

ARTICLE

Ubrogepant Is Not Associated With Clinically Meaningful Elevations of Alanine Aminotransferase in Healthy Adult Males

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Ubrogepant is a novel, oral calcitonin gene-related peptide (CGRP) receptor antagonist intended for the acute treatment of migraine attacks. Ubrogepant has a chemical structure distinct from previous small-molecule CGRP receptor antagonists that were associated with elevated serum alanine aminotransferase (ALT) in clinical trials. Here, we report overall and hepatic safety data from two placebo-controlled phase I trials of ubrogepant, spray-dried oral compressed tablet (SD-OCT) in healthy male volunteers. Trial A was a pharmacokinetic (PK) trial of single (100–400 mg) and multiple (40–400 mg) ascending doses. Trial B was a dedicated hepatic safety trial assessing daily use of ubrogepant 150 mg for 28 days. Serum ALT (as hepatotoxicity biomarker) and PK data are reported. Ubrogepant was well-tolerated in both trials, with a low incidence of adverse events that did not differ greatly from placebo. Changes in mean ALT levels were minimal and similar to placebo. Over 28 days of treatment, the mean percentage change in ALT from baseline was < 5% at all time points. No participant in either trial demonstrated ALT $\geq 3\times$ upper limit of normal at any time. Ubrogepant SD-OCT demonstrated linear PK appropriate for acute treatment of migraine, with rapid uptake (time of maximum plasma concentration (t_{max}): 2–3 hours) and no accumulation with daily use. Overall, there was no evidence of ubrogepant-associated hepatotoxicity with daily doses up to 400 mg for 10 days or with daily ubrogepant 150 mg for 28 days. Supratherapeutic dosing is a useful strategy for characterizing hepatic safety in early drug development.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

✓ Ubrogepant is an orally delivered, potent, and specific calcitonin gene-related peptide (CGRP) receptor antagonist that is anticipated to be a first-in-class CGRP-targeted acute treatment for migraine attacks. The impact of ubrogepant on changes in alanine aminotransferase (ALT) has not yet been evaluated in a dedicated clinical trial.

WHAT QUESTION DID THIS STUDY ADDRESS?

✓ What, if any, effect does oral ubrogepant have on ALT levels in healthy adult men?

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

✓ Single and multiple daily doses of ubrogepant up to the supratherapeutic dose of 400 mg were found to be safe and well-tolerated, with no evidence of drug-related ALT elevations in healthy men.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

✓ These findings will provide clinicians with the knowledge that ubrogepant, a small-molecule CGRP antagonist, is unlikely to be associated with hepatotoxicity.

Migraine is a highly prevalent neurological disease characterized by recurrent attacks of unilateral and pulsating headaches, which are often accompanied by other debilitating symptoms, including nausea, photophobia, and/or phonophobia.^{1–3} Migraine is associated with a high personal, familial, and societal burden.^{4–8}

During migraine attacks, activation of the trigemino-vascular system leads to increased release of vasoactive neuropeptides, including calcitonin gene-related peptide

(CGRP) and substance P, as well as nitric oxide, resulting in meningeal blood vessel vasodilation.³ The principal goals of acute treatment for migraine attacks are to provide rapid and durable relief of headache pain and associated symptoms while preventing recurring attacks and restoring the ability to function.^{2,9} However, despite the widespread availability of acute treatment options for migraine, treatment optimization remains difficult or impossible for many individuals due to limited effectiveness, poor tolerability,

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or contraindications to existing therapies.^{9–12} As a result, migraine remains one of the most undertreated neurological diseases and continues to be a leading cause of disability worldwide.^{7,13}

Several lines of evidence have implicated CGRP in the pathophysiology of migraine.^{14–16} Elevated levels of CGRP have been found in the external jugular outflow, but not in the cubital fossa, during migraine attacks.^{17,18} In addition, a sustained elevation in serum CGRP levels has been reported between attacks in some people with chronic migraine.^{19,20} Furthermore, infusion of CGRP can elicit moderate to severe headache pain in people with migraine and in healthy individuals.^{21–23}

