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Title: Estimating the clinical effectiveness and value-based price of erenumab for the prevention of migraine in patients with prior treatment failures: a US societal perspective

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Abstract

Background: Frequent migraine with four or more headache days per month is a common, disabling neurovascular disease. From a U.S. societal perspective this analysis models the clinical efficacy and estimates the value-based price (VBP) for erenumab, a fully human monoclonal antibody that inhibits the calcitonin gene–related peptide receptor.

Methods: A Markov health state transition model was developed to estimate the incremental costs, quality-adjusted life-years (QALYs) and value-based price range for erenumab in migraine prevention. The model comprises "on preventive treatment", "off preventive treatment" and "death" health states across a 10-year time horizon. The evaluation compared erenumab to supportive care (SC); i.e. no preventive treatment, in patients that have failed at least one preventive therapy. Therapeutic benefits are based on estimated changes in migraine day (MD) frequency from erenumab pivotal clinical trials and a network meta-analysis of migraine studies. Utilities were estimated using previously published mapping algorithms. A VBP analysis was performed to identify maximum erenumab annual prices at willingness to pay (WTP) thresholds of $100,000 - $200,000 per QALY. Estimates of VBP under different scenarios such as choice of different comparators, assumptions around inclusion of placebo effect, and exclusion of work productivity losses were also generated.

Results: Erenumab resulted in incremental QALYs of 0.185 versus SC and estimated cost offsets due to reduced MD frequency were $8,482, for an average treatment duration of 2.01 years. The estimated VBP at WTP thresholds of $100,000 - $200,000 for erenumab compared to SC ranged from $14,238 - $23,998. VBP estimates including the placebo effect and excluding work productivity ranged from $7,445 - $13,809; increasing to $12,151 - $18,589 with onabotulinumtoxinA as a comparator in chronic migraine**.**

Conclusion: Erenumab offers consistent and meaningful reductions in MD frequency, related direct and indirect costs, and increased QALYs compared to SC.

Keywords: value based-price, episodic migraine, chronic migraine, economic evaluation, productivity, indirect costs, CGRP, erenumab, cost-effectiveness analysis

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Conflicts of interest

RBL has received research grants from NIH, the Migraine Research Foundation and the National Headache foundation, has received consulting fees from the American Academy of Neurology, Alder, Allergan, American Headache Society, Amgen, Avanir, Biohaven, Biovision, Boston Scientific, Dr. Reddy's, Electrocore, Eli Lilly, eNeura Therapeutics, GlaxoSmithKline, Merck, Pernix, Pfizer, Supernus, Teva, Trigemina, Vector and Vedanta. RBL serves on the editorial board of Neurology, as an Associate Editor of Cephalalgia and as senior advisor to Headache. RBL receives royalties from Wolff's Headache, 8th Edition, Oxford Press University, 2009, Wiley and Informa, and holds stock in eNeura and Biohaven.

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SP has received consulting fees from Amgen.

AJH was an employee of BresMed Health Solutions when the study was conducted, who have received consulting fees from Amgen.

JKP is an employee of Amgen. SS, GV and NS are employees of Amgen and hold stock.

INTRODUCTION

Frequent migraine is a highly disabling neurovascular disease characterized by severe, typically unilateral headache, commonly accompanied by nausea, photophobia, phonophobia, and aura.[1] Migraine prevalence is 3 times higher in women than in men[2-7] and is most common between the prime productive working ages of 18 and 59, with the peak prevalence of migraines occurring at around 40 years of age.[8-10]

Migraine can be broadly classified as episodic (EM) or chronic migraine (CM) based on the number of migraine days (MD) and headache days (HD) per 28 days. EM is characterized by <15 HD per 28 days and accounts for more than 90% of migraine in the US population. In contrast, CM is defined by ≥15 HD per 28 days, including at least 8 days with migraine and accounts for approximately 5% – 8% of migraine.[11] Previous studies have indicated that about 90% of migraine patients are functionally impaired during an

attack, 53% are severely impaired and require bedrest, and subjects have reported being only about half as productive while working with migraine.[9, 12]

Acute medications are used to abort migraines pre/ during onset and manage pain during the migraine episode. Frequent use of acute migraine medication used to manage migraine attacks risks causing a disabling condition called medication overuse headache (MOH).[13-15] Suboptimal treatment and under-diagnosis may lead to patients seeking treatment in emergency or urgent care settings, and prescription opioids are administered in the majority of migraine-related emergency department (ED) visits (59% in 2011).[16] The number of migraine-related ED visits per year in the US has increased from 1.1 million in 1998 to 1.2 million in ED visits in 2010.[16]

Preventive therapies are recommended by US guidelines for people who experience four or more MD per 28 days, who are overusing acute medication, or who have headache-related disability.[17] The mainstay of migraine prevention has been re-purposed anti-epileptic drugs (topiramate and divalproex), antidepressants (amitriptyline), and beta-blockers (propranolol), but only 13% of eligible patients seek preventive therapy[18]. In addition to not being specifically designed to alter the underlying physiology of migraine, existing treatments are associated with significant side effects, and it is estimated that more than 80% of treated patients discontinue their preventive medication within 12 months of initiation.[19] OnabotulinumtoxinA was approved by the US Food and Drug Administration (FDA) in 2010 for preventative use, but is restricted to use in CM patients only. There is no recommended standard of care or published data in patients who try current prevention and fail either because of tolerability, lack of effectiveness, or both. There is therefore an unmet need in these migraine patients. This analysis deploys a US societal perspective, since migraine is atypical in that indirect costs (absenteeism/disability) and presenteeism (being less productive while at work) account for up to approximately 70% of total costs.[20] Each employee with frequent migraine costs employers thousands of dollars every year, with estimates between $2,400 and $7,000 for women and $4,000 and $13,000 for men.[21, 22] Developing novel

treatments for migraine prevention with better efficacy or tolerability profiles is a priority for improving migraine outcomes. One promising approach targets the calcitonin gene-related peptide (CGRP, a sensory neuropeptide implicated in migraine pathogenesis) pathway. Erenumab is the only fully human mAb in development targeting the CGRP pathway and the only fully human mAb in development that targets the CGRP receptor. Pivotal studies in EM and CM have completed, and the data package is under review by regulatory agencies at the time of this writing (Feb 2018). The efficacy of erenumab 140 mg was demonstrated versus placebo in pivotal studies in EM and CM.[23, 24] The primary efficacy endpoint in both pivotal studies was the change from baseline to the end of the double-blind treatment period in the mean number of MD per 28 days. In the EM study, linear mixed-effects regression models predicted a least squares mean (LSM) change from baseline versus placebo for the erenumab 140 mg group of -1.85 monthly migraine days (95% CI: -2.33, -1.37; $p < 0.001$) over the final 12 weeks of the double-blind period.[23] In the CM study, the LSM change from baseline for erenumab 140 mg versus placebo at week 12 was -2.45 monthly migraine days (95% CI: -3.51, -1.38; $p < 0.001$).[24] In pre-specified subgroup analysis in the clinical studies, erenumab demonstrated a numerically greater reduction in MD per 28 days compared to placebo in patients who had previously failed ≥1 prior preventive treatment, than was observed in the overall trial populations. Erenumab has therefore demonstrated efficacy in patients who have tried and failed preventive therapies, a population of patients with greater unmet medical need.[25]

The value of novel health technologies is typically assessed via cost-effectiveness modeling, comparing the ratio of incremental health outcomes to incremental costs, known as the incremental cost-effectiveness ratio (ICER). Erenumab is not approved for use, and pricing is not known at the time of this writing (Feb 2018), so a direct analysis of its cost-effectiveness is not possible. However, it is useful to consider what level of price is justifiable given the additional benefits of erenumab over current options and the potential to displace suboptimal therapies. To do this, one can estimate the value based-price (VBP) based on accepted value metrics.[26] The VBP is the maximum price at which the drug would still be

considered cost-effective versus a comparator, when using a defined willingness to pay (WTP) threshold for additional benefits. In the US, WTP thresholds per incremental quality adjusted life year (QALY) that have been commonly used to assess the cost-effectiveness of novel medical interventions are $100,000 - $200,000.

