AIMED ALLIANCE
Alliance for the Adoption of Innovations in Medicine

December 21, 2017

Steven Pearson, MD
Institute for Clinical and Economic Review
2 Liberty Square, Ninth Floor
Boston, MA 02109

Dear Dr. Pearson:

The Alliance for the Adoption of Innovations in Medicine ("Aimed Alliance") is a nonprofit organization that works to expand access to quality health care in the U.S. On behalf of Aimed Alliance, I respectfully submit the following comment in response to the "Calcitonin Gene-Related Peptide (CGRP) Inhibitors as Preventive Treatment for Patients with Episodic or Chronic Migraine: Effectiveness and Value Draft Background and Scope," ("Migraine Scoping Document") published by the Institute for Clinical and Economic Review ("ICER").

Over 37 million Americans have migraines, with two to three million individuals experiencing chronic migraines.[1] Despite common misperceptions, migraines are not just "bad headaches"—they are a major cause of disability, with symptoms such as severe pain, nausea, vomiting, light sensitivity, throbbing, and visual disturbances.[2] When left untreated, more than 91 percent of individuals who experience a migraine are unable to function.[3] Given that 63 percent of individuals with migraines have an attack one or more times per month, the condition can substantially limit the ability to lead a normal life, maintain relationships, and sustain a sense of well-being.[4] Coverage of migraine treatment is of vital importance, and therefore, we make the following recommendations regarding the Migraine Scoping Document.

A. The Patient Populations Should Be Narrowly Tailored

ICER should consider narrowing the patient populations so that appropriate individuals are compared to each other. Otherwise, the benchmark calculation will be skewed by inaccurately reflecting the number of individuals who truly need preventive migraine treatment.

ICER intends to consider both individuals with chronic migraines (those with 15 or more episodes per month) and acute migraines (those with between 4 and 14 episodes per month). As mentioned above, over 37 million Americans have migraines. Yet, only two to three million individuals (five to eight percent) experience chronic migraines.[5] Of those 92 to 95 percent who experience episodic migraines, not all of them need preventive medications. The determination to provide an individual with acute migraines with a preventive medication is made on a case-by-case basis taking into consideration not only the frequency of episodes, but also whether any of the following factors exist:

[1] https://www.womenshealth.gov/publications/our-publications/fact-sheet/migraine.html#i
[2] http://www.huffingtonpost.com/2013/01/17/migraine-stigma-social-epilepsy_n_2488913.html
[3] http://www.huffingtonpost.com/2013/01/17/migraine-stigma-social-epilepsy_n_2488913.html
[4] http://www.health.harvard.edu/blog/the-stigma-of-chronic-migraine-201301235828
[5] https://www.womenshealth.gov/publications/our-publications/fact-sheet/migraine.html#i

- Recurrent migraines are significantly disabling despite acute treatment;
- Acute medications are contraindicated or cause side effects;
- Acute medication is at risk of overuse; or
- Special circumstances exist (*e.g.*, hemiplegic migraines).[6]

Therefore, ICER should narrowly tailor the acute patient population to those for whom preventive care has been clearly indicated.

Additionally, as ICER acknowledged, migraine disorders disproportionately affect women. Approximately 85 percent of individuals with migraines are women, and three times as many women experience migraines in adulthood than men.[7] Moreover, 10 percent of school-age children experience migraines.[8] However, very few medications are indicated for children.[9] Finally, there is a decreasing prevalence of migraines based on age among men and women, respectively, as follows: 21 to 34 years, 92 percent and 74 percent; 55 to 74 years, 66 percent and 53 percent; and after age 75, 55 percent and 22 percent.[10] Therefore, subpopulations based on gender and age should also be considered.

Finally, ICER should limit the scope of the patient population to those individuals who are stable on their preventive medications. Individuals with migraine disorders require treatment that is appropriate for their individualized needs. As the Migraine Scoping Document notes, "patients on preventive therapy frequently discontinue or switch treatments due to lack of efficacy or tolerability," and "adequate therapeutic trials of preventive therapies generally require three to four months of treatment."[11] Therefore, in order to better account for individualized needs, ICER should consider only stable patients who have been on their medication for more than four months.

B. ICER Must Consider Patients' Perspectives

Given that patients are directly impacted by a report that seeks to define the effectiveness and value of their treatment options, they must have a meaningful role in the discussion of value. Therefore, accounting for how patients define the value of treatment options should be critical to ICER's analysis. As such, ICER should consider more than just the health care system's perspective and direct costs when determining the value of treatment.

Contrary to common misperceptions, migraines are more than bad headaches. Yet, limiting an analysis of medication effectiveness to the number of headache days patients experience perpetuates this misperception.

As ICER acknowledged in the Migraine Scoping Document, patients "frequently report feeling

[6] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3444218/
[7] http://migraineresearchfoundation.org/about-migraine/migraine-facts/
[8] http://migraineresearchfoundation.org/about-migraine/migraine-facts/
[9] http://migraineresearchfoundation.org/about-migraine/migraine-in-kids-and-teens/
[10] https://www.webmd.com/migraines-headaches/geriatric-headaches#1
[11] https://icer-review.org/wp-content/uploads/2017/11/ICER_Draft_Migraine_Scope_120417.pdf

frustrated, depressed, defeated, isolated, or a burden to society; some patients have express suicidal thoughts." All of these indirect costs associated with patients' mental state must be considered. Moreover, ICER should consider individuals' ability to conduct daily activities as well as work place performance and absenteeism.

Moreover, even if ICER were to consider only direct costs, there are other direct costs that ICER should consider in addition to number of headache days reduced, including reduction in the duration of headache and in accompanying symptoms, including nausea; vomiting; dizziness; sensitivity to touch, sound, light, and odor; abdominal pain; and mood changes.[12]

C. Use of QALYs Is Inappropriate

Aimed Alliance reiterates its longstanding recommendation against relying on quality-adjusted life year ("QALY") measures to evaluate preventive migraine treatments. The use of QALY measures to evaluate migraine disorders raises significant ethical concerns. QALY measures put a price tag on the value of a human life that merely reflects the individual's diagnosis and deems those with chronic, debilitating, and rare conditions, as being worth less than those with common diseases. They treat individuals' lives and health as a commodity and ignore patients' and practitioners' individualized concept of the value of treatment.

As ICER acknowledged, individuals with migraines often have difficulties obtaining coverage of their treatment. Health plans may impose high copays, prior authorization, step therapy, or pill quantity limits.[13] As a result, patients ration their medications, and this lack of adherence to the treatment plan can result in deteriorating health and adverse events.[14] In fact, those who cannot access their medications are more likely to attempt to access opioids.[15] QALYs are used to justify coverage limitations that prevent individuals from obtaining treatments most appropriate to their individualized needs. For these reasons, we recommend against using the QALY.

Conclusion

Thank you for the opportunity to comment on the Migraine Scoping Document. We are available for discussion to address our shared goals of access to high quality health care at a price that accurately reflects public and personal benefits in the final version of adapted methods.

Sincerely,

Stacey L. Worthy
Executive Director

[12] https://www.mayoclinic.org/diseases-conditions/migraine-headache/symptoms-causes/syc-20360201
[13] https://icer-review.org/wp-content/uploads/2017/11/ICER_Draft_Migraine_Scope_120417.pdf
[14] https://americanmigrainefoundation.org/understanding-migraine/role-adherence-triggers-headache-management/
[15] https://www.webmd.com/migraines-headaches/news/20171018/skip-opioid-treatment-for-migraine-in-the-er#1

December 21, 2017

Via Electronic Mail

Steven Pearson, MD
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RE: Comments submitted during the Migraine Draft Scoping Document Review

Dear Dr. Pearson,

On behalf of Allergan plc, the manufacturer of BOTOX® (onabotulinumtoxinA),[1] approved for the preventive treatment of headaches in adult patients with chronic migraine, we are submitting this letter in response to your request for comments on the Draft Scoping Document for a review titled "Migraine Treatment: Effectiveness and Value."