Recognition of the role of CGRP in migraine pathogenesis has led to the evaluation of CGRP antagonists (targeting either CGRP itself or the CGRP receptor) for the treatment of migraine over the past 2 decades.^{24–26} Telcagepant, the first oral CGRP receptor antagonist to reach clinical evaluation, demonstrated efficacy for the acute treatment of migraine attacks in several clinical trials.^{27–29} Single doses of telcagepant were well-tolerated, with dry mouth, nausea, dizziness, and somnolence as the most commonly reported adverse events (AEs).^{27–29} However, some participants experienced elevated alanine aminotransferase (ALT) levels following treatment with telcagepant once daily for 7 days or twice daily for 12 weeks.^{30,31} Concerns regarding hepatotoxicity led to the discontinuation of telcagepant development, despite its clinical efficacy in the treatment of migraine.³⁰ Another oral small-molecule CGRP receptor antagonist, MK-3207, was associated with delayed liver test abnormalities in phase I trials. ALT elevations were observed following the discontinuation of MK-3207 administration, leading to the discontinuation of the MK-3207 development program.^{31–33}

The mechanism of the observed liver toxicity associated with telcagepant and MK-3207 is unclear. It does not appear to be a CGRP receptor antagonist class effect, given that liver problems were not observed in CGRP knockout mice, and there is no evidence of liver toxicity with CGRP neutralizing antibodies.^{34,35} Available mechanistic data suggested that hepatic risk with MK-3207 and telcagepant was related to a bioactivation-mediated mechanism attributable to reactive metabolites. Subsequent drug development research focused on identifying a small-molecule CGRP receptor antagonist with characteristics hypothesized to be important for reducing the potential for hepatotoxicity, including greater drug potency, lower dosing for clinical efficacy, and reduced potential to form reactive metabolites.³⁵

Ubrogapant is a small-molecule CGRP receptor antagonist that is chemically distinct from MK-3207 and telcagepant. Ubrogapant was developed for the acute treatment of migraine attacks with the goal of providing maximal efficacy with minimal impact on safety, including an absence of vasoconstrictive effects and a greatly reduced hepatic risk. The results of preclinical studies showed that ubrogapant had higher potency than telcagepant (E. Moore, M.E. Fraley, I.M. Bell, C.S. Burgey, R.B. White, C.-C. Li *et al.*, unpublished data), suggesting that therapeutic efficacy could be attained at lower doses and

a smaller chance of exposure to reactive metabolites (i.e., body burden).

Ubrogapant has demonstrated significant efficacy in the acute treatment of migraine attacks in two phase III placebo-controlled clinical trials (ACHIEVE I and ACHIEVE II) that enrolled over 2,500 adults with migraine. Participants treated a single migraine attack of moderate/severe pain intensity with ubrogapant (25 mg (ACHIEVE II), 50 mg (both trials), or 100 mg (ACHIEVE I)) or placebo.^{36,37} The 50 mg and 100 mg doses of ubrogapant were significantly more effective than placebo on both coprimary end points of pain freedom and absence of most bothersome migraine-associated symptom (e.g., photophobia, phonophobia, and nausea) at 2 hours postdose. Overall, ubrogapant was well-tolerated, with no safety concerns identified.^{36,37}

The potential hepatotoxicity observed with the early small-molecule CGRP receptor antagonists^{30–32} warranted vigilant monitoring of hepatic safety signals in the clinical program for ubrogapant. Two early phase I trials conducted in healthy volunteers included hepatic safety assessments, focusing on ALT elevations as a biomarker for liver toxicity. Trial A was a single-ascending and multiple-ascending dose trial that evaluated the pharmacokinetic (PK) profile, safety, and tolerability of increasing doses (40–400 mg) of ubrogapant spray-dried oral compressed tablet (SD-OCT). Trial B was a dedicated trial to assess changes in ALT over 28 days of daily dosing with ubrogapant SD-OCT at a dose of 150 mg, which is 1.5-fold greater than the highest anticipated clinical dose. The primary objective of this report is to present the overall and hepatic safety data from these two phase I trials. To characterize drug exposure, key PK data from both trials are also reported.

