Modelling monthly migraine day distribution: A case study of Fremanezumab Japanese-Korean clinical trials for migraine prevention

Xinyu Wang[1], Kentaro Yamato[1], Yoshitsugu Kojima[1], Josef J. Paris[2], Elisabeth F.P. Peterse[3], Claire Simons[4], Anuja Chatterjee[4], Craig Bennison[4]

1. Otsuka Pharmaceuticals Co., Ltd., Tokyo, Japan. 2. OPEN Health, Oxford, United Kingdom. 3. OPEN Health, Rotterdam, The Netherlands. 4. OPEN Health, York, United Kingdom.

INTRODUCTION

- Migraine is a neurological condition, characterized by a throbbing headache. Migraine is the third most prevalent and the sixth most disabling illness in the world.[1]
- Worldwide, approximately 92% of people diagnosed with migraine have episodic migraine (EM) (<15 days of migraine per month including ≥ 4 migraine days) and 8% have chronic migraine (CM) (≥15 days of migraine per month including ≥ 8 migraine days).[2]
- Of the approximately 40% of patients suffering from migraine for whom these prevention treatments are appropriate, only 13% are currently receiving therapy.[3]
- Fremanezumab (FREM) is an investigational calcitonin gene-related peptide monoclonal antibody for the preventive treatment of both EM and CM.[4]
- FREM has demonstrated statistical superiority in mean reduction in monthly average number of migraine days compared to placebo, as well as a ≥50% reduction in average number of monthly headache days and reduction in monthly use of acute headache medication for those with EM and a history of treatment failure.[5]
- Three local Phase III clinical studies in Japan and South Korea have demonstrated similar efficacy and safety as the global trials.[6-8]

OBJECTIVES

- Otsuka have developed a cost-effectiveness model (CEM) for the Japanese country specific setting to demonstrate the cost-effectiveness of FREM in Japan.
- Analyses of the number of monthly migraine days (MMD) was needed to inform health state distributions in the CEM. The poster presents the outcomes of the analyses

RESULTS

- Due to low numbers, month 6 and 12 measurements were excluded from the MMD analyses.
- All 6 models underwent a stepwise AIC optimization to find the best fit model. The results of the model selection indicate that the ZIBB fits the data best, followed by ZINBI and ZAGA. This is concluded based on the AIC being comparably smaller on the fits using the same datasets. For EM, model fits of ZIBB (AIC: 5442.7) and ZINBI (AIC: 5443.7) were very similar. (see Table 1)
- The resulting models have been visually compared against the observed data. Model fit comparison of EM and CM patients for treatment groups placebo, monthly injection and quarterly injection are shown in Figure 1.

Table 1. MMD final fit covariates

Covariate	Episodic Migraine			Chronic Migraine		
Distribution	ZINBI	ZAGA	**ZIBB**	ZINBI	ZAGA	**ZIBB**
AIC	5443.7	5467	**5442.7**	10399.5	10478.8	**10203.5**
Baseline	✓	✓	✓	✓	✓	✓
Month 2	✓	✓	✓	✓	✓	✓
Month 3	✓	✓	✓	✓	✓	✓
Quarterly injection	✓	✓	✓	✓	✓	✓
Monthly injection	✓	✓	✓	✓	✓	✓
Female	✓	✓	✓	✓	✓	✓
Japan	✓	✓	✓	✓	✓	✓
Previous medicine	✓	✓	✓	✓	✓	✓
Age	✓	X	✓	X	X	X
Quarterly X Month 2	X	X	X	X	X	X
Quarterly X Month 3	✓	✓	✓	X	X	X
Monthly X Month 2	X	X	X	X	X	X
Monthly X Month 3	✓	✓	✓	X	X	X

Abbreviations: AIC = Akaike information criterion, ZINBI = zero inflated negative binomial, ZIBB = zero inflated beta-binomial, ZAGA = zero adjusted gamma distribution. ✓ Indicates the inclusion of a covariate, X indicates the exclusion of a covariate. Bold indicate the models with the best fit.

