INSTITUTE FOR CLINICAL AND ECONOMIC REVIEW

Acute Treatments for Migraine
Response to Public Comments on Draft Evidence Report

January 8, 2020

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Manufacturers		
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1.	**Recommendation 1: Use clinical trial efficacy observations beyond 2 hours in the CEA; T**he ACHIEVE clinical trials for ubrogepant were explicitly designed to measure benefit of treatment at and beyond 2 hours.1,2 The current ICER model does not fully utilize clinical trial efficacy observations beyond 2 hours even though this data makes an important difference in key outcomes for this ICER review. Page 62 of the DER states that "patients who did not respond at 2 hours were similarly assumed to achieve response at 8 hours and 24 hours as per the placebo response from Dodick et al. 20193." Table 4.3 on page 63 of the DER presents "assumed" differences in response rates for ubrogepant versus usual care of 3.5% (57.5% vs. 54.0%) for pain freedom (PF) at 8 hours, and 3.1% (89.4% vs. 86.3%) for pain relief (PR) at 8 hours. However, these assumptions are very different from observed ubrogepant trial data. First, Dodick et al. 20193 reports statistically significant differences between ubrogepant 50 mg and placebo at 8 hours for PF of 18% (68% vs. 50%) and for PR of 10% (92% vs. 82%), respectively ($p<0.05$ for both comparisons). Second, Kaplan-Meier (KM) time-to-event analyses of the pooled ACHIEVE trials (censoring for rescue medication or optional study medication second dose in the mITT population) demonstrate increased separation between ubrogepant and placebo from 2 to 8 hours after the initial dose,1,2,4 which is illustrated in Figure 1 below. Similar trends were observed with uncensored KM time-to-event analyses of the pooled ACHIEVE trials.4 The model inputs in Table 4.3 of the DER fail to account for above defined differences in the efficacy gain beyond 2 hours for PR and PF as observed in the ACHIEVE trials and significantly underestimate the benefits of acute treatments for migraine patients. Allergan estimates that using the treatment efficacy inputs in Table 4.3 of the DER, versus the now published KM estimates, underestimates the incremental effectiveness of ubrogepant by more than 50%.	The results used in the model are based on the network meta-analysis 2-hour timepoint, which was the primary outcome of all the treatments included. To extrapolate our results to other time points, assumptions were needed. The exploratory analysis evaluating a Kaplan-Meier time-to-event analysis of pooled ACHIEVE trials had differential censoring of patients in the ubrogepant and placebo arms. While there may be a delayed effect with ubrogepant, the effect size estimated in the KM was likely biased and unreliable. As such, we did not incorporate it in the base case. We did conduct a sensitivity analysis using the estimates from the KM analysis.
2.	The KM data for time to PF are included in the primary publications of ACHIEVE I and ACHIEVE II and are core to the data package for ubrogepant trials[1,2]. Using the censored KM data represents a robust way to minimize confounding due to greater rates of rescue medication use in the placebo group observed in the ACHIEVE trials. Additionally, they provide a way to compare benefit beyond 2 hours across emerging treatments. As noted in Allergan's comments to ICER on the Model Analysis Plan, the	See above comment

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	placebo arms in the clinical trials of emerging treatments are not comparable due to differences in timing and use of rescue, allowable rescue medications, and optional second dose. Hence, Allergan recommends using censored KM data for time to PF and PR for ICER's Population 2. Allergan acknowledges ICER's efforts to create a model that is sufficiently simple and yet sophisticated enough to permit a comparable assessment across emerging treatments. However, the simplified assumptions underestimate the value of emerging products for the acute treatment of migraine. Allergan recommends that ICER revise the treatment efficacy inputs for ubrogepant to use the censored KM data to account for the benefits beyond 2 hours demonstrated in the ACHIEVE trials for Population 2.	
3.	**Recommendation 2: Use TIR data in the CEA base case to evaluate ubrogepant in Population 1. Use mITT data for Population 2.** The ACHIEVE trials included an a priori defined, stratified-randomized subgroup by TIR status with a definition identical to that defined by ICER for Population 1. Therefore, this subgroup is most clinically relevant for ICER's Population 1. Due to the alignment of the TIR definition with the definition of ICER's Population 1 and the randomization of patients by historical triptan response, the TIR results provide specific and robust evidence of ubrogepant's efficacy in this patient population (see Figure 2). Using the TIR subgroup analyses for this sub-population also addresses one of the primary concerns raised by voting panel members in ICER's 2018 review of preventive treatments for migraine regarding the generalizability of the trial results to the target population.5 As stated in Recommendation 1, censored KM analyses provide a robust approach to capture the benefit beyond 2 hours. Allergan recommends that for ICER's Population 2 base case, mITT efficacy endpoints and censored KM data should be used. Allergan further recommends using the TIR results (i.e., efficacy endpoints and censored KM data) from the ACHIEVE trials as the base case for Population 1. For comparability across emerging treatment ICER could also consider TIR based on insufficient efficacy available across the emerging treatments	Thank you for your comment. After careful evaluation of the TIR subgroup analyses done in the ACHIEVE trials, we believe the best efficacy estimate for the CEA is the one generated from the overall population in the trials. The results of the subgroup analyses presented in Blumenfeld et al. showed there was no significant difference in the benefit of ubrogepant versus placebo in the three triptan subgroups defined in the ACHIEVE trials (triptan-responder, triptan-insufficient responder, or triptan-naïve), indicating comparable treatment effect regardless of historical triptan experience.

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4.	**Recommendation 3: Implement treatment discontinuation effects into the CEA as described in the DER.** Contrary to the model description on page 64 of the DER, the ICER model does not include any effect of discontinuation due to lack of efficacy. Not including treatment discontinuation effects underestimates the value to patients who continue treatment. ICER acknowledges this on page 61 of the DER stating "Assuming patients would continue treatment, even when it wasn't effective, would bias the analysis against lasmiditan, rimegepant, and ubrogepant, when compared to usual care." Allergan recommends that ICER implement treatment discontinuation effects into the CEA as described in the DER.	The model was built with the ability to evaluate the effect of discontinuation on those who remained treatment-responsive, increasing the proportion of patients who responded to treatment at two hours. As this was solely a hypothesized effect that was not demonstrated in clinical trials and the effect size is unknown, we decided to remove this effect from the model for the draft report base-case. We have decided to add some effect (equal to half of the full effect) for the base case of the revised report. We will vary the effect from no effect (i.e. patients who discontinue for lack of effective therapy do not change the effectiveness of therapy in those who continue to take the therapy) to full effect (i.e. patients who discontinue for lack of effective therapy are removed from the denominator only for proportion respondents to therapy).
5.	**Recommendation 4: Include indirect costs in the CEA base case to fully account for the economic burden of migraine.** In ICER's 2018 review of preventive treatments of migraine7 as well as ICER's current review of acute treatments, patients and patient advocacy groups (such as the American Headache Society, the Alliance for the Adoption of Innovations in Medicine, and the Headache and Migraine Policy Forum) have urged ICER to consider indirect costs in the CEA base case to fully account for the substantial impact of lost productivity due to migraine. Migraine is a condition that affects working age adults. The highest prevalence in the United States is among adults aged 35-45 years8 and 69% of those with migraine are covered by commercial insurance.9 Due to high indirect costs associated with lost productivity experienced with migraine, it is a disease	ICER consistently reports base-case results according to their stated perspective of the health system perspective, as outlined in their Value Assessment Framework. Where possible, a societal or modified societal perspective is presented as a scenario analysis.

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	that is highly relevant to payers and employers. Despite strong opinions from these advocacy groups and ICER's recognition in the DER of the economic burden of migraine associated with lost productivity, the CEA considers indirect costs only as a scenario. Of note, indirect costs were included in the 2014 ICER Migraine review base case analysis. Inclusion of indirect costs in the base case analysis is not only essential in order to ensure consistency across migraine reviews conducted by ICER but also to more accurately evaluate cost-effectiveness in the migraine population. Allergan recommends that ICER include indirect costs in the base case analysis to fully account for economic burden of migraine.	
6.	**Recommendation 5: Include additional studies cited in Xu 2016 and include AEs related to treatment from rimegepant's Study 302 in the network meta-analysis to be consistent with the PICOTS criteria set by ICER. T**wo triptan trials, Kolodny 200410 and Pini 1995,11 were included in Xu 201612, but excluded in ICER's evaluation of comparative clinical effectiveness. Both Kolodny 2004 and Pini 1995 enrolled adults with at least a six-month history of migraine with or without aura as defined by the International Headache Society (IHS) criteria for migraine (1988).13 The efficacy data from these trials cannot be included in the NMA since Kolodny 2004 did not report data for the placebo arm and Pini 1995 reported efficacy data at 4 hours only. However, these studies meet the PICOTS criteria set by ICER and safety data are reported for patients who treated a moderate or severe migraine attack. Hence, these two trials should be included in ICER's evaluation of potential harms; exclusion of these creates inconsistency in the inclusion/exclusion criteria set in ICER's assessment of comparative clinical effectiveness. Additionally, data related to treatment-emergent AEs (TEAEs; labeled as AEs related to treatment in the source data) for rimegepant Study 302 were listed as "not reported" in Table D7 of the DER, but are publicly available in presentations made at the 2018 Migraine Trust International Symposium (MTIS)14 and the 2018 meeting of the American Headache Society (AHS).15	Thank you for your comment. We have reviewed the suggested papers and have now included data from these papers in our NMAs on adverse events.

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	Allergan recommends that ICER include the safety data in Kolodny 2004, Pini 1995, and the Study 302 data from the two rimegepant presentations in their evaluation of comparative clinical effectiveness. Raw data are provided in Table A1 of the appendix.	
7.	**Recommendation 6: Adjust for the increased placebo response rate over time reflected in triptan and emerging treatment trials in the network meta-analyses.** Any comparative effectiveness analysis that includes emerging and existing treatments should account for historical changes in the placebo response over time in the migraine category. In ICER's comparative effectiveness analysis, the average placebo response rates prior to 2014 were 9.6% for PF at 2 hours and 28.7% for PR at 2 hours. In the phase 3 trials for the new therapies placebo response rates were 14.2% for PF at 2 hours and 45.6% for PR at 2 hours, increases of 48% and 59%, respectively. Possible explanations for the increasing placebo response over the last twenty years include increase in general awareness about migraine as a disease state, higher patient expectations of treatment response due to medical advancements leading to availability of treatments, the evolution of endpoints of clinical trials for acute treatment of migraine, and changes in the perception and stigma associated with migraine. This change in placebo response over time represents a treatment effect modifier that biases the results of the NMA in favor of treatments with a lower placebo response in the source trials. Such a case was recently demonstrated in a multiple treatment comparison for psoriasis.16 Models adjusting for cross-trial heterogeneity led to different interpretations of findings than those based on the unadjusted model.	Thank you for your comment. As noted previously, we have modified our approach to conduct network meta-regression to adjust for differences in placebo group response rate in the NMAs. We presented the results of the adjusted NMA model where it showed a better fit.

