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ARTICLE

Making Better Dose Decisions: Using Exposure-Response Modeling to Integrate Efficacy Outcome of Two Phase IIb Clinical Trials of Ubrogepant for Migraine Treatment

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Ubrogepant (MK-1602) is a novel, oral, calcitonin gene-related peptide receptor antagonist in clinical development with positive phase III outcomes for acute treatment of migraine. This paper describes the population exposure-response (E-R) modeling and simulations, which were used to inform the phase III dose-selection rationale, based on ~ 800 participants pooled across two phase IIb randomized dose-finding clinical trials. The E-R model describes the placebo and ubrogepant treatment effects based on migraine pain end points (2-hour pain relief and 2-hour pain freedom) at various dose levels. Sensitivity analyses were conducted to evaluate various assumptions of placebo response in light of the high placebo response observed in one phase II trial. A population pharmacokinetic model describing the effect of formulations was included in the E-R simulation framework to assess potential dose implications of a formulation switch from phase II to phase III. Model-based simulations predict that a dose of 25 mg or higher is likely to achieve significantly better efficacy than placebo with desirable efficacy levels. The understanding of E-R helped support the dose selection for the phase III clinical trials.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?
☑ There is limited understanding of the exposure-response (E-R) relationship of calcitonin gene-related peptide (CGRP) receptor antagonists for treatment of migraine due to difficulty in characterizing pharmacokinetics (PK) during a migraine attack.

WHAT QUESTION DID THIS STUDY ADDRESS?
☑ What is the clinical dose-selection rationale for ubrogepant and its E-R relationship?

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?
☑ A clinical dose of ≥ 25 mg ubrogepant is predicted to achieve target efficacy. Outpatient dry blood spot sampling enhanced the quality of PK data and informed E-R characterization in patients with migraine.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?
☑ Findings will aid future development of ubrogepant and other CGRP-based therapies for migraine treatment. This work serves as a successful case study for integrating modeling and simulations to inform dose selection and the go/no go decision for pivotal clinical trials.

Migraine is a highly prevalent, disabling, and complex neurologic disorder characterized by debilitating headaches in conjunction with gastrointestinal and sensory alterations.[1–3] Calcitonin gene-related peptide (CGRP) is the most abundant neuropeptide in the trigeminal nerve and plays a key role in migraine pathogenesis.[3–5] Proof-of-concept for CGRP receptor antagonists (CGRP-RA) as potentially effective migraine treatment has been demonstrated with several compounds, including olcegepant (BIBN 4096), telcagepant (MK-0974), and MK-3207.[6–8] However, clinical development of both telcagepant and MK-3207 was stopped due to elevations in liver transaminase levels in a small number of patients. In a phase II clinical trial, ubrogepant (MK-1602), an oral, chemically distinct CGRP-RA, demonstrated efficacy without evidence of drug-induced liver injury when administered as a single dose.[9] The efficacy of ubrogepant was subsequently confirmed in two phase III trials (ACHIEVE I and ACHIEVE II), where clinical doses of 25, 50, and 100 mg were associated with improved efficacy compared with placebo.[10–12]

Although clinical dose selection represents a challenge for any drug-development program, clinical dose selection for ubrogepant was further complicated by: (i) difficulty in

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obtaining samples for ubrogepant pharmacokinetic (PK) analysis during migraine events, given their unpredictably episodic and debilitating nature; (ii) the need to switch formulation from a phase I/II spray-dried oral compressed tablet (SD-OCT) formulation to a phase II/III hot-melt extrusion (HME) tablet formulation with an enhanced PK absorption profile; (iii) high variability in primary clinical response end points (pain relief (PR) and pain freedom (PF) 2 hours after study drug administration); and (iv) a higher-than-expected placebo response observed in a phase II clinical trial. All of the above factors warrant careful consideration to inform the proper dose selection of the phase III clinical trials and a rational decision to invest in phase III clinical development.

We describe the model-based simulations as a framework to assess clinical dose selection and efficacy in the context of the above-mentioned uncertainty related to the trial outcome (i.e., high interpatient variability and intertrial differences in placebo response) and introduced by the drug development decision to enhance the formulation before phase III. Population PK and exposure-response (E-R) modeling were conducted to integrate clinical trial data from two parallel phase IIb trials, which were designed to collect ubrogepant PK/efficacy data: a dose-finding/efficacy study (PN006) without a PK component[9] and a smaller companion PK/efficacy study (PN007). To support the E-R characterization, an innovative dry blood spot (DBS) sampling approach was implemented in PN007 to enable outpatient self-collection of ubrogepant PK samples proximal to a migraine attack, during which altered drug absorption in patients with migraine impacts the shape of the PK profile. Detailed results and methodology for DBS-plasma PK bridging and the population PK model are described separately.[13,14]

METHODS

Study design and treatment

PN007 (MSD protocol MK1602-PN007; NCT01657370) was a phase IIb, multicenter, randomized, double-blind, placebo-controlled PK trial in participants with acute migraine. PN007 was designed as a companion study to PN006 (MSD protocol MK1602-PN006; NCT01613248), which has been described previously,[9] to generate PK data and support development of the PK/pharmacodynamic (PD) model.

