PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Long-term efficacy and safety of erenumab in Japanese patients with episodic and chronic migraine: Results from a 28-week open-label treatment period of a randomized trial
AUTHORS	Hirata, Koichi; Takeshima, Takao; Sakai, Fumihiko; Numachi, Yotaro; Yoshida, Ryuji; Koukakis, Reija; Hasebe, Miki; Yui, Daishi; da Silva Lima, Gabriel Paiva; Cheng, Sunfa

VERSION 1 – REVIEW

REVIEWER	Pensato, Umberto IRCCS Humanitas Research Hospital
REVIEW RETURNED	26-Nov-2022

GENERAL COMMENTS	The Authors reported the safety and efficacy outcomes of erenumab in Japanese migraineurs in an open-label treatment period. They showed a persistent efficacy of erenumab for up to 1 year, in line with previous literature. The methods and results are strong and the paper is well-written. The results are mainly confirmatory, yet deserve to be published. I have no major or minor revisions. Yet, it would be interesting to analyze the efficacy in results in the sub-group of treatment-naive patients, as in Europe and America only treatment-refractory patients can receive anti-CGRP mAbs, therefore solid scientific data are lacking.

REVIEWER	Mozer, Reagan Bentley University, Mathematical Sciences
REVIEW RETURNED	19-Jan-2023

GENERAL COMMENTS	This paper presents the results of a multi-center randomized trial to evaluate the efficacy and safety of once-monthly erenumab for treatment of episodic or chronic migraine among Japanese patients. The authors utilize a simple and straightforward analytical approach based on descriptive statistics for their evaluation. Their findings provide a clear and reasonably comprehensive assessment of the safety and efficacy of erenumab for the target population. The authors also discuss how the results from an open-label treatment period compare to those observed during a double-blind randomized controlled trial. I have two minor comments/suggestions regarding the statistical analysis: 1. The authors state that their analysis included patients who received at least one dose of erenumab 70mg in the OLTP (n=254).

	However, the baseline demographics presented in Table 1 include all N=261 patients enrolled in the parent study. For consistency, the authors should consider adjusting this table to include only those patients that participated in the OLTP. 2. The authors note that 10 of the original 254 patients included in their sample discontinued treatment before the end of the study period. As a sensitivity check, it would be interesting to note the extent to which the safety and efficacy results presented are affected by the inclusion of these 10 participants. That is, would an analysis based on only those patients who completed the full IP lead to any notable changes in results?

REVIEWER	Wan Sulaiman, Wan Aliaa Universiti Putra Malaysia, Neurology
REVIEW RETURNED	01-Feb-2023

GENERAL COMMENTS	I have reviewed your manuscript and overall find it well written with important findings to the Japanese / Asian migraine population. However, due to the poor reporting of methodology (it's very confusing esp to differentiate with your RCT studies vs your current open label study) and overstatement of conclusions, as well as poor discussions, I have to reject your manuscript at the current standard.

REVIEWER	Pellesi, Lanfranco University of Copenhagen Faculty of Health and Medical Sciences, Dansk Hovedpinecenter I am employed at Lundbeck.
REVIEW RETURNED	07-Feb-2023

GENERAL COMMENTS	I have no concerns regarding publication.

REVIEWER	Gobel, Hartmut Schmerzklinik Kiel Migräne- und Kopfschmerzzentrum
REVIEW RETURNED	11-May-2023

GENERAL COMMENTS	The authors evaluate the 1-year efficacy and safety of once-monthly erenumab 70 mg following a 24-week double-blind treatment period (DBTP) of a phase 3 randomized study of Japanese patients with episodic migraine (EM) or chronic migraine (CM). The results demonstrate a persistence of efficacy for up to 1 year and a safety profile similar to that reported during the DBTP. From week 24 of the DBTP to the end of the OLTP at week 52, the reduction from baseline in MMD and MSMD, and the proportion of ≥50% and ≥75% responders in MMD reduction were maintained. The study describes important experience on efficacy and tolerability in Japanese patients. The study design is appropriate. The conclusions are justified by the results.

VERSION 1 – AUTHOR RESPONSE

Reviewer #1 (Dr. Umberto Pensato, IRCCS Humanitas Research Hospital)	