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8.	Allergan acknowledges ICER's efforts to keep the comparative effectiveness analysis simple and focused by limiting the comparators to two triptans and utilizing a recent systematic review and network meta-analysis as its primary source. However, such a focused approach introduces systematic bias that unnecessarily restricts robust and credible assessments; this approach makes it more likely that adjusted models will not be able to identify the effect modifiers or may erroneously identify interactions, which are not associated with the dramatic increase seen in the placebo response over time. Allergan recommends that ICER use adjusted models for their primary analyses to account for the differences in populations evident by the change in placebo response over time. Publication year is a possible proxy for those differences, which should be consider when addressing the challenges inherent in an NMA of acute treatments for migraine. ICER should also acknowledge the limitations of their comparative efficacy analysis in the Evidence Report to ensure readers accurately interpret the NMA results.	We are unaware of evidence that shows placebo response has uniformly changed over the time period reflected in these studies. Thus, using publication year as a proxy adjusted models was deemed not appropriate. However, as noted previously, we have modified our NMA to account for the actual placebo response rate associated with the individual trials included in our analyses. We believe this better reflects potential differences among studies.
9.	**Recommendation 7: Include adverse event costs in the CEA. A**n earlier cost effectiveness analysis of opioids for the treatment of non-cancer pain estimated that 8% of patients experiencing fatigue or dizziness will require treatment based on a Delphi panel of 9 practicing physicians experienced in pain control.17 Similarly, in the 2018 ICER review of preventive treatments for migraine, ICER assumed that each AE incurred a physician office visit.7 Using this assumption and the ICER assumption of a level 2 physician office visit (HCPCS code 99212) from the 2019 Center for Medicare & Medicaid Services physician fee schedule,1 $45.77 × 8% amounts to $3.66 per episode of dizziness and fatigue. Allergan recommends that the costs of adverse events associated with each treatment be incorporated into the economic analysis to fully account for the impact of adverse events since there are differences in safety profile of the emerging acute treatments for migraine as well as the triptans.	We do not have estimates for how frequently patients experiencing dizziness would see their physician. Patients with severe dizziness and fatigue would likely discontinue treatment, which we have included in the model. Also, it is unlikely that each episode of dizziness and fatigue would result in a physician office visit. The stated approach would dramatically overestimate the costs if applied to all patients for each migraine episode. If applied only once to each patient who discontinued therapy, the effect on the model would be negligible.
10.	**Recommendation 8: Use the same assumption for drug prices across emerging treatments in the CEA.** ICER's assumption of different prices for emerging treatments in the absence of publicly available price information impacts cost-effectiveness ratios and probabilistic sensitivity analysis (PSA) in the DER. Differing pricing assumptions used by ICER cause artificial differences in the PSA, unreliably favoring the product with an arbitrary lower price assumption. Allergan recommends that ICER use the same drug prices across all three emerging treatments until more than one price becomes known.	For the draft report base-case, we applied a differential rate based on a single individual's published beliefs of what pricing might be. As prices for these new acute treatments for migraine remain unavailable, we have applied a constant price, equivalent to a 20% premium above the price for branded Imitrex, across all emerging treatments for the revised report.

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11.	**Recommendation 9: Please clarify how the evLYG was calculated and the discrepancy between the evLYG and QALY outcomes given the lack of mortality effects in the model.** The evLYG and QALYs gained should be equal if the evaluated intervention does not affect the length of life, as in this case. We request ICER to clarify the definition, particularly to specify how evLYG and QALYs are different if an evaluated intervention does not affect the length of life.	The evLYG returns the same value as do QALYs. There was an error in the draft report table.
Biohaven		
1.	The review constitutes comparison of 14 to 28 year old studies to modern trials (i.e., of the new agents) without regard for the wealth of high-quality, real-world studies and systematic reviews on triptan cycling, lack of efficacy, discontinuations, risk for medication overuse headache (MOH) and other sequelae attributable to triptans in the decades since their approval. Biohaven maintains that this restriction is unnecessary. It is perfectly acceptable, and there is ample precedent for structuring the NMA and CEA model to permit inputs from systematic literature reviews or well-designed real-world effectiveness studies.	The methods used to select studies for the draft report are provided in the draft report. We highlight the limitations of available medications to treat acute migraine that support the need for new therapeutic options. However, it is uncertain whether the limitations associated with currently available medications such as those described will be different for these newer agents.
2.	**1. Adjustment for study-level placebo effects.** The ICER network meta-analyses for all efficacy and safety endpoints fail to account for temporal trends in placebo response due to improvements in migraine care. Biohaven maintains that the inordinate length of time between publications of the triptan studies and the new interventions will bias the NMA. Adjustment for the study level placebo effect (i.e., as a covariate to the NMA model) impacts the difference in efficacy between triptans and the newer agents. **Biohaven recommends placebo adjustment for all triptan trials included as a covariate in the NMA. Biohaven also recommends inclusion of more recent trials and high quality real world comparative effectiveness studies.**	Thank you for your comment. We have modified our approach to conduct network meta-regression to adjust for differences in placebo group response rate in the NMAs. We presented the results of the adjusted NMA model where it showed a better fit.
3.	**2. Bias from pooling drug doses.** For our NMA, we separated all drug doses, in contrast to ICER's method which pooled doses for each drug. Pooling doses can affect the choice of NMA model (i.e., between lower sample size fixed- versus larger sample size random-effects) as well as decrease the observed dose dependent variability of effect which can influence whether an effect estimate is deemed significant or not. **Recommendation: Biohaven recommends that individual drug doses reported for each trial be used in the NMA.**	Since not all of the newer drugs included different doses in the phase III trials, we decided to combine doses for those drugs in which clinicians could reasonably chose among more than one dose.

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4.	**Biohaven requests special consideration of the unique active comparator trial (see Appendix I) comparing sumatriptan versus rimegepant (multiple doses)**. This study is the only available active comparator trial of the new agents versus sumatriptan, and demonstrates comparable efficacy on sustained pain freedom at 2-24 and 2-48 hours, and sustained pain relief at 2 and 24 hours.	Thank you for your comment. As noted by the authors of the study, it was not designed with the statistical power to allow for the comparison between rimegepant and sumatriptan. As such, it's difficult for us to draw any special conclusions from this study. However, we believe the inclusion of the study in our NMA helps to provide additional, important information about rimegepant versus sumatriptan.
5.	**Cost Effectiveness Analysis (CEA): Omission of relevant comparators, treatment costs, and treatment consequences.** As described on pp. 67-68 of the DER, in modeling drug costs, ICER considers only the cost of generic, oral triptans, (i.e. excluding other non-oral formulations) and does not consider any drug costs pertaining to usual care. No mention is made of the significant bias inherent in these choices. Branded triptans, including oral and other routes of administration (e.g., subcutaneous, nasal spray, injected), are available to patients and make up meaningful shares of triptan use in the US. RED BOOK, WAC data for triptans illustrates that non-oral administration triptans cost substantially more than generic orals. Patients who are not adequately managed on triptans often take other acute, non-specific medications including anti-emetics, barbiturates, ergots, prescription NSAIDs, and opioids.3 No meaningful attempt is made to cost either these therapies or assess their potentially severe consequences in the modeling. **Biohaven considers it imperative that ICER model costs of "usual care", and consequences of same, in light of ICER's recognition of the use of various non-migraine specific agents and their serious associated health risks. It is also recommended that ICER consider the full spectrum of triptans costs (e.g. non-oral formulations) that are more representative of those used in real-world practice.**	A prevalent mix of treatments, obtained from Ford et al (Headache 2017;57:1532-1544) (table 4) was used to update the model's usual care costs. Since the costs of two triptans (sumatriptan and eletriptan) were already included in the modeled population 2 and modeled population 1 are patients who are unable to take triptans, we removed the triptan use from the prevalent mix. The lowest WAC price for each treatment was applied to the proportion of patients taking each treatment to obtain an estimated cost per person. Adverse events of these treatments would usually result in patients changing to another of the prevalent mix of treatments and is already captured in the model by the use of a prevalent mix of treatments. Costs associated with adverse events from this prevalent mix of treatments are expected to be small and would not change the model results. Therefore, these costs were not incorporated into the model. Importantly, benefits gained by these

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		usual care treatments is underestimated in our modeling of the placebo effect. As such we did not believe it was necessary to model disutility associated with adverse events of these therapies.
6.	**Underestimation of costs of productivity loss.** The ICER model also underestimates costs of lost productivity. In a retrospective observational study (4), mean annualized costs were significantly higher for patients with migraines vs. those without, including direct costs ($13,032 vs $3,234), indirect costs due to workplace absenteeism ($4,104 vs $3,531), indirect costs due to short-term disability ($1,131 vs $52), societal costs due to workplace absenteeism ($16,043 vs $6,938) and societal costs due to short-term disability ($14,278 vs $3,182). A US retrospective analysis of migraine patients found differences in medical costs by treatment status when adjusted for several comorbidities. Mean costs for patients who did not use opioids were $8,888 compared to $15,210 for high users of opioids (7+ claims). Mean costs for patients who did not use triptans were $10,753 compared to $11,517 for high users of triptans. **Biohaven recommends that ICER inform modeling of reductions in costs of lost productivity on data that Biohaven have previously provided, to better reflect the value of newer agents from the societal perspective.**	Thank you for providing this reference (Giligan 2018) as a possible estimate of lost productivity and other costs. This reference was identified in our systematic review of the literature and was rejected for use in the model because of a clear selection bias and inadequate attempts to control for such bias. Despite using a propensity matched control group, the demographic and clinical characteristics of the matched pairs showed important differences in 17 of 23 comorbid conditions. Importantly, the majority of these differences favored the control group, likely resulting in biased estimates for productivity costs, as well as total healthcare costs. When only migraine-related costs were examined, the differences in outpatient costs were $61 PPPM. These costs would include routine care not affected by effective treatment versus ineffective treatment. Therefore, it is not clear from this analysis what proportion of these costs might be reduced by effective treatment options, making this estimate unusable in the model. Regarding the second point in this comment, this referenced analysis (Silberstein et al) examined cost of treatment according to frequency of migraine attacks. We used this study to estimate the frequency of physician office visits, ED visits, and hospitalizations for patients with

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		moderate frequency episodic migraine in the model. It is not clear how these data could be used to estimate other costs in the model.
7.	**Use of a single rate of discontinuation due to lack of effectiveness for all therapies.** ICER assumes the same discontinuation rate due to lack of effectiveness for all treatments, derived solely from the lasmiditan long-term safety study. ICER's assumption that the same share of triptan patients discontinue due to lack of effectiveness as lasmiditan (21.8%) is not justified. Ample evidence from the literature demonstrates that a much larger share of triptan users discontinue rapidly after their first prescription. In a retrospective claims-data analysis, for example, Marcus et al. (2019) report that 50.8% did not refill their index triptan over the 12-month post-index period and 43.6% did not refill it over the 24-month period. The majority of the new triptan users (56.4%) had a quantity of ≤4 pills on their first fill. While such data may not derive from a controlled trial, cost-effectiveness analysis is intended to capture effectiveness in the real world. **Biohaven recommends that ICER utilize drug specific discontinuation rates reported from rimegepant, ubrogepant, lasmiditan long-term safety trials, and from recent systematic literature reviews and real-world effectiveness studies of triptans.**	This comment refers to our use of a single discontinuation rate resulting from lack of effectiveness applied to all treatments. As such, data from Marcus et al is not usable, as it did not assess the reasons for discontinuation. In the real world, patients discontinue medications for a number of reasons, including side effects, lack of effect, health-related beliefs, and cost. We do not have real-world data for lasmiditan, rimegepant, and ubrogepant. Therefore, it would be an unfair comparison to include data from this real-world study directly to data from long-term clinical trial extensions without some type of adjustment. Until real-world data emerge on refill rates for lasmiditan, rimegepant, and ubrogepant, it is not best practice to include such data in a model.
8.	**Translation of response rates to severity distributions**. In order to apply health state utilities (HSUs) which are used to derive QALYs, and which vary across migraine severity levels (none/ mild/ moderate/ severe) (see Table 4.7 of the DER), ICER's modeling requires that "pain relief" and "pain free" statistics from clinical studies be linked to severity. This approach seems arbitrary.	These data were collected at baseline in all clinical trials, suggesting that pain severity is an important factor. Furthermore, utilities have been obtained for patients based on pain severity, suggesting that pain severity is an important factor in determining patient quality of life. We could have chosen to ignore benefits of treatment in reducing pain and only evaluated pain freedom at different timepoints, but believed that this approach would underestimate the benefits of therapy by not considering an important outcome evaluated in all of the clinical trials, "pain relief." We welcomed input on alternative approaches to modeling

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		the utility of migraine from manufacturers during the open review of our modeling analysis plan and no viable alternative approaches were provided.
9.	In addition, it is likely that patients who remain on therapy and who do not require rescue medications out to 48 hours are more likely to transition from the severe to mild health state versus the severe to moderate health state. The literature suggests that the high discontinuation rates and lack of sustained response for triptans would lead to a lower percentage of patients transitioning from the severe to mild health state. A consequence of this methodology is that ICER models response estimates for triptans greatly exceeding those reported from (as example) a 133 trial meta-analysis.	Similar to other meta-analyses, we have included estimates for sustained response in our meta-analysis and model outcomes. Loss of response (as measured by sustained response in those responding at 2h) is a step function, whereby it is likely that patients will regain "response" at some later time. None of the studies we assessed evaluated or reported at what time patients regained response (or the migraine resolved). However, approximately 65-70% of patients on placebo continued to become pain free throughout the first 24 hours, suggesting that many patients who lost response would be likely to regain response within 24 hours. We have assumed that patients lost response at 8 hours and regained response by 24 hours. We believe that this approach is conservative and overestimates the loss of utility due to lack of sustained response to medications.

