Original article

Three-year patient-reported visual function outcomes in diabetic macular edema managed with ranibizumab: the RESTORE extension study

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Abstract

Objective:
To determine the impact of ranibizumab 0.5 mg on patient-reported visual function over 36 months in individuals with visual impairment from diabetic macular edema.

Methods:
RESTORE comprises a phase 3, randomized, multicenter, 12 month core study and a 24 month open-label extension study. Eyes assigned to ranibizumab in the core study received ranibizumab for 36 months; eyes assigned to laser monotherapy in the core study received ranibizumab during the extension. The primary outcome was least-squares mean change in National Eye Institute 25-item Visual Functioning Questionnaire (NEI VFQ-25) overall composite and subscale scores.

Results:
Of 303 core study participants, 240 (79%) entered the extension, comprising 83 (35%) participants initially assigned to ranibizumab, 83 (35%) assigned to ranibizumab plus laser combination therapy, and 74 (31%) assigned to laser monotherapy. Least-squares mean (standard error) change in NEI VFQ-25 composite score from baseline to month 12 (+5.9 [1.5]; +5.0 [1.5], for the ranibizumab and combination therapy groups, respectively) decreased by month 36 (+4.1 [1.7]; +4.0 [1.7], respectively, from baseline to month 36) following reduced injection frequency relative to the core study. At 36 months, the least-squares mean (standard error) change in the laser monotherapy group was similar to that in the ranibizumab groups (+4.1 [1.8]). Most subscale scores showed outcomes similar to that for the composite score. The greatest NEI VFQ-25 gains were consistently observed in participants for whom the study eye was the better-seeing eye.

Limitations:
Patients entering the extension were not randomized, and 21% of the core study participants did not enter the extension, which may have affected the results.

Conclusions:
Gains in patient-reported visual function at month 12 among eyes receiving ranibizumab in the core study decreased slightly by 36 months. Eyes originally receiving laser monotherapy for 12 months then ranibizumab for 24 months achieved similar gains by 36 months to eyes receiving ranibizumab for 36 months.

Trial Registration:
ClinicalTrials.gov: NCT00687804 and NCT00906464.

Introduction

Diabetic macular edema (DME) is the leading cause of permanent vision loss in people with diabetes mellitus1–3. When DME is associated with reduced visual
acuity (VA) in one or both eyes, it has been found to contribute substantially to reduced patient-reported visual function. The National Eye Institute 25-item Visual Functioning Questionnaire (NEI VFQ-25) is the instrument most widely used to assess patient-reported visual function, and has been employed in many clinical trials, including the RESTORE study and other studies of treatments for diabetic retinopathy. Typically, NEI VFQ-25 results are collated into 11 subscale scores as well as an overall composite score; improvements in the subscale or composite scores represent clinically meaningful improvements in best-corrected VA (BCVA), based on an assessment using the Logarithm of the Minimum Angle of Resolution chart among patients with the neovascular form of age-related macular degeneration. Notably, this questionnaire gives an overall measure of improvement, taking into consideration the fact that patients with eye diseases typically have a better-seeing eye (BSE) and a worse-seeing eye (WSE).

The RESTORE core study was a phase 3, 12 month study, in which patients with visual impairment due to DME were randomized to ranibizumab plus sham laser, ranibizumab plus laser, or sham injections plus laser. Patients managed with intravitreal ranibizumab, either alone or in combination with laser therapy, demonstrated significant improvements in both BCVA and patient-reported visual outcomes between study entry and final assessment compared with patients managed with laser monotherapy. These findings were corroborated by the REVEAL study, which showed that ranibizumab monotherapy or ranibizumab combined with laser therapy showed superior BCVA improvements over laser treatment alone in Asian patients with visual impairment resulting from DME.

The RESTORE extension study was a phase 3b, 24 month, open-label, multicenter study conducted in patients with DME who had completed the 12 month core study. Ranibizumab was administered according to a pro re nata (‘as-needed’) regimen, guided mainly by BCVA stability, with monthly monitoring.

The objective of the current analysis was to examine the effect of ranibizumab vs laser therapy on patient-reported visual function, as assessed by the NEI VFQ-25 questionnaire, over the combined 36 month period of the RESTORE core and extension studies.

