in left eye of patient 4 of cohort 2.
The heat maps generated by the Macular Integrity Assessment Instrument software (A-D) and fundus images showing the sensitivity value at each retinal location (E-H) are shown for the pretreatment test with highest mean sensitivity (A and E) and the tests at weeks 12, 24, and 36. There was severe loss of sensitivity at baseline with only a small central area remaining, but there is some slight expansion temporally after initiation of treatment. The loci circled in yellow on the pretreatment fundus images (E) show loci at which sensitivity increases ≥ 6 dB after the onset of treatment. On subsequent fundus images, green circles indicate that sensitivity at that location is increased ≥ 6 dB from pretreatment and a change back to yellow indicates a decline below the 6 dB threshold. There were two loci that showed some improvement but overall little change.

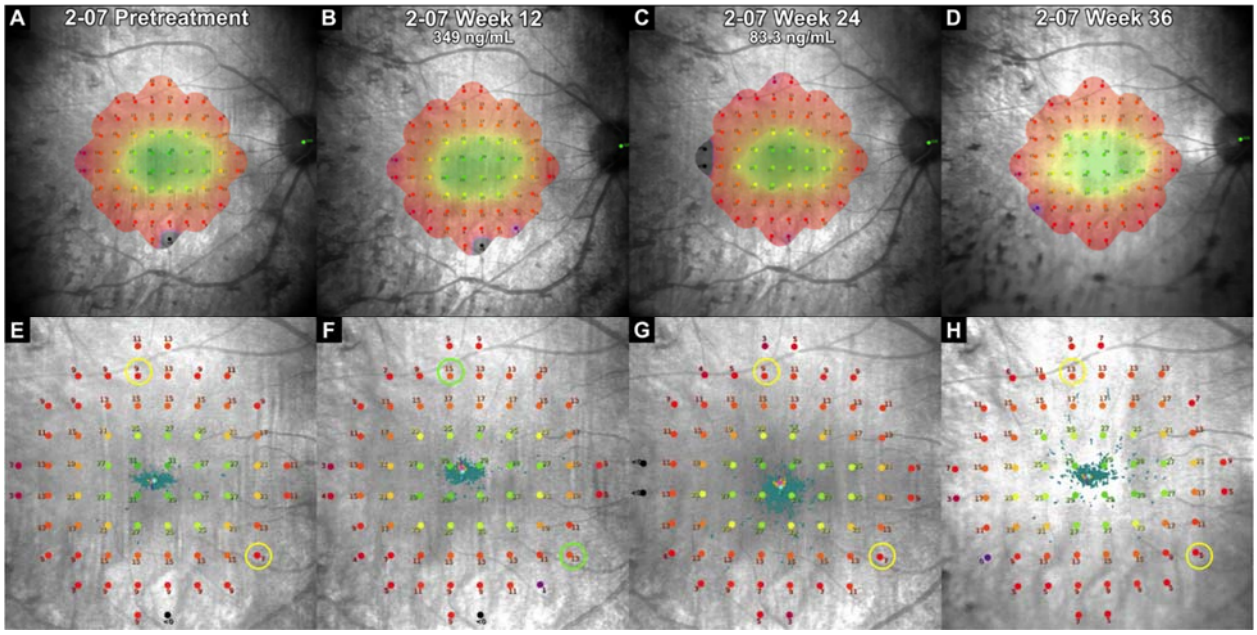
Supplemental Figure 27



Supplemental Figure 27. Change in retinal sensitivity during treatment and post-treatment observation in the left eye of patient 5 of cohort 2.
The heat maps generated by the Macular Integrity Assessment Instrument software (A-D) and fundus images showing the sensitivity value at each retinal location (E-H) are shown for the pretreatment test with highest mean sensitivity (A and E) and the tests at weeks 12, 24, and 36. In heat maps, the arrows point to regions where the retinal sensitivity improved after the onset of treatment. A change from an arrow to an arrowhead indicates improvement had occurred, and any subsequent decline is noted by a change from arrowhead to arrow. The loci circled in yellow on the pretreatment fundus images (E) show loci at which sensitivity increased ≥ 6 dB after the onset of treatment. On subsequent fundus images, green circles indicate that sensitivity at that location was increased ≥ 6 dB from pretreatment and a change back to yellow indicates a decline below the 6 dB threshold. There was mild improvement during treatment with regression after stopping treatment.

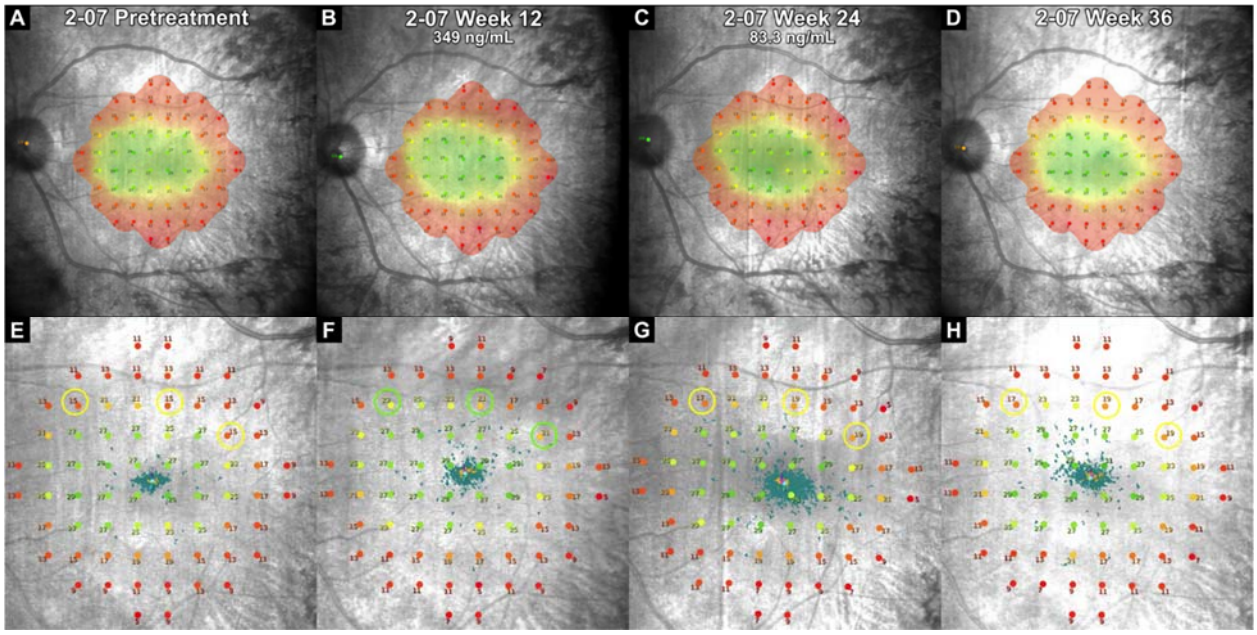
Right eye of patient 2-05 is shown in Figure 6I-P.

Supplemental Figure 28



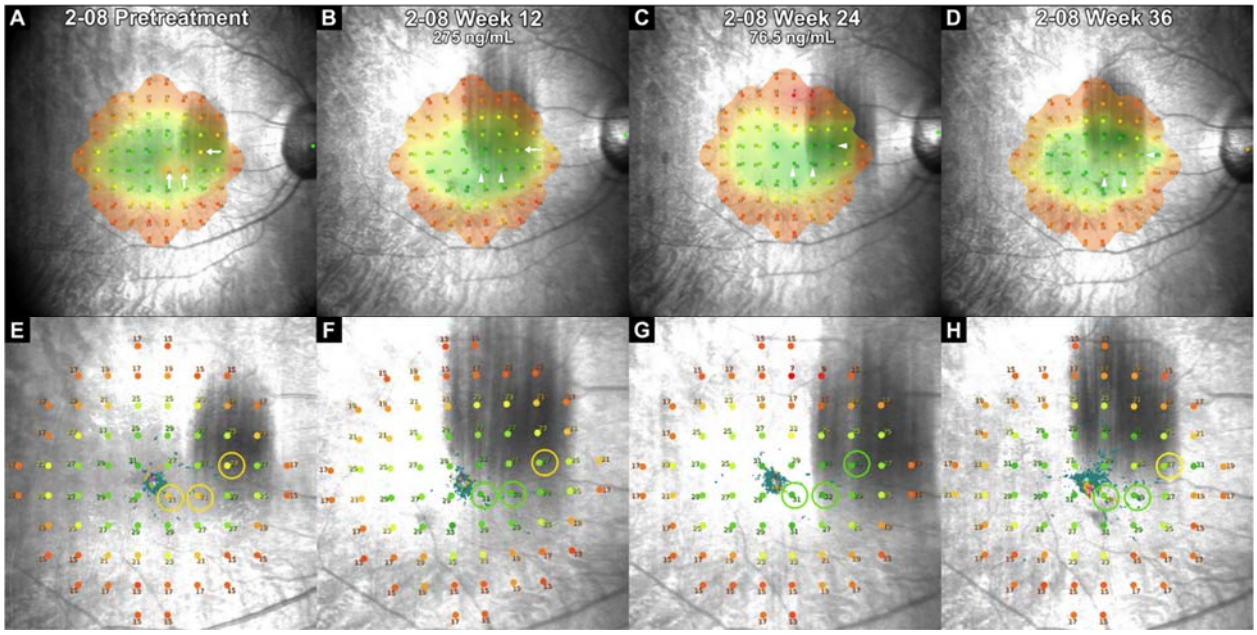
Supplemental Figure 28. Change in retinal sensitivity during treatment and post-treatment observation in the right eye of patient 7 of cohort 2.
The heat maps generated by the Macular Integrity Assessment Instrument software (A-D) and fundus images showing the sensitivity value at each retinal location (E-H) are shown for the pretreatment test with highest mean sensitivity (A and E) and the tests at weeks 12, 24, and 36. The locus circled in yellow on the pretreatment fundus images (E) show loci at which sensitivity increased ≥ 6 dB after the onset of treatment. On subsequent fundus images, green circles indicate that sensitivity at that location was increased ≥ 6 dB from pretreatment and a change back to yellow indicates a decline below the 6 dB threshold. There was good sensitivity at baseline with little change during treatment.

Supplemental Figure 29



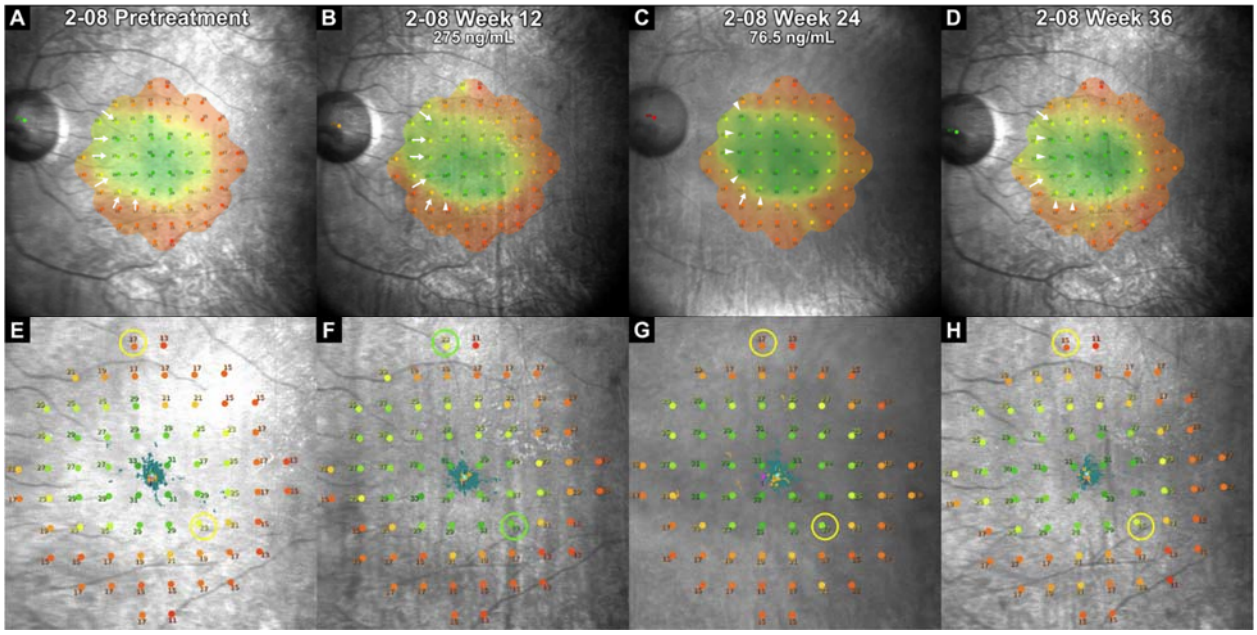
Supplemental Figure 29. Change in retinal sensitivity during treatment and post-treatment observation in left eye of patient 7 of cohort 2.
The heat maps generated by the Macular Integrity Assessment Instrument software (A-D) and fundus images showing the sensitivity value at each retinal location (E-H) are shown for the pretreatment test with highest mean sensitivity (A and E) and the tests at weeks 12, 24, and 36. The loci circled in yellow on the pretreatment fundus images (E) show loci at which sensitivity increased ≥ 6 dB after the onset of treatment. On subsequent fundus images, green circles indicate that sensitivity at that location was increased ≥ 6 dB from pretreatment and a change back to yellow indicates a decline below the 6 dB threshold. There was good sensitivity at baseline with little change during treatment.