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10.	**Biohaven recommends that ICER use observed response rates from trials, systematic reviews and high quality real world studies for all treatments. Biohaven further recommends that as an alternative to HSU estimation based on modeled severity, that ICER derive HSUs based on frequency of monthly migraine days, cited[10,11] as the strongest determinant of HSUs, and a clear indicator of migraine severity.**	Unfortunately, trials evaluating lasmiditan, rimegepant, ubrogepant, sumatriptan, and eletriptan did not uniformly report patient status for those who were not pain free at 2 hours. The failure of these studies to report patient outcomes in 75-80% of patients enrolled in the clinical trials makes the direct use of these data impossible without additional assumptions. We have used the results from responders at 2 and 24 hours and extrapolated these findings to 48 hours based on published literature from the few studies that have reported more detailed results. Studies for acute treatment of migraine did not evaluate changes in monthly migraine days in randomized controlled trials and these drugs were not approved based on findings from non-controlled longer-term open label studies with high patient dropout, that suggest that migraine frequency may be reduced. Therefore, modeling HSUs based on changes in the frequency of monthly migraine days is not possible. Furthermore, such methodology ignores the impact of treatments on migraine pain.

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11.	**Deviation of modeled response distributions from published evidence** ICER appears to have modeled loss of response from observed response at 2 hours, then applied the same assumptions across treatments to derive estimated responses at 8/24/48 hours (p. 62 of the DER).Biohaven maintains that ICER's methodology for translating response rates to severity levels (as ICER reflects in Table 4.3 of the DER) leads to counterintuitive increases in response for the triptans that are not consistent with the literature, as shown in the table below **(see comments for table)**	We agree that after 2 hours, the ability of patients to take rescue medications and differences among studies in their protocols for the use of rescue medications create challenges in modeling drug response relative to placebo after two hours. Migraine pain is known to resolve over time, even when patients take placebo. Trials involving acute treatments for migraine have not consistently evaluated what happens to patients who have had a response at 2 hours and then subsequently lost response. We have applied the same assumption to all treatments (i.e. that migraine pain resolves by 24 hours). As with all other therapies evaluated, we assume that patients who lose response over 24 hours will take additional doses, additional therapies, or will regain response even without treatment. Nothing in the cited paper contradicts these assumptions.
12.	Improvements associated with triptans modeled by ICER dramatically exceed those reported by Cameron et al. at both 2 and 24-hours.12 Cameron et al. show that pain freedom and relief both fall in frequency from 2hr to 24hrs. Further, Cameron et al. report that use of rescue medication occurs ~21% of the time on eletriptan and ~34% of the time on sumatriptan, and ICER fails to account for any use of rescue medication. Results from the recent OVERCOME study report that the majority of patients on oral triptans report poor or very poor efficacy of their current treatment, the proportion being as high for patients on their 1st (52.1%) as on their 2nd (55.8%) or later oral triptan.13 The use of non-preferred treatments (i.e., opioids 29.6%, barbiturates 16.9%) and care sought at emergency rooms (66.1%) highlight the substantial unmet needs in the eligible population.	The methods used to select studies for the draft report are provided in the draft report. We highlight the limitations of available medications to treat acute migraine that support the need for new therapeutic options. Outcomes used in our model came from data using all available studies that met eligibility criteria. We performed NMA and used output from these analyses in our model.
13.	Thus, ICER overestimates triptan benefit and underestimates benefit of the newer therapies with loss of response modeling. **Biohaven maintains that ICER should not model loss of response beyond 2 hours for any of the therapies, including triptans, but should utilize placebo adjusted observed data at 8/24/48 hours from Phase III trials of the new agents and more recent systematic literature reviews and real world studies for the triptans.**	The results used in the model are based on the network meta-analysis 2-hour timepoint, which was the primary outcome of all the treatments included. To extrapolate our results to other time points, assumptions were needed. The exploratory analysis evaluating a Kaplan-Meier time to event analysis in

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		Lipton et al (NEJM 2019) had differential censoring of patients in the rimegepant and placebo arms. While there may be a delayed effect with rimegepant, the effect size estimated in the KM was likely biased and unreliable. As such, we did not incorporate it in base case. We did conduct a sensitivity analysis using the estimates from the KM analysis.
14.	**Omission of time-varying effects despite modeling of a long-term horizon.** ICER employs a Markov health-state transition model with a time horizon of 2 years and cycle lengths of 48 hours, to model short-term utility and cost impacts of a single migraine attack, as well as potential long-term effects. ICER recognizes that this deviates from previous evaluations (p. 79 of the DER) An evaluation that considers all available real-world evidence would require a long-term horizon to account for phenomena such as discontinuation (and resulting greater mean effectiveness in those remaining on treatment), the reduction in monthly migraine days (MMD), and consequent reduced risk of MOH. **Given that a long-term horizon is modeled, Biohaven recommends that time-varying phenomena, including the following, be comprehensively modeled based on available real-world evidence:** a)Differences in discontinuation across treatments (derived from the literature, rather than one rate applied to all therapies); b)Differences in use of rescue doses across treatment (again based on therapy-specific dosing), and resulting costs and outcomes; c)Value for money reflecting continued use of treatment in predominantly treatment-responsive patients d) Costs of "usual care", including the significant share of patients who use(d) opioids following failure of triptans, or progress to chronic migraine/MOH as a result of lack of management e)Reduction in MMDs over time derived from the long term safety studies.	We have included all demonstrated time-varying effects where data are available: a) Differences in discontinuation due to adverse events across treatment options have been modeled. Discontinuation due to lack of treatment effect is not available for all of the therapies. b) Data regarding the use of rescue doses across treatment is not consistently reported in clinical trials, nor is the response to rescue treatment. c) Modeling continued use was the purpose of including discontinuation due to lack of treatment effect. This is the first model that has included such an outcome. However, clinical trials were designed as single dose studies and have not provided evidence of improved outcomes and value for money as treatment-responsive patients continue to take treatment while those who are not treatment-responsive stop taking medication. Therefore, we are forced to make informed assumptions regarding the impact of discontinuation due to lack of treatment effect on those who are treatment responsive. d) Costs of usual care have been added to the model (see response above). e) A reduction in MMDs over time has not been demonstrated in a controlled study. Lack of a control group means that regression to the mean cannot be ruled out as a likely cause of this observed association. High

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		discontinuation rates in long-term, open label safety studies showing reduction in MMDs over time may also contribute to this observed difference from baseline, as patients with more frequent and severe migraines discontinue treatment leaving a patient sample that is significantly different from the randomized sample.
15.	**Budget Impact Analysis: 1. Omission of rescue medication and pill burden.** With regard to the budget impact, the ICER model fails to consider the beneficial economic impact of lower pill burden for rimegepant which provides efficacy through 48 hr. with a single dose15 as compared to 3-to-4 pills needed for ubrogepant16 or triptans17 to achieve 48 hours of benefit. Allergan has presented publicly their one-year, long-term safety study of 50 mg and 100 mg ubrogepant (Study UBR-MD-04) in which "21,454 migraine attacks were treated with 31,968 doses of ubrogepant", which suggests 1.5 doses per attack treated. A recent publication further stated that 37% of patients required a redose with ubrogepant.18,19 **Biohaven recommends that the ICER model should be updated to more accurately reflect the pill burden associated with each therapy.**	We have acknowledged that one of the limitations of our analyses is the lack of data under randomization on rescue medication and subsequent doses. Given limitations in the available data, we do not have adequate information to determine the differential impact of this factor on the potential budget impact of each drug.
Eli Lilly		
1.	**1) Comparison of lasmiditan to triptans contradicts established clinical guidelines for migraine treatment.** Counter to the AHS Consensus statement (AHS, 2019), ICER has included a scenario in which lasmiditan is considered for use in all patients with migraine who require a prescription medication. Comparisons are based on direct competition with generically available oral triptans. Oral triptans are recognized as an appropriate first step for patients requiring prescription medication for migraine based on their established efficacy and low price. Innovative new medications like lasmiditan, however, offer much-needed options for the subset of migraine patients who are contraindicated to triptans or have failed to respond or tolerate a triptan. In the current landscape, these patients are left to seek relief via non-preferred options like barbiturates and opioids, or continued use of various triptans, despite the therapeutic limitations in these patients. Despite recommendations against their use, analyses of commonly prescribed acute treatments for	We agree that new medications, like lasmiditan, are needed for patients with migraines who have not responded to or are intolerant of currently available medications. ICER evaluated studies of lasmiditan and our review indicated that eligibility criteria permitted a range of patients to be enrolled including those in whom a triptan may be given. Moreover, the FDA label for lasmiditan does not restrict patients to only those described. Thus, we believe that the populations included in our review reflect individuals with migraine who may consider using lasmiditan.

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	migraine show that approximately 10% of patients are prescribed opioids. With opioid use being a significant public health concern, there is a need for additional treatment options to address the specific needs of patients suffering from migraine. Furthermore, opioids have been shown to reduce responsiveness to other migraine acute treatments, including triptans.	
2.	Post-hoc analyses of the phase 3 studies have indicated that lasmiditan has efficacy in the relevant subsets. In the SAMURAI trial, which had 40.9% of participants with at least 2 cardiovascular risk factors, significantly more patients taking lasmiditan were free from headache pain and their most bothersome migraine symptoms at 2 hours after dosing relative to placebo. There were no differences in efficacy or cardiovascular safety related treatment-emergent adverse events based on the presence or absence of cardiovascular risk factors in a pooled analysis of SAMURAI and SPARTAN (Shapiro, 2019). As demonstrated in another pooled analysis of SAMURAI and SPARTAN trials, patients' response to lasmiditan does not appear to be affected by prior triptan use or response to triptans.	See below
3.	Lilly requests that triptan comparators be removed from the final report and that all analyses based on the population of patients with attacks that do not adequately respond to non-prescription medications be removed from the final report.	As previously noted, our analyses reflect the populations studied in the lasmiditan trials as well as the FDA labeling indications. Though the trials included patients with risk factors for CVD, patients who had CVD were excluded. Thus, it has yet to be shown whether lasmiditan is safe for use in patients with existing CVD.