### Patients and methods

#### Study design

The methodologies of the RESTORE core (NCT00687804) and extension (NCT00906464) studies have been reported previously. Briefly, the RESTORE core study enrolled 345 adults with visual impairment due to DME in one or both eyes at clinical centers in 13 countries. Patients were required to have a best-corrected Early Treatment Diabetic Retinopathy Study (ETDRS) letter score between 78 and 39 (approximate Snellen equivalent, 20/32+ to 20/160) at baseline. In the core study, patients were randomized in a 1:1:1 ratio to intravitreal ranibizumab 0.5 mg and sham laser therapy (ranibizumab monotherapy), to intravitreal ranibizumab 0.5 mg and laser therapy (ranibizumab plus laser combination therapy), or to laser treatment and sham injection (laser monotherapy). After three initial consecutive monthly ranibizumab injections, patients in the ranibizumab groups were eligible to receive injections on a monthly basis until stable BCVA was reached, defined as no further improvement in BCVA over the last two consecutive visits or BCVA letter score ≥84 (approximate Snellen equivalent, 20/20 or better) over the last two consecutive visits. Patients in the laser groups received laser treatment on day 1, with repeated laser treatment administered in accordance with ETDRS guidelines, at intervals of at least 3 months, if deemed necessary by the investigator.

The RESTORE extension study was a 24 month, open-label, multicenter study of patients who completed the 12 month core study and who were then eligible for treatment with ranibizumab 0.5 mg. In order to be eligible for ranibizumab treatment, patients must have provided their written, informed consent and met none of the following exclusion criteria during the core study: history of stroke or transient ischemic event; hypersensitivity to ranibizumab; uncontrolled glaucoma; evidence of vitreomacular traction; or active proliferative retinopathy. All patients were eligible to receive ranibizumab injections according to the protocol-defined retreatment criteria used in the core study. Laser treatment could also be administered to all participants in accordance with ETDRS guidelines, at intervals of at least 3 months, if deemed necessary by the investigator. During the extension study, the investigators remained blinded to the treatment administered during the core study.

The NEI VFQ-25 is a patient-reported outcome questionnaire that provides a subjective assessment of visual function. The questionnaire was completed during the RESTORE core study (at baseline, month 3, and month 12) and during the extension study (at month 24 and month 36). The NEI VFQ-25 consists of 25 items, measuring general health (1 item) and 11 vision-related constructs (subscales): general vision, ocular pain, near activities, distance activities, color vision, peripheral vision, social functioning, mental health, role difficulties, driving, and dependency. Items are scored using 5 or 6 point response options, ranging from ‘not affected at all’ (level 1) to ‘severely affected’ (level 4), ‘stopped doing this because of my eyesight’ (level 5), and ‘stopped doing this for other reasons’ (level 6). Items are reverse-scored, so
higher scores indicate better visual function. An overall composite score is calculated by taking the mean of responses for all subscales except the general health item. Patients completed the interviewer-administered version of the NEI VFQ-25 in local languages. All translations underwent prior linguistic validation or were validated by cognitive debriefings with patients in local languages.

This study adhered to the tenets of the Declaration of Helsinki and was conducted in accordance with the International Conference on Harmonisation Good Clinical Practice guidelines. Approval was obtained from the ethics committee or institutional review board at each contributing center.

**Statistical methods**

All NEI VFQ-25 analyses in this 36 month follow-up were performed on the population of patients who enrolled in the RESTORE extension study; the baseline, 3 month and 12 month results reported here are therefore for a subset of approximately 79% of the patients enrolled in the core study.

Basic analyses included mean changes from core study baseline within each treatment group for all subscales. Subgroup analyses were descriptive in nature and focused on prospectively selected key NEI VFQ-25 subscales – near activities, distance activities, general vision, and mental health – and on the overall composite score. Additional subgroup analyses were conducted according to whether the study eye was the patient’s BSE, WSE, or neither BSE nor WSE, which was defined as a difference between the left and right eye of <5 letters among individuals with baseline BCVA letter scores ≥50 (approximate Snellen equivalent, greater than 20/100) in both eyes, or of <10 letters for those with baseline BCVA letter scores <50 in both eyes (Table 1).