Section I

Proposed MOA of BOTOX® for Chronic Migraine

The mechanism of action for BOTOX® in chronic migraine is thought to involve inhibition of sensory, and to a lesser extent motor, nerves.[2-4] The pathogenesis of chronic migraine involves the release of mediators that activate pain fibers both inside and outside of the cranium. This activation commonly leads to sensitization of central pain pathways that transmit pain signals to the cortex. To prevent chronic migraine, BOTOX® is injected in scalp tissues and muscles containing branches of trigeminal and cervical nerves. At sites of injection, BOTOX® is thought to enter nerve terminals, cleave the SNARE (soluble N-ethylmaleimide sensitive factor attachment receptor) complex, and consequently, inhibit fusion of presynaptic vesicles containing neuropeptides and neurotransmitters, such as glutamate, substance P, and calcitonin gene-related protein (CGRP), with the neuronal membrane. In the context of migraine, these actions are believed to reduce nociceptive input to the central nervous system – a critical component in the maintenance of chronic migraine state.

Summary of BOTOX® Safety and Efficacy

Across multiple etiologies, BOTOX® efficacy and safety has been established in more than 80 randomized, placebo-controlled clinical trials spanning nearly 30 years. It is currently approved in 94 countries for 26 different indications, including the prevention of headache in adults with chronic migraine. Since October 2010 in the U.S., over 2.0 million BOTOX® treatments have been given to over 500,000 (505,356) chronic migraine patients. Long-term clinical trials and real-world studies have established that BOTOX® is a consistently effective and well-tolerated treatment for the prevention of headaches in adults with chronic migraine.[5-9]

Below we highlight some of the safety and efficacy data for BOTOX® in chronic migraine patients. The Phase III Research Evaluating Migraine Prophylaxis Therapy (PREEMPT) clinical trials established the safety and efficacy of BOTOX® for the treatment of chronic migraine.[5,10-14] In this study, BOTOX® was administered over a 56-week period (24 weeks double-blind, followed by 32 weeks as open-label). The PREEMPT program demonstrated that compared to placebo-treated patients at 24 weeks (end of double blind), BOTOX® -treated patients had significant and meaningful improvements across multiple headache symptom measures, including frequencies of headache days, migraine/probable days, moderate/severe headache days, and total cumulative hours of headache, as well as greater improvements in headache related impact (HIT-6) and Migraine Specific Quality of Life (MSQ).

BOTOX® was well-tolerated in the PREEMPT trials, details of which can be found in the published papers.

More recently, the efficacy and tolerability of BOTOX® was substantiated by the results from a long-term phase 4 study - The Chronic Migraine OnabotulinuMtoxinA Prolonged Efficacy open-Label (COMPEL).[6,15] COMPEL is an international, multicenter, open-label long-term prospective study, where patients received up to nine BOTOX® treatment cycles over a period of 2 years. Just over one-half (52.1%) of the 715 patients enrolled in the study completed all nine treatment cycles (108 weeks). The results of COMPEL were consistent with the PREEMPT trials. Following BOTOX® treatment, there was a significant reduction in the frequency of headache days per month (-10.7 days; $p < 0.0001$ [primary endpoint]) relative to baseline at week 108. Sequential improvements were observed at all earlier assessments for which results were reported (-7.4, -9.2, and -9.8 days after 2, 5, and 7 cycles [corresponding with 24, 60, and 84 weeks], respectively; all $p < 0.0001$ vs. baseline). Significant ($p < 0.0001$) improvements in two exploratory measures (i.e., Migraine Disability Assessment Questionnaire [MIDAS] and MSQ) were also observed through week 108 of the study.[6] BOTOX® was well-tolerated and no new safety signals were identified in COMPEL.[6,15]

Beyond confirming the PREEMPT program findings, COMPEL assessed the impact of BOTOX® on comorbid symptoms of anxiety, as measured by the Generalized Anxiety Disorder 7-item scale (GAD-7), and depression, as measured by the Patient Health Questionnaire (PHQ-9).[16] The presence of these comorbidities can exacerbate chronic migraine and increase migraine related burden in those already impacted; therefore, addressing and treating these common comorbidities is part of appropriate management for chronic migraine.[17] Findings demonstrated that BOTOX® improved symptoms of depression and anxiety among those treated for chronic migraine. The exact causality for the effect of BOTOX on depressive symptoms and symptoms of anxiety is unknown and continues to be explored.[18]

Consistent with clinical trial findings from PREEMPT and COMPEL, several real-world studies have confirmed BOTOX®'s safety profile and demonstrated that treatment with BOTOX® significantly improved a range of headache symptom/impact assessments when used in clinical practice.[7-9,19,20] Effectiveness measures across these studies included: headache days, migraine days, and acute headache pain medication days. Additionally, HRQoL (measured by HIT-6, MSQ and EQ-5D [EuroQol five-dimensional questionnaire]) and work productivity were improved following BOTOX® treatment in clinical settings.[7-9,19,20] The totality of evidence from long-term clinical trials and real-world studies indicates that BOTOX® is a consistently effective and well-tolerated treatment for the prevention of headaches in adults with chronic migraine. We recommend ICER consider this evidence in the evaluations where BOTOX® is included as a comparator.

Section II

This section includes important considerations and clarifying questions for ICER to consider.

Network Meta-Analysis

Clarification: Limited head-to-head trials of the interventions and comparators of interest exist; therefore, ICER may conduct an indirect comparison in a network meta-analysis (NMA). Our concern is that even the most robust NMA may not account for differences in trials; hence, caution needs to be taken when interpreting the results.

Consideration: In conducting an NMA to support this review, ICER should be mindful of the following key challenges: 1) the definition for minimum length of headache varies across studies from a minimum of "30 minutes" to "at least 4 hours of continuous duration"; 2) the definition of migraine days may or may not include probable migraine days; in some instances migraine days are even defined differently; and 3) variations may exist in the definition of chronic migraine, which impacts the population included

in the trials. Keeping these in mind, we urge ICER to consider differences in the definition of chronic migraine, evaluate how differences in the definition of headache day and migraine day influence trial results, adjust for these differences in populations of the comparator trials, and evaluate/acknowledge how these differences may have influenced trial results. In addition, Allergan recommends that the most appropriate outcome for the NMA for this review may be migraine/probable migraine day, where a migraine day is defined as 4 hours of continuous headache. Our recommendation is supported by the rationale that the endpoint of migraine/probable migraine day is most commonly utilized across programs, in addition to being well accepted by the clinical community.[21-23]

Analytical Framework

Clarification 1: It is unclear from the draft scoping document if ICER will consider multiple base case comparators for this review.

Consideration: As mentioned previously, BOTOX® is indicated for prevention of headache in chronic migraine patients only[1]. Of note, BOTOX® is most often prescribed after patients have failed oral preventive treatments, including topiramate or for whom oral preventive treatments are not appropriated for other reasons. Place in treatment for BOTOX® is enforced by payer policies via the prior authorization process. With that in mind, we recommend inclusion of BOTOX® as a comparator only for the relevant chronic migraine population.