The objective of this study is to estimate VBP ranges for erenumab 140 mg, administered subcutaneously every 4 weeks, in migraine patients who have failed at least one prior preventive treatment, compared to SC, by evaluating the incremental costs and QALYs within a cost-effectiveness modeling framework.

METHODS

We built a Markov model, implemented in Microsoft Excel, based on the clinical data from the EM and CM pivotal studies for the subgroups of patients with prior treatment failures. The model comprises of on preventive treatment, off preventive treatment and death health states. In addition to the primary clinical outcome of MD frequency per 28 days, the model predicts the costs and health-related quality of life outcomes associated with erenumab as preventive treatment of migraine in patients with ≥1 prior failed treatment, compared to SC. EM and CM cohorts are modeled independently based on the clinical trial data, but outcomes are combined based on a split of the overall treated migraine population between EM and CM, based on available literature.[27] A comparison of erenumab to onabotulinumtoxinA in exclusively CM patients is presented as scenario analysis. Based on this output, ranges of the VBP of erenumab are estimated based on commonly used WTP thresholds.

The cycle length of the model is 28 days, consistent with the primary efficacy outcome (MD frequency per 28 days) and the frequency of administration of erenumab. Cost and QALY outcomes are discounted at an annual rate of 3%, in line with published US recommendations.[28] Clinical outcomes (number of MD, life years) are not discounted. The analysis is performed from a US societal perspective, including the direct

medical costs of treating migraine and the indirect costs of missed work days and lost workplace productivity. This reflects the working age of the migraine population.[23, 24] The model evaluates cost outcomes in 2017 US dollars.

Time Horizon

The time horizon in these analyses spans 10 years. Migraine prevalence peaks during the ages of 18-59 with the peak prevalence around 40 years of age. The erenumab studies were reflective of these demographics with mean age at baseline for the pivotal studies ranging from 40 – 43 years. The prevalence of migraine after age 60 falls to about 5% and is less than <1% in CM.[29] Published guidance on the design of economic evaluations also state that the time horizon of analyses should be long enough to capture all relevant differences between treatment strategies compared.[28] The model assumes that the clinical and economic outcomes of erenumab patients are equal to those in the SC arm after they have discontinued treatment. This means that there are no further differences between arms once all patients have discontinued, so incremental outcomes are limited to the duration of erenumab treatment. Based on the disease epidemiology and the erenumab time on treatment predicted by the model (full details provided in supplementary material section A), a 10-year time horizon is sufficiently long to capture the lifetime impact of the decision problem. As over 99% of patients discontinue erenumab by the end of the simulation, further extrapolation of the clinical trial data is not required.

Patient population

Erenumab studies enrolled subjects that were either naïve to preventive treatment or previously treated with preventive medication but failed due to lack of efficacy or intolerability. However, it is anticipated that erenumab and other CGRP and monoclonal antibodies will be restricted for use to patients who have failed prior preventive therapies. Therefore, the migraine populations considered in the model are the subgroups of patients who have previously failed ≥1 prior preventive therapy. In addition, chronic patients

are more likely to seek treatment and therefore in the base case analysis, the migraine population is modelled as 33% EM and 67% CM.[27] A scenario analysis is presented in which the migraine types are evenly split (50% EM, 50% CM).

Intervention and comparators

The intervention evaluated in the model is erenumab 140 mg, self-administered every 28 days by subcutaneous injection.

There is currently no defined standard of care for patients with 4 or more migraines per month who have tried and failed topiramate or propranolol, due to a dearth of demonstrated clinical efficacy and real-world effectiveness in these subgroups. There are no clinical trials or observational cohort data that are available or published with propranolol or topiramate in patients who have tried and failed these treatments. As such, neither topiramate nor propranolol are appropriate comparators in preventive treatment experienced patients with 4 or more migraine days per month. Patients that can gain disease control from currently available preventive treatments and who can persist on them, provide maximum value to both the patients and the healthcare system. Multiple clinical and insurer sources suggest that in clinical practice, erenumab will be used after failure of topiramate or propranolol or a similar beta blocker or antihypertensive, addressing the high unmet need of migraine patients who have experienced a lack of efficacy or tolerability from prior preventives.

In clinical practice, most of these patients are typically managed with acute treatments only. As such, the comparator against which erenumab is assessed in patients who have previously received preventive therapy is supportive care (SC), in which patients receive only acute treatment for migraine. OnabotulinumtoxinA is the only migraine preventive exclusively indicated for CM patients and is commonly used after the failure of prior preventive treatments. To reflect this, a scenario analysis is presented in which erenumab is compared to onabotulinumtoxinA in an entirely CM population.[17]

Clinical trials in migraine prevention have typically observed strong placebo effects,[30] but the administration of placebos, such as sham injections, does not represent a plausible treatment option in clinical practice. Therefore, we do not consider placebo a relevant comparator in the model. There is an absence of reliable real-world data on the natural history of migraine. In our modelling we examine two scenarios. In the base case, the placebo effect attributable to enrollment into the clinical studies and the administration of sham injections are excluded. It is assumed that patients in the SC cohort of the model remain at the MD frequency observed during the 4-week pre-randomization period in the clinical studies, prior to the start of the double-blind phase. This assumption is tested in a scenario where placebo effect is included.

Model structure

The model is comprised of two primary health states: "on preventive therapy" and "off preventive therapy" (Figure 1). Patients are at risk of death in each cycle, based on US general population mortality rates.[31] The risks of death are assumed to be unaffected by MD frequency or treatment, and life expectancy is identical in both arms of the model.

In each cycle, patients on treatment are at risk of discontinuation (A), after which they withdraw from treatment and lose the associated treatment effect. In the absence of real world discontinuation data for erenumab, baseline persistence rates were taken from US claims data, using onabotulinumtoxinA as the closest analog to a novel preventive. An exponential function was fitted to the proportion of patients remaining on onabotulinumtoxinA treatment over a follow up period of 52 weeks.[32] A discontinuation rate ratio of erenumab compared to onabotulinumtoxinA was derived from a network meta-analysis of all-cause discontinuation data reported in 9 clinical studies of preventives in CM. The predicted time on treatment curve for erenumab was used to drive transitions between the "on preventive treatment" and

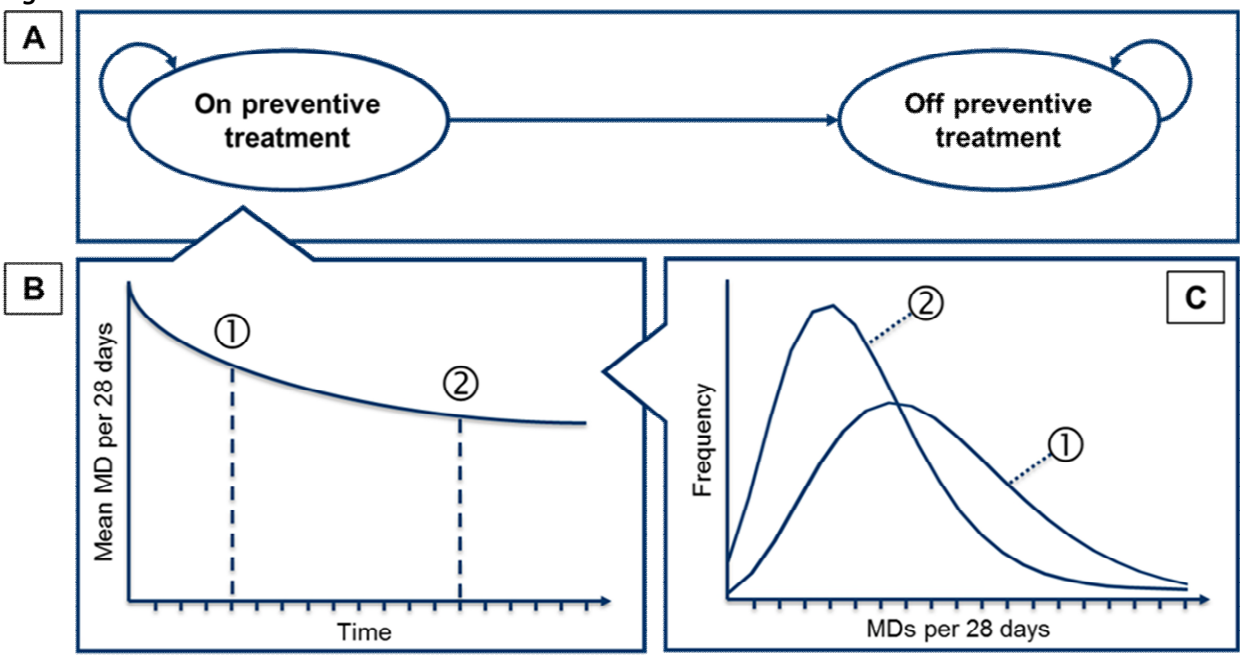
237 “off preventive treatment” health states in each cycle. The approach is described in greater detail in the
238 supplementary material. Discontinued patients are assumed to remain untreated for the remainder of
239 the simulation. Transitions between all three model health states were half-cycle corrected.