The last observation carried forward (LOCF) method was used to impute missing post-baseline data. Other methods of addressing missing data were considered, but analysis of non-LOCF results suggested that similar results would be obtained with alternative approaches. For both the overall population and subscale analyses, analysis of covariance (ANCOVA) models were adjusted for the following baseline characteristics (at entry into the RESTORE core study): BCVA in the study eye; BCVA in the fellow (non-study) eye; whether the treated eye was BSE, neither BSE nor WSE, or WSE; patient age; sex; glycated hemoglobin (HbA1c) levels; ocular coherence tomography-measured central subfield thickness (CST); and NEI VFQ-25 composite score. These models were used to evaluate differences in the least-squares mean change in NEI VFQ-25 scores from baseline across treatment groups. Least-squares mean changes and standard errors (SE) are reported. The trapezoid rule was used to derive the area under the curve for each patient at baseline and at months 3, 12, 24, and 36, and adjustments were made for duration of follow-up to provide a result on the NEI VFQ-25 scale.

**Results**

**Patient characteristics and disposition**

Of the 303 participants who completed the core study, 240 (70%) enrolled in the extension study, comprising 83 (35%) participants from the core ranibizumab monotherapy group, 83 (35%) from the core ranibizumab plus laser combination therapy group, and 74 (31%) from the core laser monotherapy group. Of these 240 participants, 227 (79, 78, and 70 in the three groups, respectively) completed the NEI VFQ-25 questionnaire at the extension study baseline visit (month 12). In total, 208 of the 240 participants (87%) completed the extension study, comprising 73 (35%), 72 (35%), and 63 (30%) participants in the three groups, respectively.

Core study baseline demographics, clinical characteristics, and NEI VFQ-25 scores among the three groups of participants who entered the extension study are shown in Table 2. Mean ages at enrollment in the core study of participants who entered the extension study were similar across the three groups, and there were similar prevalences and durations of diabetes, and similar mean HbA1c values. Mean BCVA letter scores appeared to be similar in all three groups at enrollment in the core study. The proportions of patients with a BCVA letter score <73 were

| Table 1. Definitions of ‘better-seeing’ or ‘worse-seeing’ eye used at core study baseline. |
|-----------------------------------------------|
| Better-seeing eye | Baseline BCVA letter score* | ≥50 in both eyes (Snellen equivalent ≥20/100) |
| Worse-seeing eye | Baseline BCVA letter score* | <50 in either eye (Snellen equivalent <20/100) |
| Neither-better-nor-worse-seeing eye | Study eye BCVA greater than fellow (non-study) eye BCVA by ≥5 letters |
| | Study eye BCVA less than fellow (non-study) eye BCVA by ≥5 letters |
| | BCVA of participant’s eyes differs by <5 letters |

BCVA, best-corrected visual acuity.

*This is the Early Treatment Diabetic Retinopathy Study letter score following standardized refraction.
similar in the three groups, and the three groups had similar mean CSTs as measured by ocular coherence tomography. Similar proportions of patients in the three groups received treatment in their BSE (ranibizumab, 25%; ranibizumab plus laser, 19%; laser, 18%) and WSE (59%, 61%, and 57%, respectively).

Table 3 shows clinical characteristics of participants at the time of entry into the extension study by core treatment group, including mean BCVA, mean CST, and mean numbers of intravitreal injections and laser sessions received in the study. As expected, BCVA was higher and CST was lower in the eyes originally assigned to ranibizumab monotherapy or ranibizumab plus laser combination therapy than in the eyes originally assigned to laser monotherapy.

A comparison of core study baseline characteristics in patients who entered the extension study with those who did not (Supplementary Online Table S1) indicates that the former were typically younger (mean 62.6 years vs 65.3 years), had higher mean BCVA letter score (64.5 vs 61.4 [approximate Snellen equivalent, 20/50 vs 20/63]) and a higher mean NEI VFQ-25 composite score (74.7 vs 70.3). At month 12, patients who entered the extension study had a higher mean BCVA (70.4 vs 63.5 [approximate Snellen equivalent, 20/40 vs 20/50]) and a greater mean increase in BCVA from baseline (+5.9 vs +2.1).
letters) than those who discontinued. A smaller proportion of those who entered the extension study had a BCVA letter score of 60 or worse (approximate Snellen equivalent, 20/63 or worse) at month 12 compared with those who discontinued (16.7% vs 39.0%). Additionally, patients entering the extension study had received more injections during the core study than those who discontinued (mean, 7.6 vs 5.8 injections).

Treatment distribution
The distribution of ranibizumab and laser treatments during the core study and the 24 months of the extension study have been described elsewhere. In total, 188 patients received ranibizumab 0.5 mg during the extension study (core ranibizumab group, n = 67; core ranibizumab plus laser group, n = 62; core laser group, n = 59); 52 patients did not receive ranibizumab in the extension study, including 15 in the core laser group.