Supplemental Figure 30



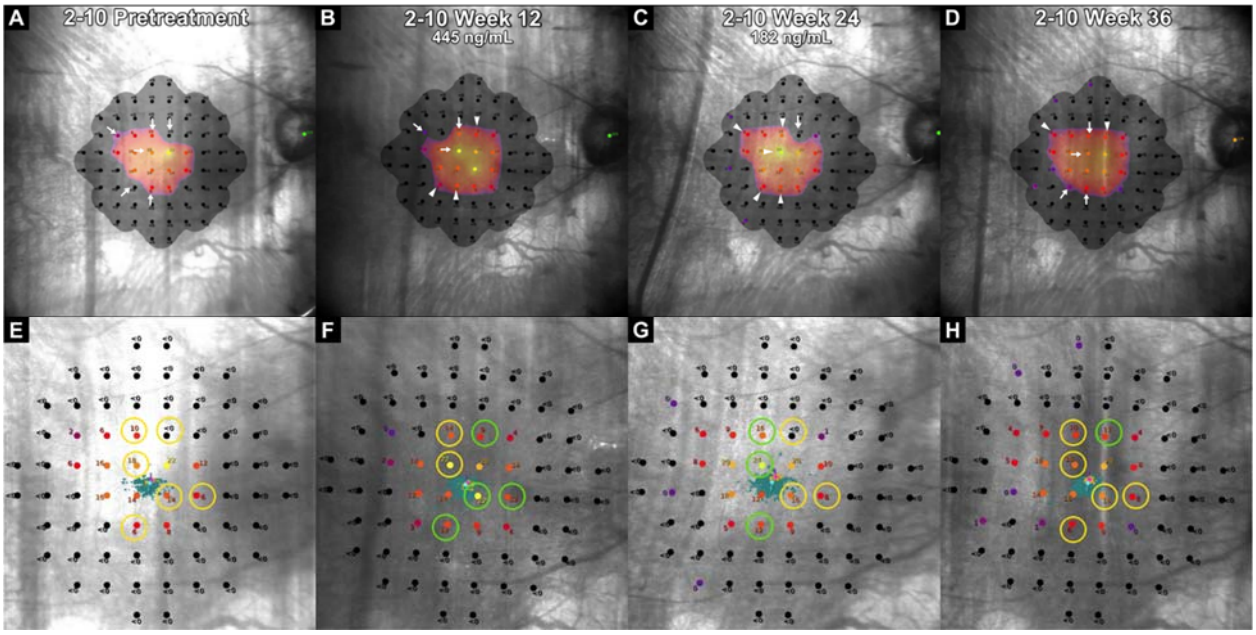
Supplemental Figure 30. Change in retinal sensitivity during treatment and post-treatment observation in the right eye of patient 8 of cohort 2.
The heat maps generated by the Macular Integrity Assessment Instrument software (A-D) and fundus images showing the sensitivity value at each retinal location (E-H) are shown for the pretreatment test with highest mean sensitivity (A and E) and the tests at weeks 12, 24, and 36. In heat maps, the arrows point to regions where the retinal sensitivity improved after the onset of treatment. A change from an arrow to an arrowhead indicates improvement had occurred, and any subsequent decline is noted by a change from arrowhead to arrow. The loci circled in yellow on the pretreatment fundus images (E) show loci at which sensitivity increased ≥ 6 dB after the onset of treatment. On subsequent fundus images, green circles indicate that sensitivity at that location was increased ≥ 6 dB from pretreatment and a change back to yellow indicates a decline below the 6 dB threshold. There was good sensitivity at baseline with mild improvement during treatment partially sustained after treatment.

Supplemental Figure 31



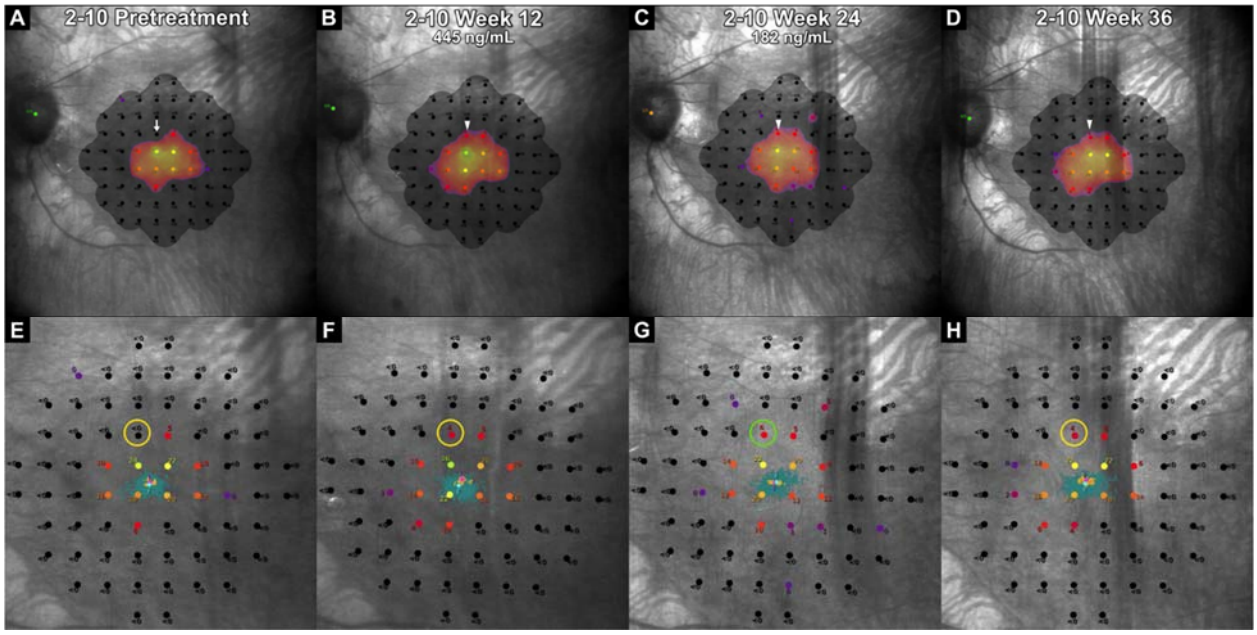
Supplemental Figure 31. Change in retinal sensitivity during treatment and post-treatment observation in the left eye of patient 8 of cohort 2.
The heat maps generated by the Macular Integrity Assessment Instrument software (A-D) and fundus images showing the sensitivity value at each retinal location (E-H) are shown for the pretreatment test with highest mean sensitivity (A and E) and the tests at weeks 12, 24, and 36. In heat maps, the arrows point to regions where the retinal sensitivity improves after the onset of treatment. A change from an arrow to an arrowhead indicates improvement has occurred, and any subsequent decline is noted by a change from arrowhead to arrow. The loci circled in yellow on the pretreatment fundus images (E) show loci at which sensitivity increased ≥ 6 dB after the onset of treatment. On subsequent fundus images, green circles indicate that sensitivity at that location was increased ≥ 6 dB from pretreatment and a change back to yellow indicates a decline below the 6 dB threshold. There was good sensitivity at baseline with mild improvement during treatment partially sustained after treatment.

Supplemental Figure 32



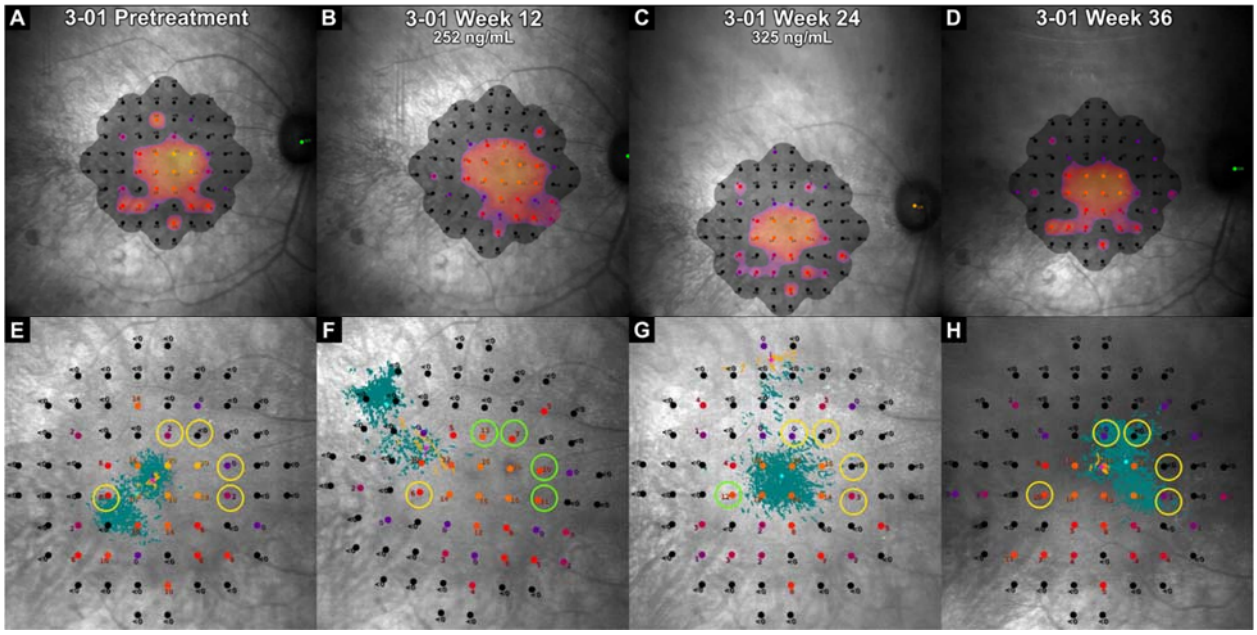
Supplemental Figure 32. Change in retinal sensitivity during treatment and post-treatment observation in the right eye of patient 10 of cohort 2.
The heat maps generated by the Macular Integrity Assessment Instrument software (A-D) and fundus images showing the sensitivity value at each retinal location (E-H) are shown for the pretreatment test with highest mean sensitivity (A and E) and the tests at weeks 12, 24, and 36. In heat maps, the arrows point to regions where the retinal sensitivity improved after the onset of treatment. A change from an arrow to an arrowhead indicates improvement had occurred, and any subsequent decline is noted by a change from arrowhead to arrow. The loci circled in yellow on the pretreatment fundus images (E) show loci at which sensitivity increased ≥ 6 dB after the onset of treatment. On subsequent fundus images, green circles indicate that sensitivity at that location was increased ≥ 6 dB from pretreatment and a change back to yellow indicates a decline below the 6 dB threshold. There was moderate improvement during treatment that regressed after treatment but was still better than baseline 3 months after stopping treatment.