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4.	**2) The NMA results are biased toward triptans because there was no adjustment for placebo response over time.** The NMA performed by ICER is flawed by the inclusion of triptans. The included studies for triptans go back more than 25 years in history. The NMA is based on the false assumption that placebo has remained a consistent comparator over these years and that, therefore, placebo response can be used to align responses among the novel acute medications and triptans. The failure to use accepted statistical methods to help mitigate the bias of changing placebo rates compounds the problem. Care should always be taken in the construction of an NMA to include placebo adjustment across studies. The placebo group across studies is a heterogeneous population due to multiple factors, including, but not limited to, route of administration, patient medical comorbidities, concomitant use of preventive medication, history of triptan non-response, migraine headache days per month, differences in dose timing, differences in second dose or rescue medication use, and differences in statistical methods for analyzing primary and secondary endpoints. Additionally, changes in scientific thinking and patient access to information over the last 25 years may have also contributed to changing perceptions of the likelihood of success. All these factors may systematically change the underlying placebo rates that are supported by the finding of increasing placebo response rates over time. Again, these issues would be eliminated should ICER remove comparisons to triptans from the final report altogether. Short of that action, Lilly requests that ICER repeat the NMA using placebo adjustment across the studies.	Thank you for your comment. The issue of differences in placebo response among different studies is an important one. The supposition that placebo response has changed over time is unproven. However, we have modified our approach to conduct network meta-regression to adjust for differences in placebo group response rate in the NMAs. We presented the results of the adjusted NMA model where it showed a better fit.
5.	**3) It is unclear whether there were any differences in how endpoints were defined across studies and whether these differences impacted the results.** ICER correctly notes that, "Due to differences in the design of the trials related to the use of rescue medication (e.g., open-label second dose vs. randomized; NSAID vs. usual acute migraine treatment)," no quantitative comparison was made. ICER fails to note, however, that these differences in trial design impacted other endpoints that were quantitatively compared such as sustained pain freedom. Accurate comparisons cannot be made unless the same definitions are used for all comparators. The lasmiditan studies used rigorous methods in which patients with missing data or those who received rescue medication, whether study drug or placebo, were considered to have failed the sustained pain	Thank you for your comment. As described in our methods section, we performed quantitative synthesis only on studies that were sufficiently similar in population, outcome definition, time point, and other important characteristics. Outcomes through 2 hours were most comparable due to similarities in analysis across studies, reflecting this being the primary time point for analysis. After two hours, differences among the studies in the use of rescue medications differed including use of study drugs, with or

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	freedom endpoint (Kuca, 2018; Goadsby, 2019; Doty, 2019). It is not clear from publicly available literature on the comparators that the same rigorous methods were applied.	without blinding, and other rescue meds. As noted in our report, we did not perform quantitative synthesis on the use of rescue medication because of differences in protocols on the use of rescue medication. However, we believe there was sufficient similarity between the assessment of sustained pain freedom across studies to allow for quantitative synthesis.
6.	Note also that the design of the lasmiditan studies may have encouraged more use of rescue medication thereby lowering the sustained response rates relative to the other comparators. The lasmiditan studies included randomized, blinded access to rescue study medication (either placebo or a second dose of lasmiditan) to explicitly test whether rescue dosing is effective. The studies did not show evidence that lasmiditan differed from placebo when used in this manner (Loo, 2019); however, the presence of readily available rescue medication may have increased the likelihood of rescue dosing and, thus decreased the number of patients who were considered sustained pain free.	See above comment
7.	Lilly requests that ICER explicitly note in the final report whether the rigorous definitions for lasmiditan were followed for the included results for other comparators and what impact any differences might have on the resulting comparisons.	See above comment
8.	**4) Data on sustained pain freedom through 48 hours were not included**. Despite availability of data on sustained pain freedom to 48 hours for lasmiditan (Doty, 2019), ICER changed course from its initial protocol to include only data on sustained pain freedom to 24 hours. This runs counter to accepted medical understanding which considers migraine a complex neurological disease, characterized by recurring attacks of moderate to severe head pain, lasting from 4 to 72 hours. Consideration of effectiveness out to 48 hours, rather than 24 hours, could affect a reduction in cost per quality-adjusted life-years (QALY), approaching roughly half of what is stated in the draft report. Lilly requests that ICER revise the analyses taking into consideration publicly available data out to 48 hours.	Please see Table 3.6. We did not perform quantitative synthesis on 48 hours sustained pain freedom because of insufficient data. However, we presented the available data on this outcome in Table 3.6 of the report.

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9.	**5) Long-term data for lasmiditan demonstrate much lower usage than what was assumed in ICER's analysis.** ICER focuses on only 1 aspect of the long-term, open-label continuation study of lasmiditan: whether or not the GLADIATOR study provides sufficient evidence of a reduction in headache episodes. Other important aspects of the interpretation of GLADIATOR are omitted. In particular, GLADIATOR suggests continued efficacy of lasmiditan over multiple episodes with lower usage of lasmiditan than what ICER incorporated into its model. While the required baseline number of migraine attacks per month required for entry was 3 to 8 attacks per month, the average number of lasmiditan-treated attacks in GLADIATOR over the course of 1 year of follow-up was fewer than 2 per month. Lilly requests that ICER revise the budget impact assessment to reflect available data on actual usage.	The draft report discussed the decrease in use of study medication over time and highlighted several limitations with these analyses that may have biased their interpretation. Given the uncertainty of this potential outcome, we elected not to include it in the cost-effectiveness analysis. However, we now report the potential budget impact both with and without an assumption of a decrease in frequency over time. For the potential budget impact analysis, we have added a scenario that builds in the decrease in utilization over time seen in GLADIATOR.
Patients/Patient Groups		
American Headache Society & American Migraine Foundation		
1.	ICER's Draft Evidence Report suggests that adverse cardiovascular events are extremely rare in clinical practice based on observational studies. However, post-marketing surveillance studies demonstrates a substantially increased risk of serious adverse events with the use of triptans. In one study evaluating the United States Food and Drug Administration (FDA) Adverse Events Reporting System database, among 2,131,688 post-marketing reports of serious adverse events, 7808 concerned triptans. The study found several reports of serious and unexpected vascular events associated with triptan use (for example: ischemic cerebrovascular events, aneurysms, artery	We agree that triptans have the potential to cause vasoconstriction and should not be used in patients with known cardiovascular disease (CVD). However, the actual risk of these medications, especially among those with varying risk factors in the absence of established CVD, remains unclear and available evidence suggests it is quite low. In addition, though these new agents have not been shown to

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	dissections, and pregnancy-related vascular events). This raises concerns about triptan use in patients with risk factors for vascular disorders and during pregnancy. As such, The American Headache Society and the American Migraine Foundation encourages ICER to continue to reference the AHS Consensus Statement during this review process and all available data for adverse cardiovascular events.	cause vasoconstriction, it is unclear if they are safe to use in individuals with migraine who have CVD since this population was excluded from phase III trials.
2.	ICER's Draft Evidence Report broadly addresses the unmet need of the patient population that would benefit from the new acute treatments early in the report; however, that focus is lost as the historical triptan data is analyzed. As stated in the ICER Draft Evidence Report, there are nonspecific and specific treatments for acute migraine attacks.	We do not believe it is contradictory to say there is a large unmet need and at the same time to compare new therapies to existing treatments. The labeling for these medications are expected to overlap with those of the triptans (as seen in the FDA labeling for lasmiditan).

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3.	The Society and the Foundation believe ICER's Draft Evidence Report falls short in appropriate acknowledgment that although the currently available acute medications are effective for some patients, they are ineffective, poorly tolerated, and/or contraindicated in many other patients. In addition, triptans remain contraindicated in patients with established cardiovascular disease (CV) and any suggestion that "decades of use" has in any way changed this contraindication or relaxed patient or clinicians' concerns of the potential for serious adverse CV events is misleading and not in the best interest of patients. Further, ICER's Draft Evidence Report de-emphasizes the potential for triptans to cause medication overuse headache (MOH). Further, triptans are used by only 15% of the US population, and over 95% of individuals with migraine in the US have at least one unmet acute treatment need. Due to these unmet needs, triptans have high discontinuation rates ranging from 55-82%. Discontinuation secondary to inefficacy ranges from 26-40% of patients, and discontinuation secondary to side effects ranges from 17-23%. Also, a large US administrative claims dataset from 2001 to 2005 demonstrated that 54% of new triptan users did not refill their index triptan, and 67% of this subgroup switched to a non-triptan migraine medication at the time of first refill. Moreover, switching among triptans is very low, ranging between 9% and 14%. More commonly, triptan users who switched therapies turned to a different medication class such as NSAIDs, opioids, and barbiturates. In a recent study involving a commercially insured population in the US, 51% of patients starting a triptan do not refill their initial triptan over 12 months of follow-up, and 44% do not refill that index prescription over 24 months of follow-up (Lipton RB et al. Submitted for publication). In keeping with previous studies, switching between triptans was uncommon, with only 9.4% of patients receiving a second triptan over 12 months and 14.0% receiving a second triptan over 24 months.	We believe the report highlights the many important points raised here. It is clear that there is need for new medications for treatment of acute migraine. This is particularly true for those individuals who are intolerant of, have failed to respond to or have contraindications to the use of triptans. However, whether these new medications are safer and more effective than triptans for those who do not have a contraindication to their use remains to be established.
4.	Use of other medications for acute treatment of migraine, such as opioids and NSAIDS, was high in the 12-month and 24-month periods among patients with and without a refill of their index triptan. The low rate of switching between triptans and high rates of opioid use in real-world practice suggests insufficient response or tolerability issues with the current standard of care. Triptan medications and NSAIDs are not recommended for those with a history of cardiovascular disease, and triptans are contraindicated for those with a history of cardiovascular and/or	We believe that the report highlights the need for new therapies for patients with the issues cited here. We are not aware of data that show the use of medications for the treatment of acute migraine decreases morbidity and mortality.

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	cerebrovascular disease. ICER's Draft Evidence Report fails to recognize that this vulnerable patient population, for whom NSAIDs and triptans are contraindicated, who may benefit from new acute treatments that do not constrict blood vessels. In addition, ICER's Draft Evidence Reports fails to identify that migraine is an independent risk factor for cardiovascular and cerebrovascular disease including ischemic stroke, transient ischemic attacks, ischemic heart disease, and myocardial infarction, as well as increased morbidity and mortality due to these events/diseases. In fact, Migraine with aura is associated with a 20% increased risk of all-cause mortality. Additionally, over 2 million people in the US have migraine and a history of greater than or equal to 1 cardiovascular event/disease that may limit the use of triptans. The unmet need in this vulnerable population results in pain, disability, and high individual, family, societal, and economic burden.	
5.	This population of patients may remain disability and having to rely on medications such as opioids, butalbital-containing, and caffeine-containing medications. Opioids, butalbital and caffeine-containing medications contribute to medication overuse headache (MOH), suboptimal acute treatment of migraine, and development of disease progression with functional and structural brain alterations. In addition, the US is in an opioid epidemic. We must reduce the use of opioid medications to save lives. New effective acute treatment options may be opioid-sparing medications. These options should be maximized, and access barriers should be lowered.	We agree that new treatments are needed to decrease use of medications such as opioid and butalbital-containing drugs. Whether these new medication result in decreased use of these other treatments remains to be seen.
6.	Finally, medication overuse headache (MOH) is a global epidemic that affects at least 1% of the population. It is among the 20 most disabling medical conditions according to the World Health Organization. All acute medications, as indicated in the ICER Draft Evidence Report, have the potential to and have been associated with MOH. The gepants, in particular, may represent the first acute migraine treatment that may not only be devoid of risk for MOH, but may actually reduce the risk of MOH. Indeed, in a recent study evaluating the efficacy of atogepant for migraine prevention, up to 60% of patients experienced a greater than 50% reduction in mean monthly migraine days when dosed daily or twice daily. This is not surprising given its unique mechanism of action (antagonist) compared to other acute treatments such as triptans and ergots (agonists).	While we recognize the potential for these newer medications, especially the gepants to decrease the frequency and severity of medication overuse headaches, this will only be demonstrated with their use over time in future studies and from outcomes of routine clinical practice.

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7.	In addition, *erenumab* a CGRP receptor-targeted monoclonal antibody that targets the same receptor as gepants, has been shown to be an effective preventive treatment in patients with chronic migraine who overuse acute medications. Finally, CGRP has been shown in experimental studies to play an integral role in the pathophysiology of MOH. Therefore, blocking the CGRP pathway with *gepants* may prevent the development of or reverse MOH.	It is unclear how the use of gepants under evaluation for treatment of acute migraine will impact outcomes when combined with monoclonal antibodies targeting the CGRP receptor. In the phase III trials of gepants, these patients were excluded.
8.	**Indirect Costs and Societal Burden of Migraine.** AHS and AMF are dialed-in to the current framework and identify it as one that may not adequately address the immense indirect costs and societal burden of migraine. Most of the direct costs due to migraine are incurred by public and commercial payors. Direct medical costs for individuals with migraine are significantly higher overall (40%) compared with matched non-migraine patients, both overall and within specific cost categories, such as emergency department (ED) visits (28%), inpatient (36%) and outpatient (45%) visits, and pharmacy expenses (36%). Indirect costs have been shown in previous studies to be substantial. In fact, migraine is unique in that a large majority of its economic burden is attributed to costs that are directly attributed to indirect costs. This translates to a significant burden on employers, as indirect costs are primarily calculated as absenteeism and presenteeism. Approximately 113 million workdays are lost annually in the United States due to absenteeism from individuals with migraine. The cost of this to employers exceeds $13 billion each year. Moreover, individuals with migraine are 2.5 and 2.4 times more likely to have a short-term and long-term disability claim, respectively, with an average cost of $26,543 per claim, compared with non-migraine individuals. In addition, more than half of those impacted by migraine 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 that are the most disabled.	We agree that migraine results in a significant societal burden. We have included estimates for indirect costs that are anticipated to be affected by these treatments in the scenario analysis. Assuming that a rapidly acting treatment would result in patients being able to continue working, we applied the full estimated labor cost to those patients whose pain was reduced to mild or no pain within two hours.

