Use of Exposure-Response Modeling to Support Regulatory Submission

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Please note: this presentation, including questions from the audience, is being recorded and may be made available.

What is Exposure-Response Modeling?

- E-R analysis most often refers to analyses where
  - Exposure variable is a summary measure (i.e., AUC, Cmax, Cavg), rather than the concentration time-course
  - Response is a clinical endpoint (efficacy or safety) or biomarker
    - Endpoints can be continuous, categorical, or time-to-event
    - Collected over time or at a key time point (i.e. end of treatment period)
  - Response and variability in the placebo group (potentially due to changes over time, concomitant medication, or a placebo effect) are incorporated
  - Typically, E-R analysis is conducted using regression analysis relating exposure directly to response (many model forms linear, non-linear, logistic regression, proportional odds, time to event, poisson regression, etc)
    - F = Baseline + Placebo Effect + Drug Effect
- The term E-R, broadly includes PK/PD modeling as a special case where the exposure variable is drug concentration.

Regulatory Support for Exposure-Response

- E-R analyses have become an integral part of clinical drug development and regulatory decision-making
- Population PK
  - Original FDA Guidance on Pop PK published in 1999, revised in Feb 2022
  - EMA Guidance on Reporting Pop PK Analyses (2008)
- E-R
  - ICH and FDA (2003) guidance for ER relationships
  - PMDA Guideline for Exposure-Response Analysis of Drugs 2020 https://www.pmda.go.jp/files/000235605.pdf

Goals of Exposure-Response

- Primary goals of E-R analyses in clinical drug development are
  - to ensure adequate dose selection and justification after each phase of development; and
  - at the time of submission, to utilize the totality of data available to quantify the benefit:risk relationship

E-R Case Studies Across Phases

- Phase 1 – early learning
  - Passarell J, Ludwig E, Liolios K, et al. Exposure-response analyses of tigecycline tolerability in healthy subjects. *Diagn Microbiol Infect Dis*. 2009;65(2):123-129.
- Phase 2 – dose justification and Phase 3 design
  - Fiedler-Kelly J, Passarell J, Morris D, Yang R, Aycardi E, Bigal ME, Cohen-Barak O. Modeling and simulation-based strategy for TEV-48125 in preventive treatment of chronic and high frequency episodic migraine. Poster presented at: 5th European Headache and Migraine Trust International Congress (EHMTIC); September 15-18, 2016; Glasgow, Scotland.
- Phase 3 – dose confirmation and submission support
  - Gidal BE, Jacobson MP, Ben-Menachem E, Carreño M, Blum D, Soares-da-Silva P, Falcão A, Rocha F, Moreira J, Grinnell T, Ludwig E, Fiedler-Kelly J, Passarell J, Sunkaraneni S. Exposure-safety and efficacy response relationships and population pharmacokinetics of eslicarbazepine acetate. *Acta Neurol Scand*. 2018 Sep;138(3):203-211.

Phase 1 Case Study

- Tigecycline (GAR-936), a first-in-class glycylcycline antibiotic, has demonstrated in vitro activity against Gram positive and Gram-negative anaerobes, atypical pathogens, and anaerobic bacteria (Stein and Craig, 2006).
- Example of early learning - first analysis of E-R for tolerability of tigecycline
- Specifically, E-R modeling of nausea and vomiting (most frequent TEAEs) was performed to select doses for Phase 2

Phase 1 Case Study Continued

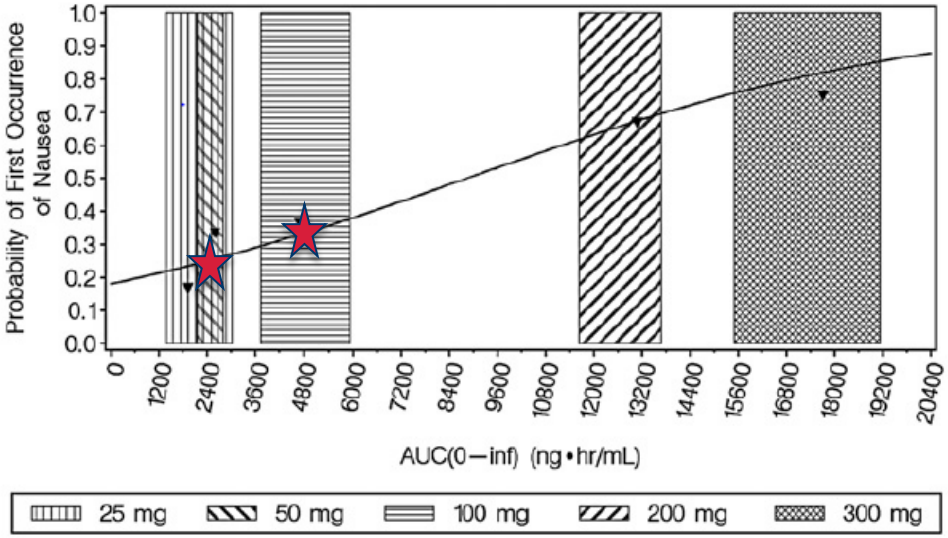
- Data from 3 single-dose phase 1 studies
- Individual tigecycline exposure measures for healthy subjects were generated using standard noncompartmental methods
  - Observed Cmax and $AUC_{0-\infty}$ were calculated for each subject
- Separate E-R models for the occurrence of nausea and vomiting
- Logistic regression analysis performed used SAS software version 8.2

Phase 1 Case Study Continued

- Data
  - Subjects who had received ondansetron as antiemetic agent were excluded from E-R
  - The occurrence of nausea and vomiting included any instance reported as “on treatment” defined as events observed between the start of the first infusion until 24 h after the last infusion
  - only events classified as definitely, possibly, or probably related to study medication were included in E-R
- Covariates included age, weight, gender, and region of treatment
  - Full model followed by backward elimination of covariates ($\alpha = 0.05$)