Supplemental Figure 33



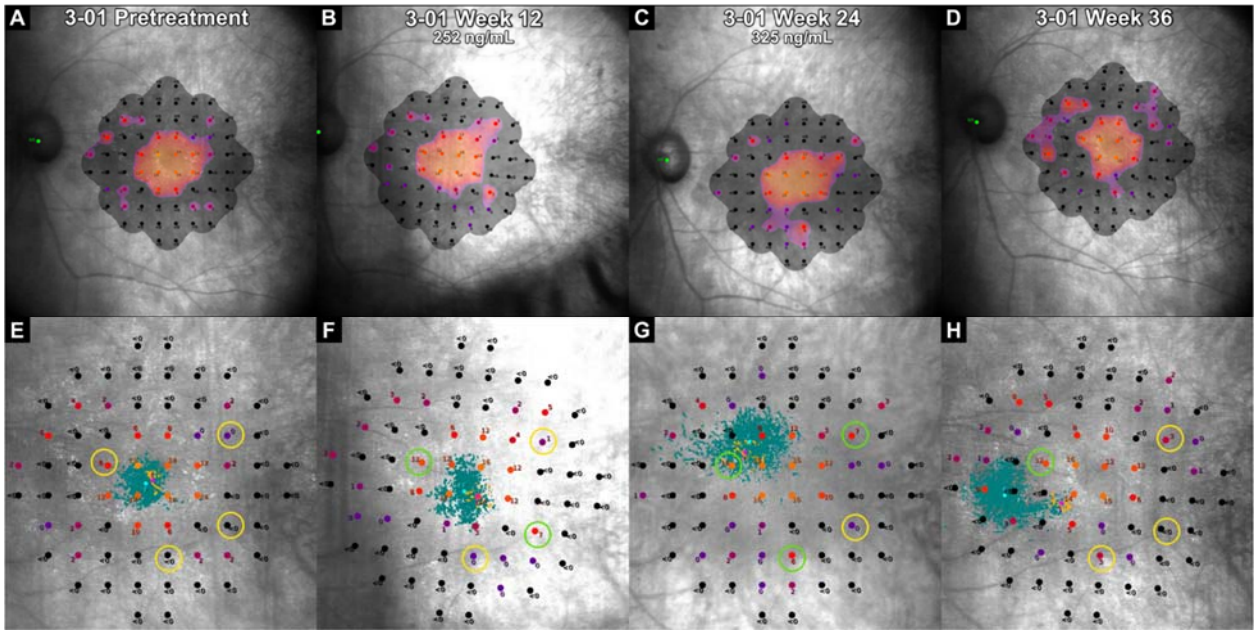
Supplemental Figure 33. Change in retinal sensitivity during treatment and post-treatment observation in the left eye of patient 10 of cohort 2.
The heat maps generated by the Macular Integrity Assessment Instrument software (A-D) and fundus images showing the sensitivity value at each retinal location (E-H) are shown for the pretreatment test with highest mean sensitivity (A and E) and the tests at weeks 12, 24, and 36. In heat maps, the arrows point to regions where the retinal sensitivity improved after the onset of treatment. A change from an arrow to an arrowhead indicates improvement had occurred, and any subsequent decline is noted by a change from arrowhead to arrow. The loci circled in yellow on the pretreatment fundus images (E) show loci at which sensitivity increased ≥ 6 dB after the onset of treatment. On subsequent fundus images, green circles indicate that sensitivity at that location was increased ≥ 6 dB from pretreatment and a change back to yellow indicates a decline below the 6 dB threshold. There was severe loss of sensitivity at baseline with minimal change during treatment.

Supplemental Figure 34



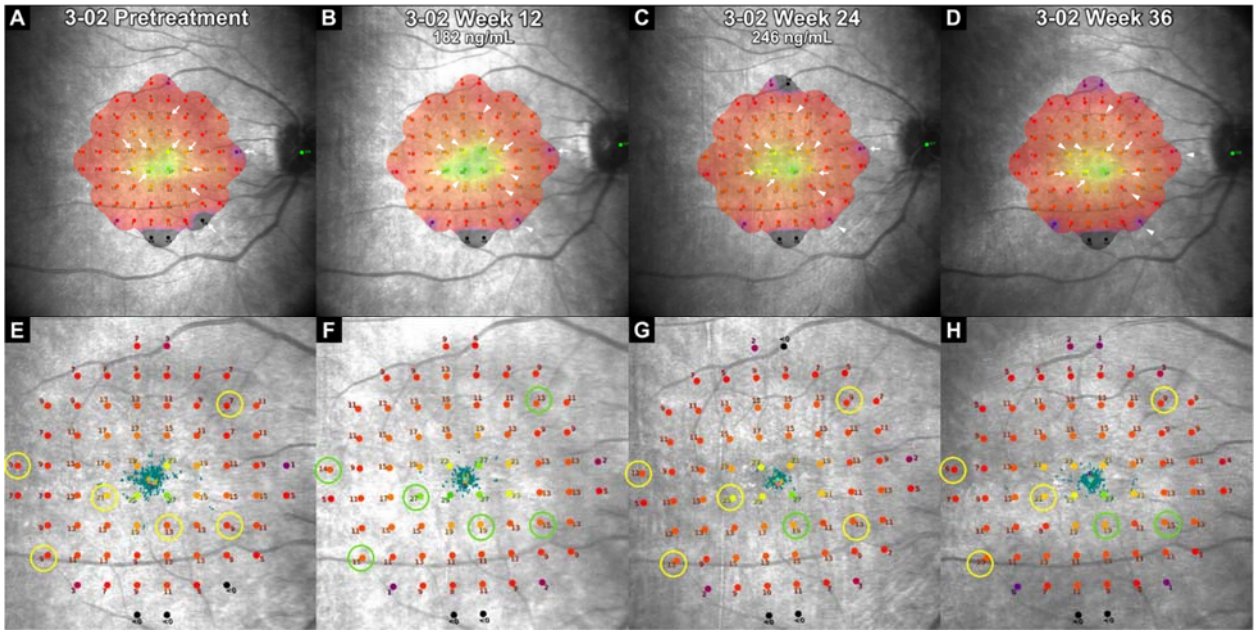
Supplemental Figure 34. Change in retinal sensitivity during treatment and post-treatment observation in the right eye of patient 1 of cohort 3.
The heat maps generated by the Macular Integrity Assessment Instrument software (A-D) and fundus images showing the sensitivity value at each retinal location (E-H) are shown for the pretreatment test with highest mean sensitivity (A and E) and the tests at weeks 12, 24, and 36. The loci circled in yellow on the pretreatment fundus images (E) show loci at which sensitivity increased ≥ 6 dB after the onset of treatment. On subsequent fundus images, green circles indicate that sensitivity at that location was increased ≥ 6 dB from pretreatment and a change back to yellow indicates a decline below the 6 dB threshold. There was significant sensitivity loss, but some improvement at week 12 with regression thereafter.

Supplemental Figure 35



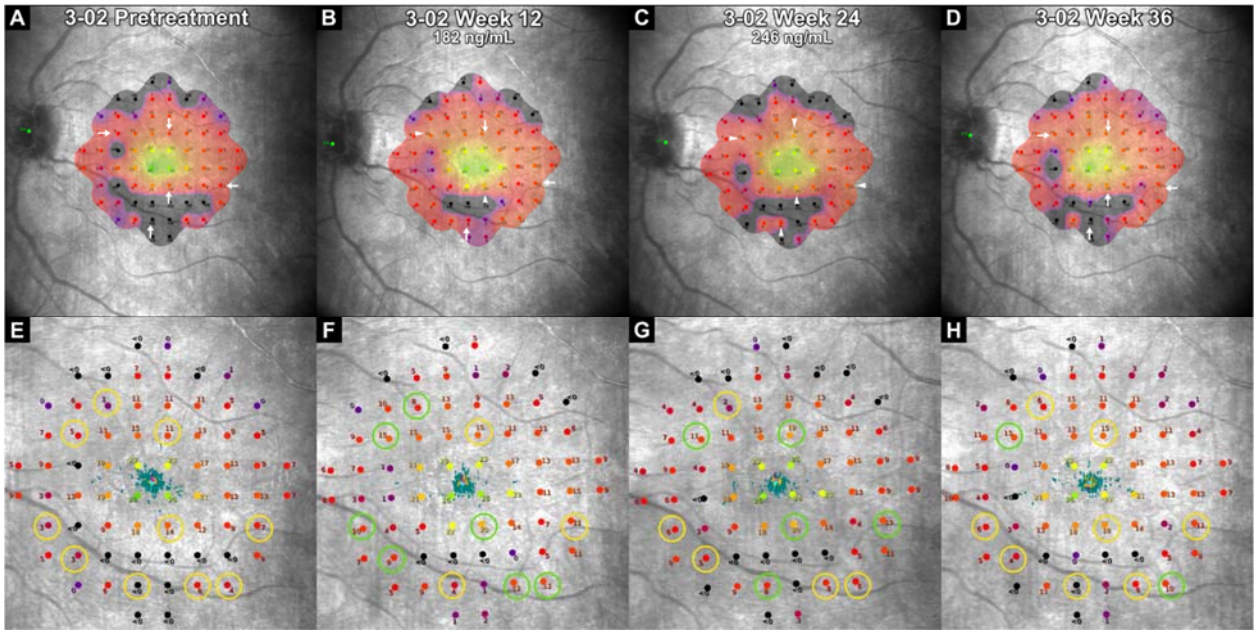
Supplemental Figure 35. Change in retinal sensitivity during treatment and post-treatment observation in the left eye of patient 1 of cohort 3.
The heat maps generated by the Macular Integrity Assessment Instrument software (A-D) and fundus images showing the sensitivity value at each retinal location (E-H) are shown for the pretreatment test with highest mean sensitivity (A and E) and the tests at weeks 12, 24, and 36. In heat maps, the arrows point to regions where the retinal sensitivity improved after the onset of treatment. A change from an arrow to an arrowhead indicates improvement had occurred, and any subsequent decline was noted by a change from arrowhead to arrow. The loci circled in yellow on the pretreatment fundus images (E) show loci at which sensitivity increased ≥ 6 dB after the onset of treatment. On subsequent fundus images, green circles indicate that sensitivity at that location was increased ≥ 6 dB from pretreatment and a change back to yellow indicates a decline below the 6 dB threshold. There was mild improvement during treatment that regressed after treatment cessation, but remained better than baseline.

Supplemental Figure 36



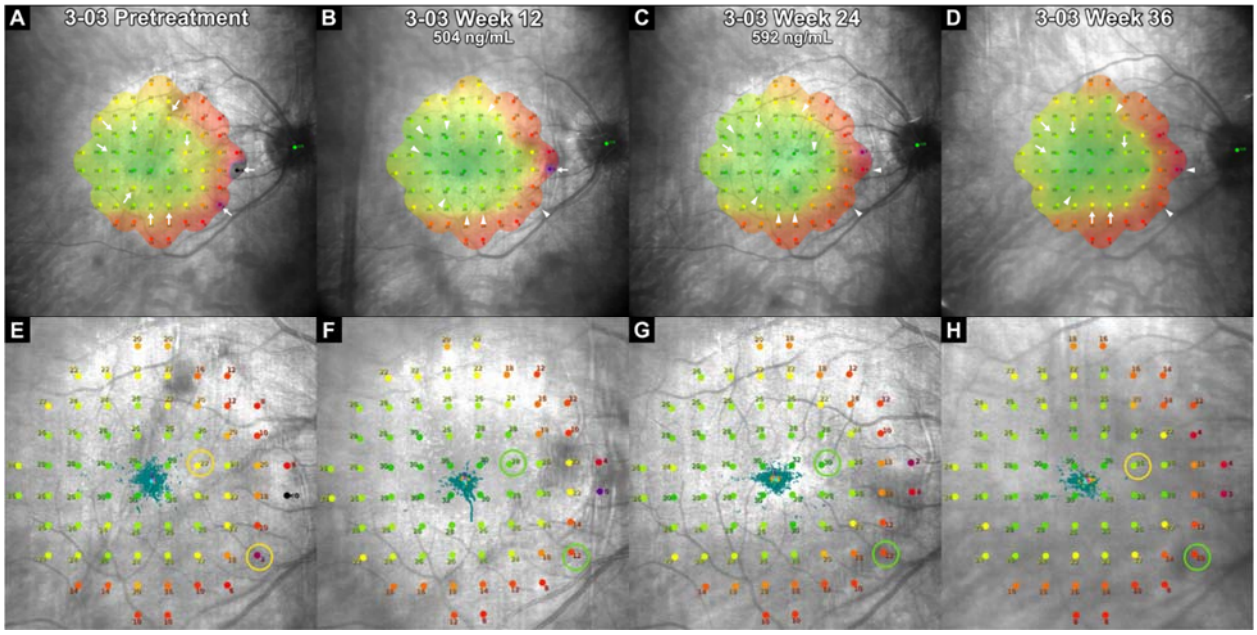
Supplemental Figure 36. Change in retinal sensitivity during treatment and post-treatment observation in the right eye of patient 2 of cohort 3.
The heat maps generated by the Macular Integrity Assessment Instrument software (A-D) and fundus images showing the sensitivity value at each retinal location (E-H) are shown for the pretreatment test with highest mean sensitivity (A and E) and the tests at weeks 12, 24, and 36. In heat maps, the arrows point to regions where the retinal sensitivity improved after the onset of treatment. A change from an arrow to an arrowhead indicates improvement had occurred, and any subsequent decline was noted by a change from arrowhead to arrow. There was a small improvement during treatment that regressed after treatment cessation but remained better than baseline.