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9.	**Lack of Long-Term Data Undervalues New Migraine Treatments.** AHS and AMF are of the opinion that the new acute treatments under review should not be viewed in isolation. The new therapeutic agents, while being used for acute therapy, will also play an important role for patients who are triptan non-responders, cannot tolerate triptans, or, and have contraindications to their use. As such, there are two distinct migraine patient populations that are considered for acute treatment: the first group: patients that are evaluated as safe to use triptan treatments and are either naïve to their use of have found them to be effective and well tolerated; and second: patients for whom triptans are contraindicated, poorly tolerated, or ineffective. The American Headache Society and the American Migraine Foundation encourages that any cost-effectiveness assessment of new therapies for the acute treatment of migraine must separate these two patient populations and conduct two separate cost-effectiveness assessments.	We agree and with feedback during the scoping phase of the project, we included these two populations and considered them separately. These newer agents appear to be effective in both groups for patients with acute migraine. However, in cost-effectiveness models, triptans dominate in the population that is triptan naive or has responded to triptans.

Institute for Patient Access		
1.	The report suffers from three deficiencies that have a material impact on the estimated value of the medicines. These deficiencies include: •Failure to incorporate the benefits of reduced comorbidities that better migraine management enables; •Methodological errors that undermine the evaluation results; and •Inappropriate or overly restrictive assumptions regarding the medicines' efficacy. Section 1.4 of the report, "Insights Gained from Discussions with Patients and Patient Groups," documents the devastating impact of migraine attacks, including the connection between migraine and higher risks for other illnesses. These other illnesses include stroke, coronary heart disease, hypertension, depression, anxiety, epilepsy and asthma.[1] These comorbid conditions create additional health care and economic costs that are linked to migraine. More effective migraine treatments help patients better manage these comorbid conditions. In fact, effective treatment of migraine early on, when patients' pain is at a lower intensity, yields significant health benefits and is an important predictor of improved outcomes.[1] The additional benefits will include better patient health outcomes, reduced economic costs on patients and their caregivers, and lower overall health care costs. Consequently, ubrogepant, rimegepant and lasmiditan will provide value by lowering the costs associated with comorbid conditions in addition to the value of reducing the direct costs associated with migraine. While acknowledging that these comorbidities exist, the report does not attempt to estimate the value of potentially reducing these comorbidities. Since the report does not quantify the benefits of reduced comorbidities, the results, by definition, underestimate the benefits patients receive from these treatments. Unless the report corrects this error and accounts for the full benefits of effective migraine treatment, ICER's analysis will be an unreliable guide for valuating the medicines.	While evidence may suggest there is a correlation between migraine and other comorbid conditions such as the ones mentioned here, there is no evidence to suggest a direct causal link. Therefore, it would not be scientifically sound to quantify the potential effects the migraine treatments may have on comorbid conditions without a direct clinical pathway indicating a causal link between migraine and these other comorbid conditions.

2.	On page 23, the report states that ICER "conducted network meta-analyses (NMAs) for each outcome of interest." According to page 24 of the report, however, ICER identified "only one head-to-head trial of one of the interventions versus a comparator of interest (rimegepant vs sumatriptan)." Using an NMA analysis when only one head-to-head study has been identified is methodologically problematic. According to a 2019 study in the Journal of Clinical Epidemiology, network meta analyses improved the precision of results only when at least two head-to-head studies are available. The precision of the results actually worsened when only one head-to-head study was available. Citing from the study's abstract: Although NMAs have the potential to provide more precise results than those only based on direct evidence, the incremental gain may reliably occur only when at least two head-to-head studies are available, and treatments are well connected. Researchers should routinely report and compare the results from both network and pairwise meta-analyses. Further, as outlined in Temple University's guide to network meta-analyses, NMAs are an evolving method that is subject to strict limitations.[1] It does not appear that the cost-effectiveness evaluation accounted for these limitations to ensure that the results are strengthened, not weakened, by the use of the NMA methodology.	We used available evidence to provide the most reliable estimates of treatment effect for use in the model comparing new treatments to placebo. While we recognize limitations of NMA, we employed the best available methods to evaluate these new drugs and compare them to existing therapies and placebo.
3.	Another concern is that the report compares modern studies for ubrogepant, rimegepant, and lasmiditan to triptan clinical studies that were conducted one-to-two decades ago. It is possible that material differences have arisen over time that make the comparison of studies from today to studies conducted up to two decades ago inappropriate. Consequently, the report needs to justify why it is appropriate to compare studies that were conducted up to two decades apart. Without such a justification, there are serious concerns regarding the accuracy of the results.	As noted previously, the methods used to select studies for the draft report are provided in the draft report. Our review of these studies supported our analyses. Though we are unaware of evidence demonstrating systematic changes in placebo response during the time period of these studies, we have addressed concern about differences in placebo response by controlling for it NMAs by controlling for the rate reported in individual studies.

4.	Ubrogepant, rimegepant and lasmiditan are novel treatments, and as a result, the clinical data regarding these medicines are limited. The desire to perform cost-effectiveness analyses prior to a medicine's availability to patients is understandable – it allows ICER to suggest a price for the medicine before patients and insurance companies must pay for the medicine. But this timing introduces an unacceptable level of uncertainty into the report and necessitates ICER to make questionable assumptions that introduce unknown errors.	We recognize that for newly approved treatments there are often limited data available. However, patients, clinicians and insurers are still faced with decisions about how best to use these new agents once approved for use. As such, we view comparative clinical effectiveness research, and cost-effectiveness modeling as a useful and important way to identify the key inputs that impact the effectiveness and cost of a new therapy. Even when there is uncertainty about the actual values used in the models, sensitivity analyses can highlight the range of plausible values and their impact on overall cost-effectiveness.
5.	As documented on page 23 of the report, "the primary efficacy endpoint in all trials was freedom from pain at two hours after treatment." This narrow definition of efficacy is problematic. For instance, two phase-III clinical trials for rimegepant administrated as a 75 mg oral dose found that 19.2% and 19.6% of patients achieved freedom from pain by two hours, (compared to 14.2% and 12% for the placebo group). But, importantly, the percentage of patients who were pain free increased over time; 66% of patients were pain freedom by eight hours compared to 47% for the placebo group. This increase in the number of patients helped at eight hours means that limiting the benefits to a two-hour period has likely resulted in an undervalued estimate of the benefit of these medicines to patients with migraine.	The clinical trials had differential censoring (defined as unreported findings or use of rescue medication) at 8 hours, leading to a potential bias in the 8-hour effectiveness estimates. However, it is possible that this increasing effectiveness over time is due to a delayed onset of effect in some patients. We are conducting a scenario analysis to attempt to address differences between our estimated effect of rimegepant and ubrogepant at 8 hours and effects observed in censored data reported from the two clinical trials.
6.	Another troubling assumption regarding pain arises because the report classifies pain into three levels: mild, moderate and severe. It is commonly understood that helping patients with migraine experience requires a much more sophisticated understanding of the type of pains they are experiencing. As just one example, patients living with migraine aura often experience the sensitivity to light and sound differently. These differences must be considered in order to effectively control a patient's migraine attack. It is not possible to account for these differences, however, when a clinical effectiveness model oversimplifies a patient's pain experience into a linear "mild-moderate-severe" categorization.	This type of granular pain stratification was not assessed in clinical trials nor in studies evaluating utilities associated with these symptoms. While this may be a true observation, there are no published data to support this statement or provide reliable estimates of these differences for incorporation into the model.

7.	According to page 44 of the report, ICER "do[es] not feel that current evidence supports a conclusion that treatment with lasmiditan, rimegepant or ubrogepant decreases migraine frequency over time." However, this assumption is based on the limitations of current studies, not based on a finding that these medicines have no impact on migraine frequency. In fact, there is growing evidence that the "gepant" class may have benefits with respect to migraine prevention. For example, atogepant, "an oral small-molecule migraine drug…showed safety and efficacy for preventing migraine headaches in a phase 2/3, dose-ranging trial with 825 evaluable patients."[1] The benefits for patients from a medicine that can prevent migraine headaches are potentially substantial, and it is troubling to assume that this benefit does not exist when the latest medical evidence indicates that the gepant drug class may actually provide these benefits. Further, this represents another instance where the report's assumptions bias the results toward a finding that the medicines have less value.	As noted in the report, we highlight important limitations with analyses examining the effect of these new medications on migraine frequency over time. We agree that if these medications are able to do this, it would be an important outcome. However, for the reasons cited, we do not believe that currently available evidence supports this claim.
8.	In Section 4.2, the methods section, the report states that the base case analysis was based only on direct U.S. health care costs. Patients living with migraine face many other costs, however. The annual quantifiable indirect economic costs alone, mostly from lost productivity and missed work, have been estimated at $2,350 per patient. Further, these costs do not include the value of being in less pain, or the value gained by having a greater ability to participate in more personally fulfilling activities. The assumption that these meaningful benefits are not worth including is another instance where the report's assumptions undervalue the benefits to migraine patients from a more effective treatment.	We agree that productivity loss is an important outcome and contributor to indirect costs for patients with migraine. Productivity loss was not included in the base case analysis because it would cause our analyses to favor working age adults (18-65) over children and elderly patients. To keep our analyses consistent and fair, we take a general population approach. However, we did include the effect of productivity loss as a scenario analysis.

9.	The chosen utility/disutility measures are important assumptions that attempt to quantify how much patients value an effective treatment and meaningfully impact the results. Page 65 of the report states that "disutilities of -0.5 were assumed for those patients who were hospitalized or required an ED visit. Hospitalizations were assumed to last for 2 days, ED visits for 1 day. We did not include a disutility score for patients suffering from nausea and/or vomiting, photophobia, or phonophobia due to lack of data." As this quote indicates, the report's chosen elasticities are predicated on several questionable assumptions that bias the results toward undervaluing the medicines. First, the assumptions of what to include in the utility/disutility scores are essential. Since the report "did not include a disutility score for patients suffering from nausea and/or vomiting, photophobia, or phonophobia", the benefits from treatments that reduce these conditions are, by definition, ignored in the report. Finally, it is not possible for one average utility score to be applicable to all individual patients, even if it were representative of the population as a whole. Therefore, the value findings from the report are not representative of how much any individual patient will value a more effective treatment.	Mean utility and disutility scores do adequately represent the entire population, but not the individual patient. We are providing evidence for policies that address care at the population level, so mean scores are appropriate. Unfortunately, we do not have utility or disutility data for the impact of nausea, vomiting, photophobia, or phonophobia. The model relies entirely on utility and disutility associated with pain and pain management.

Partnership to Improve Patient Care		
1.	PIPC would like to reiterate our concern with ICER's use of the QALY. As we have noted in several past comment letters, the QALY is not an appropriate methodology for use in value assessments, particularly where the patient population is very heterogenous, as in migraine. The Headache and Migraine Policy Forum also touches on this heterogeneity in their report noting that the experience of migraine exists on a spectrum more than other chronic disease. It is also important to note that a recent review suggested that generic PROs have been shown to have less reliability and validity than disease-specific PROs in migraine evaluation such as HIT-6, MSQv2.1 and the PPMQ-R. The QALY is also widely acknowledged to discriminate against those with disabilities and chronic illnesses. In fact, they have long been precluded from use in public health programs for this very reason. The QALY is not an appropriate metric to use when evaluating treatments for a chronic condition that is the sixth leading cause of disability. Migraine is considered an invisible disability with an impact on quality of life that may not be appreciated by the general population.	We appreciate the concerns about relying solely on QALYs. ICER agrees the QALY should not be used to discriminate against individuals with chronic illnesses or disabilities. In fact, people with serious illness and disabilities benefit most from cost-effectiveness analyses. Because the QALY captures the degree to which a treatment improves patients' lives, cost-effectiveness analyses of treatments for people with serious disability or illness have the greatest opportunity to demonstrate more QALYs gained and therefore justify a high price. In addition, to safeguard against the misuse of the QALY, every ICER report also provides a complementary measure: the Equal Value of Life Years Gained (evLYG). The evLYG ensures that any treatment's ability to lengthen life is calculated as being just as valuable for all patients – regardless of those patients' various health conditions. ICER's reports provide both QALY and evLYG metrics to ensure all stakeholders have a broad, patient-centered perspective on value when making consequential decisions around pricing and coverage. In the case of migraine, however, treatments do not offer life extension.