Phase 1 Case Study Continued

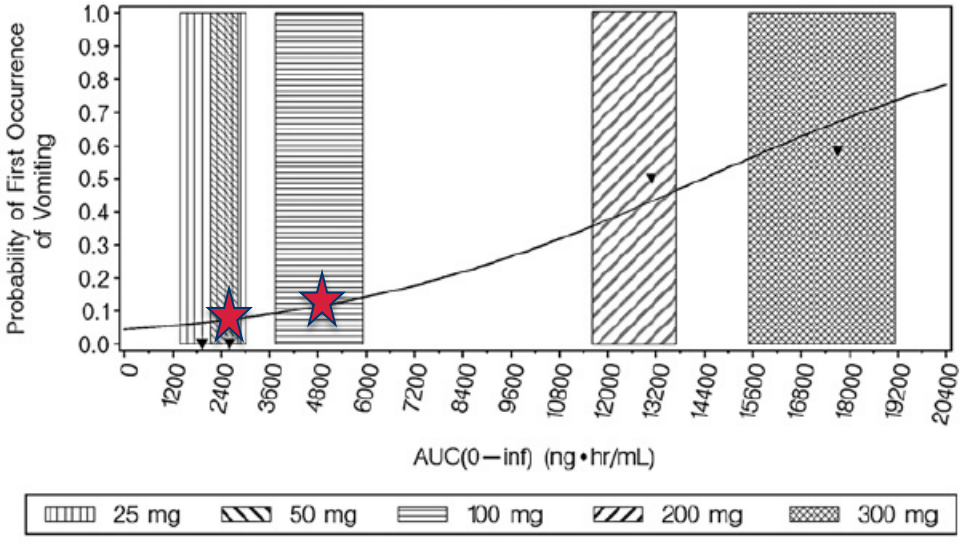
- Results Nausea –
  - $AUC_{0-\infty}$ was the most significant exposure measure
  - No covariates were statistically significant
- At the median $AUC_{0-\infty}$ for 50- and 100-mg (loading dose used in the therapeutic regimen) dose groups, model-predicted probabilities of first nausea occurrence are 0.2558 and 0.3303, respectively.



The line represents the model–based predicted probability of the first occurrence of nausea.
The bars represent the 25th to 75th percentiles of AUC for each dose group.
The triangles represent the observed probability of nausea in each dose group.

Phase 1 Case Study Continued

- Results Vomiting –
  - $AUC_{0-\infty}$ was the most significant exposure measure
  - No covariates were statistically significant
- At the median $AUC_{0-\infty}$ for 50- and 100-mg (loading dose used in the therapeutic regimen) dose groups, model-predicted probabilities of first vomiting occurrence are is 0.0746 and 0.1125, respectively.



The line represents the model—based predicted probability of the first occurrence of vomiting.
The bars represent the 25th to 75th percentiles of AUC for each dose group.
The triangles represent the observed probability of vomiting in each dose group.

Phase 1 Case Study Conclusions

- E-R models developed to describe the first occurrence of nausea and vomiting associated with tigecycline exposure predict that these events will occur at tolerable rates after 50-mg doses of tigecycline.
- These predicted rates of nausea and vomiting were comparable with those observed for the tetracycline class of antibiotics (Story et al., 1991).
- These analyses demonstrate the utility of examining E-R relationships to better understand the factors contributing to AEs associated with anti-infective therapy and support dose selection in clinical drug development.

Phase 1 Case Study Take Away

- Phase 1 E-R safety modeling was used to quantify nausea and vomiting to select appropriate doses to test in Phase 2
- Ultimately, Phase 2 doses tested included:
  - 100-mg loading dose followed by 50 mg every 12 h
  - 50-mg loading dose followed by 25 mg every 12 h
- Phase 2 and 3 clinical trials demonstrated the safety and efficacy of intravenous tigecycline compared with vancomycin for the treatment of complicated skin and skin-structure infections and compared with imipenem–cilastatin for the treatment of complicated intra-abdominal infections (Babinchak et al., 2005; Ellis-Grosse et al., 2005).
- Tigecycline was approved for the treatment of serious bacterial infections by the US FDA in June 2004 and, subsequently, in more than 50 other countries.
- Published clinical trials indicate that tigecycline was well tolerated, with the most frequently reported TEAEs related to the digestive system.

Phase 2 Case Study

- Example of dose selection and Phase 3 study design
- Fremanezumab (TEV-48125, humanized, murine-derived IgG2Δa monoclonal antibody) is a potent, selective anti-CGRP drug for the treatment of migraines.
- Several Phase 1 clinical trials were conducted to investigate the PK and safety of TEV-48125 in healthy subjects receiving intravenous (iv) infusions or subcutaneous (sc) injections.
- Two Phase 2b studies (LBR-101-021 and LBR-101-022) were conducted to evaluate the safety and efficacy of TEV-48125 in patients with chronic migraines (CM) and high frequency episodic migraines (HFEM), respectively.

Phase 2 Case Study Continued

- Objectives
  - Further develop and refine an existing population PK model (including covariate analysis) using data from patients with CM or HFEM.
  - Develop E-R models for the following efficacy endpoints (including covariate analysis) during the 28-day post-treatment periods ending at week 4, week 8, and week 12:
    - CM: monthly cumulative migraine days; and
    - HFEM: monthly cumulative moderate/severe headache days.
  - Perform clinical trial simulations to support dose selection and optimize the design of Phase 3 trials of TEV-48125.

