Placebo response reduction training increases assay sensitivity in clinical trials on migraine treatment

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Introduction:

- High placebo responses are a common reason why clinical trials fail to discriminate effective treatments from placebo across therapeutic areas.[1]
- The main driver of the placebo response is thought to be expectation of therapeutic benefit.[1,2]
- Discrimination between drug and placebo can be improved under conditions where patients' expectation is neutralized through exposure to balanced information about the likelihood of benefit[3], or patients are trained to attend to internal experiences rather than external cues.[4]
- Placebo Response Reduction (PRR) Training was developed to neutralize the placebo response through psychoeducational training aimed at neutralizing expectations of therapeutic benefit, and has been associated with reduced placebo effects in clinical trials in other therapeutic areas.[5]

Objective:

The objective of this study was to determine whether PRR Training was associated with a lower placebo response in 3 Phase 3 trials of a CGRP antagonist compared to a Phase 2 trial which did not use such training

Methods:

Placebo Response Reduction Training

- The PRR Training Program consists of psychoeducational materials designed to neutralize study staff and subject expectations.
- Content was developed through cognitive debriefing studies, subject interviews, feedback, and input from subject material experts.
- The PRR training program includes:
  - Presentation and live role-play at sponsor investigator meeting
  - Staff training modules and competency quiz with completion certificates
  - On-demand staff training
  - Subject training modules
  - Subject competency quiz
- To date, PRR Training has been implemented in over 40 unique clinical trials, in 45 different countries, with over 50,000 subjects trained.

Analysis

- Data were extracted from three studies that implemented PRR training as well as a comparable study that did not implement PRR training.

- The primary endpoint of all four studies was the change in migraine headache days from baseline. The difference in migraine days between placebo and CGRP antagonist was calculated across 3, phase III studies. These results were descriptively compared to the phase II study.
- The average proportion of placebo responders (≥50% reduction in migraine headache days) were calculated across the 3, phase III studies. The proportion of placebo responders between phase II and III studies was compared by using a chi-squared analysis.
- This proportion of placebo responders was a secondary endpoint for the four studies and was chosen an outcome measure of interest due to the primary research question on the efficacy of PRR on neutralizing placebo response.

Table 1. Comparison in study design between phase II and III studies

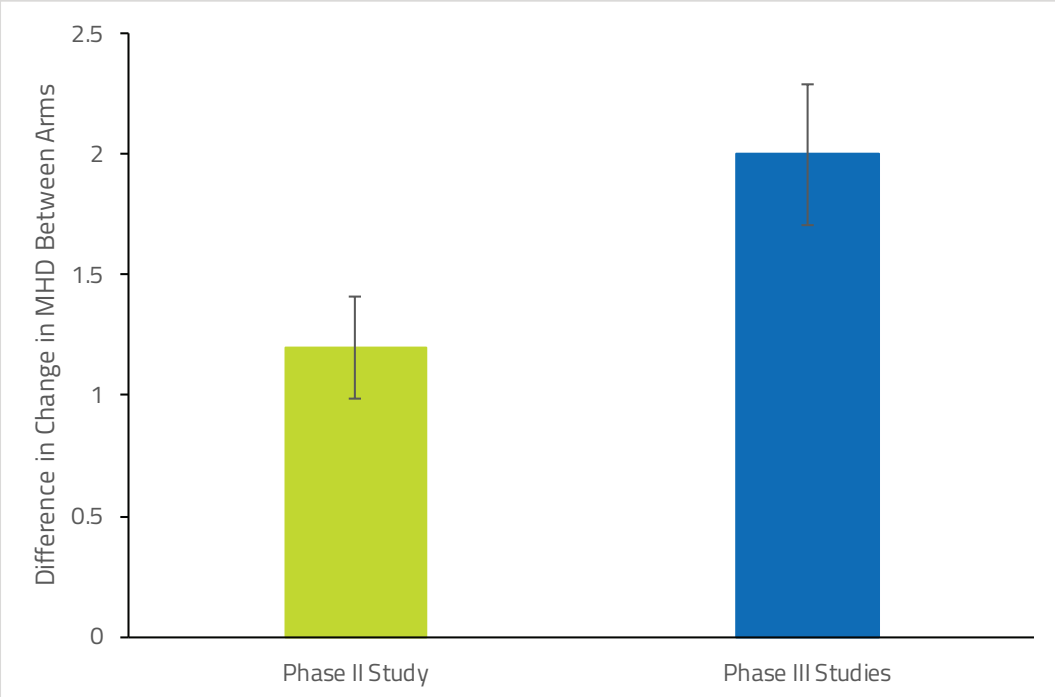
	Phase II	3 Phase III
Study design	Multi-center, randomized, double-blind, placebo controlled	Multi-center, randomized, double-blind, placebo controlled (3 studies)
Treatment	150mg every 2 weeks for 3 months	240mg loading dose, followed by 120mg monthly for 6 months (2 studies) 240mg loading dose, followed by 120mg monthly for 3 months (1 study)
Population		
Diagnosis	ICHD defined migraine	ICHD defined migraine
Migraine frequency	4-14 MHD per month	4-14 MHD per month (2 studies) ≥15 MHD per month (1 study)
*Concomitant medications	None	None (2 studies)≤1 (1 study)