240 In each 28-day cycle, the mean MD frequency is modeled for patients in the living health states (only “on
241 treatment” shown in ***Figure 1***) (B). Patients are distributed based on the mean MD frequency, across the
242 range of possible MD counts (between 0 and 28 MDs in each cycle), using previously validated parametric
243 models (C).[33, 34] As shown in hypothetical time points ① and ②, the shape of the distribution of individual
244 patients by MD frequency changes to account for both the mean MD frequency and the asymmetric
245 spread of individual patients.

246 The parametric models used in the calculation steps in components B and C are described in greater detail
247 in the supplementary material.

248

Figure 1: Model schematic



MD, migraine days. Patients can transition to an absorbing death state due to all-cause mortality at any point. **A:** Time- and treatment-dependent discontinuation rates determine time on preventive therapy, during which patients experience the MD frequency reduction attributed to treatment. **B:** The cohort of patients achieves the reduction in mean monthly MD frequency from baseline, based on clinical trial endpoints. **C:** Parametric distributions represent the variation of patients around the mean MD frequency, and allow outcomes linked to the number of MDs to be estimated.
Hypothetical time points ① and ② indicate how the distribution of patients is estimated based on the mean MD frequency of the cohort at different time points.

Costs

Drug and administration costs

Preventive therapy and acute migraine medication costs are accounted for in the model (Table 1). Erenumab is currently undergoing regulatory review by the FDA and, as such, is not yet available for purchase. In the absence of a list price, value-based price ranges are evaluated based on the model. For the scenario analysis, onabotulinumtoxinA is estimated to cost $5,035 in drug acquisition costs, and $649 in administration costs per year (CMS Physician Fee Schedule CPT 99212).

Medical resource use costs

Medical resource use in the model consists of physician office visits, emergency room visits, hospitalizations, and specialist consultations based on published unit costs (Table 1). Average annual medical resource use is taken from a published 2009 analysis of survey data from 7,437 migraine patients in the US.[35] The mean patient-reported medical resource use over 12 months was divided by the reported annual number of HD to estimate the medical resource cost per MD in the model.[35] The resource use per MD and the unit costs are combined in the model to estimate the weighted average costs of medical resource use for each cohort of patients.

Table 1: Preventive therapy costs, migraine resource use costs and acute medication costs

Medical resource	**Unit cost (2017 USD)**	**Average use per year***	**Use per migraine day†**
Physician visits (CPT99212)	$44.14 [36]	0.720	0.0379
Emergency room visits	$939.59 [32]	0.167	0.0088
Hospitalization (DRG 102 and 103)	$4,298.35 [37]	0.075	0.0039
Specialist consultations (CPT 99215)	$146.43 [36]	0.221	0.0116
Acute medication‡		**Cost per day of use - EM (2017 USD)**	**Cost per day of use - CM (2017 USD)**
Non-migraine-specific		0.99	1.76
Migraine-specific		4.94	3.99
Preventive therapy	**Cost per year (2017 USD)**	**Frequency of occurrence or dosing**	**Annual cost**
OnabotulinumtoxinA	$1,158.00[38]	12-weekly	$5,035

*Annual use reported in Munakata 2009, migraine patient cohort.

278 †Patients reported an average of 19 headache days over the previous 12 months.

279 ‡Estimation of costs per day of use based on published breakdown of medication types by frequency of use
280 and 2017 unit costs.

281

282 *Acute migraine day medication costs*

283 The distribution of the drug classes by usage and the dosages used to treat acute migraine were obtained
284 from three studies in the literature.[39-41] Using acute medication use data collected in the erenumab clinical
285 studies, the model differentiates between migraine-specific acute medication (comprised of triptans and
286 ergot derivatives), and non-migraine-specific acute medication (comprised of acetaminophen, non-
287 steroidal anti-inflammatory drugs [NSAIDs], barbiturates, opioids, isometheptene compounds and other
288 over-the-counter medications).[39] Weighted average costs per day of use are shown in Table 1, and the
289 numbers of days of acute medication use by MD frequency are presented in supplementary data.

290

291 *Indirect costs of lost work productivity*

292 The substantial impact on a patient's ability to function and associated lost productivity accounts for the
293 greatest proportion of total costs attributed to migraine.[35, 42] The productivity cost of migraine is split into
294 two types. Absenteeism days are days in which patients are unable to attend work or school due to their
295 migraine. Presenteeism days are days in which patient productivity at work or school is reduced by at least
296 50% (but less than 100%). The number of days of productivity losses in the model are based on erenumab
297 clinical trial data, and reflect the sex, age and employment status of the clinical trial populations. The
298 average costs of absenteeism and presenteeism days are calculated assuming the median hourly wage
299 obtained from the US Bureau of Labor Statistics,[43] assuming a 8-hour working day. As the degree of
300 productivity loss on each presenteeism day (i.e. days where productivity is reduced by at least 50%) is not

known,[44] the model assumes lost productivity of 50%. The costs per absenteeism and presenteeism day used in the model are presented in Table 2, and a scenario excluding productivity costs is presented in Supplementary Materials.

Table 2: Estimated indirect costs per absenteeism and presenteeism day

Parameter	Value	Source
Median hourly wage	$26.00	Bureau of Labor Statistics, Private sector December 2016
Number of working hours per day	8	Assumption
Proportion of productivity loss on presenteeism days	50%	Assumption
Estimated cost per absenteeism day	$208.00	Calculated
Estimated cost per presenteeism day	$104.00	Calculated

The number of absenteeism and presenteeism days are estimated based on patient responses to the Migraine Disability Assessment (MIDAS) questionnaire collected in the erenumab EM and CM pivotal studies.[24, 45] Question 1 of the MIDAS questionnaire refers to absenteeism, and question 2 refers to presenteeism.[44] Patient responses from both the EM and CM studies were combined to generate one complete migraine dataset, in which the relationship between MD frequency and productivity was analyzed. Zero-inflated Poisson regression models were fitted and used to predict the average number of absenteeism and presenteeism days for each possible MD frequency (0-28 MD per 28 days). As an example, a person experiencing 15 MD days in a 28-day period is estimated to have 3.94 presenteeism days and 1.40 days absence, at a total lost productivity cost of $702. The predicted values by MD frequency used to estimate absenteeism and presenteeism costs in the model are presented in supplementary materials (section B).