Phase 2 Case Study Continued

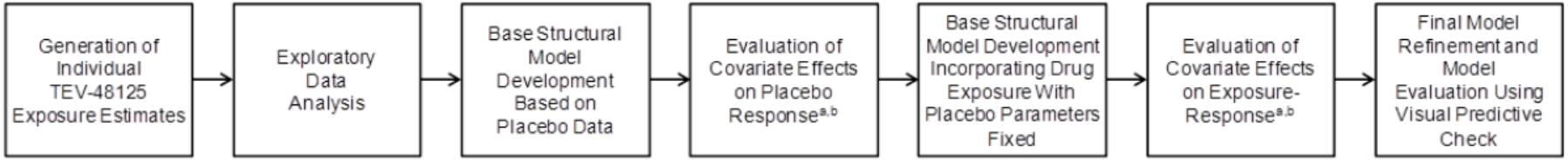
- Two Phase 2b studies (LBR-101-021 [CM] and LBR-101-022 [HFEM]) in adult men and women were pooled for E-R modeling.
- The Phase 2 studies included the following sc dosing regimens each given as 3 separate doses monthly (28 days apart):
  - CM: 675 mg/225 mg/225 mg; 900 mg/900 mg/900 mg; placebo/placebo/placebo
  - HFEM: 225 mg/225 mg/225 mg; 675 mg/675 mg/675 mg; placebo/placebo/placebo

Phase 2 Case Study Continued

- Using the pop PK model, individual measures of TEV-48125 exposure were calculated using predicted TEV-48125 concentration profiles (following each dose over 28 days for each subject) based on the individual empiric Bayesian PK parameter estimates obtained from the final PK model.
  - Monthly exposures measures calculated - average concentration [Cav], area under the concentration-time curve from time 0 to 28 days [AUC0-28], and maximum drug concentration [Cmax]
  - Exposure measures were set to zero for subjects receiving placebo
- Efficacy Endpoints based on electronic daily headache diary
  - CM: monthly cumulative migraine days; and
  - HFEM: monthly cumulative moderate/severe headache days

Phase 2 Case Study Continued

Process for the Development of the TEV-48125 Exposure-Response Models



[a] Age, race, sex, baseline weight, baseline body mass index (BMI), years since onset of disease, baseline value of the endpoint, use of analgesic medications (opioids or barbiturates), classified as yes/no, use of other migraine preventative medications, classified as yes/no, and the number of days/month of use of acute medications, specifically triptans or ergot compounds.

[b] Graphical inspection and stepwise forward selection (α=0.05 plus a reduction in IIV in the parameter of interest), followed by backward elimination (α=0.001).

Phase 2 Case Study Continued

- **Clinical Trial Simulation Methodology**
- Replicated clinical trial simulations (n=500) were used to estimate the probability of success for the planned Phase 3 trial designs.
- The simulated trial designs are provided below:
  - Phase 3 trial in CM consisted of 3-month core phase followed by 9-month safety extension phase
  - 1020 patients enrolled for 867 completers (289 per arm) with 15% dropout rate
  - 1:1:1 randomization to:
    - 675 mg loading dose followed by 225 mg sc qm
    - 675 mg sc q3m
    - placebo sc qm (switched during extension phase to loading dose of 675 mg followed by 225 mg qm)
- Similar CTS were performed for the Phase 3 trial in HFEM using different dosing regimens
- For simulation purposes, efficacy endpoints were simulated for a total of 6 months starting with the 28-day run-in period (baseline) and following monthly dosing on days 1, 29, 57, 85, 113, and 141.

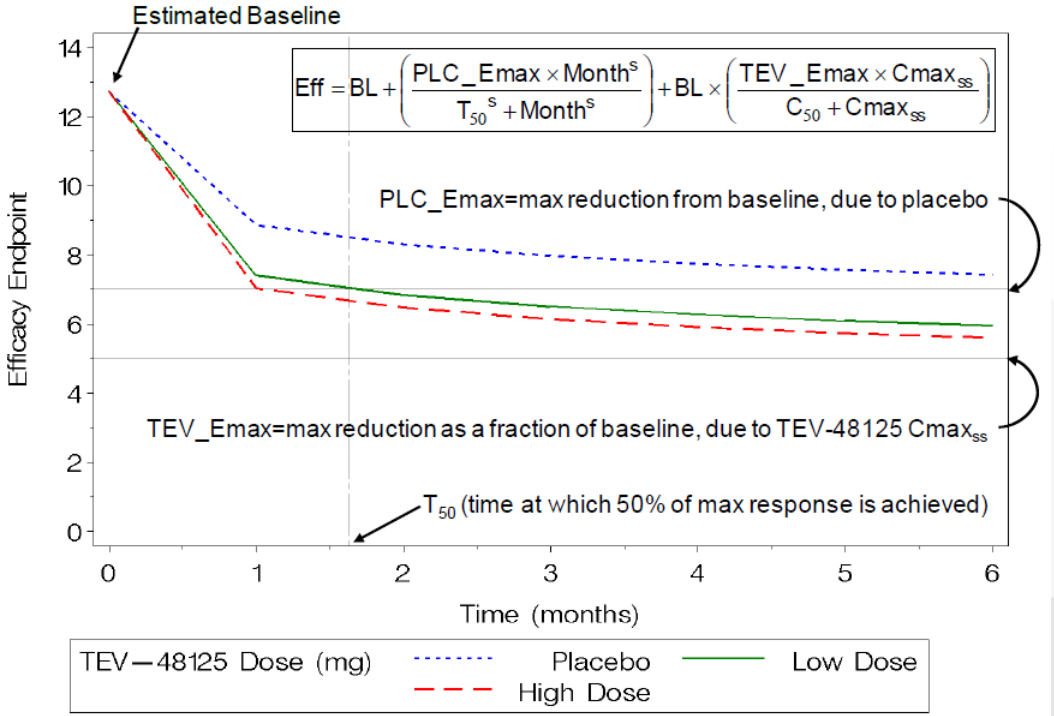
Phase 2 Case Study Continued

- **Clinical Trial Simulation Methodology Continued**
- The primary analyses of the mean change from baseline of the monthly average number of migraine days or monthly average number of moderate to severe headache days over the first 3 months (analysis of covariance [ANCOVA] model) included treatment and baseline response.
- Secondary analyses of the change from baseline in each endpoint response on each month were analyzed using a mixed effects model for repeated measures (MMRM), including treatment, visit (as a categorical variable), baseline response, and treatment by visit interaction.
- For both primary and secondary analyses, the number of positive trials (statistically significant [$P<0.05$] difference in change from baseline in each endpoint response between placebo and TEV-48125 treatment arms) was summed and divided by 500 to determine the probability of success for each design and endpoint.
- For the secondary analyses, the probability of success at each month for the first 6 months was also calculated.

