INSTITUTE FOR CLINICAL AND ECONOMIC REVIEW

CGRP Inhibitors for Migraine Prevention

Response to Public Comments on Draft Evidence Report

May 31, 2018

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Response to Comments from Individual Patients

We would like to thank the patient community for submitting public comments on our draft report on CGRP inhibitors for chronic or episodic migraine. We received an unprecedented number of comments from individuals on this review – more than 170 – and we deeply appreciated the migraine community's willingness to share how the disease has affected patients and their families.

We heard from many patients about how migraine alters their decisions due to the uncertainty in when the next migraine will occur, how living with migraine is depressing and isolating, how the "guess and test" approach to finding the right preventive therapy is frustrating, and how affordability of new treatments is a concern. We summarized these main themes in Section 1.4 of the report.

We also would like to clarify a few misunderstandings about ICER, as some commenters appeared to suggest that we either set the price of drugs, or that we create insurance coverage policies. Actually, neither is the case. ICER encourages drugmakers to set prices that align with the benefit patients receive, and when that happens, we put pressure on insurers to open up broad patient access. As part of our process, ICER hosts public meetings where all stakeholders, including patients and doctors, can participate in discussions about what insurance policies should look like and what a fair price for a treatment is. More information about ICER's work, goals, and funding can be found at https://icer-review.org/about/.

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Manufacturers		
Allergan		
1.	**Recommendation 1:** The migraine severity data of the scenario analysis in Table 4.12 of the DER should be used in the base-case analysis rather than as a scenario analysis. As noted in the Allergan letter re: comments on the model analysis plan (Recommendation 3, pages 11-12), the migraine severity data provided in Table 4.3 of the DER (page 60) do not represent proportions of migraine days that are mild, moderate and severe. Rather, they represent proportions of patients by "the severity of the pain they experience when their most severe type of headache is at its worst"1 (see the footnote to Table 4 in the source paper). The study by Blumenfeld at al. was sponsored by Allergan and the responses are based on the survey question, "When your most severe type of headache is at its worst, how severe is the pain?" The data collected address a completely different question and therefore should not be used for the migraine severity distribution. Using these data to inform the distribution of migraine severity does not simply constitute a limitation, but rather results in an erroneous assumption and an overestimation of severity that compromises the robustness of ICER's analysis.	We modified the distribution of migraine severity used in the model. The distribution of migraine severity was based on data from the American Migraine Prevalence and Prevention study, which was a mailed survey to 120,000 US households. Among those identified with migraine, information on the frequency of migraines and the severity of the migraine was reported. Data for those with more than four migraines per month up to 14 migraines per month were used to determine the severity distribution for the episodic migraine population where the categories of no impairment, some impairment, and severe impairment were summarized as mild, moderate, and severe. We selected this population for the distribution of headache severity as it was the population that was indicated as eligible for treatment in the paper. The same distribution was applied to the chronic migraine population. These distributions were similar to pooled estimates of migraine severity provided by manufacturers, which was based on

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		PREEMPT 1 and 2 and eptinezumab Phase II and III data.
2.	In contrast, the alternate data for severity of migraine used in a scenario analysis (Table 4.12, columns "Scenario Analysis", page 66, in the DER) represent an appropriate source of data and are consistent with published results for the proportions of migraine days at baseline that were mild, moderate, and severe in randomized controlled trials of chronic migraine patients. We recommend that these data be used in the base case analyses for the distribution of migraine severity to ensure the credibility and robustness of the analyses conducted by ICER. These estimates would be internally consistent with the trial populations and the efficacy estimates.	See above.
3.	**Recommendation 2:** Revise the definition of the failure population for chronic migraine to include patients who failed up to three preventive therapies. The DER defines the patient population modelled in the cost-effectiveness analysis as patients that "had at least one but not more than two prior preventive treatments result in failure" (page 51). This definition is said to be based on the anticipated place in therapy.	The data for the efficacy used in the base case model are from the patient population for whom at least one prior therapy had failed. In the base case-model, we are using these efficacy estimates to compare CGRP inhibitors to no treatment. The no treatment comparison is meant to reflect that if patients do not benefit from treatment with CGRP inhibitors, there are no alternatives.
4.	As noted in Table D5 of the DER (page 122), the erenumab and fremanezumab trials in chronic migraine did not exclude patients who had previously failed 3 preventive medications, and the PREEMPT trials of BOTOX® placed no exclusion criteria on the number of prior preventive medications. Furthermore, the payer policies summarized in Table 2.1 of the DER (page 14) do not exclude patients who have failed more than 2 prior preventive therapies from treatment with BOTOX®. Therefore, the exclusion of patients with 3 prior failures from the chronic migraine population in the cost-effectiveness analysis is neither consistent with the patient populations of the chronic migraine trials nor with representative payer policies. Allergan recommends that ICER change the definition of the failure population in chronic migraine to include patients who failed 3 prior preventive medications.	As noted above, the data for the efficacy used in the base case model are from the patient population for whom at least one prior therapy had failed.
5.	Allergan has conducted network meta-analyses (NMAs) comparing BOTOX® to the published data for erenumab 140 mg at weeks 4, 8, and 12, and at the end of the placebo-controlled period in patients who failed 1 to 3 prior preventive medications. Bayesian models were performed in WinBUGS 1.4.3. Both fixed effect and random effects models were based on code from the National Institute for Health and Clinical Excellence (NICE) Decision Support Unit. For each analysis, the model with the lower deviance information criterion and residual deviance was selected as the best fit. Allergan has also	See below.

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	conducted meta-analyses of the treatment effects for BOTOX® at weeks 16 and 20. Inverse-variance weighted fixed effect and DerSimonian and Laird random effects meta-analyses were performed using CMA software. Allergan suggests incorporating the treatment effects for BOTOX® at weeks 16, 20, and 24 into ICER's model, as the ICER model provides inputs for each cycle up to month 6.	
6.	**Recommendation 3:** Include BOTOX® PREEMPT 24-week data in the cost-effectiveness analysis. In the Clinical Effectiveness section of the DER, the NMA of the change from baseline in monthly migraine days in all migraine patients uses the PREEMPT results at week 24, the end of the placebo-controlled period (Table 3.1, page 26). However, the NMA of the change from baseline in monthly migraine days in patients who have failed at least one, but no more than two, prior preventives used in the cost-effectiveness analysis (Table 4.4, page 58) only uses the first half of the PREEMPT placebo-controlled period: week 4 through week 12. The PREEMPT trials show that the relative efficacy of BOTOX® shows further improvement after receiving a second treatment. In order to capture all the consequences of the interventions being evaluated, as guidelines recommend, this continued improvement warrants inclusion in ICER's modeling of BOTOX® efficacy. Allergan also notes that the ICER model, provided to us for review, already includes inputs for treatment effects at months 4, 5, and 6+, allowing for the inclusion of the entire PREEMPT placebo-controlled period. It is inappropriate to compare multiple treatments of the CGRPs to a single treatment of onabotulinumtoxinA, given the availability of placebo-controlled evidence from the PREEMPT trials and the model structure.	In the models, we use monthly changes in migraine days as estimates of efficacy. In the scenario analysis that includes Botox, we use the efficacy results from PREEMPT out to 24 weeks in the model.
7.	**Recommendation 4:** Include BOTOX® PREEMPT OLE data in the cost-effectiveness analysis. The PREEMPT placebo-controlled trials were followed by an open label extension (OLE) that showed further decreases of migraine days associated with continued treatment with BOTOX®. While the OLE results are acknowledged in the text of the DER (page 27), they are not used in the cost-effectiveness analysis. Allergan recommends including the OLE results with observations up to week 56 from randomization in the cost-effectiveness model, which has a two-year time horizon. Allergan previously provided a pooled analysis of the estimated treatment effect of BOTOX® in the PREEMPT 1 and PREEMPT 2 OLE for the intent-to-treat population.	We do not use open label extension data for inputs in the economic model. As noted above, we incorporate the 24-week data from PREEMPT in the scenario analysis.
8.	**Recommendation 5:** Discontinuation rates for should be revised. The cost-effectiveness analysis uses constant monthly discontinuation rates (Table 48, page 60 in the DER). As noted in our earlier letter to ICER, the results of the PREEMPT and COMPEL studies indicate that the discontinuation rate for BOTOX® decreases over time (see Recommendation 6, pages 24-25), and Allergan provided these data (Table 17, page 25). In	We use the discontinuation rates from the clinical trials in the model. We have included updated estimates of discontinuation in the models. Importantly, the discontinuation rates have very small effects on the incremental cost-effectiveness ratios as

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	contrast, the erenumab OLE in episodic migraine exhibits increasing discontinuation rates over time, biasing the current ICER model in favor of CGRPs. Allergan recommends accounting for the observed changes in the rates of discontinuation. Based on the discontinuation data extracted from Tepper 2017 (Table D13, page 142 in the DER), a patient without a post-baseline diary assessment and those who did not receive erenumab were excluded by ICER (Table D13, page 142 in the DER). To quantify discontinuation correctly, Allergan recommends inclusion of the patient without a post-baseline diary assessment, as the patient who did receive treatment. Further, ensuring an approach comparable to the discontinuation data reported in PREEMPT trials (Intent to Treat) requires inclusion of all patients who were randomized to erenumab and discontinued.	indicated in the one-way sensitivity analyses.
9.	**Recommendation 6:** Include the effect of BOTOX® on migraine severity in the cost-effectiveness analysis. The DER states that for the cost-effectiveness analysis, "it was assumed that the treatment effects result in a reduction in migraine days across all severity levels and do not change the distribution of migraine severity" (page 56). In the Allergan letter re: comments on the model analysis plan, Allergan noted that this assumption is contradicted by the evidence available for BOTOX® (see Recommendation 4, pages 15-16). A pooled analysis of PREEMPT 1 and PREEMPT 2 demonstrated that at week 24, compared to placebo patients, the proportion of headache days rated as severe was 3.9% lower in BOTOX® patients ($p<0.001$), the proportion of headache days rated as moderate was 1.4% higher ($p=0.066$), and the proportion of headache days rated as mild was 2.5% higher ($p<0.001$). The beneficial effect of BOTOX® on headache severity is also supported by a published analysis of PREEMPT patients who failed to achieve at least a 50% reduction in the frequency of headache days from baseline to week 24.14 At week 24, the proportion of severity responders was significantly higher in BOTOX® patients than placebo patients (41.1% vs 31.4%; $p=0.011$), where a severity response was defined as at least a 1-grade improvement in the item "When you have headaches, how often is the pain severe?" from the 6-domain Headache Impact Test (HIT-6). Please note that the impact of this issue is compounded by the issue raised in Recommendation 1.	We have incorporated treatment effect on the distribution of migraine severity.
10.	**Recommendation 7:** The differences in the available evidence for CGRPs compared to BOTOX® should be acknowledged as a limitation of the economic analysis. The clinical evidence currently available for the CGRPs in chronic migraine patients is limited to one Phase 2 trial for erenumab and one Phase 3 trial for fremanezumab, both of which were limited to 12 weeks in duration. In contrast, the evidence available for BOTOX® includes two Phase 3 trials with a 24-week placebo-controlled period and an open label extension through 56 weeks, as well as observational studies of up to two years in duration. The	We incorporate the 24-week efficacy estimates associated with Botox in the scenario analysis that compares the CGRP inhibitors to Botox. This is now included as a scenario analysis because of the evidence rating comparing the CGRP inhibitors and Botox.