Table 3. Characteristics of study participants at entry into the RESTORE extension study, by original treatment assignment in the core study.

|                      | Ranibizumab monotherapy + sham laser therapy (n = 83) | Previous ranibizumab + laser therapy (n = 83) | Laser monotherapy + sham injection (n = 74) |
|----------------------|------------------------------------------------------|------------------------------------------------|---------------------------------------------|
| BCVA letter score in study eye |                                                      |                                                |                                             |
| Mean ± SD [Snellen equivalent]  | 74.1 ± 9.5 [20/32]                                  | 71.3 ± 10.4 [20/40]                            | 65.2 ± 11.9 [20/50]                         |
| Median (range)       | 76 (40–93)                                           | 72 (39–90)                                     | 68 (34–85)                                  |
| Patients with BCVA letter score >73 [Snellen equivalent >20/40], n (%) | 48 (58)                                             | 34 (41)                                        | 16 (22)                                      |
| Central subfield thickness (mean ± SD), μm | 304 ± 106                               | 285 ± 94                                       | 343 ± 127                                   |
| Number of ranibizumab injections in core study | 7.4 ± 2.8                                     | 7.5 ± 2.9                                      | 0.0                                          |
| Median (range)       | 8 (3–12)                                             | 8 (3–12)                                       | 0                                            |
| Number of laser sessions in core study | 0.0                                                  | 1.8 ± 0.9                                      | 2.2 ± 1.1                                   |
| Mean ± SD            |                                                      |                                                |                                             |
| Median (range)       | 0                                                    | 2 (1–5)                                        | 2 (1–4)                                      |

Measured changes in patient-reported visual function
Changes in mean BCVA scores in the three treatment arms over the 36 months have been presented in the primary publication for the extension study. Figure 1A shows the least-squares mean change from baseline in NEI VFQ-25 composite score for the three treatment groups at months 3, 12, 24, and 36 after adjustment for participant baseline characteristics. This demonstrated a differential response after 12 months, with the greatest least-squares mean (SE) score gain from baseline in the ranibizumab monotherapy group (5.9 [1.5] points), followed by the ranibizumab plus laser combination therapy group (5.0 [1.5] points), and the lowest response in the laser monotherapy group (2.5 [1.6] points). As expected, given that all three groups were eligible to receive

Figure 1. A. Least-squares mean change from core study baseline over time in NEI VFQ-25 overall composite score among those who entered the extension study, by core treatment assignment at baseline, after adjustment for core study baseline characteristics (best corrected visual acuity [BCVA] in study eye; BCVA in fellow eye; whether eye treated was better-, worse- or same-seeing eye; age; sex; glycated hemoglobin level; central retinal subfield thickness; NEI VFQ-25 overall composite score). B. Area-under-the-curve analysis of least-squares mean adjusted change from baseline to month 36 in NEI VFQ-25 overall composite score.
runibizumab therapy in years 2 and 3, the NEI VFQ-25 overall composite score gains by month 36 were similar across the groups, with a least-squares mean (SE) overall composite score gain from baseline of approximately 4 points (4.1 [1.7], 4.0 [1.7], and 4.1 [1.8] points, respectively). Area-under-the-curve analysis (Figure 1B) did not identify a difference in visual function at 36 months between patients treated with ranibizumab throughout the core and extension studies and those initially receiving laser monotherapy in the core study who switched to ranibizumab in the extension study (least-squares mean [95% confidence interval] difference vs laser: ranibizumab +1.5 [−2.3, 5.3]). Supplementary Online Figure S1A shows the unadjusted mean change in NEI VFQ-25 composite score from baseline to month 3 and each annual visit to month 36 for extension study participants in each of the three original treatment arms. Area-under-the-curve analysis is shown in Supplementary Online Figure S1B.

Supplementary Online Figure S2 shows least-squares mean changes in NEI VFQ-25 scores over 36 months for the near activities, distance activities, general vision, and mental health subscales, adjusted for the same covariates as in Figure 1. For both the 12 month and 24 month scores on the near activities subscale, initial ranibizumab therapy, either alone or combined with laser, resulted in the greatest gain in NEI VFQ-25 scores. However, by 36 months, following a late gain in BCVA in the third year, the core laser-only group had achieved a substantial gain relative to baseline, which appeared to be similar to the overall gain in the two ranibizumab groups. By contrast, gains over time on the distance activities subscale did not appear to differ by initial treatment allocation. The NEI VFQ-25 mental health subscale showed substantial gains in all three treatment groups, particularly by months 24 and 36; no differences across treatment groups were identified. Least-squares mean results for all NEI VFQ-25 subscales are shown in Supplementary Online Figure S3.