Health-related quality of life

Utility values in the model were estimated as a function of MD frequency per 28 days. Patient responses to the Migraine Specific Questionnaire (MSQ) version 2.1, collected in the pivotal EM and CM clinical studies, were mapped to the EuroQoL 5-dimension instrument (EQ-5D) using previously published algorithms for EM and CM.[46] Gillard et al (2012) report algorithms for mapping between the MSQ and EQ-5D generated based on datasets of 5,770 and 338 participants from 10 countries in the International Burden of Migraine Study (IBMS) survey in EM and CM, respectively. MSQ responses from the erenumab EM and CM pivotal studies were pooled and the relevant EM or CM mapping algorithm applied. A longitudinal beta regression model was fitted, with mapped EQ-5D as the response variable, controlling for MD frequency and key patient characteristics. The regressions were used to generate predicted EQ-5D values for each frequency of MD per 28 days, which are used in the model to estimate the mean utility of the patient cohort, weighted by the distribution of patients by MD frequency in each cycle. As treatment status (erenumab 140 mg compared to placebo) was significantly predictive of utility, with higher utility values predicted for erenumab, the predicted values applied in the model are separated for actively-treated (erenumab, onabotulinumtoxinA) and untreated patients (SC, post-discontinuation). This approach is consistent to the assumptions made in the previous economic model for onabotulinumtoxinA,[42] which also assumed an additional treatment effect on utility of active treatment compared to SC. As an example, a person with 15 MD days in a 28-day period would have an estimated utility value of 0.589 on erenumab 140 mg and 0.571 whilst untreated. The values applied in the model are presented in the Supplementary materials.

Results

In the base case analysis, patients receiving SC were estimated to experience an average of 1,949 MD over 10 years (Table 3). By comparison, erenumab-treated patients were estimated to experience 1,805 MD, meaning a reduction of 144 MD. Because of discontinuation, this reduction is based on a mean duration of erenumab treatment of approximately 2 years. As a result of the MD frequency reductions, erenumab was associated with increased total discounted QALYs per person of 0.1849 over the 10 year horizon.

The discounted cost associated with the burden of migraine in patients on SC was estimated to be $129,889 over 10 years. By reducing the number of MD, erenumab was expected to reduce the total MD-related cost by $8,482. This does not include the incremental acquisition costs of erenumab. Disaggregated incremental MD-related costs, showing the contribution of the different cost types, are presented in Table 4.

Based on the clinical effectiveness of erenumab predicted by the model, VBP ranges were estimated. These prices represent the maximum annual treatment costs at which erenumab would be considered cost-effective at willingness to pay (WTP) thresholds ranging from $100,000 - $200,000 per incremental QALY. The estimated VBP of erenumab ranged from $14,238 to $23,998 per year.

The sensitivity of the base case analysis to model input parameter values was assessed in a deterministic sensitivity analysis based on the estimated VBP. The results of this analysis are presented in supplementary material section C.

359 ***Table 3: Base case model results per person by comparison and treatment arm, over 10 years****

Comparison	Erenumab	SC	Incremental
Mean duration of treatment (years)	2.01	N/a	N/a
Mean migraine days	1,805	1,949	-144
Mean discounted QALYs	5.1437	4.9588	0.1849
Mean discounted MD-related costs**	$121,407	$129,889	-$8,482
Societal Value based price***	$14,238 - $23,998	-	-

360 * Migraine population in the base case model is made up of 33% EM and 67% CM patients[27]

361 **Cost estimates do not include the costs of providing preventive medication, as a price of erenumab is not
362 available

363 ***Maximum acceptable price at a willingness to pay threshold of $100,000 – $200,000 per QALY

364

365 ***Table 4: Disaggregated incremental costs by comparison and treatment arm***

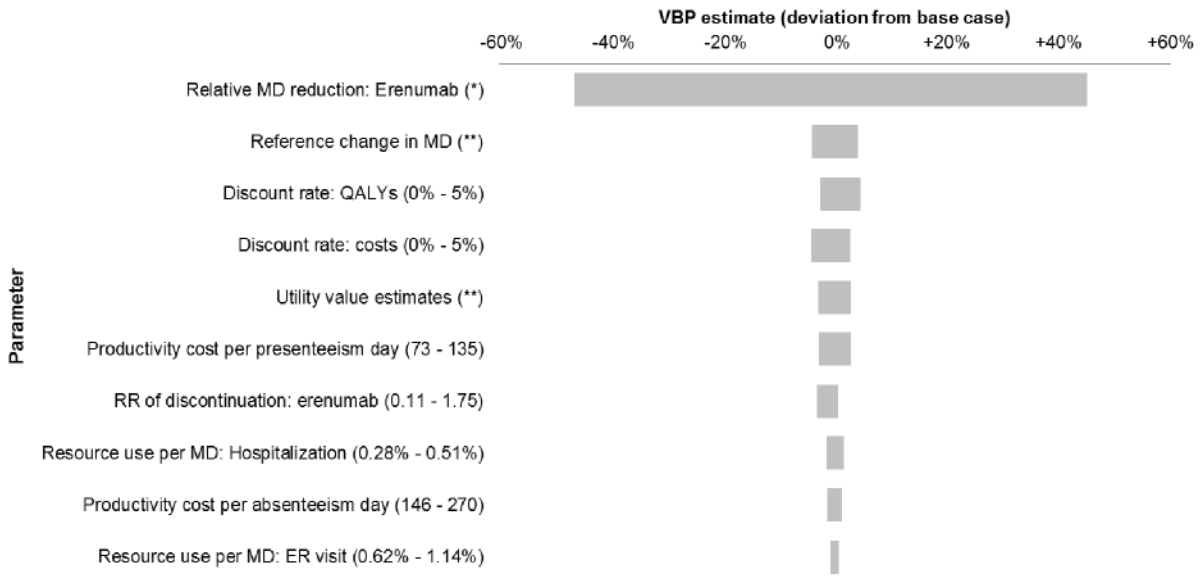
Cost category	Erenumab	SC	Incremental
Physician visits	$2,443	$2,631	-$188
Emergency room visits	$12,061	$12,988	-$927
Hospitalizations	$24,779	$26,684	-$1,904
Specialist consultations	$2,487	$2,679	-$191
Migraine-specific acute medication	$2,599	$2,820	-$221
Non-migraine-specific acute medication	$673	$708	-$36
Absenteeism	$31,339	$32,997	-$1,658
Presenteeism	$45,025	$48,382	-$3,357
Total	**$121,407**	**$129,889**	**-$8,482**

366

367 **Deterministic sensitivity analysis**

To explore the sensitivity of VBP estimates to key input parameter values, deterministic sensitivity analysis (DSA) was performed, in which upper and lower bounds of individual model parameters were tested to identify model drivers in each of the comparisons assessed. The results of this analysis were quantified as the percentage deviation from the base case VBP estimate, calculated based on a WTP threshold of $150,000 per incremental QALY. The estimate of the VBP was driven mostly by the relative reduction in MD of erenumab, reflecting uncertainty in the NMA outcomes parameterizing this. There was smaller influence of MD-related outcomes, primarily utility estimates, productivity costs and hospitalization frequency. The maximum variation in the VBP was within +/- 50% of the base case estimate (Figure 2).