Clarification 2: The draft scoping document states: "*The model will consist of discrete states including being on treatment with episodic migraine, being on treatment with chronic migraine, discontinuing treatment with episodic migraine, discontinuing treatment with chronic migraine, and death.*"

Consideration: Allergan would like clarification as to whether this statement describes all health states being considered for the model or if ICER plans to include a more granular model structure that discerns health states characterized by number of migraine/probable migraine days per month. In addition, we would like to better understand what evidence or assumptions will be used to estimate changes in monthly migraine/probable migraine days after patients discontinue treatment. Lastly, it is not clear if the model allows for patients to move between episodic and chronic migraine. If movement between migraine states is allowed in the model, Allergan recommends ICER to clearly differentiate between different types of transitions.

Clarification 3: The draft scoping document states: *"A cohort of patients will transition between states using monthly cycles over a lifetime horizon, modelling patients from treatment initiation until death."*

Consideration: With respect to treatments that are administered at quarterly intervals, will treatment costs be incurred only in the cycles in which treatment is administered? Or will they be prorated across cycles? In addition, Allergan would like to better understand what evidence or assumptions will be used to estimate changes in monthly migraine days on-treatment beyond the duration of the randomized controlled trial.

We appreciate the opportunity to engage with ICER and look forward to continued dialogue. If you have any questions, please contact Priti Jhingran, PhD, Executive Director – US Health Outcomes and Value via e-mail at Priti.Jhingran@allergan.com or Jonathan Kowalski, PharmD, Vice President US Health Outcomes and Value via email at Jonathan.Kowalski@allergan.com.

Regards,

Priti Jhingran, B.Pharm, PhD.
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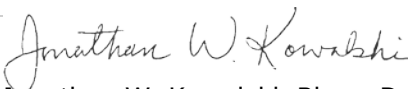

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Dear Mr. Seidner,

Thank you for sending these documents to review.

The Alliance for Headache Disorders Advocacy would like to remain involved in the Institute for Clinical and Economic Review process. We would like to suggest some edits of the migraine scoping document:

1. *Page 1*: Migraine is the 5th, not the 8th, greatest cause of years lived with disability in the United States (US), and 2nd in the world.[1]
2. *Page 1 and 3*: It is better to say migraine patients *are stigmatized* than *they feel stigmatized*.[2,3]
3. *Page 1*: Low episodic migraine patients are typically not treated. It is recognized that patients with more than 4 migraine days per month may benefit from treatment, and patients with high episodic migraine (generally 10-14 days per month, but sometimes considered to be 8-19 days a month), and chronic migraine should be treated. Nonetheless most are not, and a much higher percentage of the low episodic patients are not treated with preventives. Models should incorporate these facts.[4]
4. On *page 1*, venlafaxine is listed as a comparator. If so, lisinopril and candesartan should also be listed.
5. On *page 2*, fremanezumab and galcanezumab are humanized, not fully human, monoclonal antibodies.
6. *Page 4*: Evidence should also include retention rates on therapy based on experience from prospective clinic-based studies.[5]
7. *Page 5 and 6*: Propranolol is not an appropriate comparator for chronic migraine as there are no studies. Furthermore, it is an inappropriate choice for episodic migraine as all clinical trials but one are so old that the participating patient populations in these early trials were very different from current trials. The one newer study, which compares propranolol to topiramate and placebo, had a very poor completer rate, and was performed on a low frequency migraine population that is unlikely to be offered a biologic under any circumstances.[6]
8. *Page 5, 7*: in modeling comparative value there is no accounting for the prevention of opioid abuse and addiction as a benefit of treatment; or avoiding overusing nonsteroidal antiinflammatory drugs or other abortives, and the complications of that overuse, such as renal failure.[7,8,9]
9. *Page 7*: we are very concerned with the use of the discredited measure QALYs, which have been found to be discriminatory against persons with disabilities by the US Department of Health and Human Services.[10] Also, several studies, specifically in migraine, demonstrate the instability of the procedures that underlie the QALY measure.[11,12]
10. *Page 8*: In considering the potential cost of the new biologics to the health system we believe prescribing will be constrained by available providers and expertise. Models

should be based on the past market uptake of preventive medications, and savings from the cannibalization of current treatments should be calculated.

We hope you will consider our suggestions in your efforts to make an appropriate cost-benefit evaluation of the new preventive treatments.
Sincerely,

William B. Young, MD, FAHS, FAAN
President, Alliance for Headache Disorders Advocacy

Bert Vargas, MD, FAHS, FAAN
President-Elect, Alliance for Headache Disorders Advocacy

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ACCME ACCREDITED WITH COMMENDATION

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AMERICAN MIGRAINE FOUNDATION*

22-December-2017

Steven D. Pearson, MD, President
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Dear Dr. Pearson,

Thank you for asking for public comment on the Institute for Clinical and Economic Review: Calcitonin Gene-Related Peptide (CGRP) Inhibitors as Preventive Treatments for Patients with Episodic or Chronic Migraine: Effectiveness and Value.

The American Headache Society (AHS) along with the American Migraine Foundation are eager to improve care for our patients with migraine in a cost-effective manner. We appreciate that you are anxious for input from many stakeholders, and we are pleased to submit the following comments as you prepare to analyze the cost-effectiveness of therapies for migraine.

For nearly 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. Equally important to its professional programs is its work as the voice for patients both in the United States. Through the American Migraine Foundation, the Society advocates for, supports, educates and engages the 47 million Americans who suffer the debilitating effects of migraine. It is these efforts that makes the American Headache Society a global authority in headache and migraine medicine.

As ICER develops its Scoping Document, we emphasize the importance of keeping the patient perspective at the core of your assessment, and ask you to consider the following points:

- Migraine is a serious neurological disease that is characterized by disabling symptoms including severe pain, compromised mobility and physical functioning, attack-related cognitive impairment, nausea, vomiting, visual disturbances, and exquisite sensitivity to environmental stimuli (e.g. light, sound, odor).[1] The burden of migraine is pervasive, impacting the individuals directly afflicted by the disease, as well as family members, employers, payers and society as a whole.[2] Migraine is the 3rd most prevalent and among the 10 most disabling medical conditions in the world.[3]
- The unmet need in preventive migraine treatment is enormous. While approximately 38% of individuals with migraine should be offered preventive therapy, only 3-13% of individuals are receiving such treatments.[4] Among the most severely affected individuals with chronic migraine who do receive preventive treatment, over 80% discontinue the medication within one year.[5] While there may be several reasons for this poor treatment adherence, chief among them are suboptimal efficacy and tolerability.[6]
- No preventive drug class currently available has been designed to prevent migraine. Not surprisingly, only four oral medications have received regulatory approval for migraine prevention and only one treatment–

OnabotulinumtoxinA – is approved for the prevention of chronic migraine. All other treatments are used off-label and have substantially less quantitative and qualitative evidence to support their use.