Supplemental Figure 37



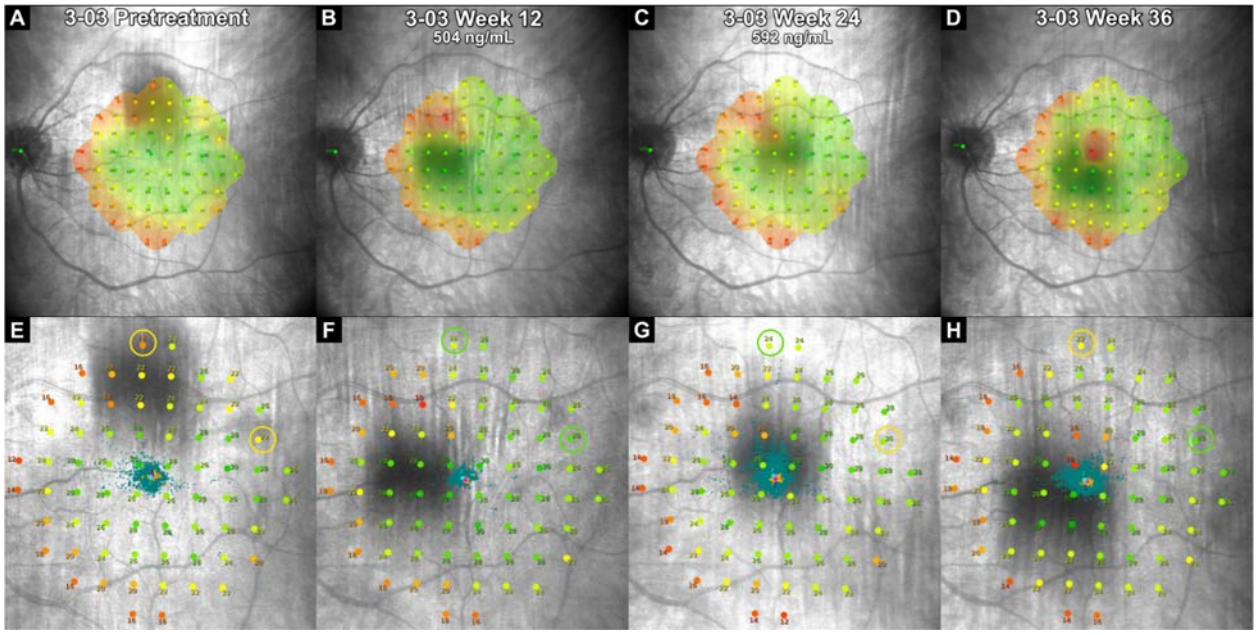
Supplemental Figure 37. Change in retinal sensitivity during treatment and post-treatment observation in the left eye of patient 2 of cohort 3.
The heat maps generated by the Macular Integrity Assessment Instrument software (A-D) and fundus images showing the sensitivity value at each retinal location (E-H) are shown for the pretreatment test with highest mean sensitivity (A and E) and the tests at weeks 12, 24, and 36. In heat maps, the arrows point to regions where the retinal sensitivity improved after the onset of treatment. A change from an arrow to an arrowhead indicates improvement had occurred, and any subsequent decline is noted by a change from arrowhead to arrow. The loci circled in yellow on the pretreatment fundus images (E) show loci at which sensitivity increased ≥ 6 dB after the onset of treatment. On subsequent fundus images, green circles indicate that sensitivity at that location was increased ≥ 6 dB from pretreatment and a change back to yellow indicates a decline below the 6 dB threshold. There was a large improvement during treatment that regressed after treatment but remained better than baseline.

Supplemental Figure 38



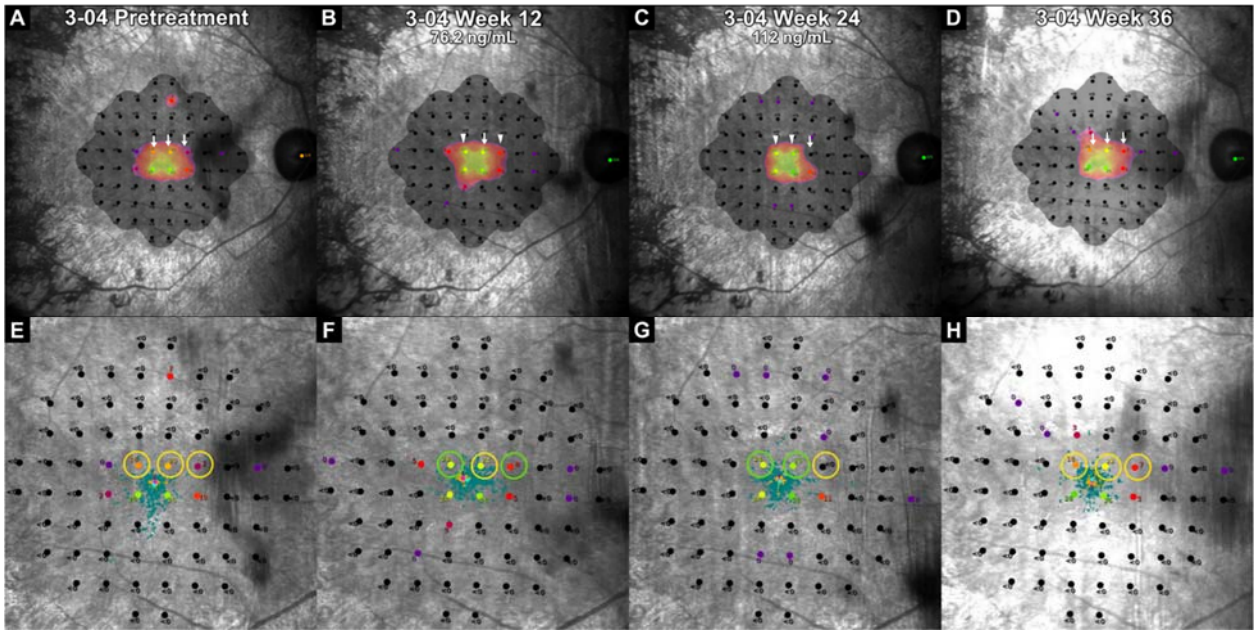
Supplemental Figure 38. Change in retinal sensitivity during treatment and post-treatment observation in the right eye of patient 3 of cohort 3.
The heat maps generated by the Macular Integrity Assessment Instrument software (A-D) and fundus images showing the sensitivity value at each retinal location (E-H) are shown for the pretreatment test with highest mean sensitivity (A and E) and the tests at weeks 12, 24, and 36. In heat maps, the arrows point to regions where the retinal sensitivity improved after the onset of treatment. A change from an arrow to an arrowhead indicates improvement had occurred, and any subsequent decline is noted by a change from arrowhead to arrow. The loci circled in yellow on the pretreatment fundus images (E) show loci at which sensitivity increased ≥ 6 dB after the onset of treatment. On subsequent fundus images, green circles indicate that sensitivity at that location was increased ≥ 6 dB from pretreatment and a change back to yellow indicates a decline below the 6 dB threshold. There was good sensitivity at baseline that improved slightly during treatment and regressed after treatment cessation, but remained better than baseline.

Supplemental Figure 39



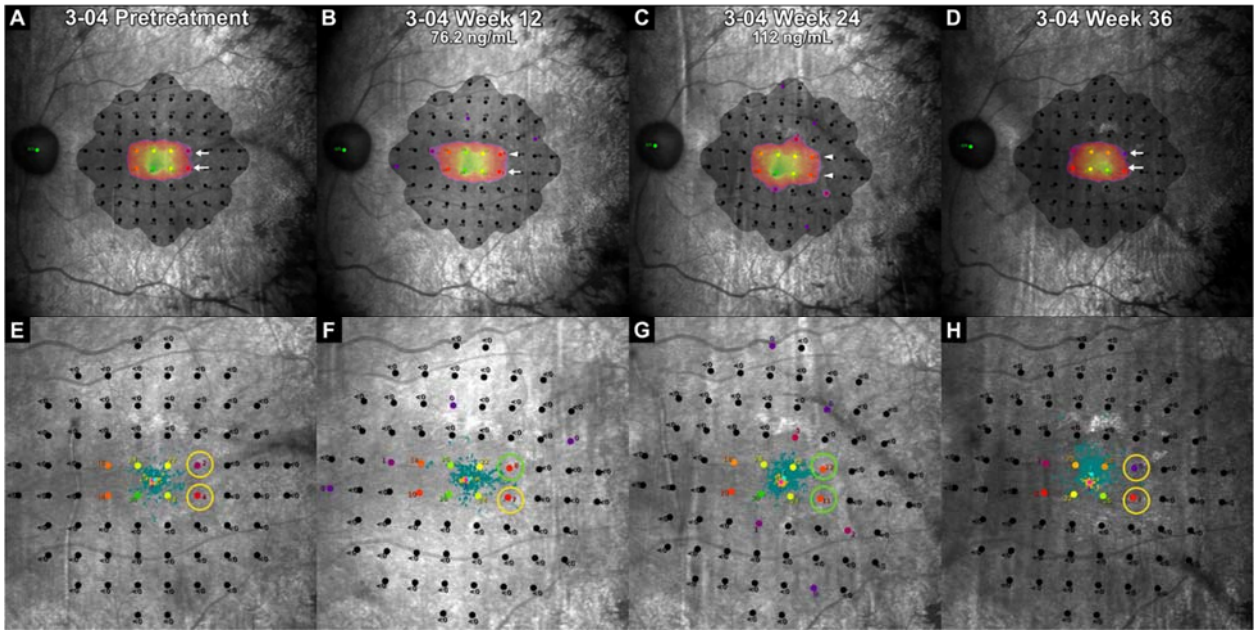
Supplemental Figure 39. Change in retinal sensitivity during treatment and post-treatment observation in the left eye of patient 3 of cohort 3.
The heat maps generated by the Macular Integrity Assessment Instrument software (A-D) and fundus images showing the sensitivity value at each retinal location (E-H) are shown for the pretreatment test with highest mean sensitivity (A and E) and the tests at weeks 12, 24, and 36. In heat maps, the arrows point to regions where the retinal sensitivity improved after the onset of treatment. A change from an arrow to an arrowhead indicates improvement had occurred, and any subsequent decline is noted by a change from arrowhead to arrow. The loci circled in yellow on the pretreatment fundus images (E) show loci at which sensitivity increased ≥ 6 dB after the onset of treatment. On subsequent fundus images, green circles indicate that sensitivity at that location was increased ≥ 6 dB from pretreatment and a change back to yellow indicates a decline below the 6 dB threshold. There was good sensitivity at baseline with little change during treatment and possible worsening 3 months after stopping treatment.