Figure 2: DSA results



* Relative MD reduction for erenumab based on NMA endpoints, combined uncertainty for EM and CM data

**Utility and reference change in MD frequency are vectors of parameters based on regression models

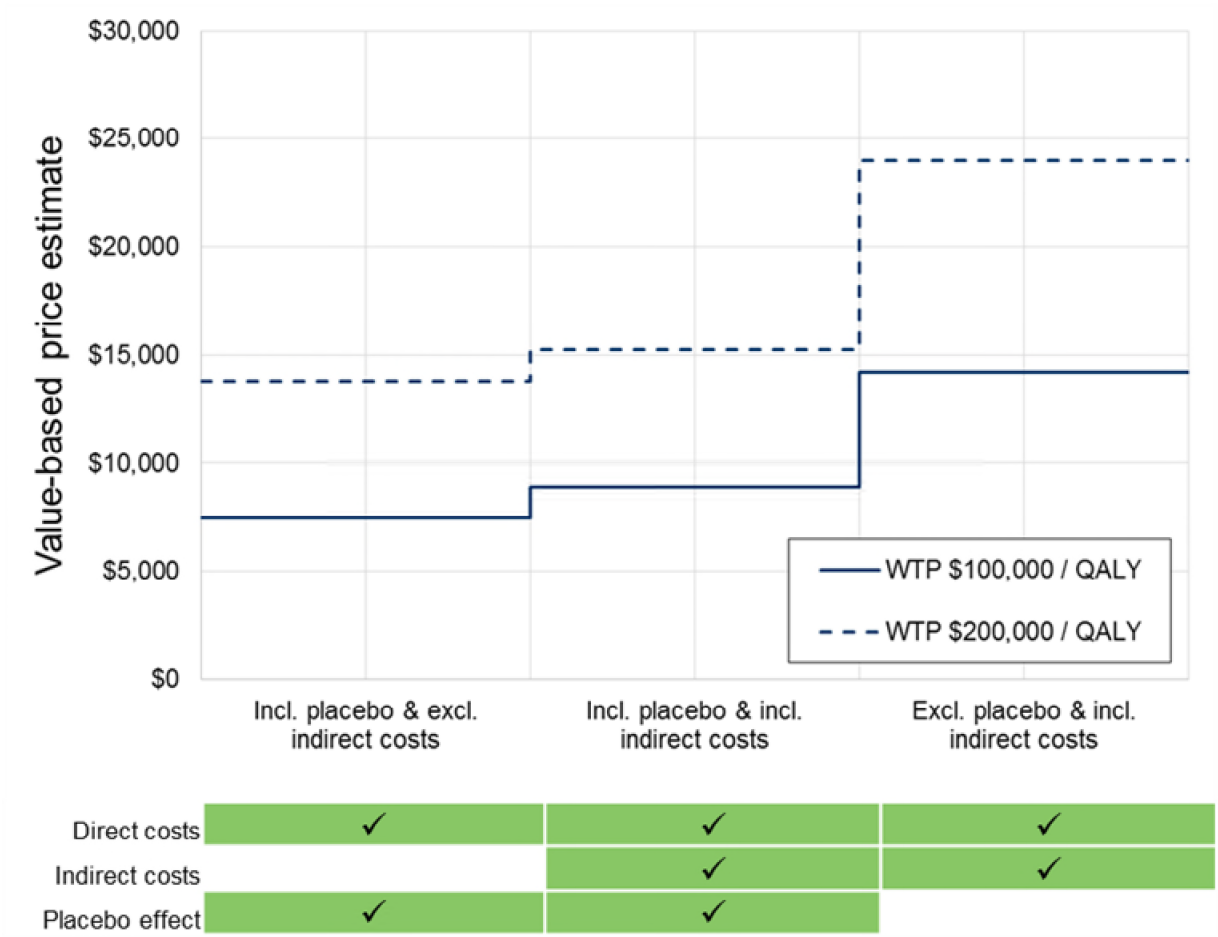
Scenario analyses

In the scenario analysis performed including the reductions in MD frequency observed in the placebo arms of the clinical studies (i.e. taking a more pessimistic estimate of the relative reductions of erenumab, full

scenario presented in supplementary material section D), the VBP ranged from $8,886 to $15,250. In the scenario in which the placebo effect is included and indirect costs are excluded, the VBP estimates ranged from $7,445 to $13,809. In the scenario in which the previously treated migraine population is assumed to be 50% EM and 50% EM, the VBP estimates ranged from $13,331 to $22,553. Finally, in the scenario in which erenumab is compared to onabotulinumtoxinA in exclusively CM patients, the VBP estimates ranged from $12,151 to $18,589.

The ranges of VBP estimated in the base case and scenarios are presented graphically in Figure 3, along with the assumptions defining each scenario.

Figure 3 Summary of VBP estimates, assuming a 33% EM, 67% CM split



WTP, willingness to pay

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Discussion

To achieve efficient allocation of healthcare resources under budget constraints, cost-effectiveness analysis is increasingly used by healthcare decision makers to prioritize societal preferences for changes in health status across competing healthcare interventions.[28] The MD frequency reductions and QALY improvements with erenumab presented here demonstrate the value of this novel migraine therapy compared to current practices in migraine patients who have failed prior preventive therapy. In people with frequent migraine, there are no published data supporting preventive treatment for patients that have failed at least one prior preventive therapy, therefore this represents an important QALY gain of approximately 0.184.

At the time of launching a new therapy, there is a necessity to satisfy not only safety and efficacy requirements, but increasingly the need to highlight economic value in relation to costs to satisfy paying organizations. Accomplishing this is challenging, considering the full economic value of a new intervention cannot be fully established before launch, due to the absence of real-word data. Attempts to estimate economic value of new interventions using only the regulatory data package (i.e. FDA filing) is limited by this data availability. The analysis described here highlights the challenges of demonstrating economic value for a new product when no price has been established and real-world evidence is not available. To circumvent the challenges of conducting an economic value demonstration on a pre-launch preventive migraine therapy, we have conducted an analysis which seeks to evaluate the annual cost of treatment that reflects the estimated clinical and economic value of erenumab, using acceptable value standards (i.e. WTP thresholds). From a US societal perspective, these are the maximum estimated 'prices' below which erenumab would be cost-effective at a WTP of $100,000 - $200,000 given the framework of a cost-effective analyses for patients who have failed at least one prior treatment and against appropriate comparators.

The modeling approach applied in this study is different to that used in previous economic evaluations in migraine prevention,[42, 47, 48] which have adopted decision tree approaches or Markov models based on health states based on defined ranges of MD or HD frequency. Modeling MD frequency as a continuous outcome better captures the outcomes of patients, by accounting for variability in MD frequency without relying on compartmentalizing patients based on response status or arbitrary categories of monthly MD frequency, which have been shown to introduce bias into MD estimates.[49] The approach allows cost and quality of life outcomes to be linked to individual migraine frequency, rather than average outcomes for compartmentalized health states. In this way, the model therefore spans the range of migraine frequency, across EM and CM and is consistent with patient presentation in clinical practice. This also permits the same model structure to accommodate combined assessments of EM and CM and for estimating the impact of each individual MD event.

Scenarios presented in this paper excluding indirect costs, such as those associated with absenteeism and presenteeism, lower the VBP range compared to the base case analyses. Consistent with US guidelines on economic evaluation,[28] the analysis here includes missed work days and lost productivity. In migraine, these costs represent a significant proportion of the economic burden of migraine, and are often paid by employers due to reduced productivity of people with migraines. We recognize that healthcare payers may not always consider these costs in assessing the value of novel preventives, despite their importance to patients and employers and hence VBP were also generated based on this scenario. Even when the monetary value of QALY gains are ignored, migraine day related costs off-sets with erenumab (ignoring erenumab drug costs) are still approximately $8,500 over the mean treatment duration of 2.01 years. These VBP estimates represent one of several factors considered in pricing decisions, and other factors, such as affordability. Cost-effectiveness models by definition do not factor in affordability and typically do not address other considerations important to payers, such as the size of the treated patient population and unmet need.

The results presented here should be interpreted within the context of the study limitations. This analysis is based on erenumab treatment practices defined by treatment protocols used in the pivotal randomized controlled trials in the pre-launch phase of drug development. However, in clinical practice, physicians and patients may adjust treatment practices to optimize outcomes, and in some cases, introduce strategies for when to discontinue therapy. It is likely that when erenumab enters treatment practice, and prior to the establishment of clinical guidelines, clinicians will adjust erenumab use to meet patient treatment goals. This may include treatment discontinuation in cases of non- or partial- clinical response. The discontinuation of patients experiencing smaller reductions in MD frequency will likely improve estimates of the clinical effectiveness and VBP ranges presented here. In a cohort of treated subjects, as non-responders or low-responders discontinue, the average MD frequency reduction of the patients remaining on treatment will increase, the total number of erenumab-treated patients will reduce, and thus cost-effectiveness will be more favorable.