The Authors reported the safety and efficacy outcomes of erenumab in Japanese migraineurs in an open-label treatment period. They showed a persistent efficacy of erenumab for up to 1 year, in line with previous literature. The methods and results are strong and the paper is well-written. The results are mainly confirmatory, yet deserve to be published.	Not applicable (no change requested)
I have no major or minor revisions. Yet, it would be interesting to analyze the efficacy in results in the sub-group of treatment-naive patients, as in Europe and America only treatment-refractory patients can receive anti-CGRP mAbs, therefore solid scientific data are lacking.	Thank you for your comment. In the current dataset, only 61 subjects with either EM or CM had never used migraine preventive treatment, thus the sample is too small for robust analysis.
Reviewer #2 (Dr. Reagan Mozer, Bentley University)	
This paper presents the results of a multi-center randomized trial to evaluate the efficacy and safety of once-monthly erenumab for treatment of episodic or chronic migraine among Japanese patients. The authors utilize a simple and straightforward analytical approach based on descriptive statistics for their evaluation. Their findings provide a clear and reasonably comprehensive assessment of the safety and efficacy of erenumab for the target population. The authors also discuss how the results from an open-label treatment period compare to those observed during a double-blind randomized controlled trial.	Not applicable (no change requested)
The authors state that their analysis included patients who received at least one dose of erenumab 70mg in the OLTP (n=254). However, the baseline demographics presented in Table 1 include all N=261 patients enrolled in the parent study. For consistency, the authors should consider adjusting this table to include only those patients that participated in the OLTP.	We thank the reviewer for their comment. Table 1 (Page 9) has been updated as suggested, as has relevant corresponding text (Page 8, Lines 171-173).
The authors note that 10 of the original 254 patients included in their sample discontinued treatment before the end of the study period. As a sensitivity check, it would be interesting to note the extent to which the safety and efficacy results presented are affected by the inclusion of these 10 participants. That is, would an analysis based on only those patients who completed the full IP lead to any notable changes in results?	All available data from the 10 subjects who discontinued the study treatment early are included in the analyses. Given the high 96% completion rate of the study, excluding these 10 subjects should not alter any conclusion of the study results. The reasons for their early discontinuation are not likely to impact the study results either. Therefore, we do not think it would be informative to conduct the suggested sensitivity analysis.
Reviewer #3 (Dr. Wan Aliaa Wan Sulaiman, Universiti Putra Malaysia)	
I have reviewed your manuscript and overall find it well written with important findings to the Japanese / Asian migraine population. However, due to the poor reporting of methodology (it's very confusing esp to differentiate with your RCT studies vs your	We appreciate your review. Where possible, we have attempted to clarify methodology (Page 5, Line 97-99; Page 6, Lines 123-124 and 130-134), provide more conservative conclusions (Page 3, Lines 46-48; Page 15, Lines 284-287), and improve Discussion (Page 14, Lines 256-259, 261-

current open label study) and overstatement of conclusions, as well as poor discussions, I have to reject your manuscript at the current standard.	265, 268-271, and 276-279; Page 15, Lines 280-281).
Reviewer #4 (Dr. Lanfranco Pellesi, University of Copenhagen Faculty of Health and Medical Sciences)	
I have no concerns regarding publication.	Not applicable (no change requested)
Reviewer #5 (Prof. Hartmut Gobel, Schmerzklinik Kiel Migräne- und Kopfschmerzzentrum)	
The authors evaluate the 1-year efficacy and safety of once-monthly erenumab 70 mg following a 24-week double-blind treatment period (DBTP) of a phase 3 randomized study of Japanese patients with episodic migraine (EM) or chronic migraine (CM). The results demonstrate a persistence of efficacy for up to 1 year and a safety profile similar to that reported during the DBTP. From week 24 of the DBTP to the end of the OLTP at week 52, the reduction from baseline in MMD and MSMD, and the proportion of ≥50% and ≥75% responders in MMD reduction were maintained. The study describes important experience on efficacy and tolerability in Japanese patients. The study design is appropriate. The conclusions are justified by the results.	Not applicable (no change requested)

References

1. Calvert M, Blazeby J, Altman DG, et al. Reporting of patient-reported outcomes in randomized trials: the CONSORT PRO extension. *JAMA.* 2013;309(8):814-822.
2. Goadsby PJ, Reuter U, Hallstrom Y, et al. A Controlled Trial of Erenumab for Episodic Migraine. *N Engl J Med.* 2017;377(22):2123-2132.
3. Ailani J, Lipton RB, Goadsby PJ, et al. Atogepant for the Preventive Treatment of Migraine. *N Engl J Med.* 2021;385(8):695-706.
4. Takeshima T, Sakai F, Hirata K, et al. Erenumab treatment for migraine prevention in Japanese patients: Efficacy and safety results from a Phase 3, randomized, double-blind, placebo-controlled study. *Headache.* 2021;61(6):927-935.

VERSION 2 – REVIEW

REVIEWER	Mozer, Reagan Bentley University, Mathematical Sciences
REVIEW RETURNED	19-Jul-2023

GENERAL COMMENTS	The authors have adequately addressed all concerns in the revised manuscript.

REVIEWER	Gobel, Hartmut Schmerzklinik Kiel Migräne- und Kopfschmerzzentrum
REVIEW RETURNED	31-Jul-2023

GENERAL COMMENTS	In a comprehensive study, the authors describe the efficacy and tolerability of erenumab in Japanese patients with episodic or chronic migraine. In the revision, all suggestions have been taken up and adequately implemented. The study provides a very important insight into the use of erenumab in Japanese patients.