Phase 2 Case Study Continued

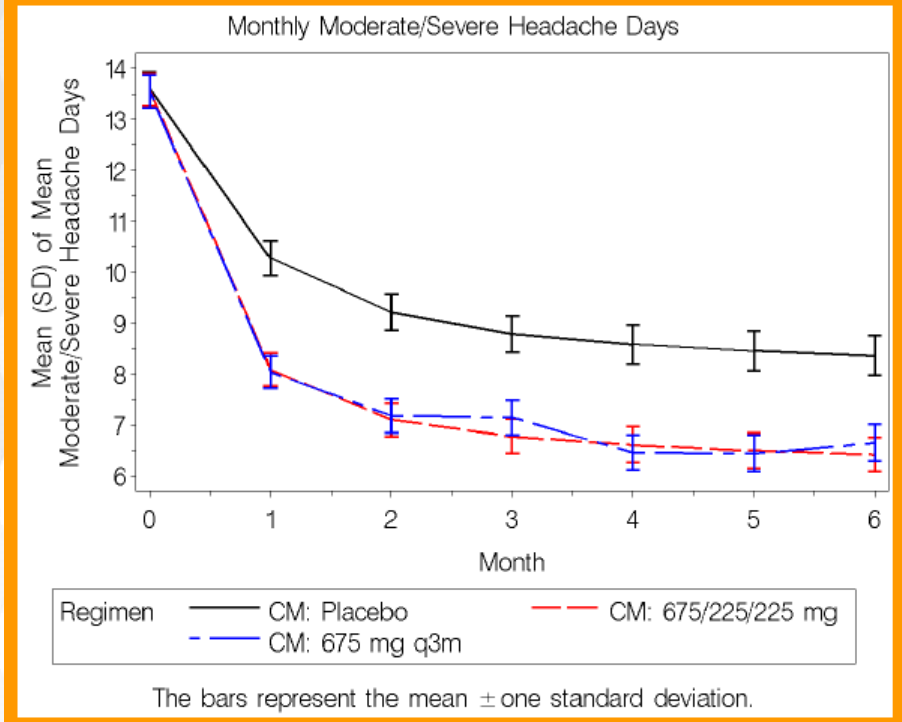
- **Modeling Results** - Separate population-specific (CM and HFEM) E-R models were developed for migraine days and moderate/severe headache days.
- The models are described by 2 components:
  - **placebo effect**: an estimated baseline for each endpoint in each indication plus a maximal reduction due to placebo and a parameter estimating the time to 50% of the maximal reduction, and
  - **exposure-response component**: maximal additional reduction due to TEV-48125 exposure, in addition to consideration of patient factors which affect the time-course of response and exposure-response relationship.

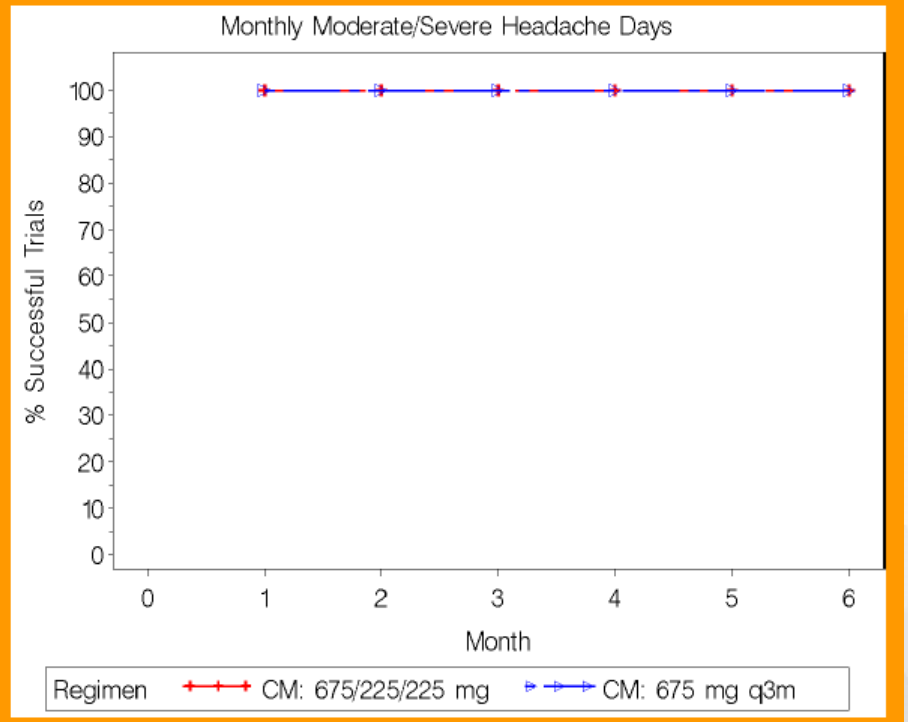
Inhibitory Maximum Pharmacologic Effect Exposure-Response Models