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	economic analysis presented in the DER omits some of the available evidence for BOTOX® due to the unavailability of data for the CGRPs for the same periods of time. This should be noted as a key limitation of the comparisons of the CGRPs with BOTOX®, as it understates the long-term benefits of BOTOX®.	
11.	Additional suggestions for clarification. The Draft Questions for Deliberation and Voting related to the Clinical Evidence and the Long-term Value for Money describe the patient populations broadly as patients "for whom other preventive therapies have failed." However, the economic analysis in the DER uses a more restricted definition of the patient population that limits the number of prior failures to at least one, but not more than two, preventive therapies (page 51). Furthermore, it should be noted that the ICER assessment focuses exclusively on monthly migraine days as the measure of treatment efficacy. In the PREEMPT trials of BOTOX®, the primary endpoint was monthly headache days, and the reductions in headache days were nearly identical to the reductions in migraine/probable migraine days used in ICER's analysis. Allergan recommends addressing these data in the final report given important implications for patients.	Data on patients with prior failures are being used to extrapolate effects of CGRPs in patients with multiple prior failures. The base case cost-effectiveness analysis looks at patients for whom other preventive treatments have failed. At the public meeting, we expect discussion of how many failures of preventive therapies need to occur before it is reasonable to treat with a CGRP inhibitor.
Amgen		
1.	**ICER's base-case does not include indirect burden**. ICER should capture patient indirect costs in the base-case so as not to underestimate the value of CGRPs to patients. ICER's exclusion of indirect burden of migraine in the base-case does not align with established, accepted methodologies in economic evaluations of new treatments. This approach is inconsistent with ICER's previous assessment of Botox® for migraine, which included indirect/lost productivity costs in all scenarios. Comprehensive capture of all productivity costs should form the backbone of the base-case rather than a scenario analysis. Lost productivity costs are 70% of total costs in migraine. Omitting these from the base-case captures only 30% of CGRP value and could result in migraine patients experiencing discrimination in favor of treatments that offset more costs to the healthcare system. The gold standard for health economic assessment methodology, the Second Panel on Cost-Effectiveness in Health and Medicine, recommends that all cost-effectiveness analyses capture both the healthcare payor 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).	The ICER-base case analysis is developed from a health system payer perspective and does not include elements of a societal perspective such as productivity loss, since this perspective is most relevant for decision-making by public and private payers, provider groups and policy makers. We have however included a modified societal perspective capturing the impact of the CGRP inhibitors on productivity loss in patients eligible for treatment with these drugs. Please refer to our value assessment framework https://icer-review.org/final-vaf-2017-2019/ for more details on this.
2.	**ICER's estimate of productivity costs is derived from patients with very low disease severity (2 MMDs as opposed to 8 MMDs in the erenumab clinical trials).** ICER should adjust these costs to the baseline severity of migraine in CGRP trials. ICER productivity costs for episodic migraine patients of $245 per month (used in the scenario analysis) underestimates the real burden in prevention-eligible episodic migraine patients by a	We have changed our approach for estimating the impact on productivity which now assigns lost productivity based on hours per migraine day. Specifically, the costs of lost productivity were based on data from the American Migraine Prevalence and Prevention study (Stewart,

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	factor of two. ICER used the International Burden of Migraine Study (IBMS) for indirect costs in which a headache day frequency per month was 2.1 for episodic migraine (EM) and 14.56 for chronic migraine (CM). In contrast, the average monthly migraine day (MMD) in the erenumab pivotal studies was 8.36 (SD= 2.5) in EM and 17.8 (SD=4.7) in CM. Moreover, EM patients in erenumab randomized controlled trials (RCTs) had to have at least 4 MMDs during the baseline period to be enrolled into these studies. Hence, ICER applies costs of a significantly less severe migraine population leading to the undervaluation of erenumab in EM, especially when applied to indirect costs. Using monthly productivity costs for EM patients with 8 MDs (derived from STRIVE) gives a productivity cost of approximately $490 per month (derived from Lipton et al., see Appendix A for further explanation).	2008), in which nearly 200,000 participants reported estimates of lost productivity time. Patients with migraine reported the average number of hours of productivity lost in the last two weeks. Data on the number of migraines experienced in the last three months and the amount of lost productivity was used to estimate the number of hours lost per migraine day. To estimate the cost, the median income rate in the US was used.
3.	The accuracy of ICER's analysis could be strengthened by incorporating data from the treated erenumab EM patient population given a wide variation observed in lost productive time (LPT) across EM patients. In a study by Stewart et al., among employed individuals with migraine, the average LPT (absenteeism and presenteeism) per worker per week specifically due to headache was: • 2.2 (SD=4.5) hours for those with 0–3 days of headache/month • (SD=6.5) hours for those with 4-9 days of headache/month • (SD=7.3) hours for those with 10-14 days of headache/month Variability in LPT is considerable, especially in the EM population. Hence, ICER's use of a single number for lost productivity across the whole EM population grossly understates the burden among these patients. Lipton et al., more accurately reflect this variation at a migraine day level in their model, calculating the average costs of absenteeism and presenteeism days assuming the median hourly gross wage obtained from the US Bureau of Labor Statistics over an 8-hour working day (the degree of productivity loss on each presenteeism day, i.e., days where productivity is reduced by at least 50%, is not known). The publication uses question two from the Migraine Disability Assessment (MIDAS) which defines a presenteeism day as lost productivity of at least 50%. We would highlight that this is not an overestimation of the impact of migraine but consistent with the definition from the well-validated MIDAS questionnaire. If ICER took this approach basing the number of days of productivity losses on erenumab clinical trial data (capturing the sex, age and employment status of the clinical trial populations and the baseline migraine days of 8 mentioned above) it would make productivity costs more accurate.	As described above, we use the Stewart study for our source of productivity-related costs.
4.	**ICER's analysis underestimates direct health care costs.** ICER should revise its hospitalization, Botox® and ED costs and rates and conduct a robust sensitivity analysis around these. ICER's	We have revised the estimates of direct healthcare costs used in the model. We use data from an analysis of the Truven

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	direct cost estimates are too low owing to underestimates in the main cost drivers of emergency department visits, hospitalization and Botox® cost summarized below: • Emergency Department (ED) cost: ICER uses $473 for migraine related ED from Messali et al. which is 1.5 to nearly four times less than the estimates from Insigna and Bonafede et al. This difference is attributable to Messali et al.'s value excluding services in the ED for migraine patients such as fees for provider administered injectables, MRI and CT scans, which the latter two references include. • ED visit rates: ICER's ED visit rates for migraine patients in EM are too low. ICER uses 14/100 patients per year in EM and 19.6/100 patients per year in CM, whereas other references estimate this as 17/100 patients/per year. 34% of migraine patients have at least one ED visit in a 12-month period compared to 14.3% among non-migraine controls. • Hospitalization rates: ICER uses a rate of 0.342 hospitalizations per day per 100 patients (from AHRQ Statistical Brief #111). This is an inaccurate reflection of migraine hospitalization rates because a) it is an ED visit rate not a hospitalization rate; and b) it is the migraine hospitalization rate as a proportion of the general US population, not the higher reported hospitalization rate among migraine patients. ICER's model input should be specific to the population it is modelling. We recommend ICER use the rate from Munakata et al., which is seven migraine-specific hospitalizations per 100 migraine patients. • Drug costs: ICER estimates the cost of Botox® based on the Federal Supple Schedule (FSS) which underestimates its cost. We recommend instead using the WAC cost which is more representative of the costs payors would incur. The current Wholesale Average Cost (WAC) or List price for a 200 unit vial for Botox® is $1,202 for an annual drug cost of $5,169 and annual administration cost of $649. These differences are important as combined, they work to diminish the costs that CGRPs offset, which results in an underestimation of the value of these innovative treatments to patients. This is especially important as these inputs are unavailable by migraine frequency and previous treatment status. Hence, we also suggest conducting robust sensitivity analyses around medical resource use and direct cost estimates.	MarketScan Commercial Claims and Encounters (CCAE) database for ED costs. We have also adjusted the denominator for estimating the rate of hospitalizations and apply the rate to costs from the same analysis of the Truven MarketScan CCAE database. Finally, we use the same analysis for costs of outpatient visits.
5.	**ICER's analysis does not quantify uncertainty in the network meta-analysis (NMA) nor its implication on clinical effectiveness results.** ICER should focus the NMA on the base-case analysis, remove the comparison in all-comers and adjust for heterogeneity in the studies analyzed. We commend ICER for recognizing the relevant patient population for CGRPs (those who have failed a prior preventive therapy) and rating the evidence as promising but inconclusive for EM and comparable or better for CM (See Appendix B, Table A). Aligning with this, in	Our assessment of the CGRP inhibitors includes the wider population of chronic and episodic migraine patients as well as the subpopulation of chronic and episodic migraine patients for whom prior therapies have failed. Based on our conversations with many stakeholders included clinicians and patients, both of these populations were of interest to evaluate in the clinical

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	evaluating clinical effectiveness we recommend that ICER removes the comparison of CGRPs to current preventive therapy (as presented in the scenario analyses). Comparison of erenumab and CGRPs against generic prevention should not be undertaken given their place in the treatment paradigm and observed heterogeneity in the results.	review. Indeed, the current CGRP inhibitor trials include patients from the wider population and not only those for whom preventives have failed. Given the anticipated place of the CGRP inhibitors in the treatment paradigm, this "prior failure" subpopulation is the main focus (the "base-case") for our economic analysis.
6.	The NMA includes studies conducted over two decades during which methods for collecting outcomes and design of clinical trials have evolved tremendously. The methods to define outcomes and included patient populations (in terms of baseline number of MMDs, medication overuse, use of concomitant therapy, etc.) vary substantially between the studies. This introduces significant heterogeneity in the networks. ICER has acknowledged that the heterogeneity in the CM model was fairly high (0.68 [0.03, 3.02]). We recommend that ICER accounts for the resulting heterogeneity in the NMA.	Without access to patient-level data, we are unable to conduct network meta-analyses to control for patient-level characteristics. As we are only able to use the study-level (aggregate) data, we excluded trials with 100% medication overuse from any analysis and did not synthesize results quantitatively where outcome definitions differed substantially (e.g,. 50% responders in the chronic migraine population).
7.	Lastly, ICER's rating of the evidence could be enhanced by: 1) adding clarity on what was considered as a comparator for each phenotype and patient subgroup; and 2) adding clarity on the derivation of the efficacy numbers highlighted in ICER's draft report, page 48, "Efficacy: Results suggest a modest reduction in monthly migraine days (1.3-2.4 fewer migraine days per month), a modest reduction in days using acute medications (0.9-2.5 fewer days per month), and a greater proportion of patients experiencing a reduction in migraine days by at least 50% (OR 1.9-2.3) with erenumab compared with placebo."	We have updated the summary to match the current evidence base in this version of the Report.
8.	**ICER's model estimates utility based on a distribution of migraine severity, which does not capture the treatment effect of erenumab.** ICER should map QALYs from quality-of-life scales measured in the relevant population (erenumab Phase III studies). Reduction of interictal burden is an important benefit with prevention which is not captured in ICER's analysis. ICER uses utilities in the model collected from patients and the general public to form a QALY for a given state of health. These utilities are not representative of the erenumab patient population recruited in the Phase III studies or patients who are eligible for prevention. ICER misinterprets Lipton et al. stating, "Lipton et al. derived utility estimates from the International Burden of Migraine Study that included participants from 10 countries," This is not where Lipton et al. derive these utilities. It is correct that the algorithm to map utilities from Migraine-Specific Quality-of-Life Questionnaire (MSQ) and Headache Impact Test 6 (HIT6) was based on the IBMS data, however, the treatment effect on utilities for erenumab and placebo map from the MSQ and HIT6 collected in erenumab Phase III trials. This is critical since as pointed out by ICER, "Lipton et al. derived utility measures that are different across placebo and treatment, such that patients had 1) a utility gain associated with the	We have conducted a scenario analysis were a small gain in utilities was incorporated for patients who were treated with CGRP inhibitors to reflect the change in depression. Specifically, we applied a 0.05 QALY gained to an estimated 20% of patients with moderate to severe depression that may have a benefit associated with CGRP inhibitor treatment. The 0.05 utility gain corresponds to a rough average of utility gain from a 2-point change in the PHQ9 for those with moderate to severe depression.

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	treatment that was independent of migraine day reduction." This treatment effect for erenumab is likely due to the effect on interictal burden, reduction of other migraine symptoms and reduced severity. ICER's approach to modeling utility does not account for this treatment benefit. Hence, ICER should map from HRQoL scales collected in the relevant population (erenumab Phase III studies) in order to capture this treatment benefit that goes beyond a reduction in MDs.	
9.	ICER overestimates baseline QALY values for chronic migraine patients when not experiencing a migraine, which underestimates the benefit of erenumab. ICER uses QALY values on pain-free migraine days of 0.95 from patients averaging 1-6 migraine attacks from Xu et al. versus 0.87 from patients averaging 5 MMDs from Stafford et al.,Stafford et al.'s value for a non-migraine day is lower than Xu et al. because patients in the Stafford et al. manuscript were more severe and are a better proxy for the patients enrolled in the erenumab Phase III trials (averaging 8 MMDs). Hence, ICER's use of Xu et al., does not adequately capture the impact of migraine on a patient's quality of life and interictal burden. Moreover, the values in Stafford et al. are consistent with other studies in representative populations that report a mean utility of migraine patients when not experiencing a migraine day (MD) as 0.82. This is further supported by Amgen Phase III studies, which measured a utility of 0.84 for patients with zero MDs.	We felt it was internally consistent to use the utility values from the same source for each of the health states. Moreover, the current approach with a larger difference between the average utility on a migraine day and that on a migraine free day will benefit the CGRP inhibitors because there will be larger gains in utility when adding additional migraine free days. Thus, using the Stafford et al. estimate would result in lower treatment effects in terms of QALYs. Finally, we conducted one-way sensitivity analyses on the utility value for migraine-free days and migraine days.
10.	**Patients seeking care for CGRPs or generic prevention will experience a placebo effect even in clinical practice. ICER** should exclude these effects in the base-case for consistency. Clinical trials in migraine prevention typically have strong observed placebo effects. Migraine placebo response is predominantly due to regression to the mean since migraine day frequency and severity vary markedly over time within individual patients.i ICER uses placebo adjusted rates from erenumab studies but not for clinical practice. These also occur in clinical practice but are not measurable because administration of placebos, such as sham injections, is not a plausible treatment option. This severely underestimates the efficacy of erenumab as it accounts for placebo effects in the erenumab clinical trials but not those in clinical practice: these occur in both settings and ICER should standardize the approach for consistency.	We believe it is appropriate to look at the benefits of a therapy compared with placebo, rather than to assign a therapy benefits that occur through the placebo effect.
11.	**ICER's model overestimates the number of CM patients treated with preventive migraine therapy in the budget impact analysis.** ICER should revise the size of the patient population that may be treated by CGRPs to be consistent with published prevalence numbers and other market analyses reports. The ICER report states that 95.6% of CM patients currently receive preventive treatment, which is an overestimate. While this number is based on the Adelphi Migraine Disease Specific Programme (DSP), a real-world, cross-sectional survey of physicians and their patients with migraine, it only samples	Thank you for your comment. We have reviewed your suggestion and revised the eligible population for the budget impact model. Unlike the eligible population in the draft version of the report, which included patients assumed to experience the failure of at least one line of preventive therapy among those estimated to currently receive preventive therapies, the current eligible population includes patients assumed to fail