In PN007, 195 participants were equally randomized via an Interactive Voice Response System to ubrogepant 1, 10, 25, 50, or 100 mg (SD-OCT formulation) or placebo. Randomization was stratified by each participant's historical migraine response to oral triptan (high-responder (current triptan user who responded ≥ 75% of the time); low-responder (current triptan user who responded < 75% of the time, or had tried but no longer used triptans); or oral-triptan–naïve).

PN006 and PN007 were conducted in accordance with the ethical principles of the Declaration of Helsinki and Good Clinical Practice guidelines. The protocols were approved by the institutional review board/independent ethics committee at each participating center. All participants provided written informed consent.

Key eligibility criteria and end points for PN007 were the same as for PN006 and are described elsewhere.[9] Briefly, eligible participants were healthy men and women aged 18–65 years with a history of migraine (with or without aura) for ≥ 1 year who had experienced two to eight moderate or severe migraine attacks per month in the 2 months before study enrollment.

PN007 participants were instructed to take three single oral doses of study medication: one dose at home at the onset of a migraine attack of moderate or severe pain intensity, and two single doses the evening before and during clinic visit 2, which was ~ 4 days following the migraine attack, for safety evaluation and PK characterization.

Participants rated headache intensity based on a 4-point scale (grade 0 = no pain, grade 1 = mild pain, grade 2 = moderate pain, and grade 3 = severe pain) at baseline and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 24 (PN006 and PN007), and 48 (PN006 only) hours after study drug administration.

Efficacy end points included PF (defined as a reduction in headache severity from grade 2 or 3 at baseline to grade 0) and PR (defined as the reduction of a moderate or severe migraine headache (grade 2 or 3) to a mild headache or no headache (grade 1 or 0)) at 2 hours postdose.

Ubrogepant concentration was determined from DBS and plasma assays (PN007 only). DBS sampling was performed at screening (visit 1), at home on the day of migraine (2, 4–12, and 24 hours postdose), and in the clinic at 3.5 hours postdose (visit 2). Plasma samples were collected at screening, predose (0 hour), and 15 minutes, 40 minutes, 1.5 hours, and 3.5 hours after study drug administration (visit 2).

Bioanalytical analyses

Ubrogepant blood concentration from DBS was determined using reversed-phase high-performance liquid chromatography with tandem mass spectrometry detection (lower limit of quantification: 0.36 nM). The plasma PK samples were analyzed using reversed-phase high-performance liquid chromatography with tandem mass spectrometry detection with two dynamic curve ranges of 0.18–182 and 1.82–1820 nM, and lower limit of quantification of 0.18 and 1.82 nM, respectively. Details of the bioanalytical analyses are described separately.[14]

Model development

Population PK model predictions as input into the E-R model. A population PK model was developed to characterize the PK of ubrogepant, as described previously.[14] Briefly, the population PK model comprised a two-compartment disposition model with absorption described as sequential zero-order infusion into the absorption depot compartment followed by lagged first-order absorption into the central compartment. The model was used to generate typical individual predictions of ubrogepant PK based on participant-specific values of PK covariates, including formulation, health status (i.e., healthy participants vs. patients with migraine), sex, and migraine attack (i.e., in-between vs. during a migraine attack). The predicted individual-level PK values were used to support E-R analysis for efficacy.[14]

E-R model development. E-R models were developed based on pain efficacy data from 793 PN006 and PN007 participants. A joint E-R model for both 2-hour PR and PF

binary responses was developed to account for the natural ordering of the PR and PF responses (i.e., a participant with PF must also have PR). To construct a joint model to directly fit the 2-hour PR and PF end points, the pain intensity (PI) scores were used to define the following dependent variable (DV):

$$DV = \begin{cases} 0 \; PI = 0, PF = 1, PR = 1 \\ 1 \; PI \leq 1, PF = 0, PR = 1 \\ 2 \; PI > 1, PF = 1, PR = 0 \end{cases} \quad (1)$$

where PF = 1 if DV = 0 denotes that the participant has PF at 2 hours (PI = 0), and PR = 1 if DV ≤ 1 denotes that the participant has PR at 2 hours (PI ≤ 1).

The general form of the 2-hour PR and PF joint model was given by the expression:

$$\text{logit}\left(\Pr\left(DV_i \leq m\right)\right) = \sum_{k=0}^{m} \beta_k + f_d\left(x\right) \quad (2)$$

where the probabilities were modeled in the logit scale, logit(p) = log(p)–log(1–p) for m = 0 or 1, β_0 denotes the placebo logit-probability for PF, $\beta_0 + \beta_1$ denotes the placebo logit-probability for PR, and $f_d(c)$ is a function describing the drug effect that depends on the ubrogepant concentration (c).