METHODS

Trial objectives

The primary objective of this study was to evaluate the safety and tolerability of rising single and multiple oral doses of ubrogapant (trial A) and the safety, tolerability, and effects on ALT levels of multiple oral doses of ubrogapant (trial B) in healthy male volunteers. The secondary objective of both trials was to estimate the serum PK parameters following single-dose and/or multiple-dose administration of ubrogapant.

Trial designs and ethical conduct

Trial A (MSD Protocol MK-1602-002) was a two-part, randomized, double-blind, placebo-controlled trial. Ubrogapant was administered as an SD-OCT. Two additional formulations of ubrogapant were also tested, but the results are not included here. Participants were randomized 3:1 to ubrogapant ($n = 6$) or placebo ($n = 2$). During part 1, the first panel of participants (panel A) received single once-daily rising oral doses of ubrogapant (100–400 mg) or placebo under fasting conditions, and 100 mg with a high-fat meal in five treatment periods, with a minimum 7-day washout between treatment periods. In part 2, the next four serial panels of participants (panels B, C, D, and F) were administered once-daily oral doses of ubrogapant (40–400 mg) or placebo, under fasting conditions, for 10 consecutive days.

Trial B (MSD Protocol MK-1602-004) was a randomized, double-blind, placebo-controlled, single-center, multiple-dose trial; participants were randomized 2:1 to once-daily ubrogepant 150 mg (1.5 times greater than the planned clinical dose) or matching placebo, administered as an SD-OCT, orally once daily for 28 consecutive days. The 150 mg dose was selected for evaluation in trial B because it was expected to be higher than the anticipated efficacious dose for acute treatment of migraine, which was estimated using an empirical maximal effect (E_{max}) population PK/pharmacodynamic (PD) model for capsaicin-induced dermal vasodilation (CIDV) (E. Moore, M.E. Fraley, I.M. Bell, C.S. Burgey, R.B. White, C.-C. Li *et al.*, unpublished data). In this assay, inhibition of CIDV was measured by laser Doppler scan at 1 and 5 hours after single oral doses of ubrogepant (0.5, 5, and 40 mg) that were selected to capture the expected dynamic range of the exposure-response curve based on the estimated half-maximal effective concentration of 3.2 nM from CIDV experiments in rhesus macaques. The CIDV PK/PD modeling results indicated that the threshold concentration of ubrogepant associated with efficacy (effective concentration 90%) is 23 nM.

Each trial was performed in accordance with the Declaration of Helsinki and the principles of Good Clinical Practice. The conduct of each trial was approved by the relevant institutional review boards and/or ethics committees, and all participants provided written informed consent prior to enrollment.

Trial population

Both trials enrolled healthy nonsmoking men aged 18 to 50 years. Additional inclusion criteria were general good health with body mass index ≤ 30 kg/m² (trial A) or between 18 and 32 kg/m² (trial B); no clinically significant electrocardiogram (ECG) abnormalities; ALT and aspartate aminotransferase (AST) below the upper limit of normal (ULN); total bilirubin less than twofold ULN and (if total bilirubin is greater than the ULN) direct bilirubin within normal limits at screening and prior to first trial drug dose. Potential participants were excluded if they were mentally or legally incapacitated or had significant emotional problems or a history of mental illness that may have confounded trial results; had an estimated creatinine clearance (Cockcroft-Gault equation) of ≤ 80 mL/minute; had a history of hepatic disease; had a history of stroke, chronic seizures, or major neurological disorder (including migraine); or had a history of excessive intake of alcohol or caffeinated beverages or inability to refrain from prohibited medications.