Supplemental Figure 40



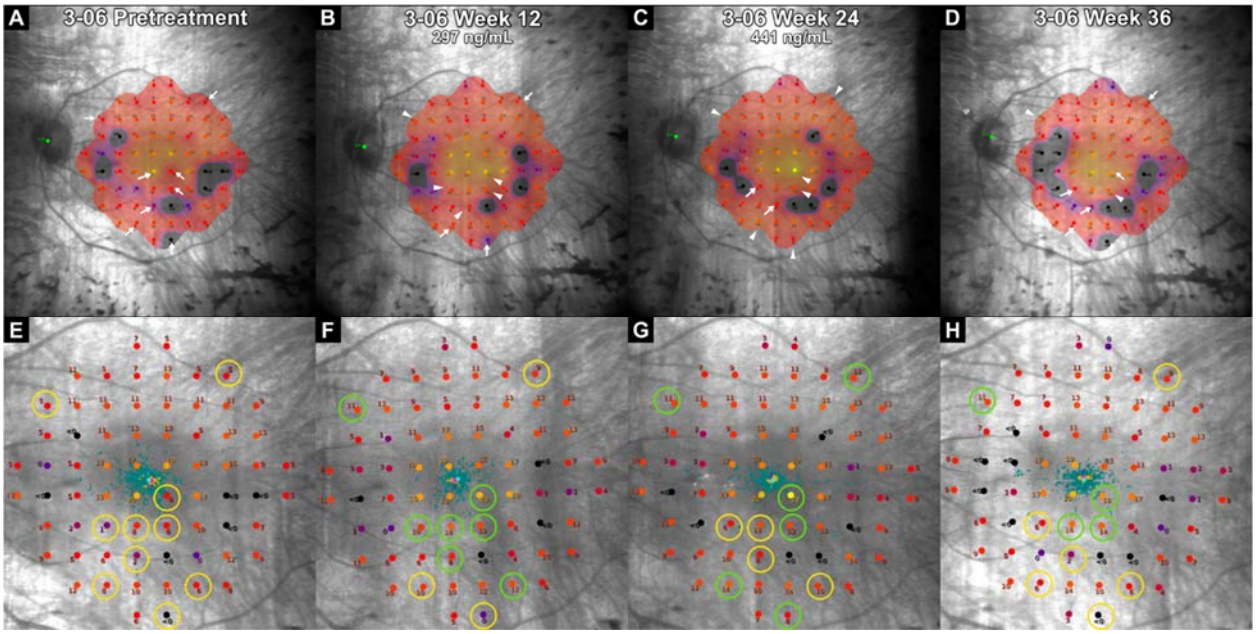
Supplemental Figure 40. Change in retinal sensitivity during treatment and post-treatment observation in the right eye of patient 4 of cohort 3.
The heat maps generated by the Macular Integrity Assessment Instrument software (A-D) and fundus images showing the sensitivity value at each retinal location (E-H) are shown for the pretreatment test with highest mean sensitivity (A and E) and the tests at weeks 12, 24, and 36. In heat maps, the arrows point to regions where the retinal sensitivity improved after the onset of treatment. A change from an arrow to an arrowhead indicates improvement had occurred, and any subsequent decline is noted by a change from arrowhead to arrow. The loci circled in yellow on the pretreatment fundus images (E) show loci at which sensitivity increased ≥ 6 dB after the onset of treatment. On subsequent fundus images, green circles indicate that sensitivity at that location was increased ≥ 6 dB from pretreatment and a change back to yellow indicates a decline below the 6 dB threshold. There was severe loss of sensitivity at baseline with mild improvement during treatment that regressed after treatment.

Supplemental Figure 41



Supplemental Figure 41. Change in retinal sensitivity during treatment and post-treatment observation in the left eye of patient 4 of cohort 3.
The heat maps generated by the Macular Integrity Assessment Instrument software (A-D) and fundus images showing the sensitivity value at each retinal location (E-H) are shown for the pretreatment test with highest mean sensitivity (A and E) and the tests at weeks 12, 24, and 36. In heat maps, the arrows point to regions where the retinal sensitivity improved after the onset of treatment. A change from an arrow to an arrowhead indicates improvement had occurred, and any subsequent decline is noted by a change from arrowhead to arrow. The loci circled in yellow on the pretreatment fundus images (E) show loci at which sensitivity increased ≥ 6 dB after the onset of treatment. On subsequent fundus images, green circles indicate that sensitivity at that location was increased ≥ 6 dB from pretreatment and a change back to yellow indicates a decline below the 6 dB threshold. There was severe loss of sensitivity at baseline with mild improvement during treatment that regressed after treatment.

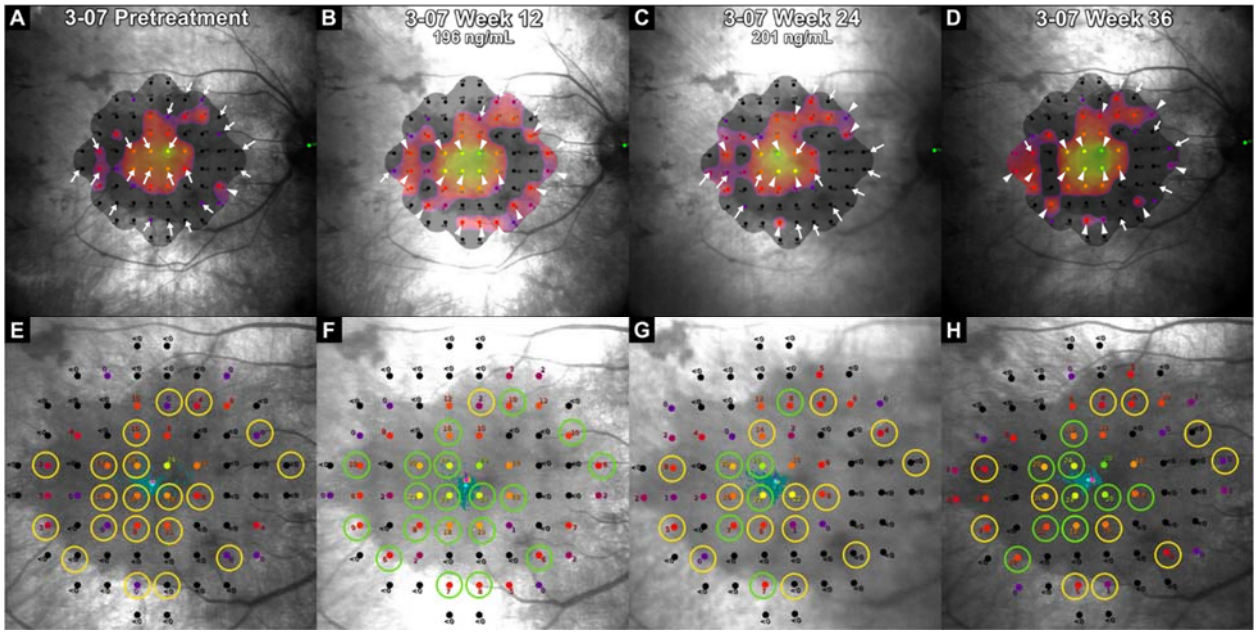
Supplemental Figure 42



Supplemental Figure 42. Change in retinal sensitivity during treatment and post-treatment observation in the left eye of patient 6 of cohort 3.
The heat maps generated by the Macular Integrity Assessment Instrument software (A-D) and fundus images showing the sensitivity value at each retinal location (E-H) are shown for the pretreatment test with highest mean sensitivity (A and E) and the tests at weeks 12, 24, and 36. In heat maps, the arrows point to regions where the retinal sensitivity improved after the onset of treatment. A change from an arrow to an arrowhead indicates improvement had occurred, and any subsequent decline is noted by a change from arrowhead to arrow. The loci circled in yellow on the pretreatment fundus images (E) show loci at which sensitivity increased ≥ 6 dB after the onset of treatment. On subsequent fundus images, green circles indicate that sensitivity at that location was increased ≥ 6 dB from pretreatment and a change back to yellow indicates a decline below the 6 dB threshold. There was a large improvement during treatment that was partially sustained after treatment cessation.

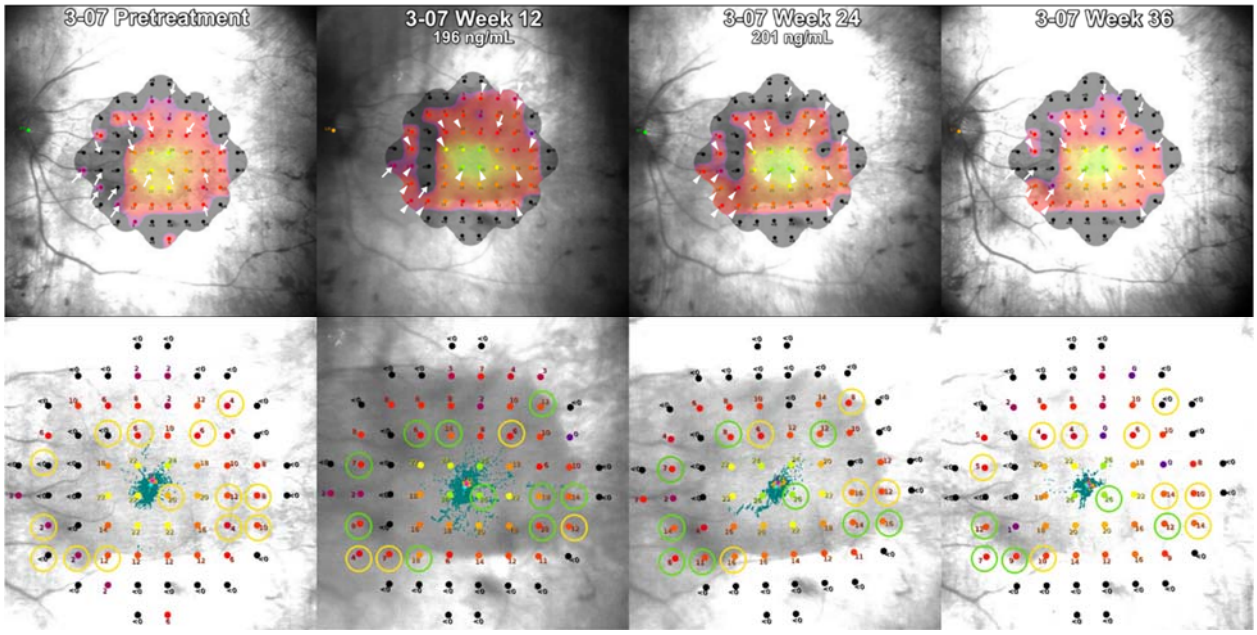
The right eye of patient 3-06 is shown in Figure 7A-H.

