ACCME ACCREDITED WITH COMMENDATION

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ICER OPEN COMMENT PERIOD ON CGRP INHIBITORS FOR MIGRAINE

Submitted electronically to: publiccomments@icer-review.org

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Dear Dr. Pearson,

The American Headache Society (AHS) and the American Migraine Foundation (AMF) appreciate the opportunity to comment on ICER's Draft Evidence Report - **Calcitonin Gene-Related Peptide (CGRP) Inhibitors as Preventive Treatments for Patients with Episodic or Chronic Migraine: Effectiveness and Value**.

For 60 years, the American Headache Society has been and continues to be the leading professional society of health care providers dedicated to the study and treatment of migraine, headache and face pain. With over 1400 members and associates, the Society's education, research and advancement programs engage medical professionals throughout their careers, from the world's most sought after thought leaders to those at the beginning of their professional work in headache medicine. As the largest professional headache society of health care providers in the United States, and holding the distinction of CME credit provider with commendation from ACCME, AHS uses its strengths to design and deliver programs that teach, train and advance the field, whether designed to train professionals on the latest diagnostic methods, supporting and promoting the latest in headache research or educating on the newest of migraine and headache therapies, the Society is committed to advancing the expertise of its members and the field of headache. The American Migraine Foundation advocates for, supports, educates and engages the 47 million Americans who suffer the debilitating effects of migraine and other headache diseases. Founded by AHS in 2010, the AMF strives to mobilize a community for patient support and advocacy, as well as drive and support impactful research that translates into treatment advances.

We appreciate ICER's engagement with various stakeholders from the migraine community and the ongoing communication between ICER and AHS and AMF throughout this process. We provided feedback via email communication on March 16 after reviewing a pre-publication summary of ICER's economic model. After reviewing the full Draft Evidence Report, we have remaining concerns over the current quantitative analysis. We urge you to please consider the following points:

Patient Values Should be Top Consideration in Evaluation

The most important treatment outcomes for those living with migraine are improved quality of life and functional performance through the relief of the pervasive and disabling symptoms of migraine. AHS/AMF believes that the use of QALY as a methodology for a value assessment doesn't account for these important treatment outcomes. We highlight that any treatment that provides improvements to those living with migraine, including greater quality of life, productivity at work and at home, and more time spent with loved ones, provides enormous value

to this community. A successful therapeutic outcome depends not only on a reduction in migraine headache days (MHD) frequency, but also on the persistence and severity of pain and associated symptoms, level of disability and functional capacity. AHS/AMF urges ICER to utilize a more patient-centered approach with endpoints that represent incremental gains valued by patients.

The DER Does Not Fairly Account for Indirect Costs and Societal Burden of Migraine.

We remain concerned that the current framework will not adequately address the immense indirect costs and societal burden of migraine, and reemphasize our argument submitted to you in our December 2017 comment letter. The majority of direct costs due to migraine are incurred by public and commercial payors. Direct medical costs for individuals with migraine are significantly higher overall (40%) compared with matched non-migraine patients, both overall and within specific cost categories, such as emergency department (ED) visits (28%), inpatient (36%) and outpatient (45%) visits, and pharmacy expenses (36%). Indirect costs have been shown in previous studies to be substantial. In fact, migraine is unique in that a large majority of its economic burden is attributed to costs that are directly attributed to indirect costs. This translates to a significant burden on employers, as indirect costs are primarily calculated as absenteeism and presenteeism. Approximately 113 million workdays are lost annually in the United States due to absenteeism from individuals with migraine. The cost of this to employers exceeds $13 billion each year. Moreover, individuals with migraine are 2.5 and 2.4 times more likely to have a short-term and long-term disability claim, respectively, with an average cost of $26,543 per claim, compared with non-migraine individuals. In addition, more than half of migraine sufferers state that their work or school productivity is reduced by at least 50%. In addition, because 10% of children and adolescents experience migraine and some develop chronic migraine, clinical experience suggests there is a significant impact on career choices and wage growth among those the most disabled.

Lack of Long-Term Data Undervalues New Migraine Treatments.