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	patients who present at a doctor's office, i.e., are trying to access care for their migraine. Hence, this number vastly overstates the percentage of patients with chronic migraine who are receiving preventive migraine therapy. Considering a one million patient plan, approximately 3% of patients currently or previously on migraine preventive therapy would start an anti-CGRP in year one. These estimates are consistent with independent analyst estimates at 2%. This would apply to the base-case scenario where patients with at least 4 MMDs and experience with one prior preventive therapy are eligible for an anti-CGRP. Another study, estimates that only 12-13% of patients who need prevention are currently receiving it.	at least one line of preventive therapy among all patients eligible for preventive therapy.
12.	**Areas for further clarification.** Since the efficacy estimates for the base-case analysis were not transparent, we are unable to comment if the efficacy data were used appropriately. Amgen provided ICER data in treatment experienced patients from Amgen publications. However, it is not clear what the efficacy estimates are for this base-case. It is also unclear if NMA results for efficacy for treatment experienced patients were used in the base-case analyses. It is unclear how the erenumab open label extension (OLE) data were incorporated in the clinical and value assessments. Erenumab is the only CGRP with robust published data. We recommend that these data be included in the evaluation of benefit that erenumab brings to patients.	For the subgroup of patients for whom preventive therapies have failed in the base-case, treatment effects for monthly migraine data were utilized from the subgroup results submitted by the manufacturers in confidence (Amgen/Novartis and Teva). Originally, we used the OLE discontinuation rates for erenumab but currently use the discontinuation rates from the trials included in the NMA.
Eli Lilly and Company		
1.	As noted in the Evidence Report, CGRP inhibitors have not yet been FDA-approved. In addition, there is limited information (e.g., pricing not set) on which to base a comprehensive assessment of product efficacy and value, and no data on effectiveness. For these reasons, we previously requested that ICER delay conducting this review until results have been published for all pivotal clinical trials for all CGRP inhibitors being evaluated. In particular, we requested that galcanezumab be removed from this assessment until Phase 3 randomized controlled trial (RCT) data have been published in peer-reviewed journals. The results presented in this assessment highlight the limitations associated with prematurely conducting a review without all of the pivotal clinical trial and other data needed for this purpose. As a result, it is our opinion that ICER has conducted a suboptimal assessment that lacks appropriate scientific rigor and full transparency.	The first of the CGRP inhibitors, erenumab, was approved by the FDA on May 17, 2018, and a price announced. We have updated our cost-effectiveness analysis to reflect this price. Patients, clinicians, and insurers will now be making decisions about erenumab and other CGRP inhibitors in anticipation of a FDA decision later this year. This is an active research space, and we have identified and synthesized the current literature to date to aid in the decision-making process. As noted, due to the limited data availability for galcanezumab at this time, we have only included it in our clinical review but not the economic assessment. We look forward to seeing the full results and publications of additional trials in the future.
2.	**Limited published data from Phase 3 RCTs across all compounds leading to inconclusive findings.** • Multiple Phase 3 RCTs have been conducted across the CGRP inhibitors; however, at this time, only a few articles have been published for erenumab and fremanezumab and none for galcanezumab.	Thank you for noting the missing trial from our ongoing trials section. We have updated the appendix with this trial and data.

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	• Although grey literature may provide some insights into efficacy and safety, it does not provide the same level of detail (e.g., baseline characteristics, inclusion/exclusion criteria) as peer-reviewed published articles that would be needed to conduct a comprehensive assessment. In addition, although ICER policies state that they will consider grey literature as part of their review, it is apparent that it was not factored into this particular review despite the fact that the evidence is rapidly evolving. Numerous abstracts are available on galcanezumab Phase 3 data (citations provided to ICER in correspondence dated February 6, 2018); however, only Phase 2b data were used in the comparative clinical assessment with the exception of a mention of Phase 3 trials/results in the appendix. Thus, when comparing clinical efficacy, only Phase 2b data for galcanezumab were shown in tables that included both Phase 2 and Phase 3 data for other molecules without adequate documentation of this key difference. To improve transparency, a column should be added to the comparative clinical tables that clearly shows when Phase 2 or Phase 3 data are being used. At minimum, a footnote should be added to the tables to highlight this issue. • On page 22, you mention the galcanezumab Phase 3 chronic migraine (REGAIN) trial and state that the results are shown in Appendix C; however, information on the REGAIN study is not included in Appendix C. Please include a summary of this trial in the Appendix. We acknowledge the data in confidence policy that ICER developed during this review; however, we believe that a redacted report would not meet the appropriate standards of transparency. In addition, it is our opinion that the current policy does not adequately mitigate the risks associated with jeopardizing future publications.	
3.	**No pricing information.** Currently, there is no pricing information available for the CGRP inhibitors. It is premature to conduct cost effectiveness or budget impact modeling and to draw conclusions on the potential value of the products without pricing information or other contributors to price (e.g., labeled dose).	While this was noted as a limitation in the draft evidence report, it is important to note that the threshold analyses do not require a list price to be calculated. Rather, they illustrate the price that could be charged to meet a given cost-effectiveness threshold range. Erenumab was approved in the period between the posting of the draft and revised evidence reports and ICER's analyses have been updated with its list prices.
4.	**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 the products. As a result, there is no way for ICER to know which of the many efficacy and safety results are relevant. In the assessment, ICER used galcanezumab 120mg in the comparative clinical section; however, Phase 3 trials evaluated both 120mg and 240mg.	In the economic model, we selected the dose with the highest efficacy estimates for estimating the incremental cost-effectiveness ratios and the value-based price.

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	Given that ICER only used a Phase 2b dose ranging study in the evaluation of galcanezumab, the 240mg dose that was used in subsequent Phase 3 trials was not even acknowledged in the comparative clinical section.	
5.	**Confusing use of the term "insufficient" in the summary and comments.** In the summary of the results, ICER refers to the evidence of net benefit for galcanezumab and the other two CGRPs as being "insufficient." The use of this term may be confusing because in Figure 3.1 ICER defines "insufficient" as "any situation in which the level of certainty in the evidence is low." In the case of galcanezumab, in particular, ICER does not have published Phase 3 data to adequately evaluate the evidence. Thus, it is not uncertainty in the efficacy and safety evidence that is the issue, but rather the timing of the assessment which is resulting in a lack of evidence that ICER has access to use in the review. We respectfully request that ICER clarify this point and not "rate" galcanezumab in this assessment. If ICER chooses to rate galcanezumab, then we would strongly suggest the following editorial change to ensure clarity in interpretation: "Given the limited data currently available for galcanezumab, the amount of evidence upon which its net benefit could be assessed was rated as insufficient ("I")."	We have rephrased the summary to "Given the limited amount of data currently available, we rated the evidence on the net benefit of galcanezumab as insufficient ("I") for all populations and comparisons." We look forward to seeing the full results and publications of additional trials in the future.
6.	**Cost Effectiveness.** The model includes utilities based on migraine severity. Consider doing a scenario analysis evaluating utilities based on migraine frequency similar to the Lipton et al (2018) article that you reference in the report. Health care resource utilization in the model is based on a proportional reduction in migraine days. It is unclear how a correlation can be made between reduction of migraine days and reduction in health care resource utilization such as emergency room visits or hospitalizations. It would be more appropriate to consider HCRU reduction associated with the use of preventives. The model is based on a health system perspective with a scenario analysis using the societal perspective. Given the substantial impact of migraine on workplace productivity and other indirect costs it would be important to emphasize those results in the conclusion or to consider using a societal perspective as the base case.	We felt that the data available to us, mostly originating from published literature, were most consistent with the approach that we used for utilities and migraine severity. We did not have the data used in the Lipton paper for migraine frequency and utilities. We do incorporate a shift in the severity distribution of migraines for individuals treated with the CGRP inhibitors. From the clinical trials we do not have the changes in resource use associated with the use of the preventive medications. It was necessary to use a treatment effect based on migraine days to proxy the reductions in health care resource use. The ICER base-case analysis is developed from a health system payer perspective and does not include elements of a societal perspective such as productivity loss, since this perspective is most relevant for decision-making by public and private payers, provider groups and policy makers. We have however included a modified societal perspective capturing the impact of the CGRP inhibitors on productivity loss in

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		patients eligible for treatment with these drugs.
Teva Pharmaceuticals		
1.	**Impact of Treatment on Severity of Headache.** The current modeling framework has accounted for a reduction in migraine days due to the use of preventive migraine therapies. However, the treatment-specific impact on the severity of subsequent migraines or headaches is not considered. Different therapies have different mechanisms of action and may have a unique impact on severity of headaches post-treatment. We strongly suggest to include any impact of preventive therapies in not only reducing the number of migraine/headache days but also for reducing the severity post preventive therapy use based on treatment-specific available data. Including this effect of therapies in the analysis will allow for a more complete estimation of treatment benefits.	We have incorporated a shift in the severity distribution of migraines based on the data made available to us.
2.	**Accounting for Differences in Baseline Migraine Days.** The ICER model also relies on the mean reductions in monthly migraine days as a measure of clinical benefit to estimate the cost-effectiveness of preventive therapies in chronic and episodic migraine. The same absolute change in monthly migraine days may mean different things to patients across the distribution of migraine days per month at baseline. Differences in baseline migraine days have been observed across trials that were included in the analysis for estimation of treatment efficacy of therapies. For example, in chronic migraine, the baseline monthly migraine days across different trials were: • fremanezumab trials (monthly dosing arm) (Silberstein 2017, Bigal 2015a): 16.0 and 16.4 days • erenumab trial (140 mg dose) (Tepper 2017): 17.8 days onabotulinumtoxinA trials (Aurora 2010, Diener 2010, Cady 2014): 19.1 to 23.4 days.	We used an absolute reduction in migraine days which were the primary endpoints in the clinical trials used for the NMA. Relatively small differences are seen in the absolute treatment effect across chronic and episodic migraine populations. Therefore, we chose to use a constant absolute effect for each of the CGRP inhibitors. We include sensitivity analyses around the treatment effects which can be used to address differences in efficacy.
3.	For two different therapies with the same reduction in absolute number of migraine days, the corresponding percent reduction in the number of migraine days would be greater with the therapy that was used in patients with fewer number of baseline migraine days. Given the observed differences in baseline migraine days as noted above, efficacy estimates that are adjusted to account for differences in monthly migraine days at baseline would allow a more robust comparison of efficacy across these preventive agents. **We suggest that percent change in monthly migraine days from baseline be used in place of the absolute change in migraine days from baseline to allow for a more valid comparison across trials with different baseline migraine days.**	The data from the episodic and chronic population show a similar absolute treatment effect which is counter to the notion of a constant relative effect within each of the CGRP inhibitors. Therefore, it seemed most accurate to use the absolute effect for each of the drugs in the models.
4.	**Phase 2 Data Considerations.** In the comparative effectiveness analyses, evidence from Phase 2 and Phase 3 studies were given equal consideration (ICER 2018, Table 3.1 in appendix). It should be noted that trial phase may have an important impact on the observed treatment effect. The FDA itself notes that "pre-	Trials were only included in a quantitative synthesis if they had similar study designs, baseline characteristics, intervention dosages, and outcome definitions, regardless of Phase. For example, we did

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	market clinical testing usually progresses in phases, with increasingly rigorous methods at each phase" (FDA 2017) thereby potentially leading to an overestimation of treatment effects in Phase 2 as compared to Phase 3. Indeed, in one example from oncology, there was a significant overestimation of the mean difference in response rates for Phase 2 as compared to the subsequent Phase 3 trials (Zia 2005). This "phase effect" is further supported by a recent FDA report (FDA 2017) and a recent review of over 200 drug candidates 2013-2015 (Harrison 2016). Using data on efficacy estimates of a therapy with only Phase 2 trial data (e.g., erenumab in chronic migraine) and comparing it to efficacy estimates of therapies pooled from both Phase 2 and Phase 3 data (e.g., fremanezumab in chronic migraine) may be biased given the potential for overestimating the efficacy in Phase 2. A more robust approach would be to test the sensitivity of results to the potential bias introduced due to overestimation of efficacy in Phase 2.	not include the erenumab 7 mg dose from a Phase II study in our analyses of clinical benefits, but we did include the 70 mg dose. All available evidence, including from Phase II trials, can help inform effect estimates. However, due to smaller sample sizes or larger variances, the results from the Phase II trials are given less weight in the NMAs.
5.	**Treatment Discontinuation Rate Considerations.** Treatment discontinuation is one of the variables impacting cost-effectiveness outcomes. ICER calculated monthly discontinuation rates using the odds ratios estimated in the network meta-analysis of clinical studies in episodic migraine and chronic migraine. However, the estimated results lack face validity. For example, in the ICER analysis the monthly discontinuation rate for the fremanezumab monthly arm in episodic migraine is estimated to be 17.5% (ICER 2018, Table 4.8, p60), whereas the discontinuation rate for the fremanezumab monthly dosing regimen observed over a 12 week period in the fremanezumab episodic pivotal trial is substantially lower. The ICER analysis should ensure that the discontinuation rate estimates are appropriately derived and used in the analysis. In addition, to reflect discontinuation rates that are more indicative of those observed in real world clinical practice, the impact of a lack of therapy response on discontinuation should also be included in the discontinuation estimation and economic modeling.	We have incorporated the additional data on the discontinuation rate for fremanezumab in the model.
6.	**Therapy Cost Estimates of onabotulinumtoxinA.** The current analysis uses the therapy cost of onabotulinumtoxinA as per the Federal Supply Schedule which is very relevant for the US Federal Government and Veteran's Administration (VA). Though this is an important audience, to make the results more relevant to the commercial payers, a more relevant price estimate that reflects the likely cost of onabotulinumtoxinA cost to the commercial payers should be used in the analysis.	We use SSR data whenever estimating net price for a drug. However, in some case where drugs are physician administered, as in the case of Botox, sampling errors occur since these drugs move through less-common institutional channels. The sampling error tends to artificially lower gross sales and implied discount rate. In such cases, we use the Federal Supply Schedule price to represent a discount from WAC. However, we are happy to consider estimates on discounts for Botox if available.