The model is also limited by the consideration of MD frequency as the only metric of disease status, and other dimensions of migraine, such as duration and severity, are not explicitly considered beyond their contribution to the definition of a MD. Any residual impact during non-MD such as interictal burden, prodromal symptoms, anxiety, and depression is not captured in our analysis[50]. Improvement in the other dimensions may be indirectly captured by the application of utility values stratified by treatment (i.e. separate values for patient on erenumab/onabotulinumtoxinA versus SC), but these are not isolated as separate treatment effects. The model is also subject to limitations in available data. In particular, there is no evidence of time to discontinuation for patients treated with erenumab in clinical practice, and the comparative discontinuation rates applied in the model are derived from available clinical trial data. Furthermore, the use of cost data from Munakata 2009 is likely to result in an underestimation of medical resource use costs.[35] Firstly, the source data reported resource use across the US migraine population, and the resource use among patients who have failed a previous preventive therapy is likely to be greater.

Secondly, the study reported only headache days, only a proportion of which will be migraine days (MD), so the resource use per MD will also be an underestimation.

The model is also limited by several simplifying assumptions, most notably the assumption that patients remain untreated after discontinuation. Whilst this may not be reflective of clinical practice, the lack of long-term, sequential treatment data prevents other scenarios from being explored. Finally, it is not certain that the MD frequency of patients treated only with acute medication would be constant over time. Whilst the inclusion of the placebo reduction is essential in assessing the treatment effect of erenumab in a clinical trial context, its relevance to economic evaluation as a potential comparator is limited. It is also possible that patients whose migraines are not controlled with preventive therapy, and instead rely only on acute medication, may experience increased MD frequency over time, due to pain medication overuse.[14]

Conclusion

The VBP ranges presented in this manuscript suggest that erenumab would most likely be considered cost effective within the represented scenarios and under robust, widely accepted approaches. However, cost-effectiveness is just one criterion against which value can be assessed and affordability and other factors also impact final price. The novel mechanism of action of erenumab represents the first targeted migraine preventive therapy especially in patients who cannot derive a benefit with current prevention. In this study, erenumab showed consistent and meaningful improvements in MD frequency and QALY compared to SC for patients who have failed at least one prior generic preventive therapy. The results presented provide the range of prices at which erenumab would be considered a valuable addition as migraine prevention in people with migraine, based on established WTP thresholds in the US. The value demonstration framework based on willingness to pay for health gains offers a meaningful approach

to understand product value in relation to potential prices. Our analysis also highlights potential cost savings that can be achieved for people with migraine attributed to acute MD treatment costs, physician costs and improved productivity output, suggesting benefits for both health services and broader societal impact. In the post-launch period, the economic results described here can be enriched to more accurately define clinical and economic value.

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Author Contributions

RBL: Conception and design of Study; Analysis and interpretation of data, drafting and final editing manuscript

AB: Conception and design of Study; Analysis and interpretation of data, drafting and final editing manuscript

SP: Conception and design of Study; Analysis and interpretation of data, drafting and final editing manuscript

AJH: Conception and design of Study; Analysis and interpretation of data, drafting and final editing manuscript

JKP: Conception and design of Study; Patient data collection/Data acquisition; Analysis and interpretation of data, drafting and final editing manuscript

SS: Conception and design of Study; Patient data collection/Data acquisition; Analysis and interpretation of data, drafting and final editing manuscript

GV: Conception and design of Study; Patient data collection/Data acquisition; Analysis and interpretation of data, drafting and final editing manuscript

NS: Conception and design of Study; Patient data collection/Data acquisition; Analysis and interpretation of data, drafting and final editing manuscript

ST: Conception and design of Study; Analysis and interpretation of data, drafting and final editing manuscript

DD: Conception and design of Study; Analysis and interpretation of data, drafting and final editing manuscript

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Supplementary materials

A) Modeling approaches

Migraine day frequency analysis

The primary endpoints of the clinical studies were the reduction in the mean MD frequency from baseline. However, change in mean MD frequency across a cohort of patients does not capture all clinically meaningful impacts of migraine preventive therapy.

Modeling the distribution of patients by MD frequency allows the application of outcomes stratified by the number of MD in each cycle, with outcomes estimated as a function of MD observed. In doing this, the model can account for non-linear relationships between MD frequency and associated cost and quality of life outcomes, for example patient utility, where the marginal disutility of each incremental MD increases towards the upper end of the frequency range.

The parametric approach adopted in the model estimates both the change in mean MD frequency over time and the distribution of the MD counts of individual patients over each 28-day cycle. Discrete probability distributions are assumed, in which a MD is considered a “success” and a non-MD is considered a “failure”, supporting the range of possible numbers of MDs observable within each cycle: a minimum of 0 and a maximum of 28. The distributions of patients in each cycle are used to estimate the weighted average cost and quality of life outcomes of the cohort, based on the proportions experiencing each number of MD, and the respective outcomes for each frequency.

The MD frequencies of patients in each health state are estimated via four steps. Firstly, the baseline MD frequency of the cohort is derived from the pre-treatment baseline phase of the clinical studies. Secondly, a reference change in MD is determined by the reductions in frequency observed in the placebo arms of the erenumab clinical studies. Thirdly, the treatment effects of active preventive medication (erenumab

and onabotulinumtoxinA), relative to the placebo reductions, are then applied to estimate the mean MD frequencies in each model cycle. Finally, the distribution of patients by MD frequency is then estimated using the distribution parameters derived from the patient-level data.

Estimation of placebo change in migraine day frequency

The changes in MD frequency for placebo (to which the treatment effects of active preventives are applied) are based on a longitudinal analysis of MD count data from patients in the placebo arms of the EM and CM clinical studies (20120296 and 20120295) who had failed at least one prior preventive therapy at baseline.[24, 45] Longitudinal non-linear, hierarchical regression models were fitted to patient-level MD frequency data from these patients over the studies' double-blind treatment phases. The response variable (the number of MD reported in each 28-day observation period) was assumed to follow negative binomial or beta-binomial distributions. These distributions have previously been shown to accurately approximate the distributions of MD count data from the erenumab clinical studies.[33, 34] In addition to the mean MD counts over 28 days (28 Bernoulli trials), the negative binomial and beta binomial distributions are characterized by additional parameters which account for the spread of individuals by MD frequency (the dispersion parameter and intra-class correlation coefficient, respectively). The longitudinal regressions provide estimates of these parameters, which are assumed constant across the patient population, irrespective of treatment and time. The fits of the negative binomial and beta binomial regression models were compared, and the negative binomial models are adopted in the base case analyses.

In the EM comparison to SC, patients are assumed to receive no reduction from their baseline frequency at the start of the clinical studies, and their MD frequency is assumed constant at their pre-randomization baseline observation. In the scenario analyses including the placebo effect, the placebo change from

689 baseline in MD frequency from the clinical study is assumed to represent the natural history of migraine
690 over the course of the model.

691

692 **Application of relative treatment effects**

693 The reductions in MD frequency associated with erenumab and onabotulinumtoxinA are derived from the
694 results of a network meta-analysis (NMA) of RCT data for migraine preventives.[32] The relative effects are
695 applied to the regression models which were fitted to the placebo arms of the erenumab clinical studies,
696 to generate comparable estimates of MD frequency, based on the indirect comparison performed as part
697 of the NMA.