The drug effect is described with an E_{max} model, where E_{max} is the maximum drug effect, C_{2hour} is the typical individual prediction of 2-hour plasma concentration of ubrogepant based on the population PK model, and EC_{50} is the typical individual C_{2hour} corresponding to 50% of the maximum drug effect.

$$f_d\left(c_{2hour}\right) = \frac{E_{max} c_{2hour}}{EC_{50} + c_{2hour}} \quad (3)$$

During model building, various exposure metrics were evaluated for E-R characterization, including dose, C_{2hour}, and area under the curve from time zero to 2 hours ($AUC_{0–2hour}$). All three metrics resulted in similar model fits. C_{2hour} was chosen strategically as the exposure metric to model and to enable extrapolations between formulations (from SD-OCT to HME), given the known differences in absorption rate of ubrogepant that may plausibly impact the clinical end points, which are acute pain measurements at 2 hours postdose.

NONMEM version 7.2.0 software (ICON plc, Dublin, Ireland) was used in all model fittings. Processing of data, NONMEM output, and simulations were performed using SAS version 9.3 (SAS Institute, Cary, NC), R Version 2.15.1 or S-Plus version 8.2 (TIBCO Software, Palo Alto, CA).

PD covariates evaluated included: baseline pain intensity score, triptan responder status (naïve, low, high), baseline age, sex, and caffeine usage (yes, no). The final parsimonious covariate model was developed by selecting a subset of 15 reduced E-R models relative to the full covariate model based on the Wald's Approximation Method using Schwarz's Bayesian Criterion.[15] The parsimony of the final model selected by the Wald's Approximation Method procedure was confirmed using a combined forward selection (P = 0.01) and backward elimination procedure (P = 0.001).

The adequacy of the final E-R model was assessed based on standard goodness-of-fit plots and visual predictive checks (VPCs) stratified by study, dose, and covariates included in the final model.

Placebo-delinked model for sensitivity assessment of placebo response

As the observed placebo 2-hour PR response for PN006 (~ 45%)[9] is relatively high vs. historical values (ranges ~ 32%),[16–20] exploratory modeling was conducted to assess scenarios of various placebo-response rates in the event that the observed placebo response may not be reproduced in a future clinical trial. Specifically, a placebo-delinked model was evaluated with two separate parameter values for β_1 in Eq. 2: one for the placebo group and one for the active treatments.

Simulations

Clinical dose-response predictions and probability of achieving target values. Simulations were performed to generate predictions and 90% confidence intervals of the 2-hour PR and PF proportions for the SD-OCT and HME ubrogepant formulations for a range of ubrogepant dose levels from 0–30 mg in 5-mg increments and 40–100 mg in 10-mg increments.

Simulations were also conducted to quantify probability of achieving target value (PTV) for 2-hour PR (0–50%, 50% and higher) and 2-hour PF (0–18%, 18% and higher) as a measure of the technical viability of ubrogepant at each dose for the HME formulation. These targets were prespecified based on expert opinions, including clinical and commercial input.

Simulations for placebo sensitivity assessment. Three simulation scenarios assessed the potential sensitivity of PTV to the assumed placebo response. Scenario A (nominal case) assumes the observed placebo data from PN006 and PN007 (interim data) reflect true placebo response. Scenario B (worst case) assumes a lower placebo response based on a review of the literature (Merck, Kenilworth, NJ, unpublished data), while assuming the placebo-subtracted drug effect from the clinical trial is reproducible for future trials. Scenario C (best case) uses the placebo-delinked model, which treats the observed placebo response from PN006 as spurious, and uses a model-extrapolated placebo value (based on active doses of ubrogepant), which predicts a lower placebo response and, thus, a higher placebo-subtracted drug effect.

Figure S1 outlines the simulation procedure for the dose predictions (90% confidence intervals) and PTV for each simulation scenario.

Phase II/III clinical trial simulations. Clinical trial simulations were performed based on the final PK and E-R models to inform dose selection for the phase II/III trial. One-thousand virtual trials were simulated based on a putative phase II/III design of four treatment arms (placebo, 25, 50, and 100 mg ubrogepant) with 380 participants each. Baseline covariates were obtained by nonparametric

bootstrap from the data set (765 participants, including PN006 and PN007).

The following statistical success criteria were proposed: (i) a statistically significant improvement in 2-hour PR and PF for one or more ubrogepant doses relative to placebo; and (ii) a statistically significant difference between successive ubrogepant dose levels (e.g., 25 vs. 50 mg and 50 vs. 100 mg).

The probability of success (POS) for achieving these criteria was estimated based on summarizing the 1,000 virtual trials. To understand the robustness of the proposed phase IIb/III study design, the POS was estimated for various scenarios based on three different assumptions of placebo response (nominal-case, worst-case, and best-case) and baseline headache severity distribution (67:33% vs. 50:50% for moderate:severe headaches, as nominal and hypothetical worst-case scenarios, respectively, for treatment response). In all simulations, the phase II/III HME formulation was used.

Two-sided statistical tests ($\alpha = 0.05$) for the difference between active treatment (ubrogepant) and placebo were performed without adjusting for multiple comparisons. Two-sided statistical tests ($\alpha = 0.10$) for the differences between successive ubrogepant dose groups (25 vs. 50 mg and 50 vs. 100 mg) were also performed.

The clinical trial simulation procedure for evaluating POS for the statistical criteria for each simulation scenario and dose level is summarized in **Figure S2**.