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7.	**Including Efficacy Data Over the Entire Observation Period.** In the estimation of efficacy, it is important to consider the benefit of therapy over the entire observation period (e.g., over the entire 12 week period) as opposed to efficacy observed only at a latest observation period (e.g., over last 4 weeks at week 12). This is important because including efficacy observed over the entire observation period ensures that the estimates of early benefits of therapy are reflected in the assessment and also ensures that the efficacy estimate is not an artifact of the treatment observation period selected. Failure to account for observed differences at these earlier time points disregards potentially meaningful benefits of therapy across the entire course of treatment, and underestimates the overall treatment effect and impact. This assessment approach should be applied consistently across all preventive therapies included in the assessment.	We disagree, and in the model we use the monthly changes in migraine days at 4, 8 and 12 weeks (inflated to 30 day periods). We use the 12 week estimate for the duration of the model thereafter because we feel this estimate is the best representation of subsequent treatment effects.
8.	**Inclusion of Efficacy Data on Impact on Comorbidities.** Impact of reducing migraine days and severity can have significant positive impact on migraine related comorbidities like depression and anxiety. Recently, fremanezumab therapy has been shown to decrease the score on the Patient Health Questionnaire (PHQ-9) in patients with moderate to severe depression in chronic migraine patients (Cohen 2018). Cost and quality of life implications of such benefits of preventive therapies should be modeled to assess the full benefit of preventive therapies in the evaluation.	We have conducted a scenario analysis where a small gain in utilities was incorporated for patients who were treated with CGRP inhibitors to reflect the change in depression. Specifically, we applied a 0.05 QALY gained to an estimated 20% of patients with moderate to severe depression that may have a benefit associated with CGRP inhibitor treatment based on data on PHQ9 scores.
9.	**Consistency of Outcome Time Point.** Time point of follow-up utilized in the comparative effectiveness assessment is an important factor in determining the magnitude of the effect relative to baseline. ICER's analysis of change in monthly migraine days by time point presented in Appendix D (ICER 2018, Tables D28-D30, pp173-175) suggests that time point of assessment has an impact on the derived efficacy estimate. This emphasizes that analyses using data from consistent periods of observation (e.g., 4, 8, 12 weeks) across trials should be used in the assessment. In the primary analysis for chronic migraine, onabotulinumtoxinA trial results at 24 weeks were compared to topiramate at 16 weeks and the other drugs at 12 weeks. The validity of the analysis comparing onabotulinumtoxinA at week 24 to the other drugs at 12 or 16 weeks is questionable. Consistency in time point of assessment across trials would allow for a more meaningful comparison of efficacy estimates across trials.	We conducted scenario analyses including analyses by time point (4, 8, 12 weeks) and analyses with covariate adjustment for follow-up. The results from these analyses lead to similar conclusions as the analysis at last follow-up (e.g., 12-24 weeks).
10.	**Consistency in Estimates for Monthly Cycles in Cost-Effectiveness Model.** Estimation of monthly costs and rates for use in the cost-effectiveness model should be carried out in a consistent way. This includes specifying a common definition for a "month" and applying this definition consistently throughout the analyses. For example, it appears as if the effectiveness rates are estimated based on reported 4-week (28-day period) data,	We believe that we are consistent in our approach. We used monthly costs and we used efficacy estimates that are scaled to 30-day periods.

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	scaled to a 30-day period and applied accordingly. Whereas cost inputs are calculated assuming a 30-day month. In any given cycle, this imprecision may seem insignificant, however, over the course of the model calculations (analysis time horizon - 2 years) inconsistencies in benefits and cost estimations may add up to significant levels.	
Clinical Societies		
R. Allan Purdy, MD, Chair, American Headache Society; David Dodick, MD, President, American Migraine Foundation		
	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 QALY accounts for the impact of a health technology on the health-related quality of life besides its impact on length of life. The QALY is a widely used metric in cost-effectiveness analyses in the US and in other countries as well, to capture disease burden and levels of alleviation of this burden using specific health technologies.
	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	The ICER-base case analysis is developed from a health system payer perspective and does not include elements of a societal perspective such as productivity loss, since this perspective is most relevant for decision-making by public and private payers, provider groups and policy makers. We have however included a modified societal perspective capturing the impact of the CGRP inhibitors on productivity loss in patients eligible for treatment with these drugs. While the impact of migraines on career choices and wage growth, may be possible, there are no available data linking the potential treatment effects to these sorts of potential long-term changes.

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	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 >50%, >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 >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 drugslong-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.	Our assessment is based on evaluating the existing evidence for CGRP inhibitors. As noted, the current evidence base is limited to short-term follow-up with only one interim analysis of an ongoing, open-label extension study. Additional trials and open-label extension studies are on-going and we look forward to seeing these results in the future.
	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	We believe it is appropriate to look at the benefits of a therapy compared with placebo, rather than to assign a therapy benefits that occur through the placebo effect.

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	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.	Randomization is an assignment mechanism wherein the distribution of effect modifiers is the same, in expectation, across groups. Because the distribution of these characteristics is the same at baseline, any differences in the trial results between the groups can be attributed to the assigned treatment. This difference between groups, not the arm-level results, is an unbiased estimate of the causal effect of treatment assignment. We agree that future randomized trials comparing active interventions head-to-head, particularly of the CGRP inhibitors versus oral preventive therapies, are of interest. However, at this time we are unaware of any such efforts.
	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	The treatment effects observed in the clinical trials demonstrate an effect that is consistent across the study period. If patients were discontinuing due to a lack of effect we would have expected to observe an increase in efficacy across the study

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	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.	period. Further, based on input from clinicians it is not clear that patients are advised to discontinue based on a specific threshold of response and it may even be possible that very high responders would discontinue therapy as they may receive sustained benefit.
Seymour Diamond, MD, Executive Director, et al., National Headache Foundation		
1.	The impact of migraine on an individual is not fully represented in the ICER report's current models. They do not account for the impact of the prodromal symptoms that may occur several days before the migraine attack, which themselves can impair quality of life. They also do not account for the impact of psychiatric disorders that may result from attacks of migraine headache that are not adequately treated by existing preventative therapies.	We do not have data specifically delineating the impact of the prodromal symptoms on quality of life. We used data on migraine severity that may include some aspects of prodromal symptoms when patients were reporting utility values.
2.	Both acute and chronic migraine are compared to onabotulinum toxin A in the report. Since this therapy is not indicated for episodic migraine, this represents an inadequate comparator for these analyses. A more appropriate comparator would have been currently indicated preventative therapies for episodic migraine as well.	We have conducted analyses separately for episodic and chronic migraine, and only included onabotulinum toxin A in the chronic migraine assessment. For both populations, we also compare the CGRP inhibitors to other preventive therapies (topiramate, amitriptyline, propranolol). We also have conducted subgroup analyses for the patients for whom existing preventive therapies have failed. For this population, we compare the CGRP inhibitors to placebo only in episodic migraine and to placebo and onabotulinum toxin A in chronic migraine. Indeed, this “prior failure” population is the main focus (the "base-case") for our economic analysis.
3.	We are concerned that analyses were performed separately for only two groups of migraine patients -those with episodic and chronic migraine. This dichotomization may not be entirely justified as those with high migraine frequency (10 to 15 days per month) have a similar disability to those with chronic migraine. We understand that these population definitions are not conceived or implemented by ICER, but we feel that though they may be useful for clinical trial design, they have little	Our decision to conduct separate analyses for chronic and episodic migraine was informed in part by existing clinical diagnoses (e.g., chronic migraine), trial designs, and input from stakeholders. Patients with "high-frequency episodic migraine" may receive benefits somewhere between those observed in episodic and

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	applicability in the real world. The ICER report should take this into account.	chronic migraine trials. Analyses with patient-level data may help to explore these potential benefits. However, we do not have the data available that characterize a treatment effect in this population.
4.	The effect of migraine on a given individual depends not only on the frequency of migraine days, but on the effectiveness of their abortive treatments that can vary from patient to patient. Models should have been done to stratify for differential response rates to abortive medication s.	In generating the incremental cost-effective ratios we rely on population averages to estimate the most likely value. We realize there is variability across many of the parameters used in the model. We attempt to quantify this variability through sensitivity analyses, both one-way and probabilistic.
5.	Opioids are frequently used to treat persons with migraine, which can lead to abuse and dependence in a small percentage of persons with migraine. These costs should have been included in the economic analyses. We feel that the CGRP antibodies could play a significant role in reducing the impact of the opioid crisis in the U.S.	Opioids are included in the mix of medications used for acute treatment of migraines in the model. There is a reduction in the use of these acute treatments associated with the CGRP inhibitors. We also capture reductions in ED visits and hospitalizations associated with migraine use that may include opioid utilization and therefore a reduction associated with CGRP inhibitors. However, there are no data linking the use of CGRP inhibitors with reductions in long-term opioid abuse and misuse.
6.	The current economic analysis includes costs for every person started on CGRP monoclonal antibodies and assumes all individuals will continue on this medication for 1 year. One year might be too long of a time period to assess efficacy. You may want to limit its use to 6 months in the analysis, which would be a more appropriate duration for a preventive trial.	The model does not require that patients are continued on medications for 1 year. In fact, discontinuation rates from the clinical trials are relatively high and patients are allowed to stop treatment beginning after the first month. Using a shorter time horizon in the model would not change the results.
7.	It is likely that only 40 to 60% of those with migraine may actually be responders (e.g. those with a 50% or more reduction in migraine days) to this therapy. Costs will be much lower in this group as response rates are much higher. You may want to consider performing a separate analysis in the responders to determine cost per quality of life year saved. This will be much more reflective of ongoing costs for CGRP monoclonal therapies.	The treatment effects observed in the clinical trials demonstrate an effect that is consistent across the study period. If patients were discontinuing due to a lack of effect it would be expected to observe an increase in the efficacy across the study period. Further, based on input from clinicians it is not clear that patients are advised to discontinue based on a specific threshold of response.
Amy Miller, PhD, President and Chief Executive Officer, Society of Women's Health Research		
1.	Because migraine is more common in women and affects women differently than men, data should be stratified by sex. In	Our model incorporates the demographics of the current migraine population in the

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	previous reports, ICER has shown a willingness to stratify the cost-effectiveness results by subpopulation. Given the ways that migraine and migraine treatments affect women differently than men (as described above), we strongly encourage ICER to stratify the final results of its cost-effectiveness analysis (CEA) by sex.	United States. The goal of the economic evaluation is to provide the population level estimate of the incremental cost-effectiveness ratio and value-based price. We do not believe there would be separate value-based prices based on sex and therefore a single estimate seems to have the most policy relevance.
2.	Migraine quality of life data used in ICER's analysis may not adequately capture the disproportionate effect this disease has on women. The Headache Impact Test 6 (HIT-6) and Migraine Disability Assessment Test (MIDAS) are two of the most commonly used quality of life questionnaires for migraine, but they are not without flaws. For example, the HIT-6 and MIDAS ask about the quality of life from the past four weeks and three months, respectively, which may not appropriately capture lost productivity and missed work that occurred prior to these windows of time. Importantly, these instruments only evaluate the effects on the person with migraine and only during attacks, meaning the burden of migraine on the family is not adequately captured, nor is the burden of disease in between attacks. Individuals with migraine may have lost productivity and/or miss family or social obligations in between migraine attacks because of prodromal symptoms or anxiety about the uncertainty of the next attack. Limitations in the current quality of life measures for migraine are important for ICER to recognize and account for in its analysis given the significant effects migraine has on physical, emotional, and social aspects of daily life for women.	Thank you for raising these limitations with the commonly used quality of life measures. These productivity issues are noted in our Other Benefits and Contextual Considerations section and will likely be discussed during the public meeting.
3.	CEA based on quality-adjusted life years (QALY) may not adequately capture the differences in preferences and clinical characteristics of women with migraine. While we recognize that ICER has committed to using CEA as the basis for its value framework, we would strongly encourage ICER to develop novel approaches to assessing value. Many stakeholders have acknowledged the limitations of QALY-based CEA, particularly in accounting for heterogeneity. Women with migraine vary in age, employment, caregiver status and socioeconomic status. A simple cost-effectiveness ratio cannot capture those differences.	The inputs for the model were intended to be representative of the population with migraine in the United States. This is represented by the proportion of women relative to men in the model and the sex-specific mortality rates. Importantly, the studies used for inputs in the model contain a mix of women and men and therefore are intended to be representative of the overall migraine population.
4.	Flawed assumptions used by ICER regarding the price of migraine treatments may have significant implications for a woman's access to care. ICER's estimation of the budget impact of migraine treatments (and therefore the number of women and men who can access treatment) is based on the wholesale acquisition cost (WAC) of a drug. Not taking the rebates and discounts frequently negotiated between payers and pharmaceutical manufacturers into account may lead to inaccurate estimations of the budget impact of these treatments. Similarly, the CEA appears to be based on a placeholder WAC estimate, which is likely to result in incorrect estimates for the value of these treatments. If payers rely on	Our estimation of budget impact in the draft evidence report was based on a placeholder price of the CGRP inhibitors, as estimated by market analysts since a WAC wasn't available at the time of publishing the draft report. We now have an official list (WAC) price for erenumab which we will extend to fremanezumab in the absence of a list price for the latter. In the final version of our report, the cost-effectiveness analysis will use a net price based on assumed discounts from the list price. Additionally, our budget