*Concomitant preventative migraine medications
MHD Migraine headache days; ICHD International Classification of Headache Disorders

Results:

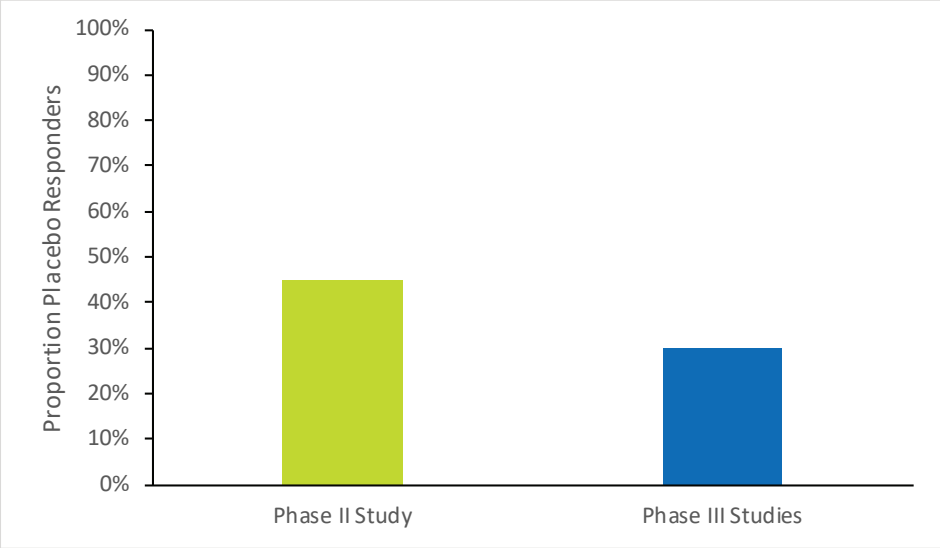
- The phase II clinical trial had 219 subjects and the 3, pooled, phase III studies had 2,954 subjects.
- The mean difference in change in migraine headache days per month between placebo and active drug for the phase II study was 1.2 (SE+/- 0.21, p=0.003).
- The mean difference in change in migraine headache days between placebo and active drug for the pooled phase III studies was 2.01 (SE+/-0.29, p<0.001).
- In the phase II trial, 45% of subjects in the placebo group were considered responders (≥50% reduction in migraine headache days), whereas only 30% of subjects the placebo group were considered responders for the phase III studies.
- There was a statistically significantly lower proportion of placebo responders in the pooled phase III trials than in the phase II trial (-15%; x2=21.2, p<0.001).

Figure 1. Difference in change in migraine headache days between arms for phase II and phase III studies



MHD Migraine headache days

Figure 2. Proportion of placebo responders in phase II and phase III studies



Placebo responder (≥50% reduction in migraine headache days)

Discussion:

- The 3, phase III studies that implemented PRR training had 15% lower placebo responders than the phase II study that did not implement PRR training, a clinically and statistically significant difference (p<.001).
- These results are supported by a meta-analysis examining the placebo response rate in clinical trials on chronic low back pain. In this analysis, the study that implemented accurate symptom reporting (ASR) and PRR training had the lowest proportion of placebo responders (19.1%) compared to studies that did not implement this training (average 37.7%).[5]
- The results of these studies, taken together, suggest PRR training may successfully neutralize the placebo response resulting in greater assay sensitivity and protection of study endpoints.
- Because there were likely other differences between these studies aside from PRR Training, such as differences in details of study design and population, we cannot claim a causal relationship between the PRR Training and the lower observed placebo response; however these results are consistent with similar studies in the literature.
- Further research is needed on controlling the placebo response in clinical trials. Meanwhile, sponsors should consider PRR Training in clinical trials with subjective outcomes.

References:

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