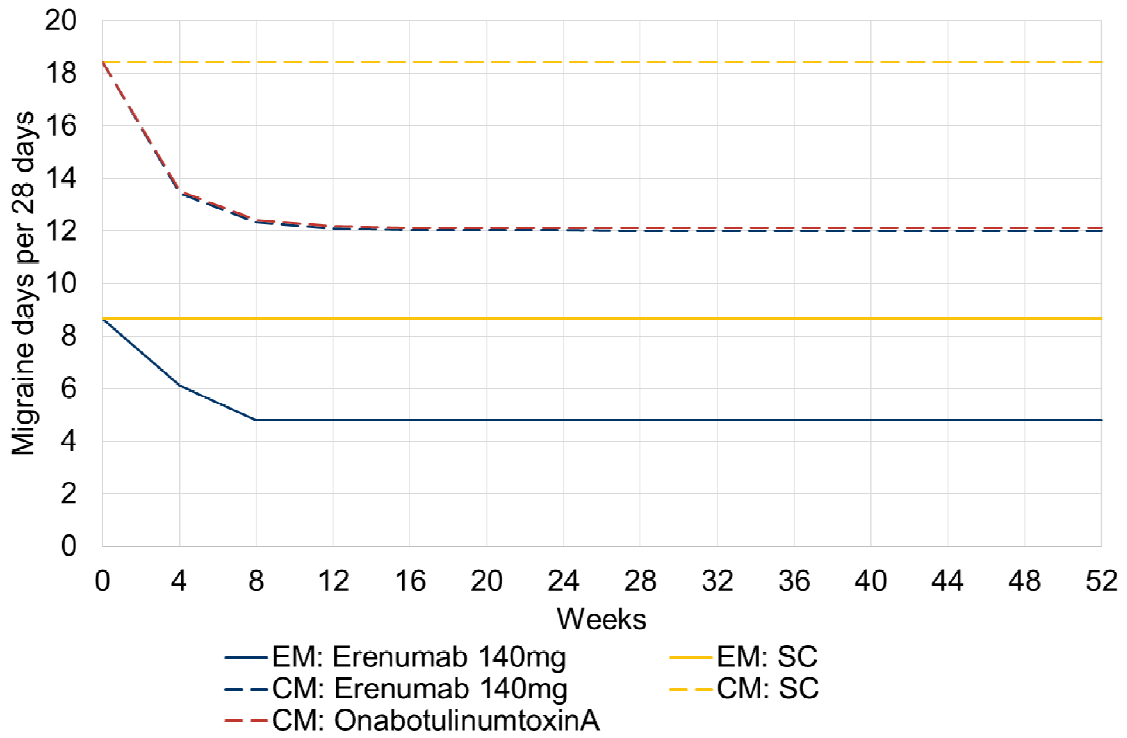
698 The NMA assessed absolute differences in MD frequency reductions from baseline in 15 EM clinical studies
699 and 22 CM studies. The results of the NMA are used to derive the additional reductions in MD per 28 days
700 for erenumab and onabotulinumtoxinA in EM and CM, relative to the reductions in the combined placebo
701 arms. In EM, erenumab 140mg was estimated to reduce MD per 28 days by 1.9 (95% CrI: 0.8 – 3.0)
702 compared to placebo. In CM, the estimated reductions versus placebo were 2.3 (95% CrI: -1.0 – 5.6) and
703 2.2 (95% CrI: 0.6 - 4.3) for erenumab and onabotulinumtoxinA, respectively.

704 Although there was some variation in the duration of the double-blind phases of the studies (EM: 12-26
705 weeks, CM: 12-24 weeks), the estimates of relative reductions in MD frequency are applied at the end of
706 the erenumab studies (EM: 24 weeks, CM: 12 weeks). When applying the relative effects in the model,
707 the additional reduction of active prevention is applied gradually over time, proportional to the reduction
708 estimated in the placebo longitudinal regression models, such that at the start of the model the treatment
709 effect is 0%, and at the time point equal to the end of the relevant double-blind phase (EM: 24 weeks,
710 CM: 12 weeks) the treatment effect is 100% (i.e. the full relative reduction is applied).

As the NMA assessed MD frequency reductions in published clinical studies, the results reflect the mix of treatment naïve and treatment experienced patients enrolled in each, and not the prior failure subgroup that is the subject of this evaluation. To account for this in the model, the absolute changes from baseline for erenumab and onabotulinumtoxinA in patients who have failed prior therapy are assumed to be equal to those observed in the full clinical study group. This assumption is supported by the fact that the absolute changes from baseline for erenumab in the pivotal EM and CM studies were consistent across patient subgroups based on the number of failed prior preventive treatments.[25]

Finally, the mean MD frequencies predicted by the longitudinal regression models are extrapolated up to a maximum of 2 years. The extrapolations are performed assuming a logistic function, the best fitting of four parametric functions tested for goodness of fit (exponential, logistic, log-logistic and Gompertz). Although the reductions for all comparators were extrapolated up to 2 years, MD frequency plateaued quickly and was constant from around 6 months.

Figure 4: Modeled migraine day frequency per 28 days over first year of the model, EM and CM patient subgroups with ≥1 prior treatment failure at baseline



EM, episodic migraine; CM, chronic migraine;

Discontinuation

OnabotulinumtoxinA discontinuation rates applied in the model are derived from real world persistence data from 2017 US prescription claims data.[38] An exponential distribution was fitted to the proportion of patients remaining persistent on onabotulinumtoxinA over 1 year, and this was used to derive the transition probabilities of onabotulinumtoxinA patients between the "on preventive therapy" and "off preventive therapy" health states.

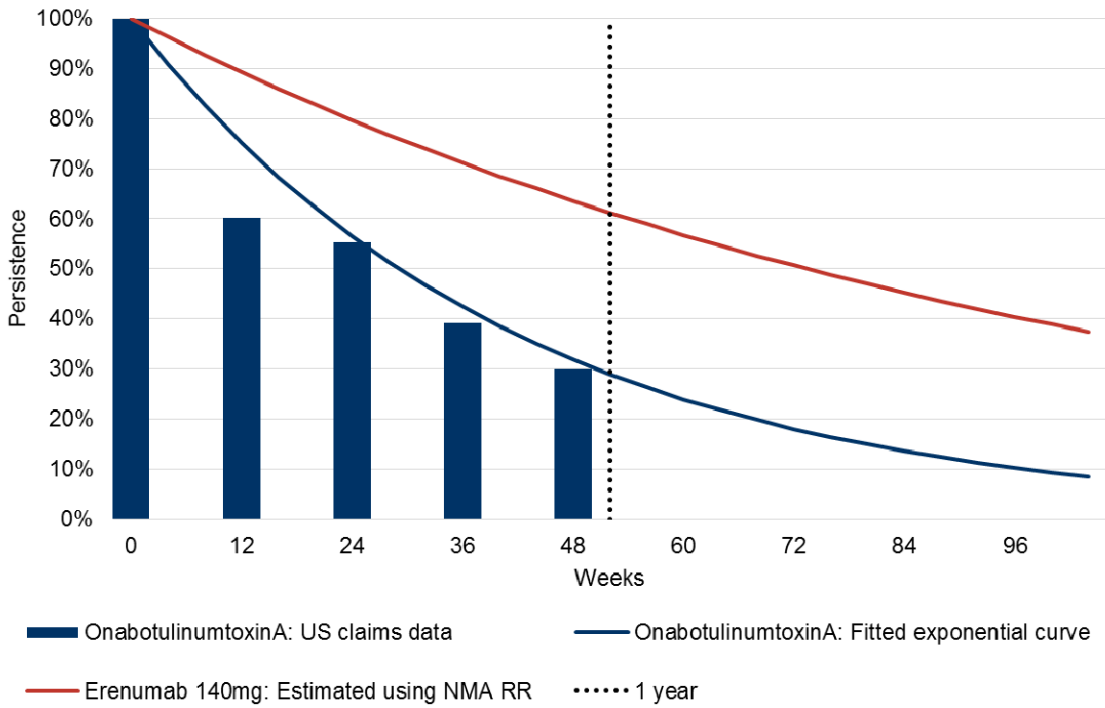
No data is currently available on real-world persistency with erenumab. However, data were available from an NMA of migraine clinical trial data on the comparative rates of all-cause discontinuation. To account for differences in the duration of included studies, discontinuation was converted to a rate of discontinuation per 4 weeks, assuming a constant rate over the reported trial duration. The NMA included

data from 22 EM studies and 9 CM studies, and reported a median rate ratio (RR) of discontinuation every 4 weeks for erenumab compared to onabotulinumtoxinA of 0.40 (95% CI: 0.11 – 1.75). This RR was applied to the exponential discontinuation curve fit to the onabotulinumtoxinA data to estimate the expected real-world persistence of patients treated with erenumab (Figure 5).