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	flawed estimates, it could have significant implications for women's access to important treatments for migraine. We encourage ICER to consider accounting for likely rebates and discounts in its estimates.	impact analyses will estimate the budget impact of the CGRP inhibitors based on the published list price, the assumed net price, as well as the prices to reach different cost-effectiveness thresholds in eligible patients.
5.	ICER's analysis should accurately reflect the direct health care costs of migraine. Emergency department visits, hospitalization, and therapeutics are the main direct cost drivers of migraine. An underestimation of their combined costs will result in an incorrect valuation of CGRP treatments. We urge ICER to conduct robust sensitivity analysis around medical resource use and direct cost estimates using published sources.	We have modified the direct costs that are used in the model in response to the comments that we have received. We believe these new cost estimates are representative of the direct costs associated with migraine. We evaluate the impact of the direct costs in one-way sensitivity analyses.
Individual Clinicians		
Andrew Blumenfeld, MD		
1.	While I am pleased that the International Burden of Migraine Study (IBMS) was referenced in the report, I am concerned that the data for headache pain severity have been misinterpreted and as a result, used incorrectly by ICER. The data cited in the IBMS publication represent responses to the survey question, "When your most severe type of headache is at its worst, how severe is the pain?" The respondents' data did not represent the proportions or frequency of migraine attacks or days with attacks that were mild, moderate, or severe, as shown in Table 4.3 of the Draft Evidence Report. As the first author of this paper and on behalf of my co-authors, it is important for me to highlight that the way these data have been used in the ICER model results in an error in ICER's evaluation and significantly overestimates the proportion of migraines that are severe in the patient population, because a patient who experienced one severe migraine is counted as though all the patient's migraines are severe. The IBMS survey question is not an appropriate data source to inform ICER's assumption of the distribution of severity for the cost-effectiveness evaluation of migraine preventive treatments. I recommend that ICER use an alternate source of data, specifically daily diary data reported at baseline from clinical trials of migraine preventive treatments. Daily diary data from trials more accurately represents the distribution of migraine severity in the patient population of interest for ICER's evaluation. In addition, the distributions are fairly consistent across trials.	Thank you for the clarification. Based on this the source for the distribution of the severity of migraines was changed.
Patient Organizations		
Stacey L. Worthy, Counsel, Alliance for the Adoption of Innovations in Medicine		
1.	**ICER Must Consider Patients' Perspective.** While ICER acknowledges the patient perspective, it should incorporate the direct and indirect costs to patients into its calculations. As ICER notes in the Migraine Draft Report, patients expressed that migraine disorders prevent them from living normal lives. They	The ICER-base case analysis is developed from a health system payer perspective and does not include elements of a societal perspective such as productivity loss, since this perspective is most relevant for

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	often experience depression, anxiety, and difficulties in interpersonal relationships. One study found that as many as 40 percent of patients with migraines also experienced depression, and that depression often preceded the migraine diagnosis. The economic costs of depression and anxiety are among the highest of any health conditions in the workforce. Yet, only one study considered by ICER evaluated patients with such comorbidities. Additionally, migraines can impact an individual's ability to make a living. In addition to missed work days or loss of productivity, many individuals are unable to attend school due to their migraine disorder. School absenteeism should be taken into account because the inability to finish a degree significantly impacts an individual's ability to make a living. Moreover, unemployment rates are high due not only to the inability to work during an episode, but also from the resulting stigmatization and feelings of frustration, depression, and isolationism. Additionally, due to the loss of productivity at work, individuals may not eligible for the promotions that their peers receive. These factors should be considered in the indirect cost analysis.	decision-making by public and private payers, provider groups, and policy makers. We have, however, included a modified societal perspective capturing the impact of the CGRP inhibitors on productivity loss in patients eligible for treatment with these drugs. In addition, we conducted a second scenario analysis that allows for an additional utility gain based on data showing an improvement in depression scores for patients treated with CGRP inhibitors. The base case analysis includes consideration of data on changes in quality adjusted life years associated with the treatment. While imperfect, quality adjusted life years remain the gold standard in economic evaluation of the long-term cost effectiveness of a drug. Quality adjusted life years are based on patient preferences about underlying health states that incorporate how the condition impacts their overall health. For something like the potential impact of CGRP inhibitors on school work, job promotions, and other possible indirectly related life choices and events it would require data that demonstrate a treatment effect due to the CGRP inhibitors related to those potential occurrences in the model which are not available.
2.	**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 on coverage. As a result, patients ration their medications, and this lack of adherence to a treatment plan can result in deteriorating health and adverse events. In fact, those who cannot access their medications are more likely to attempt	ICER's value assessments do not rely solely on the QALY, which is not used in the assessment of the comparative clinical effectiveness of these medications. Furthermore, ICER's economic analyses also report the incremental costs per life year and migraine-free day gained to facilitate discussions around the value of these therapies. Many of the considerations mentioned toward the latter portion of this comment are captured in the sections describing input received from patients and advocacy organizations and in Section 5, which describes the other benefits and contextual considerations surrounding migraine and its treatment. These are essential components

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	to access opioids. 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 QALYs.	of any assessment of a medical intervention's value.
3.	**A Value Assessment Is Premature.** While clinical trials have provided evidence of the safety, effectiveness, and value of CGRP inhibitors, these treatments are still in their infancy. The U.S. Food and Drug Administration has not yet approved any CGRP inhibitors, and therefore, none are for sale in the U.S. market yet. Over time, valuable data will fully emerge in clinical practice. However, if CGRP inhibitors are deemed inadequately cost-effective now, then the likelihood of third-party payers covering these treatments without imposing significant benefit utilization management policies increases, creating barriers to access for individuals who need them. Without market uptake, data cannot be collected and analyzed. Therefore, we recommend that ICER refrain from making a determination on the value of treatments until mature data emerges.	At the time the revised report is being published, the FDA has approved the marketing of one of the CGRP inhibitors (erenumab), and a decision on fremanezumab is anticipated in the coming months. Clinicians, patients, and insurers will need to make decisions on the appropriate use of these treatments, despite the availability of only short-term data. Therefore, it is important to understand the value of CGRP inhibitors, even with the uncertainty in estimates of the comparative clinical- and cost-effectiveness of these interventions. ICER may revisit its analyses as important new evidence emerges in the coming years. Furthermore, Amgen has published a cost-effectiveness model for erenumab (Lipton et al., 2018, *J Med Econ*), suggesting that they acknowledge the importance of a value assessment at product launch.
Kevin Lenaburg, Executive Director, Coalition for Headache and Migraine Patients (CHAMP)		
1.	We are disappointed that ICER declined our request that the CTAF Voting Panel include a migraine patient and a headache specialist physician. In medicine, it just doesn't make sense to exclude both patients and disease specialists from making determinations that impact care. Because the CTAF Voting Panel does not have a personal or specialist understanding of migraine disease, this is why we have been so active in engaging people with migraine to share their stories and struggles with ICER, so those who vote better understand the widespread and desperate need for access to improved migraine medicines.	ICER has followed the same approach for this meeting as it does for all of its reports and public meetings. The voting panels for each of its three public programs do not change from meeting to meeting, and are composed of clinicians from a variety of medical specialties, health services researchers, and patient advocates. This approach, which is similar to the one taken by other organizations such as the United States Preventive Services Task Force, is designed to limit the bias that may be introduced when a therapy is evaluated solely by specialists from the same field of medicine. That being stated, we agree that any evaluation must be informed by expert clinicians from the relevant specialty and patients with the condition at hand. To this end, ICER engaged in conversations with these and other stakeholders from the outset of its review, a draft version of its

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		report was reviewed by several migraine experts and a patient advocate, and independent clinical experts and patient advocates will participate in the upcoming public meeting to discuss this review. Further, the analyses were subject to several periods of public comment and revision, the proceedings of which will be shared with the voting panel prior to its deliberations. We believe that this approach will provide sufficient background to permit a reasoned evaluation of the value of the CGRP inhibitors.
2.	**Ensuring the ICER Model Has Appropriate Discontinuation Rates**. CHAMP is very concerned about how the DER models discontinuation rates for CGRP inhibitors. The model assumes that all patients will stay on the CGRP inhibitors for a year, minus a small discontinuation rate of those who experience adverse side effects. The importance of this model choice is that the DER assumes many patients who are experiencing little or no benefit from the CGRP inhibitors will stay on them for the full year, which adversely skews the cost-benefit analysis. It is well known that many patients fail to take prophylactic medication for sustained lengths of time. The HMPF letter shares data about high discontinuation rates by migraine patients for the preventive medicines topiramate, amitriptyline and divalproex sodium. It is our understanding that the DER does not include discontinuation rates from those who aren't experiencing medicine efficacy because supposedly studies with Botox don't show high discontinuation rates. While it is true that the PREEMPT Phase 3 studies for Botox did have high completion rates of about 90%, a recent poster presented at the American Academy of Neurology conference in Los Angeles looked at real-world and longer-term usage rates of Botox and this data is a better predictor of what ICER should model for CGRP inhibitors. The poster was titled, "Long-Term Safety and Tolerability of Onabotulinumtoxin A Treatment in Chronic Migraine Patients: COMPEL Analysis by Treatment Cycle." The authors are Paul K. Winner, Andrew M. Blumenfeld, Eric J. Eross, Amelia Orejudos, Aubrey Manack Adams and Mitchell F. Brin. This COMPEL analysis is a post-approval study looking at OnabotulinumtoxinA treatment by 716 enrolled participants over a 108-week period. Only 52.1% of the enrolled patients completed the study, meaning that there was a discontinuation rate of almost half over the less than two-year time period. The study provides information about the causes of discontinuation, and lack of efficacy (4.9%) was a higher cause of discontinuation than adverse events (3.5%).	The comment infers that discontinuation rates would be influential on the incremental cost-effectiveness ratios or the value-based price generated from the model. In fact, as demonstrated in the one-way sensitivity analyses, discontinuation rates have a relatively small effect on the ICERs. In addition, the discontinuation rates are relatively high based on data from the clinical trials for the CGRP inhibitors.

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	This COMPEL analysis reinforces that discontinuation rates for migraine preventives are high and that lack of efficacy is a bigger factor than adverse events. Therefore, it is misleading to assume that all patients who try CGRP inhibitors will use them for a full year (minus a small rate of those who experience adverse events). Instead, the patient population on CGRP inhibitors will over time self-select towards including a higher percentage of patients that are positively responding to the medicines (while non-responders stop taking medicines that aren't providing any clinical benefit for them). The ICER model must be updated to reflect that patients who are not experiencing benefit from CGRPs will discontinue use over the course of a few months. We suggest the model and medical practice allow for six months of opportunity for patients and doctors to determine the effectiveness of CGRP inhibitor treatments for individual patients.	
3.	**Feedback on the Draft Voting Questions.** For the first two sections of DVQs on Clinical Evidence (questions 1-3 and 4-5), CHAMP suggests that the questions should be phrased more specifically to say, "patients that have been failed by two or more other migraine treatments." As detailed in the HMPF joint letter, it is our understanding that payors will likely require two levels of step-therapy prior to approving access to these CGRP inhibitors. While step-therapy (also known as fail-first) is a process that we generally disagree with, if it is what the payors will require, then this is the population that should form the base case for ICER's analysis. Compared to patients with just one documented failed therapy, this will have the effect of reducing the efficacy of the placebo, while the efficacy of the CGRP inhibitors stays consistent, resulting in a higher efficacy rating for the treatment. We understand that there are limitations in the clinical trial data that is available to ICER, but we request that an analysis of CGRP cost-effectiveness also be conducted for the sub-population of high-frequency episodic migraine patients (10-14 headache days per month). Multiple pieces of research establish that high-frequency episodic migraine patients are more similar to chronic migraine patients in the disability and functional impact of their migraine disease, than they are to low-or-medium-frequency episodic migraine patients.	To the degree that patients with 10-14 migraines are more similar to chronic migraine patients, then the results for the chronic migraine patients would apply to these individuals. However, we do not have the data available that characterizes a treatment effect in this population that is different than the overall episodic population that participated in the clinical trials. In terms of the voting questions, the data for the efficacy used in the base case model are from the patient population for whom at least one prior therapy had failed. In the base case model, we are using these efficacy estimates to compare CGRP inhibitors to no treatment. The no treatment comparison is meant to reflect that if patients do not benefit from treatment with CGRP inhibitors, there are no alternatives.
4.	For Question 6, we request the specific addition of two "other benefit(s)" to be voted on: • "This intervention will reduce the exposure of migraine patients to opioids and the risks and costs of substance abuse disorders that are associated with opioid treatment." • "This intervention will reduce the incidence of co-morbid conditions with migraine, and these co-morbid reductions will contribute to reducing health costs and increasing quality of life."	Thank you, but while such issues can be discussed at the public meeting, we are aware of no data that would allow the CTAF to vote on these questions.