In both the core and extension studies, only 21% of participants had their BSE as the study eye, while 55% of participants in the core and 60% in the extension study had their WSE as the study eye, and for 21% of participants in the core and 19% in the extension study, the study eye was neither the BSE nor the WSE. Data were missing for two patients at baseline. Baseline NEI VFQ-25 overall composite and selected subscale scores are shown in Table 4 for these analyses. For each subscale, baseline scores tended to be lower when the study eye was the BSE. Supplementary Online Figure S3 shows the least-squares mean changes from baseline for the BSE, WSE, and neither BSE nor WSE subgroups for the overall composite and the near activities, distance activities, general vision, and mental health subscales. The greatest gains in NEI VFQ-25 scores were typically seen for participants treated in their BSE, particularly for participants assigned to ranibizumab monotherapy during the first

Table 4. Baseline NEI VFQ-25 composite and selected subscale scores according to study eye status as the better-, worse-, or neither-better-nor-worse-seeing eye in each treatment arm.

| Subscale                | Better (n = 12) | Same (n = 10) | Worse (n = 40) |
|-------------------------|----------------|--------------|---------------|
| Composite               | 67.1 ± 2.5     | 70.9 ± 1.9   | 70.2 ± 2.1    |
| Near activities         | 59.8 ± 2.1     | 69.6 ± 2.6   | 69.2 ± 2.1    |
| Distance activities     | 64.5 ± 2.4     | 74.0 ± 2.7   | 74.4 ± 2.6    |
| General vision          | 65.2 ± 2.4     | 70.0 ± 1.7   | 69.0 ± 1.8    |
| Mental health           | 60.0 ± 2.5     | 70.5 ± 2.9   | 70.1 ± 2.3    |

NEI VFQ-25, National Eye Institute 25-item Visual Function Questionnaire.

Data are presented as mean ± SD.
year. This gain was seen in the near activities subscale, and persisted in the core ranibizumab monotherapy group throughout the 3 years. Differences in NEI VFQ-25 scores among treatment groups were less evident for participants treated in their WSE and for participants whose treated eye was neither their BSE nor their WSE.

Discussion

To the best of our knowledge, this is the first study to assess long-term (3 year) effects of a specific treatment for DME on patient-reported visual function, using the validated NEI VFQ-25 instrument. The results of this multicenter, international extension study demonstrate that the substantial improvements in patient-reported visual function achieved with ranibizumab, as monotherapy or combined with laser therapy, over the 12 months of the core study were generally maintained, albeit with a slight decrease in magnitude, over 36 months. These findings suggest that the therapeutic benefits of ranibizumab in the long-term treatment of DME translate into improvements in patients’ confidence in their ability to perform the daily activities of life that require VA, such as reading, cooking, and driving. These outcomes were noted regardless of whether a participant’s treated eye was the BSE, WSE, or neither BSE nor WSE. Nevertheless, improvements in scores were anticipated to be greatest among participants treated in their BSE and, indeed, the NEI VFQ-25 gains recognized were typically of highest magnitude in this group. These results are consistent with those of Bressler et al. 17, who reported that the percentage of ranibizumab-treated patients experiencing a ≥10 point gain in NEI VFQ-25 overall composite and subscale scores was greater for the BSE than the WSE in patients with neovascular age-related macular degeneration. In the current study, mean baseline scores were consistently higher among participants who contributed their WSE to the study, compared with those contributing their BSE. Participants who contributed a study eye that was neither BSE nor WSE generally had scores in between the WSE and BSE values.

Gains from baseline in key NEI VFQ-25 subscale scores (prospectively selected because these vision-specific domains were considered most likely to be responsive to treatment of DME) were generally of lower magnitude for the distance activities subscale and for the composite score than for the near activities, general vision, and mental health subscales. Gains in different subscale scores may be associated with particular benefits; for example, gains in an individual’s near activities subscale score may mean that he or she has recovered reading vision, or gains in an individual’s mental health subscale score may be associated with alleviation of depression. Subclinical or overt depression may accompany vision impairment in a proportion of individuals with visual impairment 18. A reduced effect on NEI VFQ-25 scores for participants who showed evidence of more chronic DME (worse baseline BCVA and greater CSF thickness) was found after 1 year in the core study 12.