In the base case analysis, patients in the SC arm are not receiving preventive therapy and therefore do not discontinue. Once patients with erenumab or onabotulinumtoxinA discontinue, they transition to the "off preventive therapy" health state and are assumed to experience the MD frequency equal to that of SC (i.e. the incremental treatment effect is lost instantaneously), and patients return to their pre-treatment MD baseline. It is assumed that discontinued patients receive no further preventive therapy. This assumption is required in the absence of clinical study data on the sequential use of preventive treatments.

In the scenario analyses in which untreated patients are assumed to receive the placebo effect from the clinical studies, patients are assumed to also experience the placebo reduction post-discontinuation, rather than returning to their baseline frequency.

Figure 5: Estimation of erenumab and nabotulinumtoxinA discontinuation rates



NMA, network meta-analysis; RR, rate ratio

Mortality

General population mortality in the model is based on US life tables.[31] Annual risks of death reported are converted to a per-cycle risk of death and inform the transitions to the death health state. Treatment effects and migraine frequency do not affect the risks of death in the model, as migraine is not associated with an increased mortality risk.

B) Outcomes applied by migraine day frequency per 28 days

Table 5: Outcomes applied by migraine day frequency per 28 days, summary table

Migraine days	Mean resource use				Migraine Specific Acute med days	Non-migraine Specific Acute med days	Absenteeism days	Presenteeism days	Utility - On treatment (Erenumab/ OnabotulinumtoxinA)	Utility - Off treatment
	Physician visits	**Emergency room visits**	**Hospital stay**	**Specialist consultation**						
0	0.000	0.000	0.000	0.000	1.474	1.833	0.633	1.259	0.823	0.812
1	0.038	0.009	0.004	0.012	1.611	1.931	0.668	1.358	0.811	0.799
2	0.076	0.018	0.008	0.023	1.759	2.034	0.704	1.466	0.799	0.786
3	0.114	0.026	0.012	0.035	1.922	2.143	0.743	1.582	0.786	0.773
4	0.152	0.035	0.016	0.047	2.099	2.258	0.783	1.707	0.773	0.759
5	0.189	0.044	0.020	0.058	2.293	2.378	0.826	1.841	0.758	0.744
6	0.227	0.053	0.024	0.070	2.504	2.505	0.871	1.987	0.744	0.729
7	0.265	0.062	0.028	0.081	2.736	2.639	0.919	2.144	0.729	0.713
8	0.303	0.070	0.032	0.093	2.988	2.780	0.969	2.313	0.713	0.697
9	0.341	0.079	0.036	0.105	3.264	2.928	1.021	2.496	0.696	0.680
10	0.379	0.088	0.039	0.116	3.565	3.084	1.077	2.693	0.680	0.663
11	0.417	0.097	0.043	0.128	3.894	3.249	1.136	2.906	0.662	0.645
12	0.455	0.105	0.047	0.140	4.254	3.423	1.198	3.136	0.645	0.627
13	0.493	0.114	0.051	0.151	4.646	3.605	1.263	3.384	0.626	0.608
14	0.531	0.123	0.055	0.163	5.075	3.798	1.332	3.651	0.608	0.590
15	0.568	0.132	0.059	0.174	5.544	4.001	1.405	3.939	0.589	0.571
16	0.606	0.141	0.063	0.186	6.056	4.214	1.481	4.251	0.570	0.551
17	0.644	0.149	0.067	0.198	6.615	4.439	1.562	4.586	0.551	0.532
18	0.682	0.158	0.071	0.209	7.225	4.676	1.647	4.949	0.531	0.512
19	0.720	0.167	0.075	0.221	7.892	4.926	1.737	5.340	0.512	0.493
20	0.758	0.176	0.079	0.233	8.621	5.189	1.832	5.762	0.492	0.473
21	0.796	0.185	0.083	0.244	9.416	5.466	1.932	6.217	0.472	0.454
22	0.834	0.193	0.087	0.256	10.286	5.758	2.037	6.708	0.453	0.434
23	0.872	0.202	0.091	0.268	11.235	6.065	2.148	7.238	0.433	0.415
24	0.909	0.211	0.095	0.279	12.272	6.389	2.265	7.810	0.414	0.396
25	0.947	0.220	0.099	0.291	13.405	6.730	2.389	8.427	0.395	0.378
26	0.985	0.229	0.103	0.302	14.642	7.090	2.519	9.093	0.377	0.359
27	1.023	0.237	0.107	0.314	15.994	7.468	2.656	9.811	0.359	0.341
28	1.061	0.246	0.111	0.326	17.470	7.867	2.801	10.587	0.341	0.324

C) Scenario analysis results

In addition to the base case results, four scenarios are presented to test major model assumptions.

The first includes the reduction from baseline in MD frequency in the placebo cohorts of the clinical studies. Patients in the SC arm are assumed to achieve this reduction, and patients who discontinue erenumab are assumed to retain the proportion of the reduction observed in the placebo groups.

The second scenario also includes the placebo reduction, but also excludes the indirect costs of lost productivity, considering only costs that would be incurred by a healthcare payer. By combining the exclusion of these costs with the placebo reduction, this is expected to be the most conservative scenario with respect to the cost-effectiveness of erenumab.

The third scenario assumes that the migraine population is split evenly between EM and CM, assuming 50% EM and 50% CM.

The final scenario considers only CM patients, and compares erenumab to onabotulinumtoxinA in previously treated CM patients.

Scenario analysis 1: comparison including placebo effect

Table 6: Scenario analysis: inclusion of placebo effect

Comparison	Erenumab	SC	Incremental
Migraine days	1,554	1,632	-78
QALYs	5.3612	5.2407	0.1205
MD-related costs*	$108,877	$113,654	-$4,777
Value based price	$8,886 - $15,250	-	-

*Cost estimates do not include the costs of providing preventive medication, as a price of erenumab is not available

Scenario analysis 2: comparison including placebo effect and excluding indirect costs

Table 7: Scenario analysis: inclusion of placebo effect and exclusion of indirect costs

Comparison	Erenumab	SC	Incremental
Migraine days	1,554	1,632	-78
QALYs	5.3612	5.2407	0.1205
MD-related costs*	$40,241	$42,289	-$2,048
Value based price	$7,445 - $13,809	-	-

*Cost estimates do not include the costs of providing preventive medication, as a price of erenumab is not available

Scenario analysis 3: Assuming 50% patients EM and 50% patients CM

Table 8: Scenario analysis: Assuming 50% patients EM and 50% patients CM

Comparison	Erenumab	SC	Incremental
Migraine days	1,606	1,739	-133
QALYs	5.3474	5.1728	0.1747
MD-related costs*	$110,478	$118,261	-$7,783
Value based price	$13,331 - $22,553	-	-

*Cost estimates do not include the costs of providing preventive medication, as a price of erenumab is not available

Scenario analysis 4: Comparison of erenumab to onabotulinumtoxinA in 100% CM patients

Table 9: Scenario analysis: Comparison of erenumab to onabotulinumtoxinA in 100% CM patients

Comparison	Erenumab	OnabotulinumtoxinA	Incremental
Migraine days	2,200	2,301	-101
QALYs	4.7374	4.6155	0.1219
MD-related costs*	$143,198	$149,084	-$5,886
Value based price	$12,151 - $18,589	-	-

*Cost estimates do not include the costs of providing preventive medication, as a price of erenumab is not available