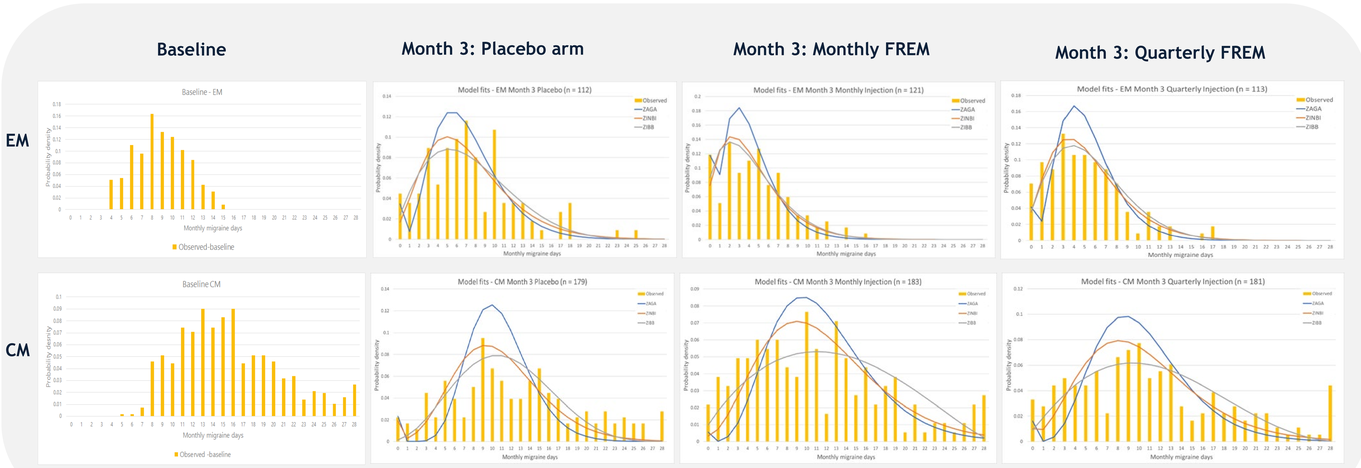

Figure 1. Model fit comparisons for baseline and month 3 MMD – EM and CM per treatment group

METHODS

Trial data

- The trial data being used for the CEM adaptation is made-up of three sets of patient level data: 406-102-00001, 406-102-00002 and 406-102-00003. They report on the use of FREM for CM, EM, and FREM's long-term safety and tolerability, respectively.

Monthly migraine day (MMD)

- In both the 406-102-00001 (CM) and 406-102-00002 (EM) trials, MMD were assessed at baseline (i.e. the month prior to starting the trial), month 1, month 2 and month 3. In the 406-102-00003 (long-term) trial, additional assessments were made at month 6 and month 12.
- We used MMD data from every assessment point for all arms in the 3 trials to inform our parametric distributions for FREM and placebo arms. These parametric distribution were used to estimate health state distributions in the economic model, where analyses were done separately for EM and CM patients.
- MMD characteristics were explored separately for the EM and CM population, we evaluated these characteristics separately by treatment arm (placebo, FREM monthly and FREM quarterly) and by timepoint (month 1, month 2 etc.).

Modeling approach

- Models were fitted to capture the treatment effect. Hence, no models were fitted to the baseline.
- For each of these models, we fitted a single model over all time points (and for all patients). For both patient groups, 3 different statistical distributions to describe the MMD were tested:
  1. Zero inflated beta-binomial (ZIBB)
  2. Zero inflated negative binomial (ZINBI)
  3. Zero adjusted gamma distribution (ZAGA)
- The choice of distributions was guided by the pre-existing TEVA model and its corresponding NICE submission (TA631)[9] as well as the similar modeling approaches for MMD data in the NICE submission of Erenumab (TA682).[10]
- Zero inflated distributions allow for the distributions to have additional weight on the zero value. Preliminary work showed that without this inflation, zero migraine days would be severely underrepresented in the modeling.
- These distributions have been shown to provide reasonable approximations for the observed distributions of migraine day count data over other clinical trials, with a negative binomial distribution implemented in a recent migraine prophylaxis CEM publication.[11,12]
- The parameters used in the distributions undergo transformations when being implemented into the model.

Zero inflated beta-binomial model (ZIBB)

- The ZIBB distribution is a discrete probability distribution which generates non-negative integers which arise from a series of Bernoulli trials (when the probability of success is either unknown or random). It has four parameters: n (number of Bernoulli trials) and three shape parameters, μ, σ and ν.

Zero inflated negative binomial model (ZINBI)

- The ZINBI distribution is a discrete probability distribution that models the number of successes in a sequence of independent and identically distributed Bernoulli trials before a specified (non-random) number of failures occurs. It is a three-parameter distribution, μ, σ and ν.

Zero adjusted gamma model (ZAGA)

- Unlike the beta-binomial and negative binomial models, the ZAGA is a continuous (non-negative) distribution. It is a three-parameter model, described by μ, σ and ν.

- The parameters used in the distributions undergo transformations when being implemented into the model. Mu (μ), Sigma (σ) and Nu (ν) were transformed using either log or logit.
- Only fixed effects models were used due to non-convergence issues with the random effects models.
- Model selection was determined by AIC, forward and backward selection were used to determine which coefficient considered for final model.
- Due to the paucity of data for patients with a follow-up of over 3 months, it was decided long-term treatment waning analysis could not be adequately analyzed. Long-term waning in the model will be based on expert opinion.

CONCLUSIONS

- Covariates included in the final model, selected based on AIC, were treatment, baseline MMD, scheduled visit, age, sex, previous medication use and country.
- Both AIC and visual fit inspections revealed the ZIBB model as the best performing distribution.
- The distribution shifts between fremanezumab and placebo demonstrated fremanezumab's efficacy at reducing MMD for both EM and CM patient groups.

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