As with all new and emerging therapies, long-term data regarding the safety and efficacy of the anti-CGRP monoclonal antibodies (mAbs) is limited. However, long-term open-label extension studies do provide some important evidence of long-term efficacy and safety. For the first of these antibodies expected to be approved, erenumab safety and efficacy are being evaluated over 5 years. In an interim analysis of one-year data, 383 patients had a median exposure of 575 days (28-822 days). The mean monthly migraine day at baseline was 8.2 and after 64 weeks, declined to 3.7. At the 64-week time point, after patients had first been randomized to either placebo or erenumab and then continued in the open-label phase, the $\geq$50%, $\geq$75%, and 100% responder rates were 65%, 42%, and 26%, respectively. Safety profile in the open-label phase was similar to the double-blind phase. Overall, safety of erenumab has been evaluated in 2,310.3 patient years exposure, including 2,066 patients who have received the treatment for $\geq$6 months. We use erenumab as an example as efficacy and safety profiles of the three additional anti-CGRP monoclonal antibodies since the efficacy, safety and tolerability profiles are similar, and since approval is expected within weeks for erenumab. Given the high rate of adherence compared to currently available oral preventive drugs' long-term outcomes, as seen in this interim analysis, are expected to be robust and accrue over time. Therefore, we respectfully disagree with the ICER grade on efficacy and safety as being "inconclusive". We believe the long-term data on these new treatments will support our point of view.

The Emphasis on "Therapeutic Gain" Values from Placebo-Controlled Trials May Lead to Underestimation of Efficacy

Placebo-controlled trials in pain (especially those delivered via injection) have a high and highly variable placebo response. However, the anti-CGRP monoclonal antibodies studies were powered to detect a clinically meaningful and minimally important difference between the active intervention and placebo. There has not been a single

controlled trial with any of the antibodies in either episodic or chronic migraine that has failed to meet its primary endpoint and demonstrate highly statistically significant superiority of active intervention over placebo.

The use of placebo-subtracted responses or 'therapeutic gains" to extrapolate the clinical impact of an active intervention has severe limitations. The response to active intervention has been remarkably consistent with and between each of the anti-CGRP monoclonal antibodies and it is the magnitude of the treatment response, the proportion of patients who respond, and the impact on the quality of life and disability of the patient that determines the clinical utility of a treatment. This has been expressed by The Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT). The recommendations from this consensus initiative involved representatives from academia, regulatory agencies (US Food and Drug Administration, European Medicines Agency), US National Institutes of Health, US Veterans Administration, consumer support and advocacy groups, industry, and more than multiple scientific, legal and medical disciplines. Their mandate was to develop consensus reviews and recommendations for improving the design, execution, and interpretation of clinical trials of treatments for pain. IMMPACT recommends that when evaluating the clinical meaningfulness of a treatment benefit, statistically significant group differences in a primary efficacy endpoint cannot be considered in isolation, as this may obscure meaningful individual patient improvements and other benefits and risks. Rather, the overall body of evidence with regard to outcomes must be considered to fully understand therapeutic benefit. We highly recommend ICER adopt an approach and model that follows these recommendations to determine the real-world value of any active intervention, especially for those where the primary endpoint is a pain measurement.

Acute and prophylactic treatment for migraine, in both historical and contemporary clinical trials are consistent for individual drugs and within drug classes. The placebo-response however varies considerably from trial to trial for preventive migraine medications. Therefore, it is difficult to compare different treatments with very different placebo responses unless they are studied in head-to-head trials. Furthermore, placebo-subtracted response rates provide an incomplete picture that typically underestimates the overall efficacy. In addition, those that respond to the treatment should be considered when calculating the QALY. When considering all patients randomized, it artificially and dramatically lowers the number of days gained over 2 years down.

Lack of Consideration of Discontinuation of Migraine Treatments Overestimates Costs

Most patients discontinue prescribed oral preventative medication within a year because of lack of efficacy, side effects or improvement. Most, if not all payers, stop covering more expensive treatments such as onabotulinumtoxinA if there is not significant improvement in 6 months. Thus, you must cut the number of patients receiving drug by at least 50 to 60 % and raise the efficacy of those who remain with greater than 50% improvement. This is the only way to give an honest estimate of QALY. As stated above, only those that respond to the treatment should be considered when calculating the QALY since non-responders will not continue to receive the treatment.

There remains an enormous unmet need in preventive migraine treatment. While approximately 38% of individuals with migraine should be offered preventive therapy, only 3-13% of individuals are receiving such treatments. Among the most severely affected individuals with chronic migraine who do receive preventive treatment, over 80% discontinue the medication within one year. While there may be several reasons for this poor treatment adherence, chief among them are suboptimal efficacy and tolerability. The recommendations for when to initiate preventive therapy are unchanged. Patients with migraine should be considered for preventive therapy in any of the following situations:

- Attacks significantly interfere with patients' daily routines despite acute treatment
- Frequent attacks (>4 headache days/month)

- Contraindication to, failure, or overuse of acute therapies
- Adverse events with acute therapies
- Patient preference

The American Headache Society and American Migraine Foundation will soon publish a consensus document that outlines the criteria for selecting patients who should be eligible to receive an anti-CGRP mAb for migraine prevention. We hope this will guide patients, clinicians in practice who prescribe for patients with migraine, and the payor community.

