**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 9% of people diagnosed with migraine have episodic migraine (EM)<15 days of migraine per month including ≥ 4 disabling days) and 8% have chronic migraine (CM) (>15 days of migraine per month including ≥ 4 disabling days).1

Of the approximately 40% of patients suffering from migraine for whom Otsuka have developed a cost-effectiveness model (CEM) for the Analyses of the number of monthly migraine days (MMD) was needed to respect.

**OBJECTIVES**

- Otsuka have developed a cost-effectiveness model (CEM) for the Japanese-Korean clinical trials to inform our parametric distributions for FREM 102-00003 (long-term) trial, additional assessments were started (trial), month 1, month 2 and month 3. In 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 distributions were used to estimate health state distributions in the economic model, where analyses were done separately for each arm and CM patients.

- MMD characteristics were explored separately for the CM 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.).

**METHODS**

- **Trial data**
  
  The data trials 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.

- **Modeling approach**
  
  Models were fitted to calculate the treatment effect. However, 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 binomial (ZIB) 2. Zero inflated negative binomial (ZINB) 3. Zero adjusted gamma distribution (ZAGA)

  - The choice of distributions was guided by the pre-existing TEVA model and its corresponding NCE submission (Table 1) as well as the similar modeling approaches for MMD data in the NICE submission of Erenumab (TA682).10

  - These parametric 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 distribution of migraine days count data over other clinical trials, with a negative binomial distribution implemented in a recent migraine prophylaxis CEM publication.11,12

- **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, ν and ρ.

- **Zero inflated negative binomial model (ZINBI)**
  
  The ZINB 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, ν and ρ.

- **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 and ν.

**RESULTS**

- **Zero inflated beta-binomial model (ZIBB)**
  
  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.

- **Zero inflated negative binomial model (ZINBI)**
  
  Only fixed effects models were used due to non-convergence issues with the random effects models. The model selection was determined by AIC and forward and backward selection were used to determine which coefficient considered for final model.

- **Zero adjusted gamma model (ZAGA)**
  
  Due to the paucity of data for patients with a follow-up of over 3 months, it was decided long-term treatment analysis could not be adequately analyzed. Long-term warning in the model would be based on expert opinion.

**CONCLUSIONS**

- Converges 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 distributions shifts between fremanezumab and placebo demonstrated fremanezumab’s efficacy at reducing MMD for both CM and CM patient groups.

**REFERENCES**