RESULTS

Participants

Of 834 and 195 participants randomized in PN006 and PN007, respectively, a total of 793 participants with 2-hour PR and PF binary responses were included in the final analysis data set. Participant disposition for PN006 has been previously reported[9]; participant flow for PN007 is presented in **Figure S3**. Baseline characteristics, stratified by study and pooled across both studies, are summarized in **Table 1**. Most participants were female (87%) and the mean (SD) age was 40 (12) years. Approximately two-thirds had experienced moderate migraine at baseline.

Ubrogepant was generally well tolerated when administered during a single, acute migraine attack. No serious adverse events were reported.

E-R model for 2-hour PF and 2-hour PR

The parameter estimates for the final and placebo-delinked E-R models are provided in **Table 2**. The E-R model predicted 2-hour PR proportions of 43.5% and 30.5% for placebo-treated participants with moderate and severe baseline headaches, respectively; the 2-hour PR proportions corresponding to the maximum drug effect were 70.3% and 57.4%, respectively, for ubrogepant-treated participants. The placebo predictions for the 2-hour PF proportions were 11.0% and 6.6% for moderate and severe baseline headaches,

Table 1 Baseline covariate summary statistics for participants included in the exposure-response analyses

	Study		
Covariate	**PN006**	**PN007**	**Total**
Age, years			
N	630	163	793
Median (range)	41.0 (18–65)	35.0 (18–65)	40.0 (18–65)
Weight, kg			
Median (range)	75.6 (41.7–175.5)	75.9 (46.0–167.8)	75.8 (41.7–175.5)
Sex, *n* (%)			
Female	552 (87.6)	138 (84.7)	690 (87.0)
Race, *n* (%)			
White	456 (72.4)	102 (62.6)	558 (70.4)
Black	83 (13.2)	24 (14.7)	107 (13.5)
Asian	6 (0.9)	3 (1.8)	9 (1.1)
Hispanic	60 (9.5)	30 (18.4)	90 (11.4)
Other	25 (4.0)	4 (2.5)	29 (3.7)
Food intake, *n* (%)[a]			
Yes	332 (52.7)	98 (60.1)	430 (54.2)
Caffeine consumption, *n* (%)[b]			
Yes	108 (17.1)	27 (16.6)	135 (17.0)
Triptan response status, *n* (%)			
Naïve	223 (35.4)	65 (39.9)	288 (36.3)
Low	226 (35.9)	53 (32.5)	279 (35.2)
High	181 (28.7)	45 (27.6)	226 (28.5)
Baseline pain intensity, *n* (%)[c]			
Moderate	427 (67.8)	109 (66.9)	536 (67.6)
Severe	203 (32.2)	54 (33.1)	257 (32.4)

[a]Food intake within 2 hours prior to dosing; 22 participants (21 in PN006 and 1 in PN007) had missing food intake imputed with the mode. [b]Caffeine consumption within 2 hours prior to dosing. [c]One participant in PN007 had missing baseline pain intensity imputed with the mode.

Table 2 Summary of exposure-response model parameter estimates ± SDs (in parentheses: % SEs)

Parameter	Final model[a]	Placebo-delinked model[a]
Placebo logit-probability		
β_0 (%PF)	–2.09 ± 0.16 (11.0)	–2.32 ± 0.21 (8.9)
$\beta_{1,pbo}$ (%PR)	1.83 ± 0.10 (43.5)	2.30 ± 0.24 (49.5)
$\beta_{1,trt}$ (%PR)	–	1.76 ± 0.10 (36.4)
Headache severity	–0.563 ± 0.151	–0.575 ± 0.151
Drug effects		
E_{max}	1.12 ± 0.27	1.31 ± 0.24
EC_{50} (nM)	41.9 ± 33.1	20.2 ± 16.1

β_0, placebo logit-probability for 2-hour PF; $\beta_0 + \beta_{1,pbo}$, placebo logit-probability for 2-hour PR; $\beta_0 + \beta_{1,trt}$, placebo logit-probability for 2-hour PR based on extrapolated/estimated placebo from data in active arms; EC_{50}, 2-hour plasma concentration (C_{2hour}) corresponding to 50% of E_{max}; E_{max}, maximum drug effect; PF, pain freedom; PR, pain relief.
[a]Covariates with missing values were not included in the final parsimonious model per the model-selection procedure.

respectively; these proportions were predicted to increase to a maximum response of 27.5% and 17.8%, respectively, for ubrogepant-treated participants. The EC_{50} was a C_{2hour} concentration of ~ 42 nM, with an estimated 79% RSE.

The placebo-delinked model was used to estimate the placebo rate based on extrapolation from the treatment groups. The model estimated a lower 2-hour PR (36.4%) for a typical placebo-treated participant with moderate baseline headache, compared with the placebo response estimated directly from the placebo group (43.5%). Given the lower estimated placebo rate, the placebo-delinked model estimated a higher drug potency (EC_{50} ~ 20 nM) compared with the final E-R model (EC_{50} ~ 42 nM). The model-predicted maximum responses are similar between the placebo-delinked and final models.