- 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%).[7]
- We urge ICER in their economic analysis to evaluate both the direct as well as the indirect cost of migraine. These indirect costs must be part of the analysis and 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.[8] This translates to a significant burden on employers, as indirect costs are primarily calculated as absenteeism and presenteeism.[9] 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. Presenteeism and the financial cost incurred by lost productivity is a growing concern among employers.[10] It is estimated that presenteeism during a migraine attack will result in 4 additional days of lost work productivity each year.[12] 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.[7] In addition, more than half of migraine sufferers state that their work or school productivity is reduced by at least 50%.[13] 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.
- Despite the low quality of evidence and widespread recommendations against their use for migraine by professional headache and Neurology societies as well as leading experts, opioids continue to be administered for more than 50% of all ED visits for migraine.[11] Emergency department visits for migraine are considered costly but largely preventable, as optimal migraine management with preventive therapy has been shown to reduce such visits. Almost half (46%) of all individuals with migraine had at least one opioid claim in the first year after diagnosis, with the mean number of claims being 5.8.[7] This is of grave concern in the midst of an opioid abuse and mortality epidemic. Preventive treatments, including the monoclonal CGRP antibodies, have been shown to reduce the consumption of acute medications.
- The prescribing of emerging and novel preventive treatments for migraine should not be restricted to specialty (Neurology/Headache) care. There are not nearly enough headache specialists in the country to treat the number of people living with migraine. Estimates are that there is one specialist for every 80,000 individuals with migraine in the United States.[14] Since the majority of patients with migraine are evaluated and managed in primary care, there should not be undue barriers that impede the primary care physician's ability to prescribe the most appropriate treatments for their patients with migraine.
- Adequate preventive medication trials are generally 2-3 months.[15] Patients may therefore fail 2-3 preventive treatments within a 6-month period, especially if no efficacy or intolerable side effects occur. We believe that a 6-month trial of each preventive treatment trial is unnecessary and not patient-centered, particularly if partial efficacy within 2-3 months is not achieved.
- 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. 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[16-18]:
  - 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

Prevention should also be considered in the management of certain uncommon migraine conditions, including hemiplegic migraine, migraine with brainstem aura, migraine with prolonged aura, and migrainous infarction, even if there is low attack frequency.[16-18]

- Determining the efficacy and tolerability of a preventive treatment is a patient-driven decision that may not exactly mirror the endpoints used to measure effective therapeutic outcomes in clinical trials. In general, a

significant reduction (e.g., 50% reduction) in migraine headache days (MHDs) or moderate and severe headache days (MS-HDs) is a useful benchmark in both clinical trials and practice. However, efficacy is variable between patients, and a successful therapeutic outcome depends not only on a reduction in MHD frequency, but also on the persistence and severity of pain and associated symptoms, level of disability and functional capacity. Therefore, patient-centric and validated outcome measures that evaluate the effect of treatment on functional capacity, disability, and quality of life are important for determining meaningful efficacy and guiding clinical decision-making with respect to the need for changes in dose, additional preventive medication(s), or switching to an alternative treatment. Examples of these measures include the:

- Patient Global Impression of Change scale (PGIC)
- Functional Impairment Scale (FIS), a 4-point scale that evaluates functional status and degree of impairment during daily activities
- Migraine Functional Impact Questionnaire (MFIQ), a 26-item self-administered instrument for the assessment of the impact of migraine on physical functioning, usual activities, social functioning, and emotional functioning over the past 7 days
- Migraine-Specific Quality of Life questionnaire (MSQ v2.1)
- Headache Impact Test (HIT-6)
- Migraine Disability Assessment (MIDAS)
- Health-related quality of life (HRQoL) reflects the overall effect of an illness and the impact of therapy on a subject's perception of their ability to live a useful and fulfilling life

We certainly agree that cost effective care is essential and all stakeholders need to be responsible stewards of health care resources. We therefore believe that emerging biologics, such as the monoclonal CGRP antibodies, should not be considered first-line for the majority of patients. Affordable and widely available generic preventive medications that are approved and/or guideline recommended for migraine prevention should be considered first for patients who should be offered preventive treatment. However, patients who fail to respond or tolerate two or more preventive medications/treatments from distinct drug classes, that are approved or guideline recommended, should be considered candidates for new and emerging preventive therapies. This will help contain the cost of care and ensure that access is reserved for those in whom it is truly needed.

In conclusion, the impact of migraine is complex, debilitating and far-reaching. As ICER prepares this important analysis, we urge you to consider and incorporate our input and ask that you please keep us and the larger migraine community engaged throughout each step of the process.

On behalf of the Executive Board of the American Headache Society,

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President, American Headache Society

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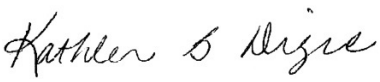

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Amgen Response to ICER's Draft Scoping Document on CGRP Preventive Therapy for Migraine

SUMMARY OVERVIEW

Amgen and Novartis appreciate the opportunity to comment on ICER's draft scoping document for Calcitonin Gene-Related Peptide (CGRP) Inhibitors as preventive therapy in migraine. Migraine is a serious debilitating disease which is overdue for innovation. A fair assessment of new migraine preventive treatments is incredibly important to patients, and needs to be framed carefully based on the unique patient experience, disease burden, and impact to society. Based on our review of ICER's draft scope, our recommendations are as follows:

1) **Employ a patient-centered approach – the base-case should be the patient and employer perspective that factors in the missed work days and reduced productivity of migraine patients, as opposed to a payer perspective.**
2) **Assess erenumab only in treatment-experienced patients – those who have tried and failed topiramate or propranolol as opposed to treatment-naïve patients.**
3) **Factor in treatment discontinuation rates with currently available preventives in the analysis and in the impact on efficacy.**
4) **Incorporate responder rates *i.e.*, a fifty percent responder rate assesses the proportion of patients who saw their migraine days reduced by half or more.**
5) **Apply full continuous modelling techniques rather than a fixed health state model to more accurately capture the complexities of migraine burden and treatment benefit.**

A more comprehensive discussion of these recommendations is below.

KEY RECOMMENDATIONS

1) Employ a patient-centered approach – the base-case should be the patient and employer perspective that factors in the missed work days and reduced productivity of migraine patients, as opposed to a payer perspective.

ICER's healthcare system perspective should not just reflect the payer perspective but be inclusive of all those who are incurring costs due to migraine, most notably the patient and employer. The adoption of a payer perspective, as opposed to a broader societal perspective, is at odds with established accepted methodologies in the economic evaluation of new treatments.[1,2,3,4] The gold standard for health economic assessment methodology, the Second Panel on Cost-Effectiveness in Health and Medicine, recommends that all cost-effective analyses capture both the healthcare payer and the societal perspective (in this case, societal is defined as all costs incurred by society due to migraine, including the often overlooked costs to patients).[5,6] These include, for example, patient co-payments for treatment, employer costs, and providers costs of services and transactions not covered by insurance. Moreover, there are higher overall total costs associated with this debilitating disease that impact the healthcare system including the impact on patient physical, psychological and social lives which are not captured in an assessment that is only payer centric. Patients with migraine have much higher average healthcare expenditures averaging 1.5 times matched controls.[7] While these are high costs to the healthcare system, they are unlikely to be captured in ICER's base-case. ICER's current base-case leaves out one of the largest healthcare payers of migraine costs, the self-insured employer. Self-insured plans cover 83% of all employees at private sector companies with >200 employees.[8] Each employee with frequent migraine costs employers as much as $13,000, a hidden cost representing nearly three times what individuals pay in insurance premiums.[9,10,11] ICER should define the healthcare perspective as greater than the payer to be inclusive of all stakeholders (*e.g.*, patients and employers): this more comprehensive approach will more accurately capture the full value of CGRP's to patients.

Failure to include a broader perspective may inadvertently lead to migraine being deprioritized over conditions that incur significant payer costs. Health economists have recommended this broader perspective for over 20 years[12] to ensure that untreated conditions that incur very little comparative cost to payers are not deprioritized.