Supplemental Figure 43



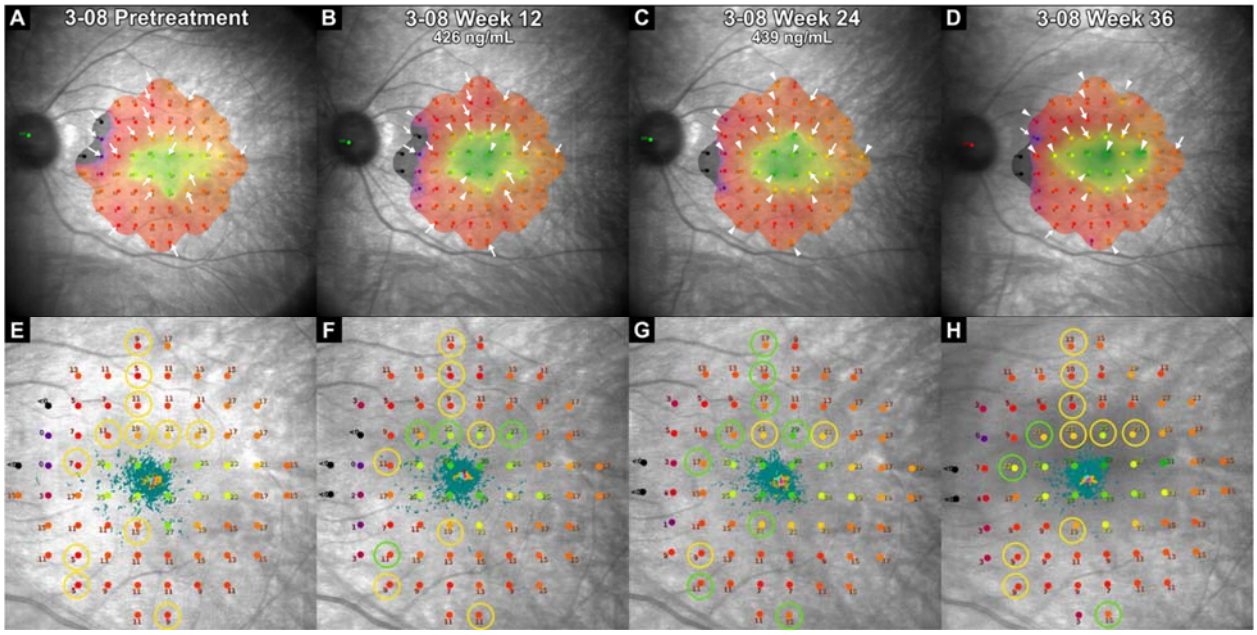
Supplemental Figure 43. Change in retinal sensitivity during treatment and post-treatment observation in the right eye of patient 7 of cohort 3.
The heat maps generated by the Macular Integrity Assessment Instrument software (A-D) and fundus images showing the sensitivity value at each retinal location (E-H) are shown for the pretreatment test with highest mean sensitivity (A and E) and the tests at weeks 12, 24, and 36. In heat maps, the arrows point to regions where the retinal sensitivity improved after the onset of treatment. A change from an arrow to an arrowhead indicates improvement had occurred, and any subsequent decline is noted by a change from arrowhead to arrow. The loci circled in yellow on the pretreatment fundus images (E) show loci at which sensitivity increased ≥ 6 dB after the onset of treatment. On subsequent fundus images, green circles indicate that sensitivity at that location was increased ≥ 6 dB from pretreatment and a change back to yellow indicates a decline below the 6 dB threshold. There was a large improvement during treatment that was partially sustained after treatment cessation.

Supplemental Figure 44



Supplemental Figure 44. Change in retinal sensitivity during treatment and post-treatment observation in the left eye of patient 7 of cohort 3.
The heat maps generated by the Macular Integrity Assessment Instrument software (A-D) and fundus images showing the sensitivity value at each retinal location (E-H) are shown for the pretreatment test with highest mean sensitivity (A and E) and the tests at weeks 12, 24, and 36. In heat maps, the arrows point to regions where the retinal sensitivity improved after the onset of treatment. A change from an arrow to an arrowhead indicates improvement had occurred, and any subsequent decline is noted by a change from arrowhead to arrow. The loci circled in yellow on the pretreatment fundus images (E) show loci at which sensitivity increased ≥ 6 dB after the onset of treatment. On subsequent fundus images, green circles indicate that sensitivity at that location was increased ≥ 6 dB from pretreatment and a change back to yellow indicates a decline below the 6 dB threshold. There was a large improvement during treatment that regressed after treatment cessation but remained better than baseline.

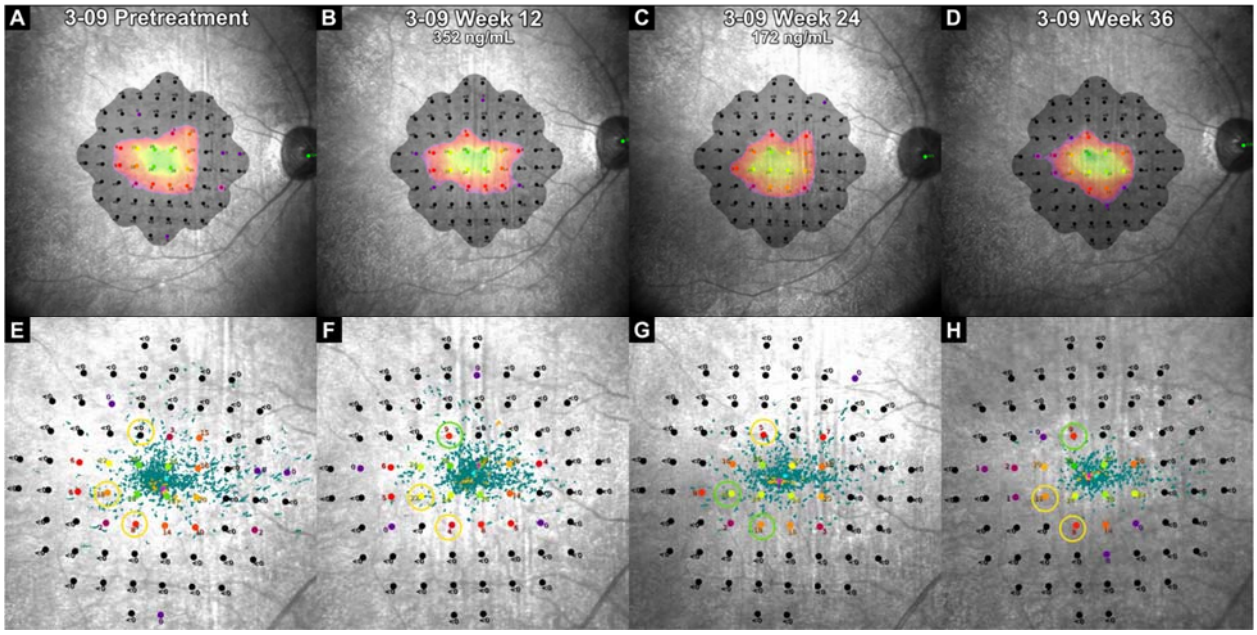
Supplemental Figure 45



Supplemental Figure 45. Change in retinal sensitivity during treatment and post-treatment observation in the left eye of patient 8 of cohort 3.
The heat maps generated by the Macular Integrity Assessment Instrument software (A-D) and fundus images showing the sensitivity value at each retinal location (E-H) are shown for the pretreatment test with highest mean sensitivity (A and E) and the tests at weeks 12, 24, and 36. In heat maps, the arrows point to regions where the retinal sensitivity improved after the onset of treatment. A change from an arrow to an arrowhead indicates improvement had occurred, and any subsequent decline is noted by a change from arrowhead to arrow. The loci circled in yellow on the pretreatment fundus images (E) show loci at which sensitivity increased ≥ 6 dB after the onset of treatment. On subsequent fundus images, green circles indicate that sensitivity at that location was increased ≥ 6 dB from pretreatment and a change back to yellow indicates a decline below the 6 dB threshold. There was large improvement during treatment that regressed after treatment cessation but remained better than baseline.

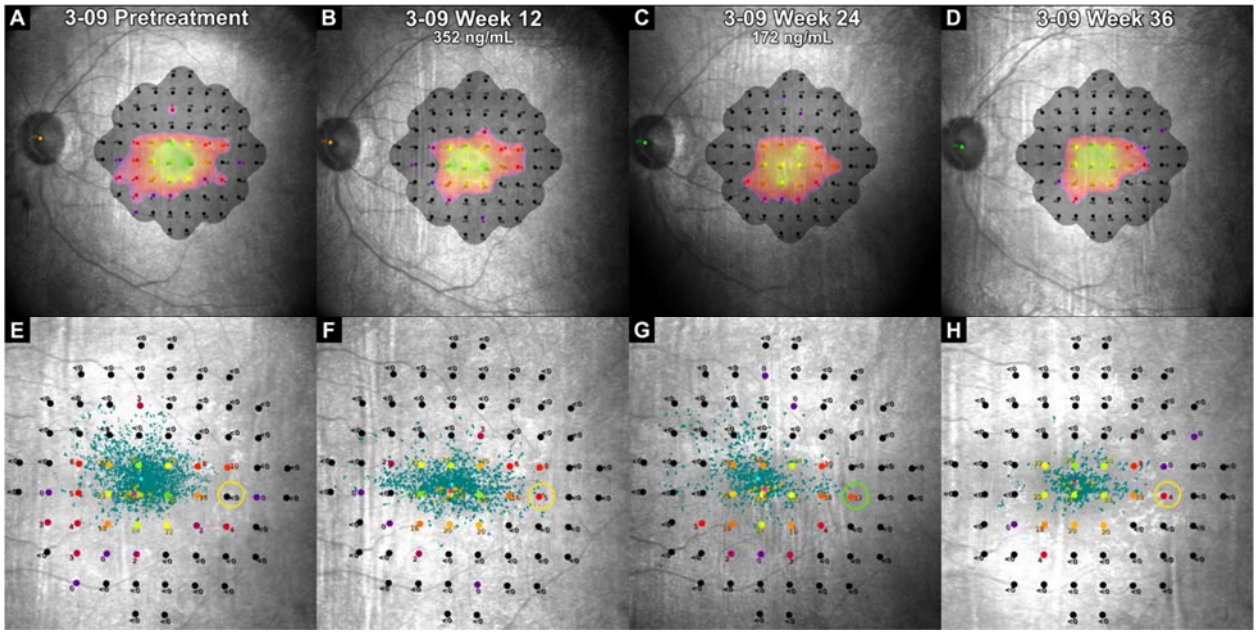
The right eye of patient 3-08 is shown in Figure 7I-P.

Supplemental Figure 46



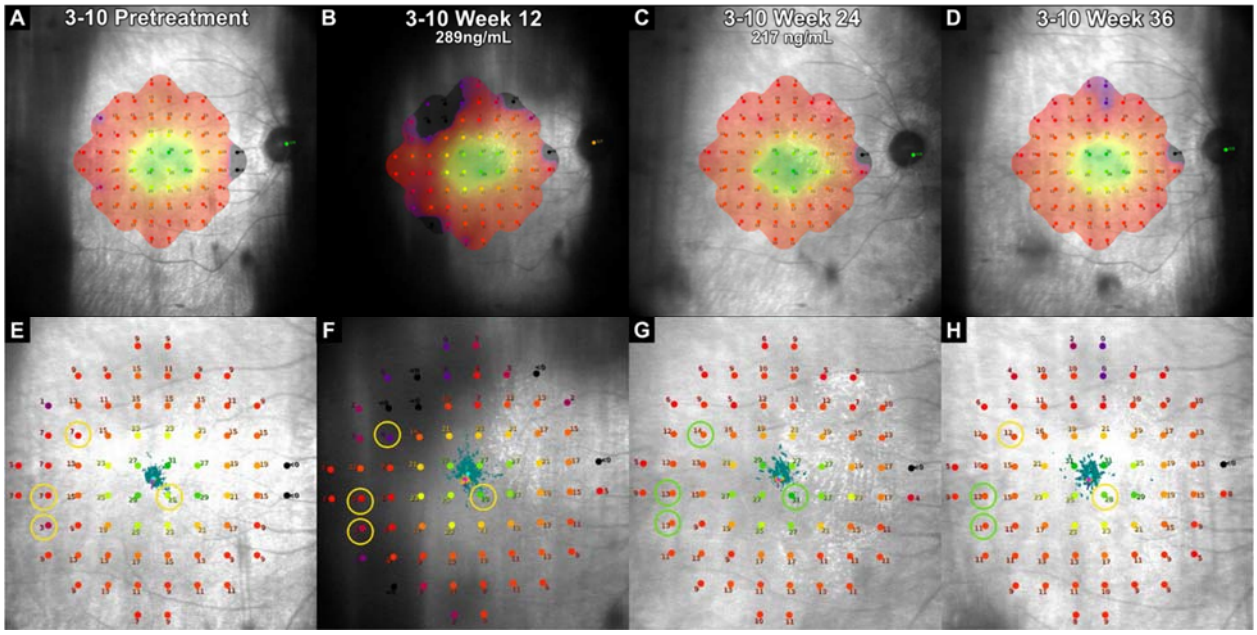
Supplemental Figure 46. Change in retinal sensitivity during treatment and post-treatment observation in the right eye of patient 9 of cohort 3.
The heat maps generated by the Macular Integrity Assessment Instrument software (A-D) and fundus images showing the sensitivity value at each retinal location (E-H) are shown for the pretreatment test with highest mean sensitivity (A and E) and the tests at weeks 12, 24, and 36. The loci circled in yellow on the pretreatment fundus images (E) show loci at which sensitivity increased ≥ 6 dB after the onset of treatment. On subsequent fundus images, green circles indicate that sensitivity at that location was increased ≥ 6 dB from pretreatment and a change back to yellow indicates a decline below the 6 dB threshold. There are a few loci that showed improvement during treatment and regressed after treatment cessation.