With the exception of the baseline headache severity effect on the magnitude of the placebo effect, none of the covariates on the placebo and drug parameters (including sex, age, triptan responder status, and caffeine usage) were predictive of the 2-hour PR and PF responses. The final E-R model goodness-of-fit plots with the 2-hour PR and PF proportions plotted vs. dose and stratified by baseline headache severity (moderate vs. severe) are shown in **Figure 1**. Goodness-of-fit plots for the placebo-delinked model are shown in **Figure S4**.

The 90% VPC intervals stratified by study and baseline headache severity with the observed 2-hour PR and PF proportions overlaid are shown in **Figures S5** and **S6**. The observed proportions across dose levels within each study for both moderate and severe baseline headaches were generally contained within the 90% VPC intervals with few exceptions, suggesting that the final model adequately simulates the 2-hour PR and PF proportions, consistent with the observed data.

Model-simulated dose response for SD-OCT vs. HME formulations

The phase II/III ubrogepant HME formulation exhibited faster absorption (k_a increased by approximately eighfold) and higher bioavailability (F1 increased by 14%) relative to the SD-OCT formulation, and, thus, resulted in a modest increase in C_{2hour} (**Figure S7**). The model-based predictions of the dose-response curves (and associated 90% prediction intervals) for both 2-hour PR and PF seemed to plateau within the dose range 25–100 mg, regardless of the formulation (**Figure 2**). In particular, for the HME formulation, the predicted 2-hour PR response rates were ~ 91%, 94%, and 97% of the maximum PR response rates at 25, 50, and 100 mg, respectively. For PF, ~ 83%, 88%,

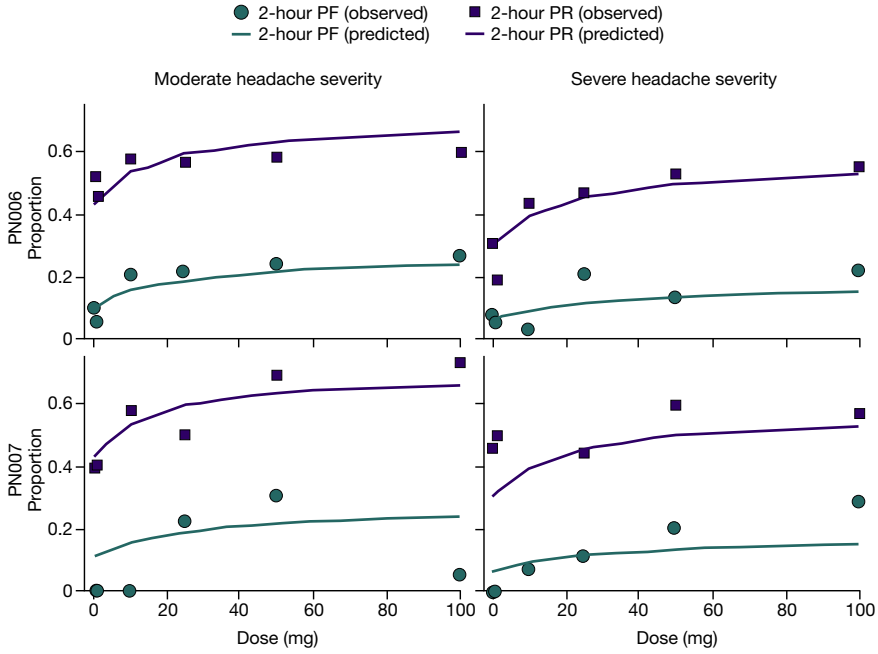

Figure 1 Final model fit vs. dose stratified by baseline headache severity. PF, pain freedom; PR, pain relief.

