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

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THE PROBLEM

High placebo responses are a common reason why clinical trials fail to discriminate effective treatments from placebo across therapeutic areas.[1]

THE SOLUTION

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.[2]

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:

- Content was developed through cognitive debriefing studies, subject interviews, feedback, and input from subject material experts.
- To date, PRR Training has been implemented in over 40 unique clinical trials, in 45 different countries, with over 50,000 subjects trained.

Analysis:

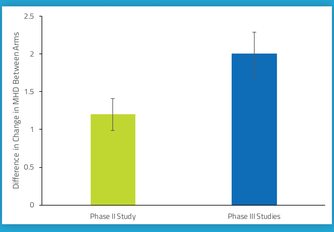
Table 1. Comparison in study design between phase II and III studies

	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

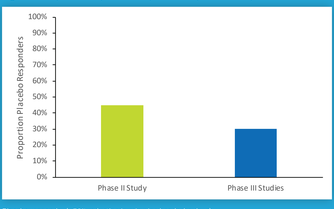
Results:

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%).[2]

References:

1. Benedetti F, Carlino E, Piedimonte A. Increasing uncertainty in CNS clinical trials: the role of placebo, nocebo, and Hawthorne effects. Lancet Neurol. 2016;15(7):736-747. doi:10.1016/S1474-4422(16)00066-1

2. Erpelding N, Treister R, Lawal O, Elder H, Katz N. Placebo response reduction training reduced placebo responses in a randomized controlled trial in chronic low back pain. Presented at the: Annual Pain and Migraine Therapeutics Summit; September 2017.

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