Author's response to reviews

Title: Unmet clinical needs in chronic migraine: Rationale for study and design of COMPEL, an open-label, multicenter study of the long-term efficacy, safety, and tolerability of onabotulinumtoxinA for headache prophylaxis in adults with chronic migraine

Authors:

Andrew M. Blumenfeld (blumenfeld@neurocenter.com)
Sheena K. Aurora (saurora@stanford.edu)
Karen Laranjo (laranjo_karen@cox.net)
Spyros Papapetropoulos (spapapetropoulos@med.miami.edu)

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Author's response to reviews: see over
Dear Dr. Shipley,

We are pleased to resubmit our manuscript, “Unmet clinical needs in chronic migraine: Rationale for study and design of COMPEL, an open-label, multicenter study of the long-term efficacy, safety, and tolerability of onabotulinumtoxinA for headache prophylaxis in adults with chronic migraine” (MS: 1543962306704543), for consideration to be accepted to *BMC Neurology*.

Below are the Reviewer Comments, with our responses. We appreciate this opportunity to revise the manuscript for your review.

Thank you for your time in reviewing this paper.

Sincerely,

Andrew M. Blumenfeld, MD
The Neurology Center
320 Santa Fe Drive, Suite 150
Encinitas, CA 92024
Phone: 760-942-1390
Email: blumenfeld@neurocenter.com
Reviewer #1:
Reviewer Comment:
I have just one amendment regarding the definition of chronic migraine, which, in the present case, include both patients with and without medication overuse.

Medication overuse is a big bias for any kind of study, since functional as well as neuroimaging tests change depending on being in the overuse phase and on the basis of the overused medication. I noticed that the criteria of response to detoxication it was pulled off the ICHD-IIIbeta. In particular, in the point 8.2 (Medication-overuse headache, MOH) it is clearly written that the MOH “usually, but not invariably, resolves after the overuse is stopped”, meaning that this *ex adiuvantibus* criteria is not essential to the diagnosis of MOH and chronic migraine should be diagnosed only when patients experience headache chronification without medication overuse. This is a clear border-line situation, however, in order to avoid misunderstanding, those patients overusing medication should be excluded or should be given both diagnoses of chronic migraine (code 1.3) and medication overuse headache (code 8.2), see ICHD-IIIbeta classification (Notes on page 650). Moreover, in order to pull off confounding effects MOH patients should be sub-classified in overusing single classes of medications (NSAIDs, triptans, combination, etc) and percentage reduction in number of tablet intake/month should be added as secondary outcome.

Author Response:
We thank the reviewer for identifying the issue of medication overuse headache, and note that a similar concern was raised regarding the inclusion of patients with MOH in the Phase 3 clinical program of onabotulinumtoxinA in chronic migraine (PREEMPT).1

The PREEMPT and COMPEL authors consulted both the Task Force of the International Headache Society Clinical Trials Subcommittee and their published guidelines, and determined from these sources that — because medication overuse is very common in patients with chronic migraine — their inclusion and stratification in clinical studies of chronic migraine patients was necessary to avoid losing the opportunity to, “address the benefits of treatment in a large group with disabling headache and an unmet treatment needs.”1 Guidance from the International Headache Society Clinical Trials Subcommittee (Silberstein 2008) specifically recommends that chronic migraine (CM) subjects with medication overuse (CM-R Criteria A-C, but not D) be included in clinical trials with consideration for stratification.

In PREEMPT, subjects were stratified at baseline for the presence of medication overuse and tracked throughout the study. A subgroup analysis was subsequently published determining the impact of baseline medication overuse on the safety and efficacy of onabotulinumtoxinA therapy.
(the subgroup results were similar to those of the ITT population for safety, tolerability, and efficacy.) COMPEL will, similarly, gather data at baseline regarding the presence of medication overuse. Primary and secondary efficacy variables will be summarized by the subgroup factors including history of medication overuse (yes versus no). Subgroup analyses will only be conducted where adequate sample size is available for each cohort of the characteristic. As suggested by the reviewer, the COMPEL study plans to identify patients by overuse of single classes of medications and combinations. Abortive headache medications used will be captured throughout the trial, allowing the investigators to determine the real-world effect of onabotulinumtoxinA treatment on the use of these medications. Additionally, while the percentage reduction in medications is not a secondary outcome, it will be captured.


Reviewer #2:
Reviewer Comment:
Major revisions: There are several points which require clarification for the reader. These deal with:
1) The labelling of visits which at times are labelled by weeks and others by visit numbers. Ideally both the week number and the visit number should be used together at each point in the report and figures for the study.

Author Response: We thank the reviewer for noting this point of clarification. We have added visit numbers under the week numbers in Figure 1. We have also added, in the text, visit numbers to existing week numbers, and week or day numbers to existing visit numbers, where appropriate for clarification.

Reviewer Comment:
2) The issue of migraine preventive medications requires clarification beyond what is in the text and would be well served with a figure indicating where and when preventative medications can be taken, started, stopped.
**Author Response:** We thank the reviewer for the suggestion, and have added a table (Table 2), that includes a full description of the criteria for starting, stopping, adding, or discontinuing oral headache prophylaxis during the study.

**Reviewer Comment:**
Additionally clarification should be made regarding what constitutes the “groups” that are going to be compared. It obviously not versus placebo and if these groups relate to the preventative medications then are these going be "lumped or split". if lumped is it going to consider those drugs that have evidence in chronic migraine, as per the table, versus those without evidence in CM and if based on evidence will it be open label or placebo or active comparator trials?

**Author Response:** We thank the reviewer for the comment. The objective of the COMPEL study is to evaluate the long-term safety and efficacy of onabotulinumtoxinA for migraine prophylaxis. The Phase 3 PREEMPT clinical program, which consisted of a 24-week double-blind phase and 32-week open-label phase, has assessed onabotulinumtoxinA vs placebo. While the goal of the phase 4 COMPEL study is to gather 2-year data on onabotulinumtoxinA treatment, a double-blind approach for such a long period of time would require denying placebo-assigned patients necessary treatment for a very long time indeed. Consequently, we have chosen an open-label design, without a comparator group. Efficacy will be assessed as mean change versus baseline. This approach is consistent with other Phase 4 studies.

**Reviewer Comment:**
Lastly since patients appear to have freedom in the use of acute medication how will the issue of medication overuse be addressed with or without regard to probable medication overuse headache.

**Author Response:** We thank the reviewer for this comment, which is similar to the primary comment made by Reviewer #1. Please see our response to that question.