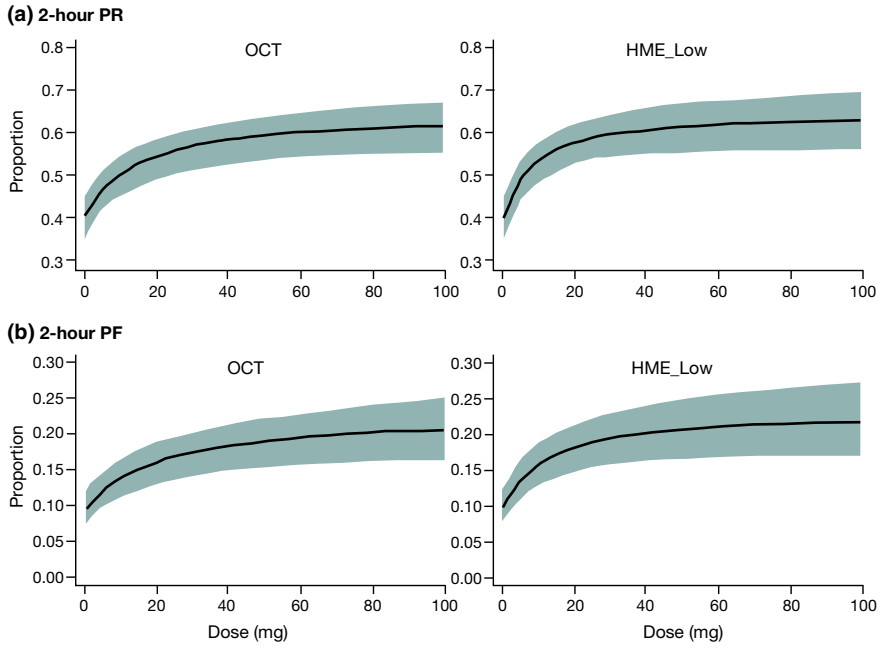

Figure 2 Dose-response predictions and associated 90% prediction intervals for 2-hour clinical end points for the SD-OCT (left panel) and HME (right panel) formulations of ubrogepant. HME, hot-melt extrusion; OCT, oral compressed tablet formulation; PF, pain freedom; PR, pain relief; SD-OCT, spray-dried oral compressed tablet. The shaded areas represent the 90% prediction intervals obtained. HME_Low indicates hot-melt extrusion low-compression formulation.

and 94% of the maximum 2-hour PF response rates were achieved at 25, 50, and 100 mg, respectively. A leftward shift in the dose-response curve was evident for the HME formulation compared with SD-OCT, suggesting higher dose potency associated with the HME formulation as a result of the improved absorption profile. However, the leftward shift was more pronounced at lower doses, suggesting the clinical benefit of switching to an HME formulation is likely appreciable only at low doses (e.g., 20 mg or lower).

Model-simulated PTV for various efficacy criteria

PTV was estimated by simulation based on summarizing data from 2,000 virtual patients with baseline covariates obtained by nonparametric bootstrap of the participants from PN006 and PN007. For each virtual patient, numerous dose levels were simulated based on the model-predicted PK parameters of ubrogepant for the HME formulation under fasted conditions and under the three placebo-response simulation scenarios (nominal-case, worst-case, and best-case).

The PTV results for 2-hour PR and 2-hour PF for the HME formulation administered in the fasted state are shown in **Figures 3** and **4**, respectively.

The model predicts a high PTV (> 90% probability) for achieving a 2-hour PR target of ≥ 50% at the 50-mg and 100-mg doses. Even under the worst-case assumption of the placebo response, a 25-mg dose is predicted to have a reasonably high chance (70%) of achieving ≥ 50% 2-hour PR.

Similarly, the PTV for achieving a 2-hour PF target of ≥ 18% is high (~ 90%) at the 50-mg and 100-mg doses, and reasonably high (~ 70%) at doses ≥ 25 mg under all scenarios.

Clinical trial simulations of dose response for HME formulations

The model-estimated POS was high (> 86% in all simulated scenarios) for demonstrating statistical improvement in 2-hour PR and PF relative to placebo based on the putative phase III study design, and at dose levels of 25, 50, and 100 mg ubrogepant, regardless of placebo model assumptions (nominal-case, worst-case, and best-case scenarios) and baseline headache severity distribution (67% moderate + 33% severe vs. 50% moderate + 50% severe).

The POS for demonstrating a statistically significant difference (α = 0.10) in 2-hour PR and PF response between successive ubrogepant dose groups for both the 25 vs. 50 mg and 50 vs. 100 mg comparisons was very low (< 22% and < 18%, respectively) across all simulation scenarios.

DISCUSSION

We describe the development of an E-R model for the primary efficacy end points (2-hour PR and PF) for acute treatment of migraine with ubrogepant. The E-R model, in conjunction with a population PK model,[14] was used to characterize and predict dose-response relationships of ubrogepant to aid in dose selection for phase III clinical trials.

The modeling and simulations suggest that switching from the SD-OCT (phase I/II formulation) to the HME formulation (phase III formulation) provided a modest increase in C_{2hour}, which translated into a slight leftward shift in the predicted dose-response curves. The faster onset of PK is predicted to translate into improved dose potency for 2-hour PR and PF of the HME formulation, predominantly at lower

