Testing rimegepant for migraine—time to revise the trial design?

We read with interest the results of the phase 3 trial by Robert Croop and colleagues[1] on the use of rimegepant for treatment of acute migraine. We feel that this study, like other similarly designed trials, has major problems in its methods, which suggests caution should be taken when examining the results.

Some of these flaws are cited by the authors—namely, a single administration of the study drug and the absence of an active comparator. These two limitations might alone invalidate the results; the generalisability of the efficacy and safety measures after a single administration is questionable and the comparison of rimegepant with placebo is hardly acceptable when active treatment is available. Other features limit the validity of the study. The included population, which is mainly composed of women with obesity, is not representative of a population with migraine alone as obesity might influence the pharmacokinetics of rimegepant and lead to changes in drug efficacy. Furthermore, although the reported effect is statistically significant, the effect size is far from satisfying, and statistically significant is not equivalent to clinically significant.[2] Additionally, the results are missing many details, including p values for comparing the two groups in terms of clinical and demographic variables and side-effects, the distribution of missing data in both groups, and results of stratified and sensitivity analyses. Overall, our opinion is that the design of clinical trials should be revised to consider the needs of clinical practice. A synthesis of this debate, although concerning clinical trials in epilepsy, was published in 2017.[3] We believe that the reformulation of study designs will add to evidence-based medicine.

We declare no competing interests.

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1 Croop R, Goadsby PJ, Stock DA, et al. Efficacy, safety, and tolerability of rimegepant orally disintegrating tablet for the acute treatment of migraine: a randomised, phase 3, double-blind, placebo-controlled trial. *Lancet* 2019; **394:** 737–45.
2 Ranganathan P, Pramesh CS, Buyse M. Common pitfalls in statistical analysis: clinical versus statistical significance. *Perspect Clin Res* 2015; **6:** 169–70.
3 Ferlazzo E, Sueri C, Gasparini S, et al. Methodological issues associated with clinical trials in epilepsy. *Expert Rev Clin Pharmacol* 2017; **10:** 1103–08.

Authors' reply

We thank Sara Gasparini and colleagues for their critique of our work.[1] In stating that single-attack studies of acute treatments for migraine with no active comparator have major problems in their methods, however, they ignore their own recommendation that clinical studies should take regulatory requirements and the needs of clinical practice into account.[2] Studies of single migraine attacks are the global standard for establishing the efficacy of acute treatments of migraine and the cornerstone of regulatory approval in the USA.[3] Furthermore, because findings from multiple-attack studies can be affected by unblinding during repeated attacks (whereby patients learn to distinguish active drug from placebo), and carryover effects, the first attack is often used to define primary efficacy endpoints.[4] We acknowledge that consistent benefit is an important attribute of acute treatment, which has been shown for rimegepant in a long-term safety study of multiple migraine attacks.[5]

Although the use of an active comparator is not considered in US regulatory guidance,[3] the rimegepant development programme includes a previous phase 2b trial with a triptan group. This study found 2 h pain-free rates of 31% (27 of 86 patients) for rimegepant 75 mg and 35% (35 of 100 patients) for sumatriptan 100 mg.[6] 2–24 h pain-free rates were 28% (24 of 86 patients) for rimegepant 75 mg and 26% (26 of 100 patients) for sumatriptan 100 mg. The proportion of patients free from nausea was 67% (58 of 86 patients) for rimegepant 75 mg and 60% (60 of 100 patients) for sumatriptan 100 mg.

Data from multiple gepant development programmes certainly suggest clinically important differences between gepants and triptans. Triptans are vasoconstrictors with cardiovascular contraindications and precautions in labelling,[7] whereas gepants are not vasoconstrictors and do not have cardiovascular contraindications. Gepants are likely to be used when triptans are ineffective, poorly tolerated, or contraindicated.

The authors claim that the sample, which had a mean body-mass index of 30·9 kg/m^2 and was 85% women, was not representative of people with migraine. However, migraine is predominantly a disease of women and, in the USA, 43% of adults aged 40–59 years are obese.[8,9] Sex and body-mass index also did not predict response to rimegepant.

Finally, Gasparini and colleagues' request for p values and stratified analyses is puzzling. The groups were balanced and the data required to compute p values are in the paper. The analyses presented in the Article were stratified and the primary endpoints were composite endpoints that incorporated missing data as failures.

Our data show the efficacy, tolerability, and safety of rimegepant in the acute treatment of single migraine attacks, a key part of a comprehensive drug development programme. The clinical significance of rimegepant will be based on an amalgam of data that have been accumulated across the entire rimegepant development programme.[10]