Phase 2 Case Study Continued

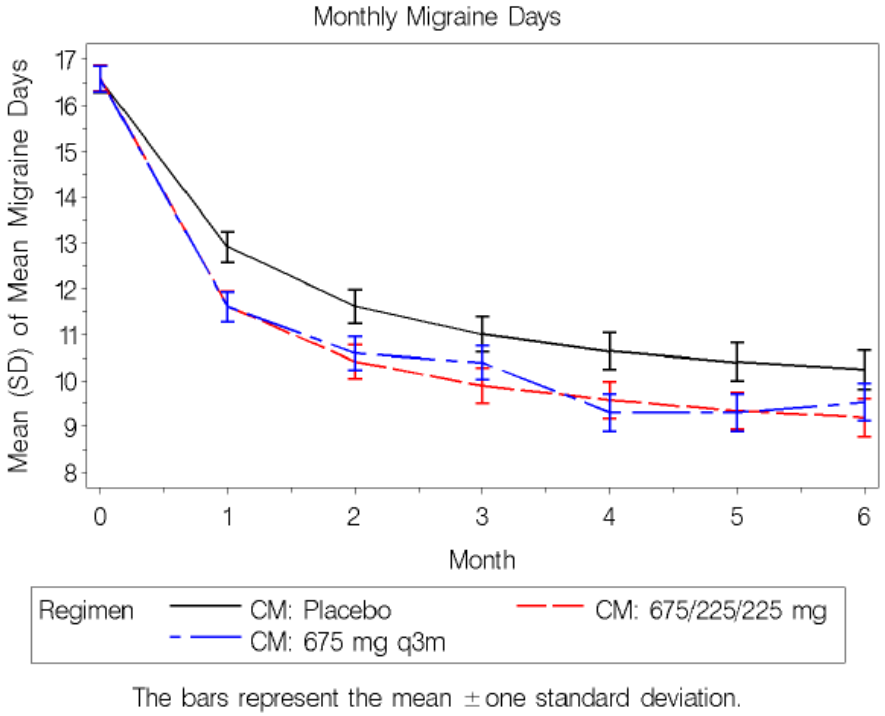
CM: **Simulated Mean (SD) Predicted PRIMARY Efficacy Responses and Probability of Success Over Time**

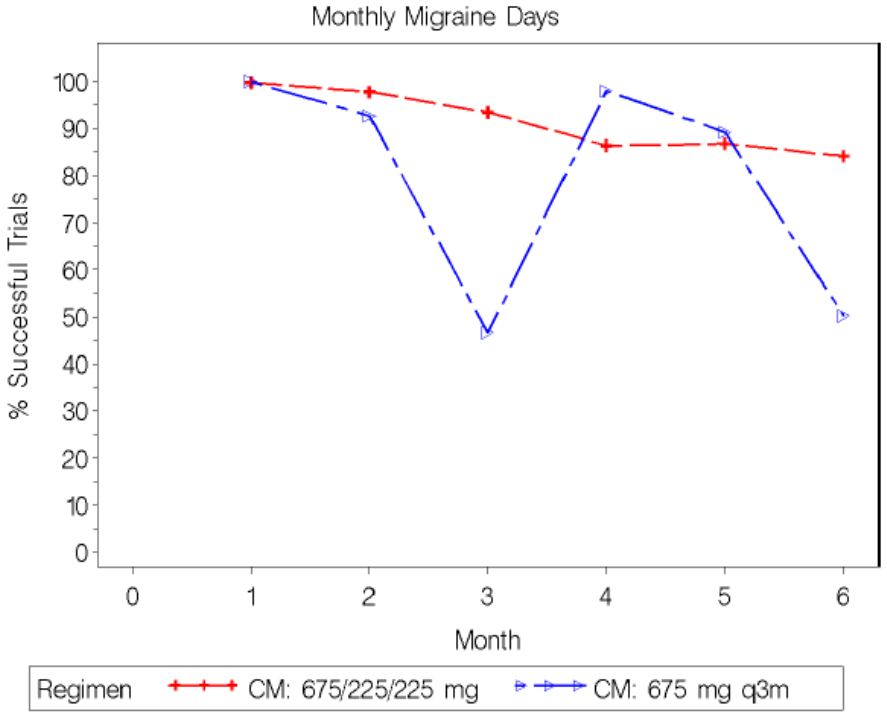




Phase 2 Case Study Continued

CM: **Simulated Mean (SD) Predicted SECONDARY Efficacy Responses and Probability of Success Over Time**