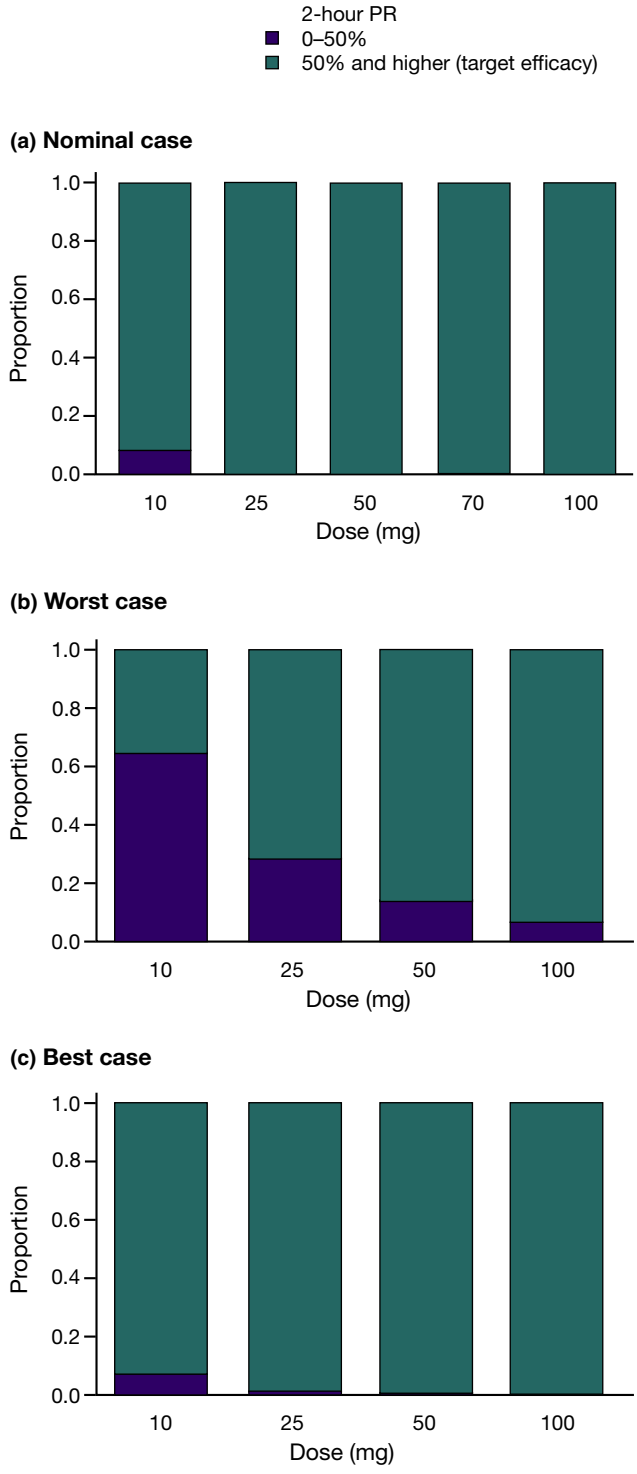

Figure 3 Model-simulated probability of achieving target values of 2-hour pain relief following administration of ubrogepant hot-melt extrusion (HME formulation) under fasted conditions. PR, pain relief.

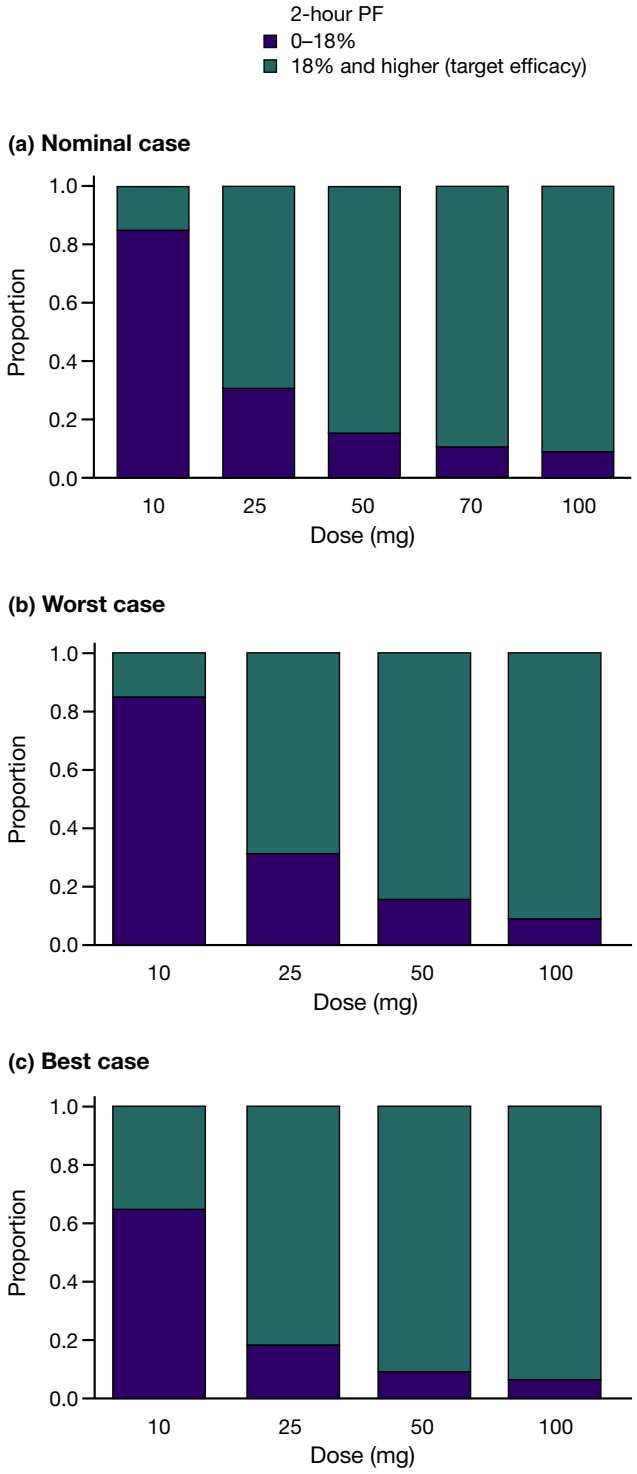

Figure 4 Model-simulated probability of achieving target values of 2-hour pain freedom following administration of ubrogepant hot-melt extrusion (HME formulation) under fasted conditions. PF, pain freedom.

dose levels associated with the dynamic portion of the dose-response curve. However, the clinical significance of the improved HME formulation may be limited at dose levels ≥ 25 mg, given the large overlap in the prediction intervals (due to intrinsically high variability in the pain end points) in the predicted responses between formulations, and given that doses > 25 mg approached the apparent plateau of the predicted dose-response curve.