Migraine qualifies as one of these as it is 1) extremely debilitating if left untreated 2) incurs little directly identifiable cost to the payer if left untreated and 3) may be more expensive to payers when effectively treated. Economists recognize that health as a merit good has benefits that go beyond the healthcare system that methodologically should be reflected in any economic evaluation, including migraine.[13]

The use of a payer perspective as the base-case is biased against a fair evaluation of therapies to prevent migraines (such as CGRPs) as it fails to capture more than half of the value to patients. As emphasized in the Amgen open comment period response, on top of the non-payer incurred direct medical costs, there are also substantial costs that lie outside of the healthcare system. Highly debilitating, migraine causes sufferers to frequently miss work and be less productive while at work, costing employers, patients and society billions of dollars per year.[14,15]Absenteeism accounts for 81%, short term disability 13%, and workers compensation 6% of costs from lost productivity due to migraine.[16,17,18,19,20] ICER should use a broader healthcare system perspective, inclusive of the patient and employer, as their base-case. Additionally, we urge ICER to make all inputs, assumptions and data available and fully transparent –especially in the event that ICER chooses to run this as a separate scenario instead of a base-case.

2) Assess erenumab only in treatment-experienced patients – those who have tried and failed topiramate or propranolol, as opposed to treatment-naïve patients.

Erenumab should <u>not</u> be assessed in populations who are naïve to migraine preventive treatment. Patients that can gain disease control from currently available preventive treatments and who can persist on them, represents maximum value to both the patients and the healthcare system. Multiple clinical and insurer sources suggest that in clinical practice, erenumab will be used after failure of topiramate or propranolol, addressing the high unmet need of migraine patients who have experienced a lack of efficacy or tolerability from prior preventives.[21,22,23,24,25] Further, in the U.S. ICER CTAF 2014 report, Botox® is reserved for CM patients who have failed topiramate or propranolol.[26] In the U.S., this reinforces the place of CGRPs in preventive treatment-experienced patients. Moreover, while ICER recommends topiramate and propranolol, the evidence on these interventions is not directly comparable to the evidence on erenumab. Studies are not comparable in terms of population, definition of endpoints and other study design elements, which weakens the comparative efficacy estimation.[27,28,29,30]

Erenumab has been shown to benefit treatment experienced patient populations including those who have <u>failed prior treatment (including topiramate and propranolol)</u>. Erenumab is an investigational migraine preventive that has demonstrated sustained efficacy specifically in these patients in clinical trials.[31,32] It is of paramount importance that ICER's assessment address the unmet needs of patients who have not benefited from currently available preventive treatments. If ICER were to assess erenumab in all patients, this is not aligned with how these treatments are expected to be used in real world practice. It may inadvertently restrict access in patients who will benefit the most and undermine the potential value of these innovative treatments.

There are several ways to model the economics of migraine prevention with CGRPS. In treatment experienced patients, one way is to model all patients with <u>≥</u> 4 migraines days per month. In this case, the appropriate comparator for erenumab in the patient populations who have tried and failed topiramate or propranolol is 'no preventive treatment'. Based on ICER's prior report on Chronic Migraine, ICER may choose to model EM and CM separately, in which case based on ICER's prior analysis, Botox in CM may be the comparator for the CM population. What is known, is that there is currently no defined standard of care for patients with > 4 migraines per month who have tried and failed topiramate or propranolol. Additionally, there are no clinical trials or observational cohort data that are available or published with propranolol[33] or topiramate [34,35,36,37,38,39] in patients who have tried and failed these treatments. As such, neither topiramate nor propranolol are appropriate comparators in preventive treatment experienced patients with 4 or more migraine days per month.

An adequate therapeutic trial with preventive therapy is approximately 2-3 months based on treatment guidelines for prevention.[40,41] Requiring failure of multiple classes of therapies for 18-24 months is overly burdensome to patients and is not supported by available evidence.[42,43,44] Treatment guidelines, published sources, real-world and clinical practice data do not to support this approach.[45] The time a patient tries a treatment can be short, reflected in persistence rates. Annual persistence rates with current preventive therapies is low: 50% of patients discontinue treatment at one month, 70-75% by month 6.[46] In another study, similar trends were observed at month 12.[47] Given that there are no data in a robust controlled setting or in current clinical practice that support a treatment paradigm of patients requiring failure of multiple classes, ICER should evaluate erenumab in migraine patients after failure of *topiramate or propranolol* with an adequate therapeutic trial.

3) Factor in treatment discontinuation rates with currently-used preventives in the analysis and in the impact on efficacy.

Discontinuation rates and poor adherence must be accurately captured since patients can only derive continued benefit when they persist with therapy. Adherence is a fundamental driver of value.[48,49] Despite discontinuation of preventive migraine medications, acute medication use persists.[50] While acute medication use is observed to decrease in the 30 days after discontinuation of the index preventive, acute medication use rebounds to pre-preventive usage in the 31-90 days after discontinuation.[51] ICER should ensure that they accurately account for and measure discontinuation rates in all treatments as they have a significant impact on efficacy in clinical practice. Failure to capture this accurately *would significantly underestimate the value of CGRPs*.

4) Incorporate responder rates (RR) *i.e.*, a fifty percent responder rate assesses the proportion of patients who saw their migraine days reduce by half or more.

Per guidelines, RR is a key measure of preventive treatment success.[52] Odds ratio (OR) and confidence interval (CI) relative to placebo, in all comers for erenumab 140-mg in EM was 2.81 (2.01 to 3.94) [53] and in CM 2.3 (1.6, 3.5). [54] In treatment experienced patients with $\geq$1 prior treatment failures, OR relative to placebo, in EM was 3.06 (1.70, 5.52) [55] and in CM was 3.30 (1.98, 5.51)[56], nominal $p<0.001$. ICER should reflect RR as an important outcome measure since it accurately captures a with-in patient response.

5) Apply continuous modelling techniques rather than a fixed health state model to more accurately capture the complexities of migraine burden and treatment benefit.

In a study comparing the modeling of migraine preventives using a health state approach versus a continuous approach, parametric continuous distributions provide more accurate approximations of migraine day frequency.[57,] ICER should use a continuous distribution approach rather than a "health state" approach to more accurately capture migraine day frequency.

CONCLUSION

The migraine prevention space has had no real innovation in two decades and patients are in need of new treatment options. As ICER has accurately reflected, migraine is one of the most debilitating diseases in the world. Its profound effects, which impact every facet of patients' lives, are frequently underestimated. Current preventive treatment options are suboptimal for many patients. We recommend that ICER focus on areas where CGRPs are more likely to be used in real world clinical practice: those migraine patients that do not have available treatments that work. Moreover, ICER should ensure that its assessment of value is inclusive of all stakeholders, not just healthcare payers, by incorporating a more comprehensive healthcare system and societal perspective in order to capture migraine costs that CGRPs could alleviate. At this time, we are also providing a supplemental data appendix with further data to support our comments here.

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Comment on ICER Draft Background and Scope, CGRP inhibitors as preventive treatments for patients with episodic or chronic migraine

Overall I agree with the Scoping document. You have obtained a good quality patient-focussed description of the impact of migraine. However I am concerned that the objective data for years lived with disability are outdated and do not provide as vivid a picture of the magnitude of this problem, both in the US and globally. I am sure that many commentees will request that you update reference 4 to the 2017 publication:

Global, regional, and national incidence, prevalence, and
years lived with disability for 328 diseases and injuries for
195 countries, 1990–2016: a systematic analysis for the
Global Burden of Disease Study 2016
GBD 2016 Disease and Injury Incidence and Prevalence Collaborators*
Lancet 2017; 390: 1211–59

Migraine is the second most common cause of years lost to disability globally. Figure 2B demonstrates graphically that across several US states and a swathe of South America, migraine is the single most common disease causing years lost to disability. Throughout most of Europe migraine is the second most common disease for YLD and the most common in France. These data emphasise the magnitude of disability better than a rather high level statement that 'Migraine is the eighth highest specific cause of years lived with disability in the US.' which is now also incorrect.