Assessments

Blood samples for PK determination were collected before dosing and at predetermined times after dosing. Following centrifugation, plasma samples were analyzed for ubrogepant concentration at Merck (West Point, PA) using liquid-liquid extraction for analyte isolation followed by liquid chromatographic-tandem mass spectrometric detection for quantitation. For trial B, the lower limit of quantitation was 1 ng/mL (1.82 nM), with a linear calibration range from 1–1,000 ng/mL (1.82–1,820 nM), whereas

a more sensitive assay with a lower limit of quantitation of 0.1 ng/mL (0.182 nM), with a linear calibration range from 0.1–1,000 ng/mL (0.182–1,820 nM), was used in trial A.

Safety assessments included tabulation of AEs and serious AEs (SAEs), as reported; and physical examination, vital sign determination, ECG, and laboratory assessments conducted at predetermined time points during the trial. Laboratory assessments included hematology, blood chemistry, and urinalysis; analyte quantitation was performed using standard established methods. Post-study safety assessments (including ALT evaluation) were conducted 2 weeks and 1 and 2 months after the final dose of study medication.

Statistical analysis

For each trial, all participants who received at least one dose of study medication were included in the analysis of safety. In both trials, hepatic safety was assessed via evaluation of percentage changes from baseline in ALT measurements at various doses and time points.

In trial A, the time to reach steady-state was assessed by using the effective rate of drug accumulation for each participant, obtained from his accumulation ratio of area under the curve from 0 through 24 hours (AUC_{0-24hr}). The effective rate of drug accumulation (η) for each individual (i) was calculated using the following relationship:

$$AUC_{X,i}/AUC_{Y,i} = (1 - \exp(-X\eta\tau)) / (1 - \exp(-Y\eta\tau))$$

where τ is the length of the dosing interval in hours, X is the total number of dosing intervals, and $Y = 1$. In addition, an exploratory dose proportionality analysis of trial A was conducted using the estimates and 95% confidence intervals (CIs) for the slope from the power law model, with $\ln(AUC)$ as the dependent variable and $\ln(\text{dose})$ as the explanatory variable. PK parameters (maximum plasma drug concentration (C_{max}), mean plasma concentration at 2 hours postdose (C_{2hr}), time to C_{max} (t_{max}), and AUC) were calculated using Phoenix WinNonlin Professional, version 6.3 (Certara USA, Inc, Princeton, NJ).

In trial B, the posterior probability that the true mean percent treatment difference in ALT (ubrogepant/placebo) exceeded 50% was calculated at the time point with the largest mean percent treatment difference. A posterior probability $< 70\%$ would provide sufficient evidence to conclude that ubrogepant does not have a clinically meaningful effect on ALT. The principal motivation for the Bayesian methods and use of posterior probability rather than classic, frequentist null hypothesis significance testing is that the latter can obscure the assessment of the target region by using null hypothesis values that are not relevant (e.g., assume 0 as the null value of the parameter) and by using habitual type I error rates (e.g., 0.05) that circumvent an appropriate assessment of risk matched to the current stage of development. Using the clinical target region (50% mean increase) and corresponding posterior probability threshold (70%), a decision rule was set to assess the probability that a clinically meaningful effect exists. The posterior probability provides the level of conditional probability based on randomly observed data. Because it uses a random variable, it is important to summarize its amount of uncertainty. In

this case, the hypothesis for this study included the interval of uncertainty (70%) that the observed effect is the true effect that would be seen in a large population.

RESULTS

Participant disposition and baseline demographics

Forty healthy participants (eight per panel) were enrolled in trial A; all 40 completed the trial. Mean age of trial A participants was 39 years (range 21–51 years), and all were non-Hispanic white men. Thirty-two healthy male participants were enrolled in trial B; all 32 completed the trial. Participants in trial B had a mean age of 38 years (range 25–49 years); the majority (69%) were African–American. Participant demographics are summarized in **Table 1**.