In conclusion, the need for improved migraine treatments is imperative. Many people living with migraine have received inadequate treatment options and outcomes for far too long. The ability for those with unmet treatment needs to have access to safe and effective therapy is our collective responsibility to patients in need. We agree that cost effective care is essential and that all stakeholders play a role. It is important that ICER establish a clear understanding with payors on the full value of these therapies.

Thank you for the opportunity to provide public comments regarding ICERs Draft Evidence Report. If you have questions, please contact Dr. David Dodick at Dodick.David@mayo.edu, Dr. Kathleen Digre at Kathleen.digre@hsc.utah.edu, or Meghan Buzby at mbuzby@talley.com.

On behalf of the Executive Board of the American Headache Society and the American Migraine Foundation,

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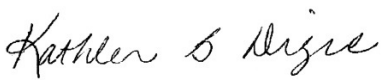

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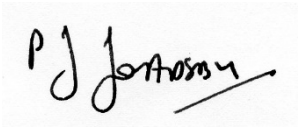

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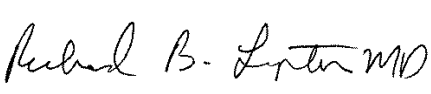

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References

Lipton RB, Bigal ME, Diamond M, et al. **Migraine prevalence, disease burden, and the need for preventive therapy**. *Neurology.* 2007;68(5):343-349.

Hepp Z, Dodick DW, Varon SF, et al. **Persistence and switching patterns of oral migraine prophylactic medications among patients with chronic migraine: A retrospective claims analysis**. *Cephalalgia.* 2017;37(5):470-485.

Blumenfeld AM, Bloudek LM, Becker WJ, et al. **Patterns of use and reasons for discontinuation of prophylactic medications for episodic migraine and chronic migraine: results from the second international burden of migraine study** (IBMS-II). *Headache.* 2013;53(4):644-655.

Bonafede M, Cappell K, Sapra S, et al. **Direct Costs Associated with Migraine in the US** (P1.180). *Neurology* 2017;88 (16 Supplement).

Hazard E, Munakata J, Bigal ME, Rupnow MF, Lipton RB. **The burden of migraine in the United States: current and emerging perspectives on disease management and economic analysis**. *Value Health.* 2009;12(1):55-64.

Burton WN, Conti DJ, Chen CY, Schultz AB, Edington DW. **The economic burden of lost productivity due to migraine headache: a specific worksite analysis**. *J Occup Environ Med.* 2002;44(6):523-529

Schultz AB, Chen CY, Edington DW. **The cost and impact of health conditions on presenteeism to employers: a review of the literature**. *Pharmacoeconomics.* 2009;27(5):365-378.

Buse DC, Manack AN, Fanning KM, et al. **Chronic migraine prevalence, disability, and sociodemographic factors: results from the American Migraine Prevalence and Prevention Study**. *Headache.* 2012;52(10):1456-1470.

Burton WN, Landy SH, Downs KE, Runken MC. **The impact of migraine and the effect of migraine treatment on workplace productivity in the United States and suggestions for future research**. *Mayo Clin Proc.* 2009;84(5):436-445.

Lipton RB, Stewart WF, Diamond S, Diamond ML, Reed M. **Prevalence and burden of migraine in the United States: data from the American Migraine Study II**. *Headache.* 2001;41(7):646-657.

Mauser ED, Rosen NL. **So many migraines, so few subspecialists: analysis of the geographic location of United Council for Neurologic Subspecialties (UCNS) certified headache subspecialists compared to United States headache demographics**. *Headache* 2014;54(8):1347-57.

Pringsheim T, Davenport W, Mackie G., et al. **Canadian Headache Society Guideline for migraine prophylaxis**. Can J Neurol Sci 2012;39:S1-S59.

Silberstein SD. **Practice parameter: evidence-based guidelines for migraine headache (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology**. *Neurology.* 2000;55(6):754-762.

Silberstein SD. **Preventive migraine treatment**. *Continuum (Minneap Minn).* 2015;21(4 Headache):973-989.

Dodick DW, Silberstein SD. **Migraine prevention**. *Pract Neurol.* 2007;7(6):383-393.

Dworkin RH, Turk DC, McDermott MP, Peirce S, et al.

Interpreting the clinical importance of group differences in chronic pain clinical trials: IMMPACT recommendations*Pain* *2009;* 146 : 238-244

. doi: 10.1212/WNL.0000000000004391. Epub 2017 Aug 23.

Ashina M[1], Dodick D[2], Goadsby PJ[2], Reuter U[2], Silberstein S[2], Zhang F, et al. Erenumab (AMG 334) in episodic migraine: Interim analysis of an ongoing open-label study. *Neurolog.* 2017;89:1237-1243

[2],