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Joseph M. Coe, MPA, Director of Digital Content & Patient Advocacy, Global Healthy Living Foundation		
1.	First a review of our previously-stated objections to ICER methodology which is used in all studies we are familiar with: (1) ICER's use of short-term or under-represented studies to create economic models. If we put this process into practice and looked at just Dr. Pearson and GHLF's Director of Digital Content and Advocacy, we would conclude that all men are balding (we looked at two), and they have been since birth (we looked at them for a few seconds). This is the result of short-term, under-represented studies. (2) ICER's exclusion of indirect costs associated with disease such as decreased or increased productivity, and the emotional burden on patients, caregivers, family, employers and society. Even in this room, the rent is reflective of the cost to construct it, maintain it, clean it, repair and replace the furniture. If the rent were based on the cost of the utilities alone, the fee would be dramatically lower, but landlords know it is prudent to include indirect as well as direct costs.	At the time of FDA-review and approval for any health technology, the evidence reviewed to aid the FDA-approval and subsequent decision-making process for payers, providers and policy makers is limited, and usually limited to trial data. ICER strives to aid these stakeholders in their decision-making process through its review of the clinical evidence and development of economic models. As more evidence is generated through long-term follow-up of patients in these trials as well as through real-world studies, ICER will update its review to include current, long term and real-world evidence when available, in a timely manner. The ICER-base case analysis is developed from a health system payer perspective and does not include elements of a societal perspective such as productivity loss, since this perspective is most relevant for decision-making by public and private payers, provider groups and policy makers. We have however included a modified societal perspective capturing the impact of the CGRP inhibitors on productivity loss in patients eligible for treatment with these drugs. Please refer to our 2017-2019 value assessment framework for more details on this.
2.	We are questioning the value assigned to direct costs. Because of your opacity, we don't know why or how ICER chose to assign a ridiculously low dollar amount to a migraine patient emergency department visit. Less than $500 is not a number anyone, much less a self-admitted data-driven group such as ICER, would credibly apply to a visit to an emergency room for any health issue. Four years ago, a 2013 National Institute of Health study put the median ED cost at $1,233. This was 40 percent higher than the average rent payment in the United States then. No one doubts that ED costs have risen since the 2013 NIH study. Starting with an unreasonably low ED visit cost is only the beginning. ICER has chosen to base its study on patients from the IBMS study with 2-3 migraine episodes a month. The CGRP study group has 8-9 episodes per month. Two episodes a month would usually not even qualify a patient for a CGRP drug. Focusing on ED visits alone, we must conclude that the difference between two and eight episodic patients will result in	In response to this comment (and others that are similar), we have changed the data source for ED visits and incorporated a higher cost associated with ED visits. Our methodology has been clarified in the report. We include a sensitivity analysis that incorporates a modified societal perspective which captures the impact of the CGRP inhibitors on productivity-related costs.

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	more ED visits, regardless of the cost basis used in the model. So not only is the individual cost understated, but the number of patients potentially visiting the emergency room who could be helped by a CGRP class drug, is, too. Worse for patients, this is not an oversight. You, ICER, are not going to say, "good point, that never occurred to us. Let's modify this so it more accurately reflects the disease, the eligible patients, and the treatment protocol we are studying." It is not an oversight. You designed the study this way – to disadvantage patients who need this drug class the most, and provide cover for payers who need to justify not respecting prescriptions written for the drug class. One area bereft of data is the impact of migraine on productivity. We have a much better sense of the impact of arthritis, diabetes, obesity, and even social media, on productivity than we do for migraine. But a lack of data is not a license to estimate low or high. It demands a responsibility to engage in range estimation. ICER is not doing this when it comes to looking at the benefit of the cost of a migraine day avoided – either directly or indirectly. Neither is ICER doing this when it calculates, or ignores, the personal, societal and economic impact of a migraine recovery day/days and the fear of a trigger or an attack.	
3.	As with our previous public comments, we are opposed to ICER's methodology as well as its appearance of objectivity, and while we are concerned about being a player in a melodrama with a dramatic arc that consistently ends at the same pro-payer, anti-patient point, we submit these comments in the spirit of improving the process that brings life-saving and life-changing medications to patients.	ICER's reviews are based in evidence and have no pre-planned outcome. Note, for instance, that in this report ICER has concluded that erenumab is fairly priced when used for patients for whom other preventive therapies have failed.
Lindsay Videnieks, Executive Director, Headache and Migraine Policy Forum		
1.	**Use of QALY Leads to Insufficient Consideration of the Patient Definition of Value.** As stated previously, 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 has been found to be discriminatory against people with disabilities by the U.S. Department of Health and Human Services. Migraine patients are more than twice as likely to be disabled compared to those without migraine. QALYs result in lower ICER valuations for regenerative or life-enhancing therapies. We emphasize that any therapy that improves outcomes for the migraine patient population that is chronic or high/medium-frequency episodic or poorly responds to existing therapies has tremendous value to this community. It is important to understand that migraine is not a homogenous	The QALY accounts for the impact of a health technology on the health-related quality of life besides its impact on length of life. The QALY is a widely used metric in cost-effectiveness analyses in the US and in other countries as well, to capture disease burden and levels of alleviation of this burden using specific health technologies. In addition to the QALY as an outcome, we have also included migraine-free days gained as an outcome when using CGRP inhibitors. We believe this outcome to be an outcome relevant to patients as well as to providers.

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	disease that all patients experience similarly. People with migraine have different symptoms, severities, limitations and responses to treatments. The migraine experience of individual patients often varies over time. This is why it is essential that migraine patients and their doctors have access to the full range of treatment options to find and use the care that best manages their specific migraine disease. 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.	
2.	**The DER Unfairly 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 does not adequately address the immense indirect costs and societal burden of migraine. Direct costs are far exceeded by indirect costs to employers including missed work and presenteeism (loss of productivity)ii; the loss of productivity can be up to 70% of the total costs of migraine, a staggering number. This is further exacerbated by the fact that migraine prevalence occurs during the most productive work years (ages 30-49) for many female patients already experiencing a wage gap.	The ICER-base case analysis is developed from a health system payer perspective and does not include elements of a societal perspective such as productivity loss, since this perspective is most relevant for decision-making by public and private payers, provider groups and policy makers. We have however included a modified societal perspective capturing the impact of the CGRP inhibitors on productivity loss in patients eligible for treatment with these drugs.
3.	**The DER Does Not Accurately Model the Likely Patient Population or Discontinuation Rates That Will Occur in the Real World, Which Skews Both the Efficacy and Cost Sides of the Analysis.** HMPF is concerned that the DER models a migraine patient population that has failed one other treatment. We know that many migraine patients have been failed by multiple preventive treatments and that payors are likely to restrict access to CGRP inhibitors to patients that have failed at least two other treatments (a restriction with which we disagree). This issue matters because the CGRP studies show an important difference in the placebo efficacy based on how many past failed treatments patients had experienced. For patients who had two or more past failed treatments, the placebo efficacy rate was significantly lower (presumably because they have less faith in medicine because they have been disappointed before), thus showing a significantly higher efficacy rate for CGRP treatment. We request that ICER update the baseline scenario model so that it focuses on patients that have been failed by two or more preventive treatments, which we believe is more likely to match the real world patient population that uses these new medicines.	The base case model is a comparison of the CGRP inhibitors compared to no treatment which is an attempt to evaluate the cost-effectiveness of the CGRP inhibitors in the population of patients who do not have other preventive treatment alternatives for their migraine. The data used for the treatment effect come directly from the clinical trials for patients who had experienced the failure of at least one prior preventive medication. Trials assessing the CGRP inhibitors in patients who have failed up to four preventive therapies are ongoing and we look forward to seeing their results.

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4.	HMPF is also concerned with how the DER models discontinuation rates for CGRP inhibitors. The model assumes that all patients will stay on the CRP inhibitors for a year, minus a small discontinuation rate of those who experience adverse side effects. The importance of this model choice is that the DER assumes many patients who are experiencing little or no benefit from the CGRP inhibitors will stay on them for the full year, which adversely skews the cost-benefit analysis. It is well known that many patients fail to take prophylactic medication for sustained lengths of time. Based on data from pharmacy claims, more than half of patients discontinue migraine prophylactic treatment by 2 months. The rate of topiramate treatment persistence at 2 months in one study was 46.4%, and the treatment persistence of other common preventatives such as amitriptyline (34.1%) and divalproex sodium (42.7%) were even lower. Another study showed that the top reason for discontinuation of migraine preventives is not side effects, but rather lack of effect.iii These studies clearly demonstrate that discontinuation of migraine preventive medicines is very high and lack of efficacy is the top reason for discontinuation. Therefore, it is misleading to assume that all patients who try CGRP inhibitors will use them for a full year; rather, the patient population on CGRP inhibitors will likely self-select towards over-representation of those who are responders - thus increasing the value of the medicines. The DER model must be updated to reflect that patients who are not experiencing benefit from CGRPs will discontinue use over the course of a few months. We suggest the model and medical practice allow for six months of opportunity for patients and doctors to determine the effectiveness of CGRP inhibitor treatment.	The comment infers that discontinuation rates would be influential on the ICERs or the value-based price generated from the model. In fact, as demonstrated in the one-way sensitivity analyses, discontinuation rates have a relatively small effect on the ICERs. In addition, the discontinuation rates are relatively high based on data from the clinical trials for the CGRP inhibitors. Finally, it is not clear that there is differential discontinuation between responders and non-responders of CGRP inhibitors. The efficacy observed in the clinical trials are relatively consistent across the study period.
5.	HMPF is also concerned that the DER does not provide an accurate comparison due to incomplete data. Phase 3 trials include data comparing CGRP inhibitors to placebo, but there is no head-to-head data within the drug class. There is also no direct data of CGRP inhibitors compared to the existing preventive therapies; importantly, Botox is only approved for chronic migraine, so it also cannot be a comparator for the episodic sub-population of migraine patients. 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 ineffective).	The CGRP inhibitor trials only compare a CGRP inhibitor versus placebo. In the absence of head-to-head data, we can compare interventions through an "indirect treatment comparison" or "network meta-analysis". These analyses synthesize the results from all available trials and allow for comparisons to be made for all interventions in the network, including those not studied head-to-head. We have conducted analyses separately for episodic and chronic migraine, and only included onabotulinum toxin A in the chronic migraine assessment. We also have conducted subgroup analyses for the patients for whom existing preventive therapies have failed. For this population, we compare the CGRP inhibitors to placebo only in episodic migraine and to placebo and onabotulinum toxin A in chronic migraine.

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		Indeed, this “prior failure” population is the main focus (the "base-case") for our economic analysis.
6.	**The DER Underestimates the Impact of a Severe Migraine Attack and Uses Wrong Utility Value for a Comparator Non-Migraine Day.** The DER model uses utility values (derived from the Xu study) that do not accurately capture the patient experience of a severe migraine attack. On a 0 to 1 point scale, a severe migraine day renders someone functionally much closer to a 0 (severe pain, limited to a dark and quiet room, cognitive impairment, unable to work or engage in household/family responsibilities) than the 0.440 score that ICER is using. We request that other studies be consulted and that the utility score of a severe migraine attack be reduced significantly below 0.440. HMPF is also concerned about the utility value ICER is using in the DER for a healthy day. The DER describes a “Pain-Free Migraine Day,” which has a utility value confidence interval of 0.896-0.967, with an oddly high mean value of 0.959. The whole concept of a “Pain-Free Migraine Day” does not make sense to the patient community. If a preventive medicine eliminates a migraine attack for a patient, then it stops the migraine attack day(s), as well as associated prodrome and postdrome days. An attack averted means that the proper comparison day to the migraine days is a “Healthy Day,” which should have a utility value of 1.000. By not properly scoring the very low utility value of a severe migraine day (should be much lower than 0.440) and not fully valuing the utility of a healthy day (should be 1.000), ICER is under-valuing the efficacy of CGRP inhibitors. Both sides of ICER’s equation must be adjusted, because the impact is significant.	We feel that the Xu study is the best source of utility values for different levels of migraine severity. We agree that a severe migraine attack can be severely disabling. Importantly, a utility value of 0.440 is a score that is associated with significant impairment. In fact, based on study from Sullivan and Ghushchyan, a value of 0.44 is worse than any mean value reported for a large set of chronic diseases in the United States (Sullivan and Ghushchyan, Med Decis Making 2006). Moreover, it is below the 25th percentile for breast cancer, psychoses, and blindness. We have changed the label applied to the days free from migraine. These were previously identified as ‘pain-free migraine days’ which was not accurate. These are days when patients do not experience a migraine.
7.	**The Omission of Costs Associated with Opioid Use / Abuse Within the Economic Model Unjustly Reduces the Value of New Migraine Therapies.** ICER’s Draft Scoping Document grossly omitted any reference to the opioid epidemic even though it is known that opioids account for nearly 10 percent of total medications prescribed to treat chronic migraine. HMPF included this in our response to ICER and it was subsequently included in the contextual section of the report but not the economic model, which is discouraging. ICER’s previous migraine assessment of Botox in 2014 included significant attention paid to opioid use and the costs associated with long-term use of opioids as rescue therapiesiv. While the DER mentions costs associated with side effects from interventional therapies, it does not explicitly indicate whether opioids and their impact on productivity / non-direct costs (broad costs associated with substance use disorders) would be included in the model, even while acknowledging that “although data are lacking on the long-term impact of CGRP inhibitors on opioid use and addiction, preventive therapies that reduce the number of migraines and acute medication use may also reduce the opioid	Opioids are included in the mix of medications used for acute treatment of migraines in the model. There is a reduction in the use of these acute treatments associated with the CGRP inhibitors. We also capture reductions in ED visits and hospitalizations associated with migraine use that may include opioid utilization and therefore a reduction associated with CGRP inhibitors. However, there are no data linking the use of CGRP inhibitors with reductions in long-term opioid abuse and misuse.