Supplemental Figure 47



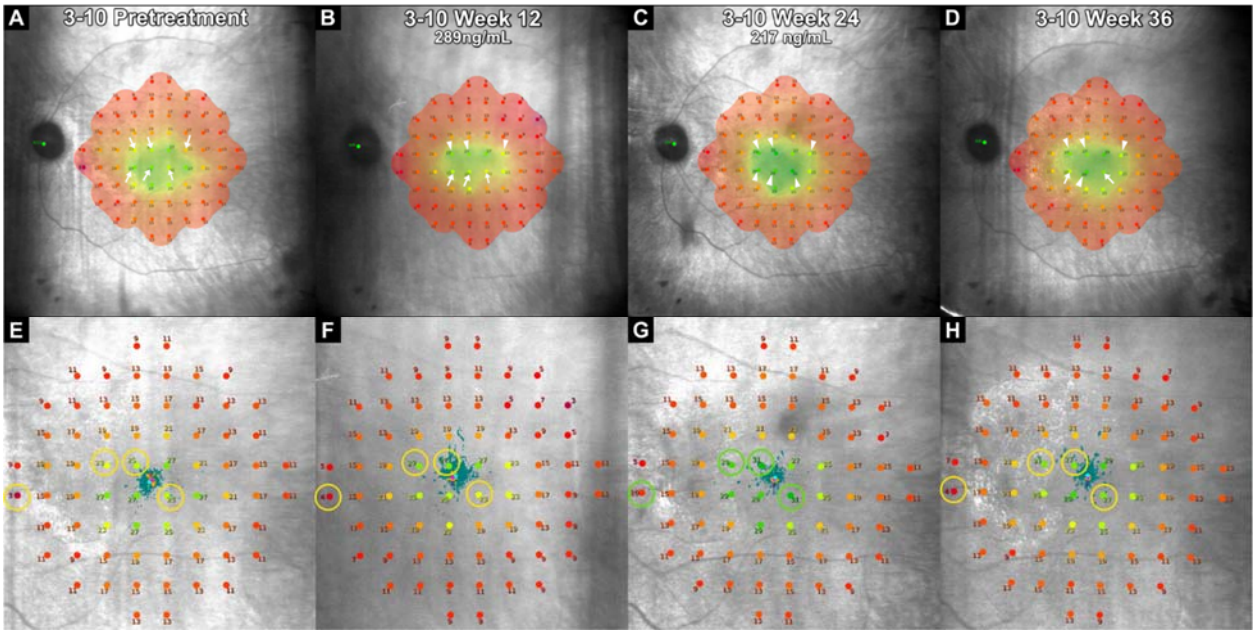
Supplemental Figure 47. Change in retinal sensitivity during treatment and post-treatment observation in the left eye of patient 9 of cohort 3.
The heat maps generated by the Macular Integrity Assessment Instrument software (A-D) and fundus images showing the sensitivity value at each retinal location (E-H) are shown for the pretreatment test with highest mean sensitivity (A and E) and the tests at weeks 12, 24, and 36. The loci circled in yellow on the pretreatment fundus images (E) show loci at which sensitivity increased ≥ 6 dB after the onset of treatment. On subsequent fundus images, green circles indicate that sensitivity at that location was increased ≥ 6 dB from pretreatment and a change back to yellow indicates a decline below the 6 dB threshold. There was mild worsening during and after treatment.

Supplemental Figure 48



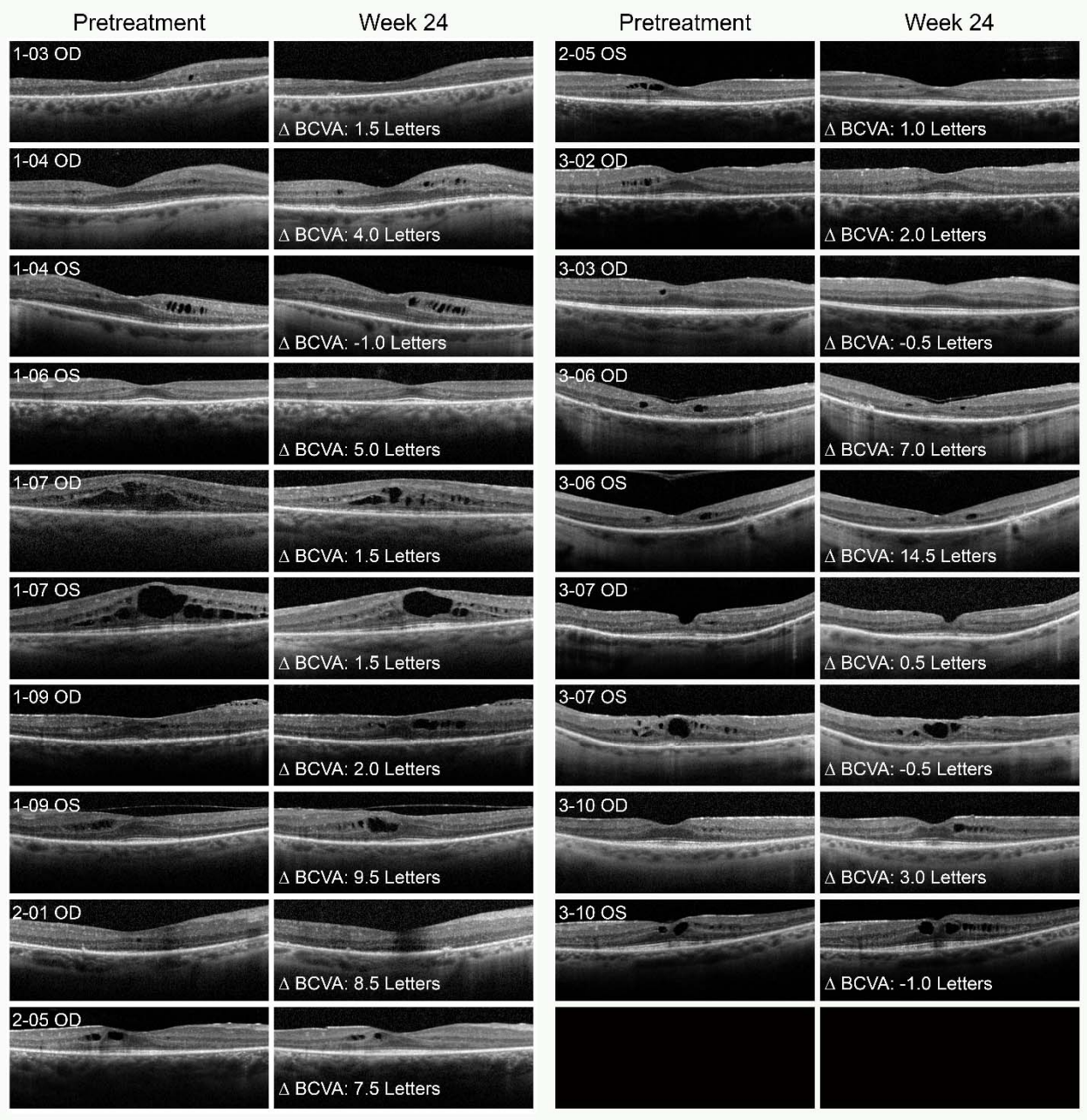
Supplemental Figure 48. Change in retinal sensitivity during treatment and post-treatment observation in the right eye of patient 10 of cohort 3.
The heat maps generated by the Macular Integrity Assessment Instrument software (A-D) and fundus images showing the sensitivity value at each retinal location (E-H) are shown for the pretreatment test with highest mean sensitivity (A and E) and the tests at weeks 12, 24, and 36. The loci circled in yellow on the pretreatment fundus images (E) show loci at which sensitivity increased ≥ 6 dB after the onset of treatment. On subsequent fundus images, green circles indicate that sensitivity at that location was increased ≥ 6 dB from pretreatment and a change back to yellow indicates a decline below the 6 dB threshold. There are four loci that show improvement by week 24. There are two areas in (B) that appear to be absolute scotomata that are artifacts due to a small pupil on the week 12 test.

Supplemental Figure 49



Supplemental Figure 49. Change in retinal sensitivity during treatment and post-treatment observation in the left eye of patient 10 of cohort 3.
The heat maps generated by the Macular Integrity Assessment Instrument software (A-D) and fundus images showing the sensitivity value at each retinal location (E-H) are shown for the pretreatment test with highest mean sensitivity (A and E) and the tests at weeks 12, 24, and 36. In heat maps, the arrows point to regions where the retinal sensitivity improved after the onset of treatment. A change from an arrow to an arrowhead indicates improvement had occurred, and any subsequent decline is noted by a change from arrowhead to arrow. The loci circled in yellow on the pretreatment fundus images (E) show loci at which sensitivity increased ≥ 6 dB after the onset of treatment. On subsequent fundus images, green circles indicate that sensitivity at that location was increased ≥ 6 dB from pretreatment and a change back to yellow indicates a decline below the 6 dB threshold. There was moderate improvement during treatment that was mostly regressed after treatment cessation.

Supplemental Figure 50



Supplemental Figure 50. Change in cystoid spaces in the macula during treatment with NAC.

Pretreatment and week 24 horizontal SD-OCT scans through the fovea are shown for all subjects who had cystoid spaces in the macula at the onset of NAC treatment. The subject identifier and indication as to whether the scan is of the right eye (OD) or left eye (OS) is shown in the upper left corner of the pretreatment scan. The change (Δ) from baseline best corrected visual acuity (BCVA) is shown in Early Treatment Diabetic Retinopathy Study letters at the bottom of the week 24 scan.

Supplemental Table 1: Baseline Information for Each Patient

ID	Age	Sex	Race	Study Eye	Cohort	Age at Onset	Disease Duration	Mode of Inheritance	Genetics	Lens		CME	
										OD	OS	OD	OS
1-01	64	M	Asian	OS	1	42	22	AD	Not Done	PCIOL	PCIOL	N	N
1-02	65	F	White	OD	1	40	25	AR	USH2A: C.2299delG and p.S1369L:c.4106C>T homozygous	PSC 1+; NS 2+	PSC 1+; NS 1+	N	N
1-03	59	F	White	OD	1	18	41	AR	PDE6A: c.2252C>T p.Thr751Met hetero 2257 rs14308057 8	PCIOL	PCIOL	Y	N
1-04	76	M	White	OD	1	27	49	AD	Not Done	PCIOL	PCIOL	Y	Y
1-05	42	F	White	OD	1	35	7	AR	USH2A: c.2898delG: p.Thr967LeufsX44(T967LfsX44) homozygous	PSC 2+	PSC 2+	N	N
1-06	39	M	Middle-Eastern	OS	1	5	34	AR	PDE6G: c.109C>T (p.Q37*) homozygous	NS 1+	NS 1+	N	Y
1-07	46	F	White	OD	1	10	36	SX	Not Done	Clear	Clear	Y	Y
1-08	21	M	White	OD	1	12	9	AR	KIZ: c.226C>T, p.Arg76* homozygous	Clear	Clear	N	N
1-09	60	M	White	OD	1	8	52	AR	PDE6B mutation c.291C>A p.Tyr97X and c.2193+1G>A	PCIOL	PCIOL	Y	Y
1-10	29	M	White	OD	1	24	5	AR	RP1: c.71_72insC (frameshift) and p.Val55Asp:c.164T>A, confirmed trans inheritance	Clear	Clear	N	N
2-01	52	F	White	OS	2	19	33	SX	Not Done	PSC 1+; NS 2+	PSC 1+; NS 2+	Y	N
2-02	57	M	White	OS	2	34	23	AR	USH2A: p.Cys3294Trp:c.9882C>G and p.Trp3521Arg:c.10561T>C	NE	Clear	NE	N
2-03	61	F	White	OD	2	38	23	AR	Not Done	PCIOL	PCIOL	N	N
2-04	50	M	African-American	OS	2	47	3	SX	Inconclusive	PSC 1+	PSC 1+	N	N
2-05	24	M	African-American	OS	2	20	4	AR	USH2A: c.2299delG (p.Glu767SerfsX21) And c.1256 G>T (p.Cys419Phe)	Clear	Clear	Y	Y
2-06	48	F	White	OS	2	29	19	AR	Not Done	PSC 1+	Clear	N	N
2-07	56	F	White	OS	2	15	41	SX	Not Done	Clear	Clear	N	N
2-08	23	F	Hispanic	OD	2	20	3	AD	Inconclusive	Clear	Clear	N	N
2-09	47	M	White	OD	2	14	33	AD	Not Done	PSC 1+, NC 1+	PSC 1+; NS 1+	N	N
2-10	56	F	White	OD	2	11	45	AR	USH2A: c.5857+2T>C and c.10661_10662delAA	PCIOL	PCIOL	N	N
3-01	69	M	White	OS	3	43	26	AR	USH2A: p.Cys3358Tyr:c.10073G>A, and p.Arg3719His:c.11156G>A	PCIOL	PCIOL	N	N
3-02	27	F	White	OD	3	15	12	AD	Not Done	Clear	Clear	Y	N
3-03	33	F	White	OD	3	22	11	AR	Not Done	PCIOL	PSC 1+	Y	N