Patients who were managed initially with laser monotherapy, of whom 80% received ranibizumab during the extension study 15, had mean NEI VFQ-25 composite scores that were lower than those in the ranibizumab groups at 12 months, but at month 36 these scores appeared to be similar to those of patients initially randomized to ranibizumab. Because many patients with DME are of working age, a delay in achieving maximum possible vision function benefits may have an important economic impact.

There are few detailed studies with which to compare our findings. The pegaptanib DME trial presented NEI VFQ-25 2 year data 1, which are supportive of the RESTORE study findings reported herein. Clinically meaningful differences (≥5 point differences between groups) were reported for some of the NEI VFQ-25 subscales at 54 weeks (near activities, distance activities, and social functioning subscales) and 102 weeks (distance activities, social functioning, and mental health subscales, and composite score) in patients treated with pegaptanib. The RIDE and RISE studies also collected data on longer-term (3 year) outcomes of monthly ranibizumab therapy in patients with DME 19, but NEI VFQ-25 data have not yet been published.

There are several limitations to this study. It was a relatively small-scale study, and approximately 21% of core study participants did not enter the extension study. Although the reasons for non-enrollment into the extension study were not formally recorded, the issues were mainly administrative 15. Compared with those who did not continue, patients who entered the extension study were typically younger and had better visual acuity at baseline and at month 12. These differences may potentially have affected the results reported here. Additional limitations were that patients entering the extension study were not randomized, and that variation in NEI VFQ-25 scores between groups at entry into the extension study was not controlled for. This may have introduced bias into the analysis as eyes with lower initial NEI VFQ-25 scores tend to show greater improvements with treatment, owing to regression to the mean effects. Missing values were imputed using the LOCF method, which can produce biased estimates of the treatment effect 20.

Most patients (approximately 60%) had treatment in the WSE. The number of patients treated in the BSE, in which the effects on patient-reported visual function were greatest, as expected, was relatively small (21%). In addition, a substantial proportion of patients in the RESTORE study had a baseline BCVA letter score of 73 or better (approximate Snellen equivalent, 20/40 or better) in one or both eyes, potentially leading to ceiling effects for
BCVA and NEI VFQ-25 changes. Together, these factors may have reduced the power to demonstrate an effect. Furthermore, the outcomes reported here are based on the protocols followed in this study; it is unknown whether the treatment regimens followed in RISE and RIDE, which evaluated patient-reported outcomes, or in the Diabetic Retinopathy Clinical Research Network studies, would result in different outcomes.

**Conclusion**

In conclusion, this study provides evidence that ranibizumab therapy provides long-term improvements in self-reported visual function in patients with vision impairment due to DME. Gains in patient-reported visual function realized at 1 year in eyes initially treated with ranibizumab in the RESTORE core study decreased slightly by 36 months. Eyes originally receiving laser monotherapy for 1 year, then ranibizumab for 2 years achieved similar gains by year 3 to eyes receiving ranibizumab for 3 years. During the 2 year extension, while there was a reduction in injection frequency relative to the core study in the original ranibizumab groups, gains in both BCVA and visual function scores were largely maintained and tended to parallel each other.

**Transparency**

**Declaration of funding**

This study was sponsored by Novartis Pharma AG, Switzerland. The sponsor participated in the design of the study, data analysis, and review of the manuscript.

**Declaration of financial/other relationships**

P.Mi. has disclosed that he has received consultancy and lecturing fees from Novartis Pharma AG, Bayer Healthcare Pharmaceuticals, and Abbott, and travel grants from Novartis Pharma AG and Bayer Healthcare Pharmaceuticals. P.Ma. has disclosed that she is a member of medical advisory boards for Novartis Pharma AG, Allergan Inc., Alimera, Sanofi-Aventis Group, and Bayer Healthcare Pharmaceuticals, has received consultation fees from Novartis Pharma AG, Allergan Inc., Alimera, and Bayer Healthcare Pharmaceuticals, and has received a research grant from Novartis Pharma AG for activities outside the submitted work. S.B. has disclosed that she has received consultation fees from GlaxoSmithKline and is Co-Investigator of grants at the Johns Hopkins University sponsored by the following entities: Bayer HealthCare Pharmaceuticals Inc.; Genentech/Roche; Novartis Pharma AG; Regeneron Pharmaceuticals Inc.; The EMMES Corporation; The National Institutes of Health; and has an independent contract agreement at The Johns Hopkins University from the American Medical Association.

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