David Bowen

CHAMP
Coalition For Headache And Migraine Patients

December 22, 2017

REGARDING ICER DRAFT SCOPING DOCUMENT FOR MIGRAINE PREVENTIVES

Submitted electronically to: publiccomments@icer-review.org

Steven D. Pearson, MD, President
Institute for Clinical and Economic Review
Two Liberty Square, Ninth Floor
Boston, MA 02109

Dear Dr. Pearson:

The Coalition For Headache And Migraine Patients (CHAMP) appreciates the opportunity to comment on the Institute for Clinical and Economic Review's (ICER) Draft Scoping Document (DSD) on therapies for migraine prevention. CHAMP is a convening and organizing entity working to unite the migraine and headache patient advocacy community. CHAMP focuses on enhancing communication, coordination and collaboration for the benefit of patients and caregivers that are confronting headache, migraine and cluster diseases.

CHAMP is a co-signer of the joint letter submitted by the Headache and Migraine Policy Forum (HMPF) that provides detailed feedback from the migraine patient advocacy community on the DSD. However, CHAMP would additionally like to flag a few points that we feel are especially important.

1) **Approach cost-effectiveness assessment from a patient-centric perspective.** A payer-focused perspective will not fully count all the societal costs of migraine disease. Migraine patients suffer from reduced earnings and society suffers from their reduced contributions. Furthermore, migraine disease has high co-morbidities and the ICER assessment should seek to identify and include data that may demonstrate benefits (both in reduced health care costs and improved societal outcomes) that correspond with reductions of co-morbidities if the migraine disease is more effectively managed. All of these costs and benefits should be holistically included in your assessment.

2) **Further break down sub-populations for cost-effectiveness assessments.** Migraine disease is a variable condition that impacts individuals differently and also can change in severity, symptoms and impact through an individual patient's life. We appreciate that ICER is planning to separately consider episodic and chronic migraine patients. We encourage further separating assessment for episodic patients to medium (approximately 5-9 headache days per month) and high (approximately 10-14 headache days per month) frequency.

3) **Selection of comparators should appropriately reflect that many migraine patients do not respond to currently available preventives.** The strong patient need for a new class of migraine preventives is because so many patients enduring the pain and disability of migraine disease have already failed on existing preventive options. Your assessment should reflect the value of these new medicines that have the potential to be effective for patients without any alternative effective comparator.

4) **Assessment should reflect demonstrated response rates and support access to trial.** The CGRP studies have generally shown that about half of patients are responders and benefit from a 50% or greater reduction in headache days. We encourage a cost-effectiveness assessment that reflects the value of allowing appropriate migraine patients to trial and discovery if they are a responder, and then assume that non-responders will not continue with the medicine and assess the ongoing value for patients that are responders.

In summary, migraine disease is complex and highly variable. We ask that ICER's assessment of CGRPs appropriately account for all the costs of migraine disease and be complex enough to reflect how these new medicines are likely to be utilized by a patient population that currently has no other effective options.

CHAMP looks forward to continuing to work with ICER in 2018 to ensure an assessment that is patient-focused and contributes to outcomes that broadly benefit society.

Sincerely,

Kevin Lenaburg
Coalition Director
Coalition For Headache And Migraine Patients (CHAMP)
HeadacheMigraine.org

Eli Lilly and Company
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Indianapolis, Indiana 46285 U.S.A.
www.lilly.com

Dec 15, 2017

RE: Response to ICER Draft Scoping Document (CGRP Inhibitors as Preventive Treatments for Migraine)

Eli Lilly and Company appreciates the opportunity to respond to ICER's draft background and scoping document titled 'Calcitonin Gene-Related Peptide (CGRP) Inhibitors as Preventive Treatments for Patients with Episodic or Chronic Migraine: Effectiveness and Value' released December 4, 2017. We believe that to be a sound value determination, efforts must be comprehensive and truly patient-centered. To that end we offer the following comments:

Background

As noted in the background section, CGRP inhibitors have not yet been FDA-approved. In addition, there is limited information on which to base a comprehensive assessment of product efficacy and value, and no data on effectiveness. For these reasons, we strongly request that ICER ***delay conducting this review until results have been published for all pivotal clinical trials for all CGRP inhibitors being evaluated. At minimum, we request that galcanezumab be removed from this assessment until Phase 3 randomized controlled trial (RCT) data have been published in peer-reviewed journals.*** This would allow for a scientifically sound evaluation across all products being considered unencumbered by uninformed assumptions for key parameters, and would greatly improve the transparency of the process as all available data would then be readily accessible to the public. Specifically, important gaps in available information include:

- ***Limited published data from Phase 3 RCTs across all compounds and outcomes of interest***

Multiple Phase 3 RCTs have been conducted across the CGRP inhibitors; however, at this time, only **two** articles have been published from the pivotal trials. Although grey literature may provide some insights into efficacy and safety, it does not provide the same level of detail as peer-reviewed published articles that would be needed to conduct a comprehensive assessment. Given the proposed timing of this review and limited data, we do not believe that ICER will be able to conduct a scientifically rigorous assessment that will meet the standards necessary to be of optimal value to health care decision makers.

- ***No pricing information***

Currently, there is no pricing information available for the CGRP inhibitors and no indication of the potential range. It would be inappropriate to conduct cost effectiveness or budget impact modeling using arbitrary thresholds to assess the value of the products with no information on price or other contributors to price (e.g., labeled dose).

- ***No final dosing information***

Each of the respective trials across the CGRPs used different doses and different dosing regimens. At this time, final dosing is not known for **any** of the products. As a result, there is no way for ICER to know which of the many efficacy and safety outcomes are relevant. In addition, it is challenging to understand the potential pricing implications associated with different doses and regimens.

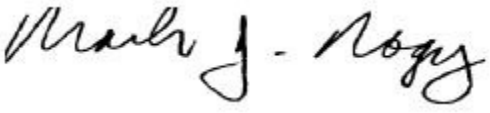
- ***No published utilities from RCTs***

The limited availability of publications from Phase 3 RCTs for CGRP inhibitors also means that there is limited or no information regarding utilities from those trials, including information that could be used for mapping.

We feel that consideration should be given to this very important issue. For the scientifically-based reasons outlined above, we recommend that the review of the entire class of CGRPs be delayed until sufficient data are available, so that

ICER can produce a scientifically-sound report without compelling companies to put their confidential information at risk. If ICER is not able to accommodate this request, Eli Lilly and Company specifically requests that galcanezumab be removed from the review. While we reserve the right to monitor activities surrounding this review, Eli Lilly and Company has made the decision to refrain from engaging in this review process.

Sincerely,



Mark J. Nagy
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December 20, 2017

Submitted electronically to: publiccomments@icer-review.org

Steven D. Pearson, MD, President
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Dear Dr. Pearson:

The Headache and Migraine Policy Forum (HMPF) appreciates the opportunity to comment on the Institute for Clinical and Economic Review's (ICER) Draft Scoping Document (DSD) on therapies for migraine prevention. The Headache and Migraine Policy Forum is a group of diverse patient advocates who advance public policies and practices that promote accelerated innovation and improved treatments for headache and migraine patients. As the second leading cause of all global disability and the second leading cause of all neurological burden, migraine is a serious public health problem affecting approximately 47 million Americans, 3 million of whom experience migraine attacks 15 or more days per month.[i] There exists an urgent need for improved migraine therapeutics.