2.	**The Draft Evidence Report Makes the Oversimplified Assumption That There are No Mortality Effects in Migraine Treatment.** The ICER Report makes a statement that it assumes there are no mortality effects in migraine treatment. This is a simplistic assumption, as a number of studies have shown people with more severe types of migraine (with aura for example) have higher rates of all-cause mortality in both men and women. Studies have also shown higher rates of both suicide and suicidal ideation in migraine patients , and more broadly in patients suffering with conditions that include chronic pain. , Considering this research, assuming a therapy that successfully reduces the pain burden for migraine patients will have no effect on mortality does not capture the full picture. Most studies that look at migraine and mortality differentiate specifically between migraine with aura (strong mortality effect) and migraine without aura (weak),[1],[2] reiterating the importance of the risk of dilution of effect by inadequate diagnosis or subgroups analysis by severity. In all it was estimated on average that people with migraine with aura had mortality rates between 10-20% higher than a matched cohort of people without the condition**.** In a scenario like this, in which the risk of mortality is higher in a particular disease state, the potential expected impact of successful therapy would be reduced risk. Even if mortality isn't an outcome in trials of migraine therapy, drawing the line between successful treatment and reduced mortality should at least be discussed and not simply assumed as null.	We are unaware of evidence showing that treatment of acute migraine decreases morbidity and mortality. We recognize that this is difficult to show for any acute treatment that is associated with a very low likelihood for any individual episode. We have highlighted this in the revised limitations of the report.

3.	**ICER Makes No Attempt to Incorporate Quality of Life Gains from Reduced Anxiety Around Migraine Attacks.** Studies have shown that HRQOL is lower for migraine patients 'between' attacks as well as during attacks as many patients shared with ICER that this constant anxiety caused them to have lower quality of life even when they were not having a migraine attack. ICER acknowledged this in their "Insights Gained from Discussions with Patients and Patient Groups" section of the report yet made no attempt in the actual model to incorporate the quality of life gains from reduced anxiety that comes from having improved options for episodic treatment. As such the construction of the ICER model, which only includes the estimation of QALY gains 'within' each acute attack, will inevitably be an underestimate of the overall effect of any therapy as it excludes those gains that are experienced outside acute attacks. This highlights our consistent concern that ICER seeks patient input but fails to give it real credence by incorporating it into the actual model. a direct result of the anxiety anticipating an attack. In one study compared with control subjects, "migraineurs perceived more symptoms and greater emotional distress as well as disturbed contentment, vitality and sleep." Another showed that "Compared with non-migraineurs and to others with chronic conditions, migraineurs report compromised physical, mental, and social functioning, particularly those with a high frequency of attack."	We acknowledge that there may be an association between migraine and anxiety. However, the new acute treatments for migraine were not demonstrated to reduce anxiety. Therefore, these outcomes have not been incorporated into the model.
4.	**ICER Continues to Use Third-Party Health Utility Estimates, which Underestimate the Effect of Treatment.** ICER continues to use third-party health utility estimates and apply them to the health states used to construct the QALY estimates rather than using health-related quality of life (HRQOL) data directly from the RCTs themselves to calculate the utilities in its QALY calculations. It has been shown that this over-translation, or categorization, of outcomes into utility sets by health state categories rather than from direct sources underestimates the effects of therapies	For health state utilities, we used EQ-5D data that were collected from migraine patients in a multicenter, double-blind study of a treatment for acute migraine in the United States. We did not have consistent data from the RCTs that would allow direct calculation of utilities.
5.	Using a translated utility from a third source as a proxy leads to an oversimplification of health states. This limits our full understanding of the effects of any therapies under investigation and can lead to them being shown to be less effective based on faulty data. We encourage ICER to cease using this type of third-party health utility estimate.	We disagree that the model oversimplifies health states, including separate utilities by pain severity.

6.	We also share the concerns of others that ICER is using clinical studies that are 25 years old and comparing them to more recent studies. Yet, we know today that the placebo response has changed over time. ICER's model cannot be accurate when ICER's literature review that underlies the cost effectiveness model relies on this 25 year old data instead of real-world data that better reflects the patient experience.	Thank you for your comment. The issue of differences in placebo response among different studies is an important one. The supposition that placebo response has changed over time is unproven. However, we have modified our approach to conduct network meta-regression to adjust for differences in placebo group response rate in the NMAs.
7.	**ICER's Model has Inherent Flaws.** When designing and executing a cost-effectiveness model, it can very quickly become a box-checking exercise: produce a Markov model that is constructed around the main outcome measures; get sources for drug cost, utilities and transitions; chose a timescale; make assumptions where data is missing; etc. This becomes quickly reductive and therefore inaccurate due to its inability to capture the real-world patient experience with the particular disease and the value of treatment.	In constructing a model, we conducted a thorough systematic reviews of the literature, and evaluated published models and studies evaluating relevant outcomes. The model that was constructed for this evaluation included the most relevant outcomes for which data was available and is one of the most comprehensive models developed for the evaluation of acute treatments for migraine. We encourage continued research to identify important outcomes for patients with migraine and their impact on patient quality of life. If and when additional data described in this comment become available, we support the development of more comprehensive models that describe the impact of the treatment of migraine. Importantly, the treatments must be demonstrated to impact the outcomes for them to be considered for inclusion in a model.
8.	While there are undoubtedly numerous inputs that are 'correct' in the ICER migraine model, it also contains structural flaws. Ultimately, the real test is whether it works, and, in many ways, this model is inconsistent with common sense based on the facts. We know migraine is a condition impacting a group of people who experience unpredictable attacks of severe pain on a minimum of a weekly basis (mean 4.8 attacks per month) which ICER's states, "can be a disabling, chronic condition that can impact all aspects of life including personal relationships and ability to work." The drugs under consideration are more effective than standard of care by orders of magnitude of 2-5 times (tables 3.3-3.7). The drugs in question are assumed in the model to cost $70.	see response above

9.	Relying on this basic set of facts, it does not meet common sense standards that the model results would find these therapies to not be cost-effective. Nor it is transparent how the aforementioned results were derived because ICER still does not publish its models or make them open source. From what we can surmise, the most significant issues seem to lie in the narrow scope of the model. Our best guess is that the underlying factor leading to this conclusion is based on how quality of life was incorporated or the source of that information. One alternative would have moderate migraine down from 0.79 to 0.53 and severe migraine down from 0.44 down to -0.20.[1] It is not clear why the chosen source of quality of life data is selected over others, or even that others are not used as part of a sensitivity analysis.	see response above
10.	Another factor for this conclusion may be the measure of the impact of reducing migraines and their severity as limited to the length of the individual attacks rather than across the entire period for the patient. This would be an oversimplification of the model that goes too far from the day-to-day reality of the disease for most patients.	see response above
11.	We would suggest a thorough review of the construct of the model and a detailed review by migraine patients themselves on how it represents the real patient experience.	see response above
12.	**Conclusion:** ICER continues to overlook outcomes that matter to patients in favor of overly simplistic QALY-based models. We urge ICER to be more thoughtful in its model construction and take seriously the feedback from patients and clinicians who are experts in migraine attacks	see response above

Patients Rising		
1.	As the draft report describes in the first part of the Background Section (1.1), and Insights Gained from Discussions with Patients and Patient Groups Section (1.4), acute migraines are a disease the affects many people (women more than men), and has profound impacts on their lives – including their workplace productivity and non-working activities and capabilities. We would like to commend ICER for reaching out to and engaging with a relatively large number of patient-facing organizations. However, we feel that this draft report illustrates the problems with ICER's overall process and methodologies because it poorly incorporates such insights into its modeling and assessments, as described below.	We did seek out input from patients and advocacy groups throughout our review and we believe that our report highlights their insights and concerns. Though it is not possible to include all of these insights into our cost-effectiveness model itself, these quantitative assessments are only one part of our report. We focus considerable attention on the data available, their limitations as well as key insights from all concerned groups including patients and their advocates. Presenting these data, along with insights from patients and other interested parties along with the quantitative results are all necessary to inform policymakers about how best to consider new therapies. The comparative clinical effectiveness, quantitative evaluation, other benefits, and contextual considerations sections of our report all feature prominently in the ICER value framework to inform all decision making by our panels.
2.	In addition, we feel it is important to reiterate some of the points we made in our May 2018 letter to ICER about some preventative treatments for migraines, as those same points apply to acute migraines: The biology of migraines is complex and uncertain. Migraines may represent multiple underlying conditions or causes leading to vascular changes and pain. As NINDS states, "There is no absolute cure for migraine since its pathophysiology has yet to be fully understood". That insight has important implications for ICER's assumptions and modeling. Until there are better diagnostics and more specific therapies, it is critically important that patients and clinicians have ready access to all options for treatment of acute migraines, because it is well known that different patients respond differently to therapeutic alternatives, and "only 29 percent of U.S. migraine sufferers are very satisfied with their treatments." Patient perspectives and clinical presentations extend well beyond pain. Migraine "is generally thought of as a headache problem, but it has become apparent in recent years that many patients suffer symptoms of migraine who do not have severe headaches as a dominant symptom. These patients may have a primary complaint of dizziness, ear pain, ear or head fullness, "sinus" pressure or even fluctuating hearing loss"	We agree that migraine is a severe and complex condition that warrants attention, especially given the lack of efficacious treatment for many patients.

3.	Unfortunately, because ICER primarily relies upon select clinical trial data to formulate its modeling, conclusions, and recommendations, and because most clinical trials (for FDA approval of migraine treatments) focus on pain measurements and assessments, other "disutility" features of migraines are not incorporated into ICER's work, even while the draft report notes that "migraine is one of the most common causes of disability worldwide."	We agree that there are limited data on the impact of migraine or therapies for migraine, on the aspects of patient quality of life outlined in this comment. We chose what we believed to be the best available evidence for the impact of migraine on health utilities. As such, clinical trials should be better designed to capture patient-important outcomes, but until then ICER makes use of the best available evidence.
4.	In looking at productivity and patients' lives in the draft report, ICER did not utilize the references we previously provided from Serrano et al., Landy, or Mandelblatt et al. While we recognize that ICER relied exclusively on Masseli's work in this draft report (and data from the American Migraine Prevalence and Prevention study for its May 2018 report on chronic migraines), we are concerned that choosing a single data source when others are available for comparison is not scientifically rigorous. Exploring and discussing multiple data sources would provide a more robust assessment, particularly for something as important to people with migraines – and their employers – as productivity-related impairments.	We conducted a systematic review of the literature to identify appropriate references and model inputs and considered all of these references for inclusion in the model. We agree that the studies conducted by Landy et al and Serrano et al were high quality, low-bias studies. Landy et al provided estimates for lost time resulting from going in to work late (2h 36 min) and time lost for leaving work early (1h 54 minutes) and a mean time of 2 hours 44 minutes lost per workday migraine, which were 64% of all migraines reported. Based on an average individual income in the US of $58,379, the resulting estimate for work lost per migraine needed for the model is $49.40. Serrano et al estimates that men with episodic migraine incur an average loss $80.08 per person per week while women incur an average loss of $46.93 per week (unadjusted for inflation). The estimates that we used were well-aligned with these estimates, with an average cost of $51 per migraine, slightly higher than what was reported in either study. This is why we chose to use the study by Messali et al to support work productivity losses with migraines and gains with treatment in the model.