In light of the higher-than-expected placebo response in the phase II trial,[9] model-based simulations were conducted to predict the dose-response relationships under various scenarios of estimated placebo and treatment effects. The simulations predict that there is a reasonably high likelihood (> 70%) of achieving the clinical efficacy targets (i.e., > 50% for 2-hour PR and > 18% for 2-hour PF) at doses ≥ 25 mg under all scenarios.

Clinical trial simulations based on the putative phase III trial design (sample size of 380 participants per arm) suggested a high POS for demonstrating statistically better response (2-hour PR and PF) compared with placebo at all dose levels (25, 50, and 100 mg) of the ubrogepant HME formulation. The simulations also suggested a low likelihood (< 22%) of demonstrating statistically significant differences ($\alpha = 0.10$) in efficacy between 25-mg and 50-mg or between 50-mg and 100-mg doses. This is not unexpected, as the rationale for the putative sample size was primarily based on adequate power to demonstrate therapeutic gain over placebo, and not to detect differences between ubrogepant dose groups.

From a dose-response perspective, the E-R relationship seemed slightly right-shifted for 2-hour PF compared with 2-hour PR. The dose of 25 mg ubrogepant is predicted to achieve 91% of the maximal 2-hour PR, indicating a dose approaching the E-R plateau of the E-R curve; however, this dose is associated with only 83% of the maximal 2-hour PF response. This suggests the potential for a gain in efficacy by a higher clinical dose of 50 mg or 100 mg with regard to 2-hour PF.

Taken together, based on available PK and E-R data, the model projected a high POS to have a positive pivotal trial compared with placebo at clinical doses ≥ 25 mg, despite the clinical formulation change and uncertainty in the placebo-response rate observed in phase II. The model also projected high PTV for achieving meaningful clinical and commercial targets based on 2-hour PR and PF. Ubrogepant is generally well tolerated, with an adverse-event profile similar to placebo, as demonstrated up to a 100-mg dose in the phase II trial.[9] The model predictions allowed the development team to have an informed assessment of the expected benefit/risk profile of ubrogepant and supported the rationale for continuing development in phase III.

One limitation of this study was that the E-R relationships were characterized using typical individual PK predictions based on the population PK model and participant-specific covariates, rather than participant-specific PK predictions. This strategy was used to leverage the substantial amount of clinical efficacy data from PN006, where PK samples were not collected. The number of participants for which both efficacy and PK data were available (PN007) was relatively small (< 200 participants), and, thus, rather than developing the PK/PD model based solely on PN007, it was determined that including data from the larger dose-ranging study (PN006) would be expected to result in more precise estimation of the E-R relationship.

Possible future research includes developing the model to analyze longitudinal data and the time course of response (e.g., to produce a model for 24-hour sustained response predictions). This was not applicable at the time for phase III dose selection, which focused on the primary efficacy end points of 2-hour PR and PF; however, such modeling could be of potential interest for the design of future migraine studies. Modeling of other clinical end points on migraine-associated symptoms, such as photophobia, phonophobia, and nausea, may also be of future interest.

In conclusion, this joint 2-hour PR and PF C_{2hour}-response model adequately described the ubrogepant E-R relationship and provides a useful platform for characterizing PK/PD relationships and predictions of dose-response relationships to aid in future development of CGRP-RA for acute migraine treatment. The E-R model enabled an accelerated clinical development timeline with an aggressive formulation development strategy by bridging the understanding of dose response between formulations with different absorption characteristics. Sensitivity analyses through simulations based on various placebo response assumptions provided further insight into the uncertainty of estimated drug effect and its impact on POS for achieving clinically and commercially meaningful targets. This work outlines the benefits of fully integrating modeling and simulation to support key clinical development decisions.

Supporting Information. Supplementary information accompanies this paper on the *Clinical and Translational Science* website (www.cts-journal.com).

Figure S1. Flowchart of simulation procedure for dose predictions and PTV.
Figure S2. Clinical trial simulations procedure.
Figure S3. Participant flow in study PN007.
Figure S4. Stage 3 (final data) placebo-delinked base model fit vs. dose.
Figure S5. Observed 2-hour pain relief and corresponding 90% VPC intervals based on the final model.
Figure S6. Observed 2-hour pain freedom and corresponding 90% VPC intervals based on the final model.
Figure S7. Clinical impact of formulation on ubrogepant plasma concentration-time profile following oral administration of 50 mg ubrogepant in fasted male participants with migraine.
Code for Exposure-response Final Model.
Code for Placebo-delinked Final Model.

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