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LETTER TO THE EDITOR Open Access

Letter to the editor: European headache federation guidelines on the use of monoclonal antibodies acting on the calcitonin gene-related peptide or its receptor for migraine prevention

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To the Editor,

We thank you for publishing the guidelines on the use of monoclonal antibodies (mAbs) targeting the calcitonin gene-related peptide (CGRP) pathway for migraine prevention [1]. We believe that these guidelines will be of great importance for clinicians in guiding treatment decisions and ultimately benefiting patients with migraine, which is a significant contribution to the field.

While reviewing the guidelines, we observed a few inconsistencies in the data presented for erenumab. On Page 20, Fig. 1 mentions "*Treatment with Erenumab 140 mg results in a small unimportant increase of serious adverse events occurrence compared to placebo*" [1]. However, as reflected in Fig. 1, the risk with placebo was 25 per 1000 and 11 per 1000 with erenumab. Hence, there is a "decrease" in serious adverse event occurrence observed with erenumab versus placebo, which we have highlighted in Fig. 1.

We also observed an inconsistency within Fig. 2 (Page 30) that provides information on binding or neutralising antibodies for all pivotal trials included in this guideline [1]. In this table, the data from the ARISE study [2] have been erroneously shown for the STRIVE study [3]. Similarly, the data from the STRIVE study [3] have been shown for the ARISE study [2]. Also, the percentage of neutralising antibodies in the ARISE study is reported as 0.3%, whereas the correct value is 0.4% (n = 1/283). The proposed correction for this swapping of data between the ARISE and STRIVE studies and for correcting the value for the neutralising antibodies is presented in Fig. 2. In addition, Fig. 2 includes frequencies of neutralising antibodies for the 7 mg and 21 mg doses, which were used in a relatively small Phase 2 proof-of-concept study [4]. These doses were ineffective, not studied further, and are not commercially available. Hence, for proper guidance to clinicians, we suggest omitting the data for 7 mg and 21 mg.

We would like to acknowledge the efforts and contributions of the consensus panel for drafting these guidelines. The data inconsistencies highlighted in this letter could have affected the final results and recommendations made in the guidelines. Moreover, the erroneous data may be cited by authors in upcoming publications, which may potentially affect the recommendations for the mAbs targeting the CGRP pathway. Hence, we request that you consider the proposed amendments to address these inconsistencies for the benefit of the readers.

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Table 14 Summary of findings table for treatment with erenumab 140 mg monthly subcutaneous injection compared with no treatment for prevention of chronic migraine

Outcomes	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with erenumab				
Reduction of monthly migraine days follow up: 3 months	The mean reduction of monthly migraine days was −4.2 days	The mean reduction of monthly migraine days in the intervention group was 2.5 days fewer (3.5 fewer to 1.4 fewer)	–	468 (1 RCT)	⊕⊕⊕○ MEDIUM[a]	Treatment with Erenumab 140 mg reduces monthly migraine days slightly compared to placebo.
Reduction of monthly acute treatment days follow up: 3 months	The mean reduction of monthly acute treatment days was −1.6 days	The mean reduction of monthly acute treatment days in the intervention group was 2.6 days fewer (3.3 fewer to 1.8 fewer)	–	468 (1 RCT)	⊕⊕⊕○ MEDIUM[a]	Treatment with Erenumab 140 mg reduces monthly acute treatment days slightly compared to placebo.
At least 50% reduction of monthly migraine days follow up: 3 months	235 per 1000	412 per 1000 (314 to 540)	RR 1.7531 (1.3359 to 2.3007)	468 (1 RCT)	⊕⊕⊕○ MEDIUM[a]	Treatment with Erenumab 140 mg results in at least 50% reduction of monthly migraine days compared to placebo.
Serious adverse events follow up: 3 months	25 per 1000	11 per 1000 (2 to 51)	RR 0.4286 (0.0900 to 2.0408)	470 (1 RCT)	⊕⊕⊕○ MEDIUM[a]	Treatment with Erenumab 140 mg results in a small unimportant decrease of serious adverse event occurrence compared to placebo.
Mortality follow up: 3 months	0 per 1000	0 per 1000 (0 to 0)	not estimable	470 (1 RCT)		No deaths were observed with treatment with Erenumab 140 mg or placebo

a. Downgraded once due to imprecision: phase II study
CI Confidence interval, *RR* Risk ratio, *RCT* Randomized controlled trial; [a]Downgraded once due to inconsistency.
GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

Fig. 1 Proposed amends for Table 14

Table 20 Binding or neutralizing antibodies directed against anti-CGRP monoclonal antibodies in available randomized clinical trials

Author, Year	Phase, setting	Participants (n)	Follow-up	Binding antibodies	Neutalizing antibodies	Clinical implications
Eptinezumab						
Dodick, 2014 [32]	II, EM	174	3 months	11/81	–	None
Erenumab						
Sun, 2016 [44]	II, EM	483*	3 months	8/104 for 70 mg	1/104 for 70 mg	None
Tepper, 2017 [45]	II, CM	667	3 months	11/190 for 70 mg 3/188 for 140 mg	0	None
STRIVE [36]	III, EM	955	6 months	8.0% for 70 mg 3.2% for 140 mg	0.2% for 70 mg 0 for 140 mg	None
ARISE [35]	III, EM	577	3 months	4.3% for 70 mg	0.4% for 70 mg	None
Fremanezumab						
Bigal, 2015 [27]	IIb, EM	297	3 months	1%§	–	None
Bigal, 2015 [26]	IIb, CM	264	3 months	1%§	–	None
HALO EM [34]	III, EM	875	3 months	1.4% for the monthly dosing 0 for single high dose	–	None
HALO CM [41]	III, CM	1130	3 months	1%	–	None
Galcanezumab						
REGAIN [31]	III, CM	836	3 months	2.7% for 120 mg 2.6% for 240 mg	2.3% for 120 mg 1.5% for 240 mg	None
Dodick, 2014 [33]	II, EM	218	3 months	15.7%#		None
EVOLVE 2 [42]	IIb, EM	936	3 months	–	–	None
EVOLVE 1 [43]	III, EM	1671	6 months	3.5% for 120 mg¶ 5.2% for 240 mg¶	0.2%	None

*The study included patients treated with erenumab 7 mg and 21 mg doses. These doses are not commercially available; §patients were positive at baseline; #including 6.2% of patients who were positive at baseline; ¶only treatment emergent antibodies

Fig. 2 Proposed amends for Table 20

Abbreviations
CGRP: Calcitonin gene-related peptide; mAb: Monoclonal antibody

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Availability of data and materials
ARISE study data publication is available online at: https://journals.sagepub.com/doi/full/10.1177/0333102418759786?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dpubmed
STRIVE study data publication is available online at: https://www.nejm.org/doi/10.1056/NEJMoa1705848?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dwww.ncbi.nlm.nih.gov

Authors' contributions
Both authors participated in the conception of the letter, read and approved the final letter.

Ethics approval and consent to participate
The study protocols were reviewed and approved by the appropriate institutional review board for each of the study sites. The studies were conducted according to Good Clinical Practice and the Declaration of Helsinki guidelines. Patients provided written informed consent before undergoing study procedures.

Consent for publication
Not applicable.

Competing interests
Daniel D. Mikol is a full-time employee of Amgen Inc. Thousand Oaks, California. Josefin Snellman is a full-time employee of Novartis Pharma A.G. Basel, Switzerland.

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