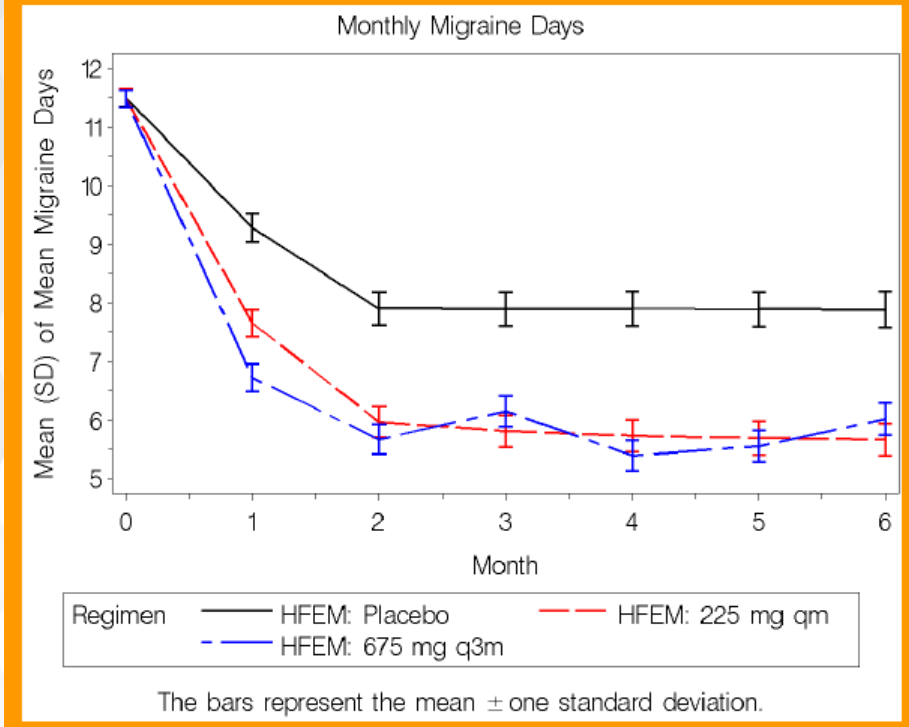


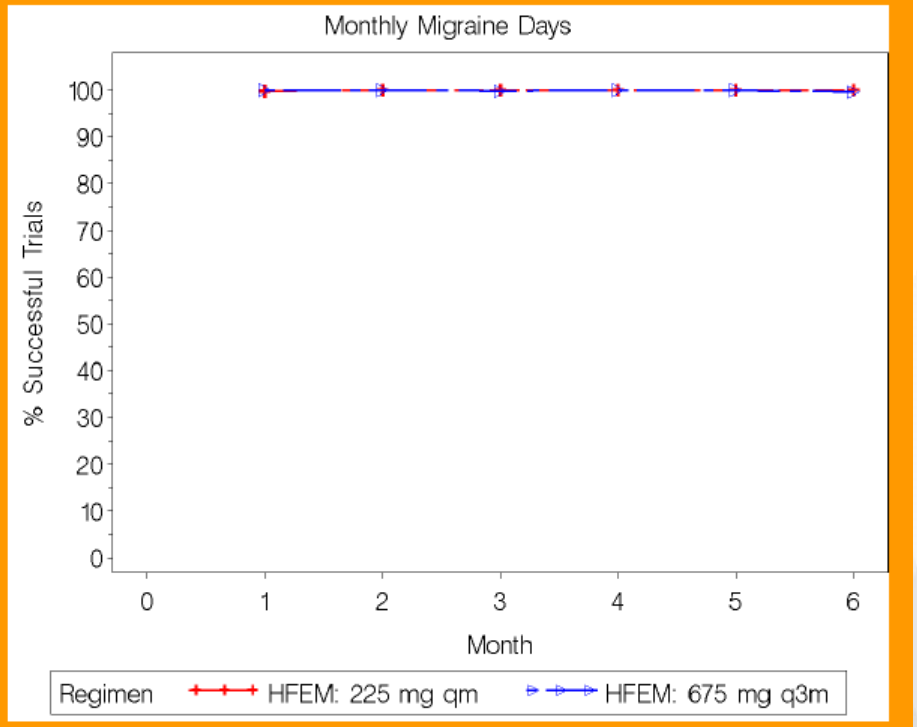


Lesser probabilities are achieved for the migraine days endpoint in CM, especially with the q3m regimen as exposure declines at month 3.

Phase 2 Case Study Continued

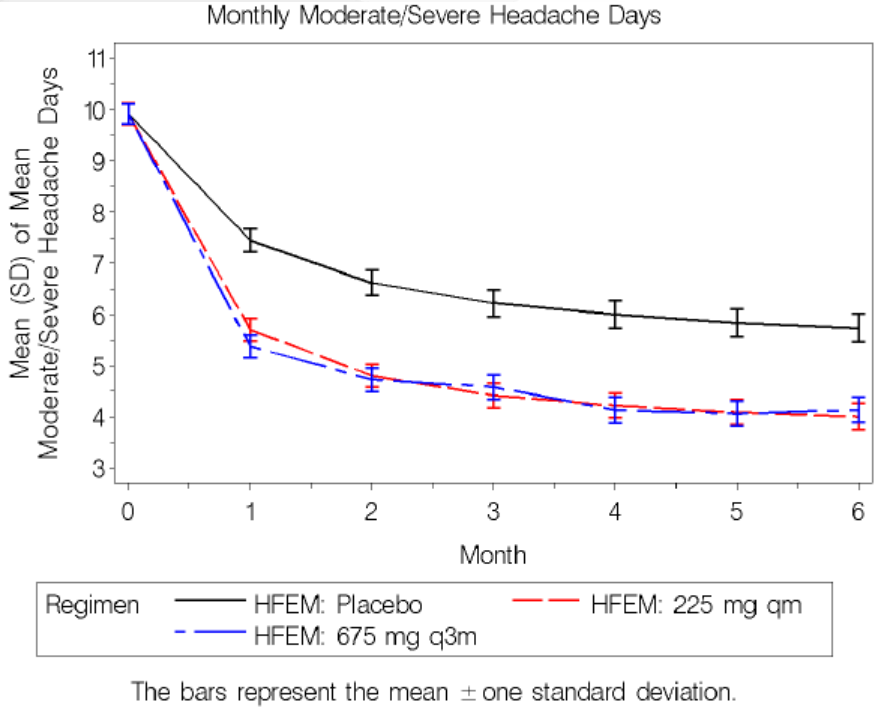
HFEM: **Simulated Mean (SD) Predicted PRIMARY Efficacy Responses and Probability of Success Over Time**