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	dependence in this population" (DER p. 83). The ICER model must be updated to account for benefit / cost reduction of reduced exposure to opioids.	
8.	**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 has in part led to the lower grade of "Inconclusive" for these new therapies. ICER has used a short time frame (a two year period) to evaluate the long-term impacts from CGRP inhibitors "…because there is a lack of data on the long term use of preventive medications for the management of migraine (DER pp. 52-53). However, ICER is still extrapolating long-term effects from this short-term data, creating unknown biases into its analysis. ICER itself admits "the models were based on clinical trial results that may not hold true for longer time horizons or in particular patient populations different than those seen in the trials" (DER p. 81).	Patients, clinicians, specialty societies, and insurers will need to make decisions about the appropriate use of these medications as soon as they are available, regardless of the maturity of the evidence base. The question of whether the evidence supports the asking price of these interventions is a natural element of these conversations, one that we believe should be informed by an independent evaluation involving all relevant stakeholders. The model is based on the best available evidence of the efficacy of the drug over the period of the clinical trials. Because discontinuation rates for preventive treatments in patients with migraine are high, the long-term changes in migraine headache frequency, common methodology used in prior economic models, and the relative importance of this timeframe for decision-makers, we felt it was most appropriate to use a two-year time horizon. However, we did include scenario analyses that looked beyond the two-year timeframe which demonstrated a very small effect on the incremental cost-effectiveness ratios.
9.	**New Data on Co-Morbidities Related to Migraine Should Have a Substantial Impact on ICER's Quantitative Model Including a New Sub-Analysis on the Link Between CGRP Reduction of Depression.** The costs of treating chronic migraine increase sharply with the number of co-morbid chronic conditions. A recent large population, long-term international study (1995-2013) showed higher risks observed among patients with migraine than in the general population. Nearly 88% of those with chronic migraine have at least one co-morbid condition that has an impact on health care costs associated with the disease, including mental disorders (37%), mood disorders (27%), and arthritis (28%), as well as heart-related problems such as hypertension (24%), hyperlipidemia (18%), and coronary heart disease (9%). One of the most expensive co-morbidities associated with migraine is cardiovascular disease including both heart attack and stroke. While medical costs for treating chronic migraine were estimated at $5.4 billion in the United States in 2015, total costs associated with migraine and co-morbid conditions exceeded $40 billion.	We have included a scenario analysis that incorporates the data that suggest a change in quality of life associated with CGRP inhibitor treatment effects in migraine patients with moderate to severe depression as determined by the PHQ-9.

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10.	Importantly, a sub-analysis of the clinical trial data presented during the American Academy of Neurology Annual Meeting held in Los Angeles last month showed that treatment with a CGRP inhibitor led to reduction in co-morbid depression (critically important as depression is a known indicator of suicide). The analysis found that CGRP treatment led to a statistically significant reduction in depression for some of the treatment groups. Using this new data, the DER model should be updated to show the reductions in co-morbidities that result from the use of CGRP inhibitors and the corresponding lower costs of treating these co-morbid health conditions. Depression, anxiety and, in the case of veterans, post-traumatic stress disorder, are common co-morbidities for patients with migraine. The ICER model should be updated to reflect that the CGRP inhibitors will improve these co-morbid conditions and the benefit/savings of these improvements needs to be factored in.	The scenario analysis noted above uses the data presented at this meeting as they are the only available data.
Jill Piggott, Co-Founder & Director, Heads Up Migraine		
1.	Your report fails to accurately describe migraine disability and makes no reference to the following facts: • Severe migraine ranks in the highest category of disability burden, alongside acute psychosis, schizophrenia, terminal-stage cancer, and quadriplegia, according to the World Health Organization's Global Burden of Disease Report. • Migraine suffers have more pain and restriction of daily activities than patients with depression, osteoarthritis, or diabetes. • Migraine far outranks every other neurological disease in years lost to disability. US migraine patients lose more than twice as many years to disability as do patients with ALS, MS, and epilepsy combined. • Migraine is the third leading cause of disability for working-age Americans.	Thank you for sharing these citations. We include the most recent Global Burden of Disease report information in our overview of migraine and restructured text to further articulate the burden experienced by patients with migraine.
2.	Your report fails to discuss disease progression and chronification. This is an astonishing error. Migraine is chronic neurological disease. For some, this disease manifests episodically, but for a significant portion of patients, migraine is a "clinically progressive disorder" in which "episodes increase in frequency over time until the individual is in nearly constant pain." The brain doesn't return to "normal" between migraine attacks because there is no "between": "Interictally, migraineurs have an enduring predisposition to attacks, abnormalities in cortical processing, and impaired health-related quality of life." Each attack makes the brain more susceptible to future attacks. This physiological progression also causes "changes in the central nervous system which manifest themselves through alterations in nociceptive thresholds (allodynia) and alterations in pain pathways (eg, central sensitization)."	We have restructured text to further articulate the burden experienced by patients with migraine.
3.	Your report fails to mention either allodynia or sensitization, which is akin to assessing cancer prevention without ever mentioning metastasis. Allodynia causes migraine patients to	We now note some patients may experience allodynia. We did not identify any comparative evidence that suggests these

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	feel pain from stimuli that "shouldn't" hurt. Some 80% of migraineurs feel pain similar when their clothes or glasses or hair or husbands touch their skin. We feel pain when we shower or when we're outside on a windy day. We feel pain when sunlight touches our skin. Just as migraine makes more migraine, allodynia makes more allodynia, and as the disease progresses, we experience allodynia not only during attacks, but constantly. Allodynia is itself responsible for significant disability.	sensations are reduced for patients receiving CGRP inhibitors.
4.	Your report also makes no mention of the anatomical progression of migraine, including the presence of brain lesions in patients. Researchers hypothesize that repeated migraine attacks are "associated with permanent neuronal damage," which cause "poor modulation to pain" and contribute to disease progression. Your final report must include an assessment of CGRP's potential to stall disease progression and protect patients from permanent damage to their brains.	We did not identify any comparative evidence that suggests CGRP inhibitors protect patients from permanent brain damage.
5.	Your report fails to detail the complexity of migraine disability, wrongly mistaking one symptom (headache) for the disease. Because most of the papers cited in your discussion of the disease date back to 2001-08, you're relying on an outdated understanding of migraine. Though officially still classified as a headache disorder, migraine is now understood as a "whole nervous system disease," "primarily affecting the sensory nervous system." During an acute attack, our brains "switch, within a few minutes, from a state of relative equilibrium to one in which there is both spontaneous pain and amplification of percepts from multiple senses." That is, we are suddenly swamped by pain (primarily in the face and head, but also throughout the body) and simultaneously completely overwhelmed by our senses.	We have added text to clarify that migraine affects individuals differently, and patients with more severe disease may experience greater disability.
6.	Your report makes no mention of the following symptoms which are central to the diagnosis of migraine: photophobia, phonophobia, hypersensitivity, and allodynia. You omit vertigo, tinnitus, hyperacusis, and aphasia. Absent, too, is the wobble of ataxia, double vision, brain fog, and coma-like deep sleeps. There's no mention of visual auras that arrive without warning and sometimes end with no pain, but obscure vision so profoundly that my own mother's life was in jeopardy when aura nearly blinded her while she was driving in heavy, 4-lane traffic. Absent, too, is any reference to hemiplegic migraine, which mimic stroke with garbled speech and loss of function—"motor weakness"—in parts of the body.	Our list of symptoms associated with migraine includes photophobia (sensitivity to light), phonophobia (sensitivity to sound), nausea, and vomiting and we have added vertigo, tinnitus, hyperacusis, and aphasia. We also note that patients may experience migraine with or without aura.
7.	While your report acknowledges the many comorbidities of migraine that contribute to disease burden and progression, you omit any discussion of migraine-associated morbidities such as suicide and increased cardiovascular and coronary heart disease mortality. Migraine patients are at least four times more likely to attempt suicide than controls, and the absolute risk of suicide attempt attributable migraine is as high as 8.6%. Chronic migraine is "an independent risk factor for suicide," even when	We did hear from migraine patients who had suicidal thoughts, which is included in our patient input section and in the other benefits and contextual considerations sections. We did not identify any evidence to suggest CGRP inhibitors reduce the risk of comorbidities.

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	the patient has no underlying diagnosis of mental illness. The risk of suicide attempts by migraineurs increases by 79% for each 1 point rise on the standard 10-point pain-intensity scale.	
8.	Likewise, your report fails to address evidence suggesting that migraine with aura increases cardiovascular and coronary heart disease mortality. Available data "indicated an increased risk of ischemic stroke in subjects suffering from migraine with aura. In addition, evidence suggests an association between migraine with aura and cardiac disease, intracerebral hemorrhage, retinal vasculopathy and mortality." Finally, like all disabled people, chronic migraineurs are more likely to be sick but less likely to "receive basic primary and preventive care others take for granted, such as weigh-ins, preventive dental care, pelvic exams, x-rays, physical examinations, colonoscopies and vision screenings."	Our report compares CGRP inhibitors to the comparators listed in Section 1.2. We did not identify any evidence to suggest CGRP inhibitors reduce mortality.
9.	Your report fails to address the disability caused by drugmakers who've overpriced triptans and insurers who've instituted artificial and harmful quantity limits on this gold-standard acute therapy. Because migraineurs have no other treatment options, insurers can stop covering our medications without seeing their costs rise. As Amgen puts it, migraine is "more expensive to payers when effectively treated." Triptan quantity limits saved insurers $12.25 per patient per month.	Thank you for this comment. We hope this issue will arise during the roundtable discussion at the public meeting.
Brian Kennedy, Executive Director, Institute for Patient Access		
1.	Due to the timing of ICER's study, data limitations meaningfully restrict the draft evidence report's ability to evaluate the cost-effectiveness of CGRP inhibitors. Specifically, the CGRPs studied were either in phase II or III clinical trials, and none had yet secured FDA approval. Therefore, the clinical and safety data that is available for these medicines is limited; and importantly, the information on these medicines that will be gained from post-marketing studies is not yet available.	See response to comment #8 from the Headache and Migraine Policy Forum for ICER's position on the timing of its reviews.
2.	As noted in the draft evidence report, a short-term time frame (a two-year period) was used to evaluate the long-term impact of CGRP inhibitors "…because there is a lack of data on the long-term use of preventive medications for management of migraine" (p. 52-53). Extrapolating the long-term effects from short-term data introduces unknown biases into the analysis. In fact, in the limitations sections, ICER notes that "the models were based on clinical trial results that may not hold true for longer time horizons or in particular patient populations different than those seen in the trials" (p. 81, emphasis added). Simply noting this limitation does not eliminate the concerns, however.	The model is based on the best available evidence of the efficacy of the drug over the period of the clinical trials. Because discontinuation rates for preventive treatments in patients with migraine are high, the long-term changes in migraine headache frequency, common methodology used in prior economic models, and the relative importance of this timeframe for decision-makers, we felt it was most appropriate to use a two-year time horizon. However, we did include scenario analyses that looked beyond the two-year timeframe which demonstrated a very small effect on the incremental cost-effectiveness ratios.
3.	When creating the five-year annualized potential budget impact, the draft evidence report states "since people with migraine tend to cycle through several preventive therapies and since we	Our cost-effectiveness model uses a two-year time horizon in its base-case to account for the lack of long-term prescribing

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	have no long-term data on CGRP usage, we assumed that each sub-cohort (i.e., 20% of the prevalent cohort) remained in the model for two years, and a new cohort entered the model every year, resulting in larger patient populations for years two through five" (p. 86). No evidence justifies whether such assumptions are valid or not. Since usage is a fundamental input into the model, it should be based on actual long-term usage data, or reasonable proxies of this data, rather than arbitrary usage assumptions.	patterns as well as outcomes with the CGRP inhibitors. We learned from clinical experts that there remains uncertainty in the long-term outcomes as well as prescribing patterns of these therapies, especially since patients cycle through multiple therapies within short time-durations. Our budget impact model also hence employs a two-year patient-time while accounting for the budget impact over a five-year period assuming a new sub-cohort of 20% of all prevalent patients entered the budget impact model each year.
4.	CGRPs do not, as of yet, have publicly available prices. To overcome this problem, ICER uses an "analyst-estimated" price of $8,500 per year for all three drugs. There is no way to know whether these estimated prices reflect the actual market prices that will prevail for the CGRP medicines once they are available. If the estimated prices vary significantly from the actual market prices, then the validity of the cost-effectiveness calculations will be compromised. The draft evidence report notes these concerns as well, stating "the placeholder price estimate for the drugs may not reflect actual market prices" (p. 81).	We now have an official list price for erenumab, from which we have calculated a net price based on past trends in discounts for branded drugs. These list and net prices have been assumed for fremanezumab in the absence of an available price.
5.	The draft evidence report assumes that "the treatments had no impact on mortality rates" (p. 60). Contradicting this assumption, large numbers of studies have linked migraine to increased health risks. For instance, migraine has been linked to higher risks of dying from heart problems and strokes. Covering this issue in 2016, a report in the Telegraph summarized the findings from "a team of German and U.S. researchers [who] followed more than 115,000 women aged between 25 and 42 for more than 10 years. They found those who suffered migraines were 50 percent more likely to die during the period." According to the National Migraine Association "migraine can induce a host of serious physical conditions: strokes, aneurysms, permanent visual loss, severe dental problems, coma and even death." The National Migraine Association further notes that "according to the New England Journal of Medicine, "migraine can sometimes lead to ischemic stroke and stroke can sometimes be aggravated by or associated with the development of migraine." Twenty-seven percent of all strokes suffered by persons under the age of 45 are caused by Migraine. Stroke is the third leading cause of death in this country. In addition, twenty-five percent of all incidents of cerebral infarction were associated with Migraines, according to the Mayo clinic. Most recently the British Medical Journal reported that after evaluating 14 major Migraine & stroke studies in the U.S. and Canada that Migraineurs are 2.2 times greater risk for stroke than the non-migraine population. That risk goes up to a	Although migraine is associated with important comorbidities, we are aware of no evidence that treatment of migraine affects these comorbidities including mortality. In the absence of such evidence, we do not feel it is appropriate to assume that a treatment for migraine will alter mortality.

