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).