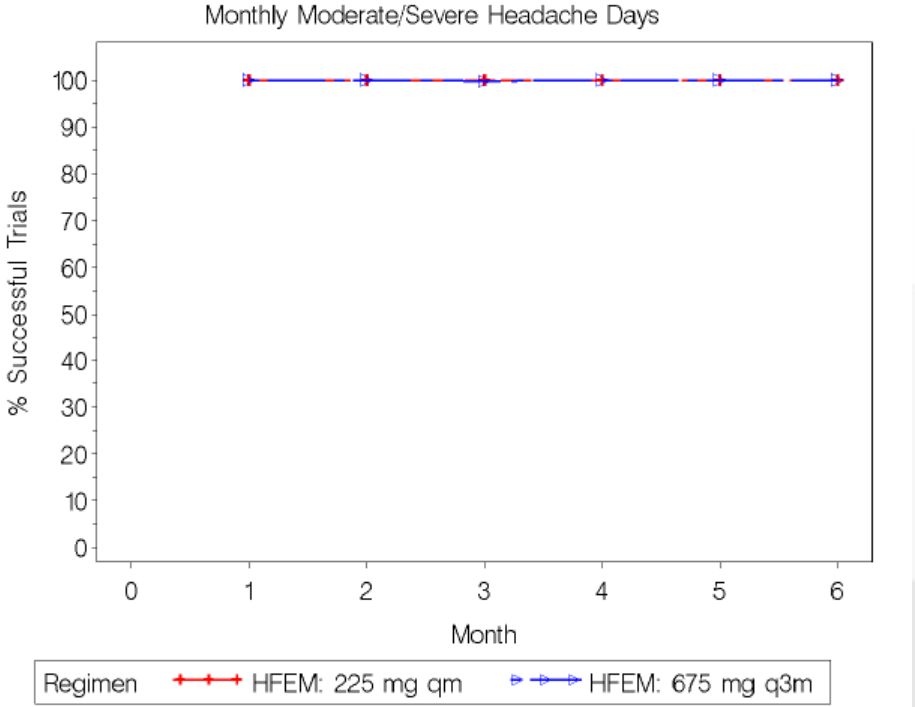




Phase 2 Case Study Continued

HFEM: **Simulated Mean (SD) Predicted SECONDARY Efficacy Responses and Probability of Success Over Time**





Lesser probabilities are achieved for the migraine days endpoint in CM, especially with the q3m regimen as exposure declines at month 3.

Phase 2 Case Study Continued

- Clinical trial simulations of the probability of success for the planned Phase 3 study designs in CM and HFEM result in a high likelihood of success (100% of replicate trials achieved $P<0.05$) in terms of differentiating between placebo and the planned dose levels for the primary endpoints
  - the average cumulative monthly moderate/severe headache days in CM over the first 3 months and the average cumulative monthly migraine days in HFEM over the first 3 months)
- Similarly, in terms of differentiating between placebo and the planned Phase 3 dose levels for the cumulative monthly moderate/severe headache days in CM and the cumulative monthly migraine days in HFEM, clinical trial simulations result in a 100% probability of success at each month over 6 months.

Phase 2 Case Study Take Away

- E-R efficacy modeling was used to quantify the relationship between clinical responses and fremanezumab exposure using Phase 2 data
- CTS were used to predict the probability of success with different dosing regimens to optimally design the Phase 3 studies
- Phase 3 studies were ultimately successful
- Fremanezumab was approved by the FDA in Sept 2018 and by EMA in April 2019 for the preventive treatment of migraine
  - Recommended dose is either 225 mg every month or 675 mg every three months

Phase 3 Case Study

- Example of dose justification and benefit:risk
- Eslicarbazepine acetate (ESL) is a once-daily oral AED for focal-onset seizures.
- Data from three Phase 3 and 11 Phase 1 studies of ESL were included in this analysis.
- The three ESL Phase 3 studies (2093-301, 2093-302, and 2093-304), were randomized, double-blind, placebo–controlled, multicenter studies assessing the efficacy and tolerability of oral QD adjunctive ESL 400 mg (Studies 301 and 302 only), 800 mg, and 1200 mg.

Phase 3 Case Study Continued

- Objectives - Develop population PK and E-R models to assess dose selection, identify significant AED drug interactions, and quantitate relationships between exposure and safety and efficacy outcomes from Phase 3 trials of adjunctive ESL.
- E-R modeling of
  - Efficacy endpoints
    - standardized seizure frequency (SSF) per 4 weeks
      - Exposure measures – steady-state AUC, Cmax, Cav
    - responder rate (proportion of patients with ≥50% reduction in seizure frequency)
      - Exposure measures – steady-state AUC, Cmax, Cav
    - weekly seizure frequency over time
      - Exposure measures – weekly Cav based on dose at that week
  - Safety endpoints
    - most common TEAEs (dizziness, headache, and somnolence)
      - Exposure measures – AUC, Cmax
    - serum sodium levels
      - Exposure measures – AUC, Cmax

Phase 3 Case Study Continued

- **Methodology** - E-R model development
  - Calculate exposure measures using pop PK model
  - Exploratory graphical analysis
  - Develop base model (placebo + drug effect)
  - Covariate analysis
  - Model Refinement
  - Model Evaluation