5.	**People-Oriented Information and Perspectives:** The findings in the draft report seem to boil down to the following points: Migraines are bad and have a significant negative impact on people who have them; The triptans and other older medications – both prescription and OTC – work for some people, but for individuals who find them not effective (or cannot use them for other reasons), there is a significant unmet clinical need; and the newer medications reviewed in the draft report provide treatment options for people with migraines when other options are ineffective, not tolerated, or not indicated. Compared to other ICER reports and projects, this draft report seems very clearly outlined by those three points. Given that the older medicines are significantly less expensive, it is the third point above that should be the crucial area of focus. And for those people, the question is simple: Are the newer medicines "worth it"? But that question needs to be asked in a more nuanced way; "worth it" is a relative term depending on the severity of the migraine for each person and their individual situation. For example, "worth it" could be very different for someone with a migraine that would only minimally impact their work productivity based upon the nature of their job, versus the impact a migraine could have on their wedding day. Unfortunately, in ICER's calculations, the former is important, but the latter is not.	The variation in the clinical value of treatments can often be tremendous, and we agree with you that an effective migraine treatment for a neurosurgeon heading in to operate, or for the President in a crisis, would be extraordinarily valuable. We hope that the perspectives of patients summarized in our reports, along with the deliberation on value that occurs at ICER meetings, helps decision-makers understand the heterogeneity of response across different types of patients and what that response can mean to different individuals. As regards our cost-effectiveness analyses, if there are specific clinical subpopulations, we often calculate separate value-based prices for them within a broader labeled indication. But most often our reports use evidence from across the entire spectrum of patients, as represented in the available clinical trials, to calculate a single price range for "all" patients. In large part we do this because manufacturers charge a single price for their drugs, and we feel that price should reflect the average benefits to a broad sample of patients. It is to help inform negotiation around that price that our work is most frequently applied. As such, when ICER talks about a fair price for a therapy it's the price that would be fair when averaged over all the patients who would be candidates for the therapy. It will always be possible to find individual patient situations where paying more -- or less -- would be reasonable, but drug pricing within health insurance systems is not structured to vary based on the value to individual patients.

6.	While pain is important, it may not be the most important factor for patients' functioning related to the symptoms of migraine. Migraine is recognized as a very difficult area of pain management for diagnosis and treatment. Therefore, the draft report faces significant challenges in comparing different types of treatment options by analyzing individual trials, or with meta-analyses. In this process, we are once again disappointed that ICER minimizes the importance to patients of improved function and quality of life, and the need for – and value of – new treatment options for people with migraines.	Please see above response regarding the lack of utility data for outcomes other than pain.
7.	Expanding on the importance of individualization of care to reflect real-world people's nuanced clinical presentations and life-concerns, the goal is to find treatments that work for patients and allow them to function in ways that they need to – which varies from person to person. For example, the impact of treating an acute migraine that occurs during the work week (or work day) could be very different if an acute migraine were to happen during a non-work day. And the consequences for an individual could depend on their work situation. For example, no one would want their surgeon operating on them while in the midst of an acute migraine, nor would they want to be on an inter-city bus when the driver is suffering from an acute migraine.	Please see answer above about not applying ICER results at the individual patient level.
8.	A related area of patient perspectives is actual costs to patients versus payer, insurance company, or nationally aggregated costs. Unfortunately, ICER clearly states that "the base-case analysis was conducted using a health care sector perspective (i.e., focus on direct medical care costs only). 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, ICER should also include estimated actual patient costs, which would be in-line with national policy makers' discussions about value-based benefit design. We strongly believe that value calculations only looking at health financing or delivery are incomplete – they must also reflect real-world value improvements for patients.	ICER utilizes the health care sector perspective because it is a well-established economic approach to health technology assessment, and because our reports are focused on the population level. While we agree that individual patient costs are important, our model is designed to inform decisions at the population level. The multiplicity of insurance arrangements in the US would likely make any particular analysis incorporating individual-level patient costs irrelevant to most patients.

9.	Another example of the problems with the draft report is the economic model, which does not include disutility of patients suffering from "nausea and/or vomiting, photophobia, or phonophobia due to lack of data. This is very problematic from a patient-focused perspective. We hope you will correct this in the final report's overall analysis, conclusions and recommendations, because we are concerned that not incorporating such important qualitative factors will lead payers and clinicians to undervalue the benefits of treating acute migraines model, which does not include disutility of patients suffering from "nausea and/or vomiting, photophobia, or phonophobia due to lack of data."	Please see above response regarding the lack of utility data for outcomes other than pain.
10.	From a technical perspective, we note that ICER states the NMA was done with binary outcomes---– but people's lives are not binary, except for death. Unfortunately, ICER did not – or could not – dig deeper into non-binary facets of how migraines affect a patient's awareness and cognition, i.e., mental fuzziness. This limitation of ICER's process is derived from its use of mathematical modelling that is based upon a narrow slice of clinical trial data, i.e., pain reduction or relief. Such a limited analytical perspective doesn't permit anywhere near a complete picture of how migraines affect patients in their overall life any more than watching a patient in a clinical office for 20 minutes reflects that person's overall capabilities, challenges, and limitations during the other 23 hours and 40 minutes of their day – or the multiple days between clinician visits. We continue to urge ICER to include a broader range of people-focused factors into its computational system, since the binary processing in this draft report severely shortchanges the value of patients' lives.	We agree that there are limitations to the NMA. However, we do our best to incorporate other patient-important outcomes in other ways that are just as important and valid in understanding the impact of migraine. We did seek out input from patients and advocacy groups throughout our review and we believe that our report highlights their insights and concerns. The NMA results are just one part of our report. We focus considerable attention on the data available, their limitations as well as key insights from all concerned groups including patients and their advocates. Presenting these data, along with insights from patients and other interested parties along with the quantitative results are all necessary to inform policymakers about how best to consider new therapies. The comparative clinical effectiveness, quantitative evaluation, other benefits, and contextual considerations sections of our report all feature prominently in the ICER value framework to inform all decision making by our panels.

11.	**Data Uncertainty:** We are a bit confused about some of the data presented in the draft report and the reliability of cross-trial comparisons, given the unavoidable differences in the groups being studied. For example, there seems to be some inconsistency about the comparability of the patient groups in the trials used in the NMA ICER conducted for this draft report.	The report presents the methods used to select studies for evaluation. We highlight the baseline characteristics of the studies selected in the appendices. Though there are differences among the studies, we included in our NMA those studies we felt were appropriate to include. As noted previously, we have modified our NMA to adjust for differences in the placebo response rate in each study.
12.	Specifically, while the body of the draft report indicates that people in the trials of eletriptan had 3-8 migraines per month, the data presented in Table D1 indicates most of the trials of eletriptan included people with less than an average of 3 migraines per month. In comparison, Table D1 also indicates that the trials involving the three newer medicines have higher rates of migraines per month. This leads us to be concerned that the population studied for the newer medicines may have had more serious migraine disease (i.e., more migraines per month), which would make cross-trial data analysis fraught with expanded uncertainty that would lead to unreliable conclusions.	As noted previously, we agree that there are some differences among the studies selected for comparison, including those mentioned here. However, we felt that these differences were not large enough to result in study exclusion.
13.	An additional foundational complication for how the draft report evaluates value and benefits of treatments for migraines is that the draft report does not consider devices or other interventions in its review or modeling. This is a problem, because in the real world, the treatment of acute migraines is not limited to OTC, triptan, and the three newer prescription medicines.	We agree that there are other treatments for acute migraine besides medications. However, to manage the scope of this project, we elected to include comparators that are similar to the new therapies in how they will be used. Feedback during the scoping phase of the project supported this decision.
14.	We also find that ICER's rationalization to justify a conclusion of regression to the mean is both convenient and unconvincing. That is, just because compounds are from different molecular or structural classes does not mean that they also have fully different mechanisms of action. Specific to the medicines involved with treating migraines that are the focus of the draft report, research has shown that they have linked physiological mechanisms of action	We do not believe that regression to the mean is limited to these newer medications. Rather we believe it reflects the principle that over time, extreme results trend toward the population's mean. That said, we raise this as one of several possible explanations for the reported results.

15.	Therefore, deriving the equivalent of a mathematical transitive association among very different trials to dismiss the possibility of any acute treatment leading to a long-term reduction in the number of migraines per month – and "explaining" that data as simply "regression to the mean" because of significant dropout rates from open extension trials – is dubious, and we find it very concerning. Couldn't some medicines – for some people with specific receptor subtypes or predispositions – yield reduced migraine frequency via changes in receptor sensitivity or up/down regulation? We see ICER's views here as an example of ICER determining what model parameters or "reasoning" best fits their pre-existing beliefs that new medicines are not valuable and do not increase the length of life – which we note ICER has declared in both written and oral statements. We are very concerned about this ongoing bias.	We agree that it is possible that these newer medications will be shown in the future to decrease the rate of migraine attacks over time among users. We also believe that studies could be designed to rigorously assess this outcome. Finally, as noted previously, we cite regression to the mean as one of several alternative possibilities to account for the reported results.
16	**Conclusions:** Patients Rising Now believes that ICER's draft report on some new therapies for acute migraine inadequately reflects quality of life, personal and work productivity, and the complexity of migraine treatments from patients' perspectives. Despite ICER engaging with a larger number of patient-connected groups in the process of compiling this draft report than it has in the past, we believe ICER needs to do a much better job of actually incorporating those perspectives into its calculations and conclusions.	Please see comment above.
17.	Specifically, patients' voices need to be a part of defining and assessing the value of their treatment plans along with the cost of all aspects of their care – including patient's direct out-of-pocket costs and indirect costs related to their ability to work and live unencumbered by migraine symptoms and complications. Overall, ICER comes up with the wrong answers because it continues to ask the wrong questions.	Please see comment above.
18.	Given the large unmet need for people with migraine for whom prior treatment options are inadequate or inappropriate, the new treatments offer significant hope. No one expects them to be a panacea for everyone who is seeking better treatments for their migraine – particularly given the uncertainty about the underlying physiological causes of migraine – but we strongly believe that payers and society should not unduly restrict access, coverage, and reimbursement for such people. We are very concerned that ICER's economically siloed conclusions will lead the gatekeepers at many insurance companies and other payers to reflexively erect such barriers.	Thank you for your comment. As stated in the report, we believe that the approval of these drugs for migraine represents a potentially important advancement for individuals with migraine. The goal of ICER's report is not to restrict access to these drugs, but to instead improve access by facilitating discussions on determining a fair price given its comparative clinical effectiveness.

19.	We would be much more supportive of analyses constructed to support patients and clinicians across the range of clinical decision making, benefit design, reimbursement policies, and coverage choices or limitation. There is a significant need, which the draft report does not fill, for assessments that encompass real patients' choices and goals, the spectrum of financial implications for new therapies, and practical options for increasing value for patients within the decision-making process across the pluralistic U.S. health care system. We are concerned that the draft report will only continue to reinforce the status quo rather than support more people-centered operations of health care delivery and insurance design.	See comment above. In addition, for each review, we seek out input from the major disease-specific patient advocacy organizations and patients who are living with the condition that is the subject of our review. Our process also includes multiple opportunities for feedback from the broader patient and advocacy communities, including explicit review of early drafts of our report. We believe our methods focus on incorporating patient-important outcomes (where possible and if data allows) and perspectives, and our approach is patient-centered.
Policy Forums		
Headache and Migraine Policy Forum		
1.	While we agree with ICER that "compared with usual care in patients for whom triptans are not effective, not tolerated, or are contraindicated, these new acute treatments for migraine provide utility gains," HMPF remains concerned that the current DER quantitative model does not adequately assess the true cost of migraine disease and neglects to consider the full potential benefits of these new therapies. Therefore, we respectfully request that ICER amend the DER to address the following:	We believe the cost-effectiveness model accounts for the cost of migraine disease and the potential benefits of these treatments to the extent that current evidence allows. We have addressed specific suggestions below.
2.	**Use of QALY Leads to Insufficient Consideration of the Patient Definition of Value.** As expressed in previous reviews, 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 also been found to be discriminatory against people with disabilities by the U.S. Department of Health and Human Services.	ICER uses the QALY as part of its assessments precisely because of its ability to take account of the balance between quality and quantity of life, allowing for comparisons of therapies on their ability to improve quality of life and lengthen life. Economic analyses using the QALY make treatments that alleviate serious illness look especially valuable.