We appreciate ICER's intent to seek multi-stakeholder input as part of its process to assess the value and effectiveness of different migraine therapies. HMPF remains concerned, however, that the DSD does not address the following:

Use of QALY Leads to Insufficient Consideration of the Patient Definition of Value.
HMPF does not support the use of QALY as a methodology for a value assessment that is meaningful to patients. For persons with migraine and other chronic and disabling diseases there is a delicate balance between quality and quantity of life. The use of QALY can be discriminatory within the disability community as it treats all patients the same in terms of their condition and value is assessed based on a patient population rather than on an individual. For individuals living with migraine, the return on investment from more time with loved ones, a higher quality of life, and increased productivity in both work and home life has great worth. HMPF respectfully requests that ICER utilize a more patient-centered approach that assigns value to endpoints that represent shorter, incremental gains that may be more meaningful to patients.

The DSD Discounts the Indirect Costs and Societal Burden of Migraine.
We are encouraged that the ICER value framework includes both quantitative and qualitative comparisons across treatments to ensure that the full range of benefits and harms - including those not typically captured in the clinical evidence such as innovation, public health effects, reduction in disparities, and unmet medical needs – but remain concerned that the framework will not adequately address the immense indirect costs and societal burden of migraine. Direct are far exceeded by indirect costs to employers including missed work and presenteeism (loss of productivity)[ii], exacerbated by the fact that migraine prevalence occurs during the most productive work years (ages 30-49)[iii].

ICER's Analytical Framework Should Identify Appropriate Subgroups to Draw Accurate Cost-Effective Conclusions.

We are pleased to see that ICER intends to separate chronic from episodic migraine patients for your assessment. However, within the episodic category there are significant differences between sub-populations with low (approximately 1-4 headache days per month), medium (approximately 5-9 headache days per month) and high (approximately 10-14 headache days per month) frequency.[iv] We ask that ICER separately assess these three episodic migraine populations during your assessment. We also hope that any cost effectiveness conclusion will not be drawn broadly and in such a way that it will unfairly penalize subpopulations.

The DSD Does Not Take Into Adequate Consideration the Cost of Treatment Discontinuation for Non-Effective Therapies Nor Does It Currently Ensure Accurate Comparators.

HMPF is also concerned that the DSD does not adequately address treatment discontinuation rates for preventatives in the analysis. Currently available therapies may have adverse side effects, causing patient intolerance of the therapy that leads to discontinuation and therefore costly ineffectiveness.

Likewise, we are concerned that the assessment will not provide an accurate comparison due to incomplete data. As you know, Phase 3 trials include data comparing CGRP blockers to placebo, but there is no head-to-head data within the drug class. There is also no direct data of CGRP blockers compared to the existing therapies; importantly, Botox is only approved for chronic migraine, so it also cannot be a comparator for the episodic sub-population of migraine patients. Finally, CGRP trials only included patients with four or more migraine days per month.

Due to the fact that many migraine patients have failed on multiple preventives, using these as comparators to the CGRP blockers is meaningless for patients who know from experience that these therapies are not effective (and therefore cost *in*effective). Instead, HMPF would recommend that any value framework and assessment of CGRP blockers for those patients who have tried and failed existing therapies use data from untreated migraine patients or those using medications at the onset of migraines. We would request that ICER's cost-effectiveness assessment include a no-treatment or placebo comparator.

The Scoping Document Should More Adequately Address the Cost Benefits of Improved Management of Comorbid Conditions.

It is conservatively estimated that the 4.2 million chronic migraine patients spend more than $5.2 billion a year—$1,251 per patient—on treatment of chronic migraine.[v] The costs of treating chronic migraine increase sharply with the number of comorbid chronic conditions.[vi] There is potential for these new therapies to have a profound effect on the chronic *atypical* form of migraine, vestibular migraine, which has a high prevalence.[vii]

In some instances, the gains in functioning associated with treating migraine may improve the individual's management of co-morbid conditions.[viii] For example, if migraine leads to social isolation and depression, treatment may enhance an individual's success in making lifestyle changes or adhering to other treatment regimens. The benefits to both improved quality of life and reduced health care costs for co-morbidities in these instances should therefore be integrated into ICER's value model.

The Omission of Costs Associated with Opioid Use and Abuse Unfairly Reduces the Value of New Migraine Therapies.

HMPF is disappointed that ICER did not include reference to the opioid epidemic given the lack of current available therapies. Currently, opioids account for nearly 10 percent of total medications prescribed to treat chronic migraine.[ix]

ICER's previous migraine assessment in 2014 included significant discussion on opioid use and the costs associated with long-term use of opioids as rescue therapies[x]. While the DSD mentions costs associated with side effects from interventional therapies[xi], it does not explicitly indicate whether opioids and their impact on productivity / non-direct costs (rescue therapies) would be included in the model. We would also request that ICER consider factoring in costs of treating addiction that develops for a percentage of migraine patients who are prescribed opioids and then become addicted.

Lack of Long-term Data Should Not Justify Undervaluing New Migraine Therapies.
We are concerned that a premature assessment based on inadequate evidence could result in delayed treatment access for migraine patients who have already waited years for a viable therapy. We are especially concerned that this could lead to a lower grade for new therapies or an "inconclusive" grade, creating an adverse impact on patient access. We therefore encourage ICER to use continuous modeling techniques that factors previous lack of innovation and captures the nuance and complexity of migraine burden in order to not unfairly undervalue migraine therapies.

We also encourage ICER to use the most updated data in its assessment. For example, citation 4 of the DSD references outdated data regarding years lived with disability in the US. However, data updating the same study and published in 2017 shows that migraine is the 5th leading cause of years lived with disability in the US.[xii]

HMPF appreciates the opportunity to provide input during this process. If you have questions, please contact Lindsay Videnieks, Executive Director of The Headache and Migraine Policy Forum, at (202) 299-4310 or Lindsay@headachemigraineforum.org.

Alliance for Balanced Pain Management
Alliance for Headache Disorders Advocacy
Alliance for Patient Access
American Migraine Foundation
Association of Migraine Disorders
Chronic Migraine Awareness
Clusterbusters
Clusterheads Documentary; *a film project currently in production*
Coalition For Headache And Migraine Patients
Danielle Byron Henry Migraine Foundation
Global Healthy Living Foundation
The Headache and Migraine Policy Forum
Health Union, LLC / Migraine.com
HealthyWomen
MigraineAgain.com
Migraine Research Foundation
Migraine World Summit
Miles for Migraine
National Headache Foundation
National Migraine Coalition
Runnin' for Research
SoldierStrong ACCESS
Southern Headache Society
U.S. Pain Foundation

[i] Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016**,** Lancet 2017 Sep 16; 390(10100): 1211–1259

[ii] Id. at 32.

[iii] World Health Organizaton Fact Sheet, "Headache Disorders" Updated April 2016. *Available at*: http://www.who.int/mediacentre/factsheets/fs277/en/

[iv] Katsarava, Z., Buse, D., Manack, A., Lipton, R. Defining the Differences Between Episodic and Chronic Migraine, Curr Pain Headache Rep. 2012 Feb; 16(1): 86–92.

[v] Messali A et al. *Headache* 2016; 56:306-322 where a recent study estimated that annual headache-related direct costs for chronic migraine and episodic migraine patients were $4,943 and $1,705, respectively. The Mean [standard deviation] total annual cost of headache among people with chronic migraine ($8243 [$10,646]) was more than three times that of episodic migraine ($2649 [$4634], P < .001). Participants with chronic migraine had significantly greater direct medical costs ($4943 [$6382]) and indirect (lost productivity) costs ($3300 [$6907]) than did participants with episodic migraine (direct, $1705 [$3591]; indirect, $943 [$2084]) (P < .001 for each).

[vi] Id. at 10, *Table 5*.

[vii] Murdin L, Schilder AGM. Epidemiology of balance symptoms and disorders in the community: a systematic review. Otol Neurotol. 2015 Mar;36(3):387–92.