3-04	32	M	African-American	OS	3	21	11	AR	ABCA4: p.Leu1970Phe:c.5908C>T	Clear	Clear	N	N
3-05	40	F	African-American	OD	3	36	4	AR	Not Done	Clear	Clear	N	N
3-06	59	F	White	OD	3	34	25	SX	Not Done	PCIOL	PCIOL	Y	Y
3-07	71	M	White	OS	3	47	24	SX	Not Done	PCIOL	PCIOL	Y	Y
3-08	48	F	White	OS	3	41	7	AR	USH2A	Clear	Clear	N	N
3-09	36	M	African-American	OD	3	32	4	SX	Not Done	Clear	Clear	N	N
3-10	56	M	White	OS	3	10	46	AR	Inconclusive	PCIOL	PCIOL	Y	Y

NE= not eligible, PCIOL = posterior chamber intraocular lens, PSC = posterior subcapsular cataract, NS = nuclear sclerosis, AD = autosomal dominant, AR = autosomal recessive, SX = simplex

Supplemental Table 2. Rates of Change in BCVA, Mean Sensitivity and EZ Width during the Week 24 to Week 36 Post-Treatment Period

	Cohort 1		Cohort 2		Cohort 3	
Post-Treatment	**Rate of Change (95% CI)**	**p-value***	**Rate of Change (95%CI)**	**p-value***	**Rate of Change (95%CI)**	**p-value ***
BCVA (ETDRS Letter Score/month)	-1.13 (-1.83, -0.42)	.002	0.13 (-0.60, 0.86)	.73	-0.17 (-0.93, 0.58)	.65
Mean Macular Sensitivity (dB/month)	-0.04 (-0.17, 0.09)	.56	-0.01 (-0.16, 0.13)	0.83	-0.15 (-0.28, -0.01)	.032
Ellipsoid Width (μm/month)	-15.18 (-40.53, 8.16)	.18	-11.43 (-36.33, 13.46)	0.35	-13.13 (-38.79, 12.53)	0.30

*P-values using linear mixed effects model for testing the hypotheses that rates of change were significantly different from 0.

After the treatment was stopped, BCVA declined in Cohort 1 at a statistically significant rate of 1.13 letters/month (the statistically significant decline however was mainly driven by the eyes that had a large drop of BCVA at week 36). BCVA did not change in Cohort 2 and Cohort 3. Macular sensitivity did not change in Cohort 1 and Cohort 2, and declined statistically significantly in Cohort 3. EZ width did not change significantly in all of the 3 cohorts.

BCVA: best corrected visual acuity; EZ: ellipsoid zone; ETDRS: Early Treatment Diabetic Retinopathy Study.

Supplemental Table 3. Rates of Change in BCVA and Mean Sensitivity, during NAC Treatment, among Eyes without Cystoid Space at Baseline (n=40 eyes)

	Cohort 1		Cohort 2		Cohort 3	
	Rate of Change (95% CI)	p-value*	Rate of Change (95%CI)	p-value*	Rate of Change (95%CI)	p-value*
BCVA (ETDRS Letter Score/month)	0.33 (0.09, 0.572)	.009	0.47 (0.24, 0.70)	<.001	0.10 (-0.18, 0.37)	0.49
Mean Macular Sensitivity (dB/month)	-0.06 (-0.16, 0.04)	0.25	0.02 (-0.08, 0.12)	0.71	0.10 (0.00, 0.20)	0.046

*P-values using linear mixed effects model for testing the hypotheses that rates of change were significantly different from 0.

BCVA: best corrected visual acuity; EZ: ellipsoid zone; NAC: N-acetylcysteine; ETDRS: Early Treatment Diabetic Retinopathy Study

TREND Statement Checklist

Paper Section/ Topic	Item No	Descriptor	Reported? ✓	Reported? Pg #
Title and Abstract				
Title and Abstract	1	• Information on how unit were allocated to interventions	×	2
		• Structured abstract recommended	×	2
		• Information on target population or study sample	×	2
Introduction				
Background	2	• Scientific background and explanation of rationale	×	3-4
		• Theories used in designing behavioral interventions	N/A	
Methods				
Participants	3	• Eligibility criteria for participants, including criteria at different levels in recruitment/sampling plan (e.g., cities, clinics, subjects)	×	5, 25-7 Fig1
		• Method of recruitment (e.g., referral, self-selection), including the sampling method if a systematic sampling plan was implemented	×	5, 25-7
		• Recruitment setting	×	5, 25-7
		• Settings and locations where the data were collected	×	5, 25-7
Interventions	4	• Details of the interventions intended for each study condition and how and when they were actually administered, specifically including:		
		○ Content: what was given?	×	25, 27-8
		○ Delivery method: how was the content given?	×	25, 27-8
		○ Unit of delivery: how were the subjects grouped during delivery?	×	25, Fig1
		○ Deliverer: who delivered the intervention?	×	25, 27-8
		○ Setting: where was the intervention delivered?	×	25, 27-8
		○ Exposure quantity and duration: how many sessions or episodes or events were intended to be delivered? How long were they intended to last?	×	25, 27-8
		○ Time span: how long was it intended to take to deliver the intervention to each unit?	×	25
		○ Activities to increase compliance or adherence (e.g., incentives)	×	21
Objectives	5	• Specific objectives and hypotheses	×	4,16
Outcomes	6	• Clearly defined primary and secondary outcome measures	×	28
		• Methods used to collect data and any methods used to enhance the quality of measurements	×	26-30
		• Information on validated instruments such as psychometric and biometric properties	N/A	
Sample Size	7	• How sample size was determined and, when applicable, explanation of any interim analyses and stopping rules	×	25
Assignment Method	8	• Unit of assignment (the unit being assigned to study condition, e.g., individual, group, community)	×	25, Fig1
		• Method used to assign units to study conditions, including details of any restriction (e.g., blocking, stratification, minimization)	×	25-6, Fig1
		• Inclusion of aspects employed to help minimize potential bias induced due to non-randomization (e.g., matching)	N/A	

TREND Statement Checklist

Blinding (masking)	9	• Whether or not participants, those administering the interventions, and those assessing the outcomes were blinded to study condition assignment; if so, statement regarding how the blinding was accomplished and how it was assessed.	N/A	
Unit of Analysis	10	• Description of the smallest unit that is being analyzed to assess intervention effects (e.g., individual, group, or community)	X	30-1
		• If the unit of analysis differs from the unit of assignment, the analytical method used to account for this (e.g., adjusting the standard error estimates by the design effect or using multilevel analysis)	N/A	
Statistical Methods	11	• Statistical methods used to compare study groups for primary methods outcome(s), including complex methods of correlated data	X	30-1
		• Statistical methods used for additional analyses, such as a subgroup analyses and adjusted analysis	X	30-1
		• Methods for imputing missing data, if used	X	30-1
		• Statistical software or programs used	X	30-1
Results				
Participant flow	12	• Flow of participants through each stage of the study: enrollment, assignment, allocation, and intervention exposure, follow-up, analysis (a diagram is strongly recommended)	X	Fig1
		○ Enrollment: the numbers of participants screened for eligibility, found to be eligible or not eligible, declined to be enrolled, and enrolled in the study	X	Fig1
		○ Assignment: the numbers of participants assigned to a study condition	X	5, Fig1
		○ Allocation and intervention exposure: the number of participants assigned to each study condition and the number of participants who received each intervention	X	5,6,7, Fig1
		○ Follow-up: the number of participants who completed the follow-up or did not complete the follow-up (i.e., lost to follow-up), by study condition	X	6,7, Fig1
		○ Analysis: the number of participants included in or excluded from the main analysis, by study condition	X	6,7, 30-1
		• Description of protocol deviations from study as planned, along with reasons	X	30-1
Recruitment	13	• Dates defining the periods of recruitment and follow-up	X	25
Baseline Data	14	• Baseline demographic and clinical characteristics of participants in each study condition	X	5,6 Table 1 Supp Table 1
		• Baseline characteristics for each study condition relevant to specific disease prevention research	X	5,6 Table 1 Supp Table 1
		• Baseline comparisons of those lost to follow-up and those retained, overall and by study condition	NA	
		• Comparison between study population at baseline and target population of interest	X	SuppTable 1
Baseline equivalence	15	• Data on study group equivalence at baseline and statistical methods used to control for baseline differences	N/A	

TREND Statement Checklist

Numbers analyzed	16	• Number of participants (denominator) included in each analysis for each study condition, particularly when the denominators change for different outcomes; statement of the results in absolute numbers when feasible	X	Table 2 Supp Table 2 Fig 3-8
		• Indication of whether the analysis strategy was "intention to treat" or, if not, description of how non-compliers were treated in the analyses	N/A	
Outcomes and estimation	17	• For each primary and secondary outcome, a summary of results for each estimation study condition, and the estimated effect size and a confidence interval to indicate the precision	x	8-15
		• Inclusion of null and negative findings	x	8-15
		• Inclusion of results from testing pre-specified causal pathways through which the intervention was intended to operate, if any	x	15
Ancillary analyses	18	• Summary of other analyses performed, including subgroup or restricted analyses, indicating which are pre-specified or exploratory	x	13 Suppl Table 3
Adverse events	19	• Summary of all important adverse events or unintended effects in each study condition (including summary measures, effect size estimates, and confidence intervals)	x	7, Table 2
DISCUSSION				
Interpretation	20	• Interpretation of the results, taking into account study hypotheses, sources of potential bias, imprecision of measures, multiplicative analyses, and other limitations or weaknesses of the study	x	16-24
		• Discussion of results taking into account the mechanism by which the intervention was intended to work (causal pathways) or alternative mechanisms or explanations	x	16-24
		• Discussion of the success of and barriers to implementing the intervention, fidelity of implementation	x	19, 21-4
		• Discussion of research, programmatic, or policy implications	No	
Generalizability	21	• Generalizability (external validity) of the trial findings, taking into account the study population, the characteristics of the intervention, length of follow-up, incentives, compliance rates, specific sites/settings involved in the study, and other contextual issues	x	23-4
Overall Evidence	22	• General interpretation of the results in the context of current evidence and current theory	x	16, 20-1

From: Des Jarlais, D. C., Lyles, C., Crepaz, N., & the Trend Group (2004). Improving the reporting quality of nonrandomized evaluations of behavioral and public health interventions: The TREND statement. *American Journal of Public Health*, 94, 361-366. For more information, visit: http://www.cdc.gov/trendstatement/