3.	Since we know that 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 contraindicated from or poorly responds to existing therapies has tremendous value to this community. It is important to understand that migraine is not a homogenous disease that all patients experience similarly. People living with migraine disease 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.	Analyses using QALYs do not result in lower ICER valuations for regenerative or life-enhancing therapies, because the QALY records the degree to which a treatment improves patients' lives. Therefore, treatments for people with serious disability or illness have the greatest opportunity to demonstrate more QALYs gained and justify a higher price. We acknowledge that there is heterogeneity among migraine patients and within patients over time, but are constrained by the lack of data on specific subgroups.
4.	For individuals living with migraine disease, 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.	ICER's evaluations strive to include as many patient-important outcomes as possible. The QALY measure in the cost-effectiveness model adjusts for changes in quality of life (or utility). We also report the cost per hour of pain avoided. Potential labor benefits from reduced migraine pain have been included in a scenario analysis in the report.
5.	**ICER Improperly Compares Decades-Old Triptan Data to Modern Studies in an Inappropriate "Apples-to-Oranges" Approach.** The DER improperly utilizes 25-year old triptan studies and compares them to modern clinical trial studies, fatally anchoring the review on a placebo response that has changed over time.[1] Therefore ICER's cost effectiveness model is a highly flawed "apples to oranges" comparison. If ICER insists on continuing to compare 25-year old studies with modern ones, we request that the model include an adjustment for the increased placebo response rate that has been documented over a very similar timeframe.	Thank you for your comment. The issue of differences in placebo response among different studies is an important one. The supposition that placebo response has changed over time is unproven. However, we have modified our approach to conduct network meta-regression to adjust for differences in placebo group response rate in the NMAs.

6.	**The DER Does Not Accurately Model the Targeted Patient Population Or Consider Discontinuation Rates That Will Occur in the Real World, Which Skews Both the Efficacy and Cost Analysis.** ICER states: "given the availability of triptans for acute treatment of migraine, we also sought to compare these interventions to triptans for patients who do not adequately respond to non-prescription medications and are eligible to use triptans." ICER's quantitative model does not take into account modern discontinuation rates because the clinical trial model for triptans unfairly skews an idealized adherence rate. Instead, the DER models a migraine patient population that does not exist. The novel acute therapies under review are primarily for patients who have been failed by triptans, yet ICER's fundamental analysis relies upon the fallacious idea that patients will have a choice between a triptan or novel acute therapy.	Discontinuation rates applied in the cost-effectiveness model were based on observed rates from clinical trials because real-world data are not available for lasmiditan, rimegepant, or ubrogepant. In order to have a fair comparison between triptans and these new acute treatments for migraine, it was essential to use data collected in a similar setting. Discontinuation rates had little to no impact on the cost-effectiveness estimates for treatments in sensitivity analyses.
7.	The reality is that for most patients who are appropriate for these new medicines, the alternatives would *instead* be either a more costly preventive therapy, taking opioids, or simply not effectively managing one's disease (thereby risking chronification, pain and/or disability). In fact, the DER contradicts the American Headache Society consensus statement last year on integrating new migraine treatments into clinical practice, stating that the target population for these novel acute therapies is those who would be contraindicated or triptan intolerant. Yet ICER insists on including within this broad group any migraine patient who needs a prescription therapy, regardless of the likelihood that the patients for whom they are intended have likely failed multiple triptans already. ICER's primary comparison of these new therapies with a generic drug like a triptan is misguided and harmful to patients. Many physicians are hesitant to prescribe triptans due to concerns about cardiovascular risks, and instead often prescribe non guideline recommended opioids. Access to these new acute therapies is vital so that clinicians can make better treatment choices.	We understand that one may be confused about including comparator patients who are triptan naïve or have had a prior response. However, our goal is to evaluate how these new medications may be used in actual clinical practice. The phase II trials of these new medications included a range of patients with acute migraine including those who are triptan naïve/ responders/ nonresponders/ intolerant/ contraindicated. Since the outcomes of these trials are favorable, we expect that FDA labeling will include the range of patients evaluated in these trials (this is the case for lasmiditan that has received FDA approval). Moreover, since clinicians are given broad discretion in how to use FDA approved medications, we believe that the comparators evaluated in our report will be relevant as these medications are introduced in the U.S.

8.	**ICER Refuses to Properly Consider That Novel Acute Therapies, Unlike Triptans, Have Been Shown to Decrease the Frequency and Severity of Migraine Attacks.** The DER states that ICER "did not perform a systematic review specifically to address […the issue of whether the novel acute therapies, when used over time, could decrease the frequency and severity of migraine attacks…] even where the results of stakeholder studies reported a decreasing frequency of migraine attacks over time. ICER's interpretation of the evidence disregards those patients with a high frequency of attacks at baseline who experience decreases in attacks. Many migraine patients experience cascading attacks; that is, once they begin additional attacks occur in sequence. Open label, long term studies by the developers of these novel acute therapies shows there is a preventive benefit. This benefit is a high value to patients, and we call on ICER to include it in your analysis.	We agree that it is possible that these newer medications will be shown in the future to decrease the rate of migraine attacks over time among users. We also believe that studies could be designed to rigorously assess this outcome. However, we do not believe that available evidence supports this benefit for the reasons stated in the report.
9.	**The DER Underestimates the Full Benefit of Novel Acute Therapies by Stopping Response at Two Hours (Assigning Responsibility to the Inevitable Differences in Trial Design).** The primary outcomes in the DER do not fully reflect the potential benefits of these new therapies. The DER describes an approach whereby ICER, in an effort to compare data among all three therapies under review, cuts short patient response data at two hours, even where clinical benefits are shown in some trial data beyond that time period, simply because of inevitable differences in trial design.	Though the primary outcome of the phase III trials of these new medications is at two hours, they continue to collect information on patients through 24-48 hours. Differences in study protocol for managing patients after two hours makes comparing these new medications to placebo more challenging. However, our model continues to evaluate patients after two hours. Moreover, we have modified how we assess outcomes after two hours based upon other feedback we received on the draft evidence report.
10.	For those patients who do not respond at two hours, ICER assumes the efficacy of those patients to be that of placebo, even where some patients are achieving pain freedom at 2.5 hours or 3 hours (or longer). Cutting short the data in an effort to compare therapies results in confirmation bias and erroneous conclusions without a complete accounting of the full benefit of these innovative therapies. ICER completely discounts the fact that migraine is a spectrum disease, where sometimes an attack or event is 72 hours or longer.	Based on the feedback we received, we have modified how we calculate the relative benefit after two hours. In the report, we clarified the limitations of studies that evaluated outcomes beyond 2 hours. We have also included a scenario analysis evaluating a potential increased impact of rimegepant and ubrogepant on pain outcomes after 2 hours.

11.	**The DER Unfairly Discounts the Indirect Costs and Societal Burden of Migraine Disease.** 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 disease**.** The DER states: "We also sought evidence on the key measures of clinical benefit including disability, health-related quality of life, employment-related outcomes, and other patient reported outcomes. We found data on disability and patient reported global impression of change but did not find any data on the other outcomes." This is inaccurate.	See response above
12.	Studies have been previously presented to ICER showing that direct costs are far exceeded by indirect costs to employers including missed work and presenteeism (loss of productivity);) ; 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.	See response above. The population from which the labor costs/benefits were derived involved surveys administered to 1101 patients with episodic migraine. The sample had a mean age of 47.2 and was 91.6% female, 91.6% Caucasian, and was highly educated. 52.8% had a total annual household income above the country's median income. Lost productivity was reported as $943 per year in 2013 USD, or $51 per migraine episode in 2019 USD. We do not believe that this underestimates lost productivity.
13.	**ICER's Refusal to Acknowledge Possible Mortality Effects Has An Undeniable Impact On Value Outcomes.** The costs of treating migraine increase sharply with the number of co-morbid chronic conditions. 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. Migraine patients are known to be co-morbid with anxiety and depression - conditions that have led many patients to suicide. ICER states, "Therapies for migraine have not demonstrated differences in mortality, nor has a mechanism for differential survival with the current treatments been proposed.	Thank you for this comment. We are unaware of evidence showing that treatment of acute migraine decreases morbidity and mortality. We recognize that this is difficult to show for any acute treatment that is associated with a very low likelihood for any individual episode. We have highlighted this in the revised limitations of the report.

14.	*Given the relatively young age of the population being evaluated and associated low mortality rate*, mortality was not included in the model." The migraine community reminds ICER that suicide prevalence in our community is much higher than in the general population, with age having *zero* correlation to mortality. Not including mortality data related to co-morbidities that increase rates of suicide has an undeniable impact on the qualitative model.	See comment above.
15.	In fact, data presented on co-morbidities related to migraine disease should have a substantial impact give a new sub-analysis on the link between migraine and suicide. A recent large population, long-term international study showed higher risks observed among patients with migraine than in the general population. Nearly 88% of those with chronic migraine had at least one co-morbid condition that had an impact on health care costs associated with the disease, including mental disorders (37%) and mood disorders (27%).	See comment above.
16.	In the largest national study designed to examine the association between migraine and suicidal behaviors and the impact of co-morbid mood (depression, anxiety) and stress (PTSD) disorders on this association among a nationally representative sample of adult inpatients from 2007 to 2012, researchers found that hospitalizations with migraine had statistically significantly increased odds of suicidal behaviors (OR: 2.69; 95%CI: 2.55-2.86; Table 2). After adjusting for confounders, people with migraine had a 2.07-fold increased odds of suicidal behaviors (95%CI: 1.96-2.19; Table 2).	See comment above.
17.	Depression, anxiety and, in the case of veterans, post-traumatic stress disorder, are common co-morbidities for patients with migraine. The final evidence report should therefore reflect that new acute therapies will improve these co-morbid conditions.	See comment above.
18	**Increased Non-Opioid Therapies Would Directly Impact the Value Outcome.** ICER states, "because of limitations of existing therapies, there are many individuals in whom no effective, reliable treatment is available. It is hoped that having more treatments for migraine can reduce the use of opioids and thus the risk for opioid misuse. Data on this are not yet available." This is misleading. The HHS Pain Task Force makes a direct correlation between additional treatment options and the reduction of opioid use. The Task Force also calls for more research that will ultimately bring more and novel therapies to patients: "As novel and proven treatment options emerge to improve acute pain and specific chronic pain conditions, they should be rapidly incorporated."	We agree that more effective therapies for acute migraine may lead to less use of therapies such as opioids. We also recognize that triptans do not appear to have achieved this important outcome. Whether these new medications are associated with decreased use of opioids remains to be seen. Since there is no evidence that these medications will decrease opioid use, this potential benefit was not included in the model.

19	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 therapies. ICER's previous CGRP DER mentions costs associated with side effects from interventional therapies and acknowledges that "therapies that reduce the number of migraines and acute medication use may also reduce opioid dependence in this population. The ICER model must be updated to account for benefit / cost reduction of reduced exposure to opioids.	The current report evaluates treatments for acute migraine. The report cited focused on patients with chronic migraine. Patients with chronic migraine were excluded from the phase III trials of these new medications. Though it is possible that future studies may show benefits for treatment of acute migraine in terms of decreasing progression to chronic migraine, use of other migraine treatments and morbidity/mortality, current evidence is lacking. For this reason, we focused on published evidence of treatments for acute migraine.
20.	HMPF appreciates that ICER encourages stakeholders to provide input on potential other benefits and contextual considerations in their public comment submissions but remains concerned that many of these issues do not carry the same weight as its quantitative model analysis. There is an urgent need for improved migraine therapeutics. Unnecessary suffering and lives will be lost if access barriers are placed in front of migraine patients. ICER has an important role in ensuring payers understand the full value of these therapies.	We hope that our report provides both a meaningful qualitative and quantitative assessment of these new treatments for acute migraine.