[viii] Thorpe, K. Prevalence, Health Care Spending and Comorbidities Associated with Chronic Migraine Patients. Feb 2017 p. 8. Retrieved at: http://allianceforpatientaccess.org/why-impact-cost-of-chronic-migraine-comorbidities-justify-whole-person-care/

[ix] Thorpe, K. Prevalence, Health Care Spending and Comorbidities Associated with Chronic Migraine Patients. Feb 2017. Retrieved at: http://allianceforpatientaccess.org/why-impact-cost-of-chronic-migraine-comorbidities-justify-whole-person-care/

[x] *Controversies in Migraine Management: A Technnology Assessment*, ICER Final Report, Aug. 2014. Retrieved at: https://icer-review.org/wp-content/uploads/2016/01/CTAF_Migraine_Final_Report_081914-2.pdf

[xi] ICER DSD, p. 8.

[xii] *Supra* note 1 at Fig. 7 & Tb. 14.

December 8, 2017

Submitted electronically to: publiccomments@icer-review.org

Steven D. Pearson, MD, President
Institute for Clinical and Economic Review
Two Liberty Square, Ninth Floor
Boston, MA 02109

Re: Draft Scoping Document

Dear Dr. Pearson:

On behalf of the Institute for Patient Access, I thank you for the opportunity to provide comments regarding ICER's draft scoping document for a review of CGRP inhibitors for migraine prevention.

About the Institute for Patient Access

The Institute for Patient Access (IfPA) is a physician-led policy research organization dedicated to maintaining the primacy of the physician-patient relationship in the provision of quality health care. To further that mission, IfPA produces educational materials and programming designed to promote informed discussion about the benefits of patient access to approved therapies and appropriate clinical care. IfPA was established in 2012 by the leadership of the nonprofit Alliance for Patient Access, a national network of more than 800 physician advocates committed to patient access. IfPA is a 501(c)(3) public charity nonprofit organization.

Draft Scoping Document Comments

The Institute for Patient Access raised several concerns during ICER's open input period. Based on the methodology described in the draft scoping document, however, it does not appear that ICER's cost-effectiveness evaluation will adequately address these issues. To reiterate, these concerns include:

(1) The vast majority of migraine patients experience comorbid conditions, such as depression, anxiety, and arthritis, in addition to the symptoms associated with migraine. The direct health care costs associated with migraine, therefore, should include the cost to treat migraine as well as the cost to treat these comorbid conditions. It is imperative that

ICER include the estimated reduction in health care costs across migraine and the comorbid conditions when evaluating the reduction in direct health care costs that the CGRP inhibitors can provide.

(2) Although the scoping document fails to discuss the connection between migraine and the current opioid crisis, opioids currently account for nine percent of the total medications prescribed to treat chronic migraine headaches. A medicine that is explicitly designed to address the pain caused by migraine headaches could be, potentially, more effective at treating migraine headache patients who currently use prescription opioids to manage their pain. If this is the case, then the CGRP inhibitors may meaningfully reduce the costs associated with the current opioid abuse crisis by reducing migraine patients' need for opioids. These benefits will include reductions in: the direct health care costs associated with opioid abuse; the work/productivity costs associated with opioid abuse; and the criminal justice costs associated with the opioid abuse crisis.

(3) The scoping document focuses on estimating the direct health care cost savings for the base-case analysis, with workplace productivity considerations relegated to a separate analysis. Focusing solely on the direct health care cost savings in the base case may underestimate (perhaps significantly) the benefit of CGRP inhibitors. As ICER's scoping document notes, episodic and chronic migraines take a large toll on patients' quality of life and significantly reduce patients' workplace productivity. Additionally, there are costs imposed on caregivers and family members living with a migraine patient.

From a patient perspective, reducing these costs is one of the primary benefits of more effectively managing migraine symptoms. It is therefore imperative to incorporate values for these "quality of life improvements" into the base model, which tends to drive ICER's overall cost-effectiveness conclusions.

(4) The scoping document confirms that ICER intends to use the QALY metric to evaluate the cost effectiveness of the CGRP inhibitors despite evidence that the metric is not appropriate for evaluating the effectiveness of medicines that treat diseases whose benefits are qualitative and, therefore, not easily quantified.

(5) The timing of this cost-effectiveness evaluation is problematic. As the ICER scoping document notes, the FDA is not expected to make a decision regarding these medicines until the second and third quarters of 2018. Therefore, significant data constraints will limit the applicability of the results from ICER's cost-effectiveness study.

Specifically, when conducting the analysis, it is likely that ICER will have access only to the clinical trial data, and (at best) initial post-marketing data. ICER will not be able to consider the more robust post-marketing data that will eventually be available. As is typically the case, the robust post-marketing data provides invaluable insight that enables researchers to more fully understand the value new drugs create. That could include the impact that CGRP inhibitors have on reducing the direct morbidities associated with

migraine, as well as the numerous comorbidities associated with migraine headaches such as depression and arthritis. It could also include the drug's potential side effects, both positive and negative.

As a consequence, IfPA remains concerned that the ICER report's findings will be unnecessarily limited due to the timing of the analysis.

Conclusion

Should ICER's evaluation of CGRP inhibitors proceed despite the problematic timing of the analysis, it is imperative that the evaluation incorporate effective estimates for all of the potential benefits associated with more effective treatment of migraine. Those include: reduced health care costs associated with treating migraine headaches, reduced health care costs associated with treating comorbid conditions, increased worker productivity, improved quality of life for patients, improved quality of life for family members or other caregivers, and the potential reduction in costs associated with the opioid abuse crisis.

Without a full accounting of these costs, the full potential benefit of CGRP inhibitors cannot be ascertained.

If IfPA can provide further detail or aid the Institute for Clinical and Economic Review in incorporating any of the above recommendations, please contact me at 202-499-4114.

Sincerely,

Brian Kennedy
Executive Director

Dec 21, 2018

Steven D. Pearson, MD, MSc, FRCP
President
Institute for Clinical and Economic Review

RE: Calcitonin Gene-Related Peptide (CGRP) Inhibitors as Preventive Treatments for Patients with Episodic or Chronic Migraine: Effectiveness and Value

Dear Dr. Pearson,

Thank you for the opportunity to review and comment on the aforementioned draft scoping document of the evaluation of CGRP inhibitors in Migraine. We have provided below a few comments for ICER to consider in the following sections – Background, Populations, Comparators, and Economic Models Focusing on Comparative Value.

Background

- It would be useful to update this section with the most recent information as presented in the recent publication on the Global Burden of Disease Study 2016.[1]
- It would also be helpful to include the migraine treatment goals in this section. This would help identifying appropriate outcomes to assess in the evaluation.

Populations

- It would be helpful to clarify on the patient populations to be examined based on available data and clinical relevance of subpopulations.

Comparators

- Differences in trial designs and data quality should be appropriately considered in conducting cross-trial comparisons of efficacy data and caution should be exercised in making assumptions about class effect on outcomes.

Economic Models Focusing on Comparative Value

- It would be useful to account for regression of migraine from chronic to episodic in the health economic model
- All efforts should be made to include productivity benefits of therapies in the evaluation as this is an important societal benefit of treating migraine

- In determination of an appropriate time horizon (including lifetime) for the analysis, the overall adherence and persistence rates over time should be considered.

Please reach out if any further clarity is needed.

Sincerely,

Sanjay Gandhi, PhD
Senior Director
Global Health Economics and Outcomes Research
Global Medical Affairs
TEVA Pharmaceticals

References

1. GBD 2016 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet 2017; 390: 1211–59.