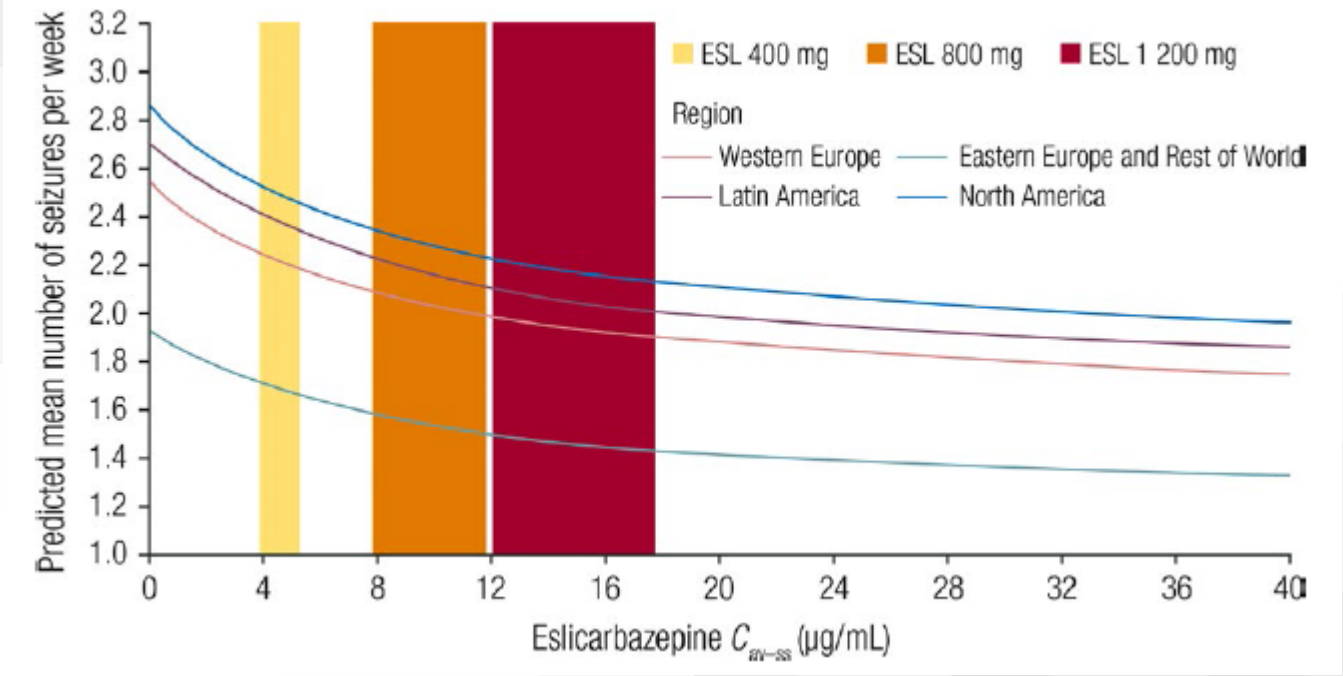
Phase 3 Case Study Continued

- **Methodology** - E-R model development
  - Efficacy
    - Direct effect nonlinear mixed effects modeling of standardized seizure frequency per 4 weeks
    - Logistic regression modeling of responder rate (proportion of patients with ≥50% reduction in seizure frequency)
    - Direct effect Poisson regression modeling of weekly seizure frequency over time
  - Safety
    - Logistic regression analysis used to evaluate E-R safety for the probability of TEAE of dizziness, somnolence, and headache
      - Exposure measures calculated from pop PK model - AUC0-24 and Cmax
      - Linear and power models evaluated
    - Direct effect nonlinear mixed effects modeling of serum sodium levels

Phase 3 Case Study Continued

- **Results** – Data for the efficacy analysis were available from 1,152 patients with 25,896 weekly seizure event records from Study 301, Study 302, and Study 304.
- Efficacy weekly seizure frequency model was a zero-inflated, Poisson regression model as a function of time-course (placebo) + drug effect
  - Time effect was a power function of week
  - Drug effect was an Emax function of Cav,ss
  - Age and region were significant covariate effects on baseline response
- The weekly seizure frequency model predicted a maximum reduction from baseline of 56% during treatment with ESL.
- Based on the model, this effect was related to both time (that is, a placebo effect accounted for 39% of the maximum reduction) and eslicarbazepine Cav-ss (accounted for the remaining 61% of the maximum reduction).
- The estimated eslicarbazepine EC50 (half maximal effective concentration) was 9.5 µg/mL; this value is similar to the median Cav-ss with ESL 800 mg QD, indicating that approximately 50% of the maximal response could be expected with an 800 mg dose of ESL.

Phase 3 Case Study Continued



The lines represent the model-predicted mean weekly seizure count at Week 14, assuming a patient of median age (37 years). The colored regions represent the 25th to 75th percentiles of Cav-ss for each randomized dose amount.

Phase 3 Case Study Continued

- **Results** - Data for the safety analysis were available from 1152 patients (306 from Study 301, 307 from Study 302, and 539 from Study 304).
- The starting dose for the first week (400 mg or 800 mg) was the strongest predictor of the risk of each of these TEAEs.
- Based on the models, the probability of a TEAE (dizziness, headache, or somnolence) for a starting dose of ESL 800 mg QD was twice that for a starting dose of ESL 400 mg QD.
- Higher exposure did not result in more TEAEs after accounting for starting dose
- Significant covariate effects included
  - body weight, sex, region, and baseline use of CBZ or lamotrigine

Phase 3 Case Study Continued

Conclusions based on the results of PK and E-R analyses -

- An improved risk-benefit profile may be achieved using a starting dose of ESL 400 mg, vs ESL 800 mg
- To improve tolerability, use of a lower dose of CBZ may be considered when taken concomitantly with ESL
- An increase in ESL dose (if tolerability allows) may be necessary for additional seizure control when ESL and CBZ are taken concomitantly ESL dose may need to be increased for additional seizure control when taken concomitantly with phenobarbital or phenobarbital-like metabolic inducers (phenytoin, primidone)
- For most adult patients, ESL dose adjustment based on body weight should not be required
- Routine monitoring of eslicarbazepine plasma concentrations does not appear useful for informing dose adjustments of ESL for efficacy, or for predicting potential tolerability issues

Phase 3 Case Study Continued

- This quantitative approach supported decision-making during the development of ESL and contributed to dosing recommendations and labeling statements, as well as providing general guidance for the use of ESL in the clinic
- ESL was approved by the FDA in Nov 2013 as an add-on medication to treat seizures associated with epilepsy
  - Initial adult dose 400 mg/day → weekly titration increments of 400 to 600 mg/day → maintenance dose 800 to 1600 mg/day
  - ESL later approved for monotherapy and in children

Conclusions

- E-R modeling is an effective tool to select doses and quantify the benefit:risk relationship and can be used throughout drug development
- Regulatory agencies recommend E-R modeling to support regulatory submissions
- E-R modeling is vital to supporting regulatory submissions and ultimately drug approval

SimulationsPlus

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Model Informed Drug Development

Q&A

Questions & Answers