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	staggering 8 times more stroke risk for women Migraineurs on the pill!" Given the mortality risks associated with migraine, the assumption that CGRP inhibitors, which based on early indications may control migraines better, will not reduce the risk of death is assuming away a very important potential benefit. The draft evidence report should instead incorporate an estimate of the benefits in terms of reduced mortality risk from better controlling migraine.	
6.	The draft evidence report does not incorporate the potential impact of CGRP inhibitors on depression and, consequently, fails to consider a significant potential benefit of the drugs. Depression is a common comorbidity of chronic migraine. Studies indicate that up to 80 percent of chronic migraine patients exhibit the symptoms of depression. Further, depression is associated with worsened migraine-related disabilities and reduced patients' quality of life. Depression is also an important risk-factor for suicide. Through improvements in the number and severity of migraine symptoms, CGRP inhibitors may also help patients' depression symptoms.	We have included a scenario analysis that incorporates recent data on changes in PHQ-9 scores that suggest a potential additional change in quality of life associated with CGRP inhibitor treatment effects in migraine patients with moderate to severe depression.
7.	Despite recognizing that CGRP inhibitors have the potential to reduce the costs associated with the opioid crisis, the draft evidence report does not attempt to incorporate the potential benefit into the analysis. Due to a lack of current effective treatment options, some patients with migraines are prescribed opioids for their headache pain despite the well documented problem of opioid abuse. In 2015 alone, over 33,000 Americans died due to opioid overdoses. The economic cost created by opioid abuse is also large – according to Altarum (a nonprofit health systems research and consulting organization) the total economic costs of the opioid crisis have exceeded $1 trillion since 2001.	Opioids are included in the mix of medications used for acute treatment of migraines in the model. There is a reduction in the use of these acute treatments associated with the CGRP inhibitors. We also capture reductions in ED visits and hospitalizations associated with migraine use that may include opioid utilization and therefore a reduction associated with CGRP inhibitors. However, there are no data linking the use of CGRP inhibitors with long-term reductions in opioid abuse and misuse.
8.	The draft evidence report also violates basic reporting standards – which is particularly relevant if these results are meant to influence actual pricing decisions. Specifically, according to the report (emphasis added), "The treatment effects for each of the medications used in the base-case analyses are listed in Tables 4.4 and 4.5, with those for the CGRP inhibitors redacted in the tables and text since they were submitted as academic-in-confidence data to ICER by the respective manufacturers."	Please see ICER's policy on using academic in confidence data. These redacted numbers will be made available no longer than 18 months after the public meeting and sooner if the results are published. We recognize the tension between transparency and the desire of manufacturers to keep data in confidence.
9.	Redacting the data on "mean reduction in migraine days" is troubling. The reduction in migraine days is a fundamental benefit that CGRP inhibitors provide patients, and releasing this data helps readers better understand the benefit analysis ICER performed. Releasing the data also helps ensure that other academics and analysts have the necessary information to reproduce ICER's results. Replicability is a core tenet of sound scientific analysis.	Please see above.

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Terry M. Wilcox, Co-Founder & Executive Director, Patients Rising Now		
1.	A complication ICER undertook in this draft report was including three biopharmaceuticals that have not been approved by the FDA – which means there is essentially only efficacy data (i.e., from ideal clinical trial situations) and scant information about the effectiveness of those treatments in real-world situations.	See response to comment #8 from the Headache and Migraine Policy Forum for ICER's position on the timing of its reviews. Furthermore, erenumab was approved by the FDA prior to the posting of the revised report, and ICER's analyses have been updated to incorporate newly-available data on cost and clinical effectiveness.
2.	An additional foundational complication for evaluating value in this area – either clinical utility or cost-effectiveness – is the great uncertainty about the biological causes of migraines. As a 2013 article stated, "the neural and vascular mechanisms underlying the development of [migraine attacks] remain to be elucidated." This is an important point because the range of existing treatment options spans multiple mechanisms of actions – ranging from systemic broad-based beta-blockers, to systemic anticonvulsants with unknown mechanism of action, to locally injected nerve toxins that prevent the release of acetylcholine, as well as FDA approved devices. While ICER included some devices and injections in its base cost calculations, it failed to discuss them as part of treatment options, also excluded were alternative and complimentary treatments that have demonstrated varying degrees of effectiveness.	The review scope was developed with input from patient advocacy organizations, clinicians, manufacturers, and insurers and includes treatments with varying mechanisms of action. The review is not intended to encompass all possible interventions for migraine, rather those that are of greatest interest for decisionmakers.
3.	**Patient-Oriented Information and Perspectives.** We are once again disappointed that ICER again minimizes the importance to patients of improved function and quality of life, even though the report states that ICER understands, "that there remains a gap between those outcomes reported in the trials and the outcomes that patients seek." As noted above, a fully formed analysis that appropriately considered patient perspectives would encompass the full scope of treatment options.	We agree that the current clinical evidence base on quality of life is limited. We hope that stakeholders, including patient advocacy groups, continue to advocate for these patient-important outcomes to be included in clinical trials and especially for those with long-term follow-up.
4.	**Limited Data Used in Analyses.** One example of how ICER's analysis skews against patient perspectives is the exclusion of Open Label Extension (OLE) data (which are the closest clinical trial data can come to real-world evidence), and the specific quality of life data – both of which were excluded from the draft report's quantitative analysis. For example, the draft report states "Our model estimates may not fully reflect the improvements in quality of life or work productivity with the CGRP inhibitors." Those omissions – as examples of the report's very narrow input data – raises serious questions about the report failing to distinguish between "outcomes" that are statistical significant versus all those that are actually important to patients.	As noted, the current evidence base for CGRP inhibitors is limited to short-term follow-up with only one interim analysis of an ongoing, open-label extension study. Additional trials and open-label extension studies are on-going and we look forward to seeing these results in the future. We received extensive input from patients, which has been summarized in the Insights Gained from Discussions with Patients and Patient Groups section. We recognize that many of these points have not been captured in a clinical trial setting, and we anticipate them to be part of the discussion regarding other benefits and considerations during the public meeting.

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5.	ICER's narrow selection of information for its analysis contrasts with the clinical guidelines from the U.K.'s NICE which states as the very first thing under prophylactic treatment, "Discuss the benefits and risks of prophylactic treatment for migraine with the person, taking into account the person's preference, comorbidities, risk of adverse events and the impact of the headache on their quality of life." In addition, an important consideration for personal choices about treatment options are potential adverse events, and as the Nottingham clinical guidelines states regarding preventative options, "The potential for teratogenic effects should be noted particularly with anti-epileptic medications." And, "Advise women of childbearing potential that topiramate is associated with a risk of foetal malformations and can impair the effectiveness of hormonal contraception. It is contraindicated in pregnancy and in women of childbearing potential if an effective method of contraception is not used." However, nowhere in ICER's draft report is this potential serious adverse effect from topiramate mentioned even though three times as many women suffer from migraines as men.	The focus of our review is on the evidence of the CGRP inhibitors. As noted, the current evidence base is limited to short-term follow-up with only one interim analysis of an ongoing, open-label extension study. Additional trials and open-label extension studies are on-going and we look forward to seeing these results in the future. We do note the concern of potential adverse events that may arise with prolonged use in the Controversies and Uncertainties section. Indeed, the concern regarding pregnancies was raised in the FDA's letter for erenumab, and pregnancy registries will be forthcoming.
6.	**Additional Areas for Offsetting Savings – Productivity and Patients Lives.** ICER requested other information about services that could be reduced or eliminated to produce savings. Therefore, we want to highlight research about lost productivity from chronic migraines from Serrano et al., that found men aged 45-54 with chronic migraine had estimated lost productive time (absenteeism and presenteeism) costs of $277 per person per week, while women in the same age group had lost wages of $137 per person per week. We also recommend reviewing the 2002 Headache article that concluded "two-thirds of the financial burden [of migraine] is linked to indirect costs," as well as Landy's work on absenteeism and presenteeism and migraines.	We have incorporated estimates of the CGRP inhibitors impact on productivity costs in a scenario analysis. The costs of lost productivity were based on data from the American Migraine Prevalence and Prevention study, in which nearly 200,000 participants reported estimates of lost productivity time.
7.	**Patients' Actual Costs.** A related area of patient perspectives is actual costs to patients versus payer, insurance company or nationally aggregated costs. Unfortunately, ICER's clearly states that "we used a health care system third-party payer perspective in which only direct medical care costs were included." We recognize that understanding the pluralistic system of private and public payers in the US, and how the resulting system of rebates, discounts, and other factors influences patient costs and access is not a simple analysis. However, if estimated net acquisition costs are included in ICER's cost-effectiveness analyses, then those analyses should also include estimated actual patient costs. That type of analysis would be in-line with discussions about value-based benefit design, and we strongly believe that value-calculations only looking at silos of health financing or delivery are incomplete unless they also reflect other aspects of health care value improvement.	As you have rightly noted, estimating patient costs is a complex analysis, especially due to the lack of robust data on what patients' out of pocket expenditures are likely to be when being treated with different health technologies. We welcome any published literature you may have on methods or estimates of patients' financial burden for different health technologies. Additionally, we use a health system third party payer perspective in our base case analysis since this perspective is most relevant for decision-making by public and private payers, provider groups, and policy makers.

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8.	**Data Uncertainty and the Utility of QALYs.** As we've previously written – and others have expanded upon – we support systematic cost effectiveness evaluations as part of determining value for patients – as long as it is done in a transparent and responsible manner. And since QALYs were developed solely for economic analysis in the UK's National Health Service, using QALYs as the core of value assessments related to the pluralistic US health care environment is very un-patient centered. As Garrison et al. noted earlier this year, "QALYs may not always fully capture the health (or well-being) of patients or incorporate individual or community preferences about the weight to be given to health gain - for example, about disease severity, equity of access, or unmet need."	The QALY accounts for the impact of a health technology on the health-related quality of life besides its impact on length of life. The QALY is a widely used metric in cost-effectiveness analyses in the US and in other countries as well, to capture disease burden the degree to which specific health technologies improve patient health. A search of the literature will reveal that the QALY is used as a key metric in conducting cost-effectiveness analyses in several countries including Canada and Australia, besides the UK and the US.
9.	We are particularly concerned about ICER's use of QALY's for migraines. As noted above, there is a disconnect between the analysis and conclusions, and the uncertainty of the input data. For example, in Section 4 of the Draft Report ("Long-Term Cost Effectiveness") much of the data cited is clearly described as uncertain, short term, or inconclusive. In simple terms, just because numbers are analyzed and yield "results" from a formula or algorithm, doesn't mean that those "results" provide accurate insights, or even if statistically significant, provide meaningful knowledge for patients and clinicians. This uncertainty, we believe, is also demonstrated in the draft report's sensitivity analyses. The extensive ranges in the sensitivity analyses – and what they mean for uncertainty of ICER's conclusions – should be highlighted in the body of the report rather than relegated to the end. This would better reflect the clinical perspectives for migraines where there is so much individual variability and uncertainty that the reality of patients' responses are best described as a curve or a cloud rather than a single data point.	We agree that uncertainty is important to consider in the economic evaluation. We have conducted a variety of both deterministic and probabilistic sensitivity analyses. These analyses provide a sense of the range of results for the incremental cost-effectiveness ratios as a function of the variability in treatment effects, costs and other important model inputs. Importantly, we believe that the expected value for the population, based on the central limit theorem, is the best estimate for the average costs and health effects that would be experienced by the population.