Pharmacokinetics

Administered as an SD-OCT, ubrogepant was rapidly absorbed, with minimal accumulation, following once-daily dosing. **Table 2** summarizes key PK parameters for oral ubrogepant SD-OCT across both trials in fasted healthy male participants. In trial A, median t_{max} for ubrogepant SD-OCT ranged from 2–3 hours, terminal half-life was ~ 3 to 4 hours after single doses, and ~ 7 to 11 hours following multiple once-daily doses. Steady-state was reached within 2 days. There was no evidence for significant accumulation following multiple daily doses. The AUC_{0-24hr} accumulation ratio (90% CI) at day 10 of daily ubrogepant dosing was 0.97 (0.82, 1.15), 1.02 (0.86, 1.20), 0.88 (0.74, 1.04), and 1.07 (0.90, 1.26) for the 40, 100, 200, and 400 mg dose groups, respectively. Mean ubrogepant plasma concentrations vs. time following single oral doses of 100–400 mg ubrogepant in fasted healthy male participants are shown in **Figure 1a**. Mean plasma ubrogepant concentrations vs. time following once-daily oral doses of 40–400 mg ubrogepant for 10 days are shown in **Figure 1b**.

Administration of 100 mg ubrogepant SD-OCT with a high-fat breakfast (fed condition) reduced the observed area

under the curve from 0 to infinity ($AUC_{0-\infty}$) by 16%, C_{2hr} by 59%, and C_{max} by 33% when compared with administration of 100 mg ubrogepant under fasted conditions. Ubrogepant t_{max} was delayed by 1 hour when administered with food (median (min, max): 4.0 hours (2.0, 6.0)) compared with the fasted state (3.0 hours (1.0, 4.0)). Following multiple oral doses of ubrogepant SD-OCT for 10 days (trial A), a C_{2hr} of > 23 nM was attained at doses of 40 mg and higher. This value is the threshold PK target predicted to be associated with efficacy for ubrogepant based on a population PK/PD model for CIDV in healthy young men (E. Moore, M.E. Fraley, I.M. Bell, C.S. Burgey, R.B. White, C.-C. Li *et al.*, unpublished data).

In trial B, $AUC_{0-24hour}$ and C_{max} values following once-daily administration of ubrogepant SD-OCT 150 mg were consistent with trial A results in the 40–400 mg dose range (**Table 2, Figure S1**). Mean ubrogepant plasma concentrations vs. time in fasted healthy adult men following once-daily 150 mg ubrogepant SD-OCT are plotted in **Figure 2**. In trial B, median t_{max} for ubrogepant SD-OCT was 2.26–3 hours and the terminal half-life was 9.9 hours at day 28. The AUC_{0-24hr} accumulation ratio (90% CI) at day 28 of daily dosing (trial B) was 1.09 (1.00, 1.18). In trial A, ubrogepant PK exposure increased with dose over the investigated dose range (40–400 mg); estimates of slope (95% CI) were 1.08 (0.90, 1.25) for AUC_{0-24hr} and 1.13 (1.00, 1.26) for C_{max} , suggesting approximately dose-proportional exposure. Because ubrogepant has minimal urinary excretion in humans, urine PK was not included in these studies.

Safety

In trial A, single (100–400 mg) and multiple (40–400 mg) doses of ubrogepant were well-tolerated in healthy male participants. There were no SAEs reported, and no participant discontinued due to an AE. No clinically significant abnormalities were noted in routine serum chemistry,

Table 1 Participant characteristics

| Characteristics | Trial A | | | | | Trial B | |
|---------------------------|---------|--------------------|---------|---------|---------|---------|--------|
| | Panel A | Panel B | Panel C | Panel D | Panel F | Placebo | 150 mg |
| No. of participants | 8 | 8 | 8 | 8 | 8 | 10 | 22 |
| Men, % | 100 | 100 | 100 | 100 | 100 | 100 | 100 |
| Age (years) | | | | | | | |
| Mean | 37 | 42 | 40 | 35 | 43 | 39 | 38 |
| Median | 35 | 45 | 45 | 38 | 46 | 40 | 38 |
| Range | 24–49 | 22–51 ^a | 22–50 | 21–48 | 26–50 | 30–48 | 25–49 |
| Race, % | | | | | | | |
| White | 100 | 100 | 100 | 100 | 100 | 20 | 14 |
| Black or African American | 0 | 0 | 0 | 0 | 0 | 70 | 68 |
| Multiple | 0 | 0 | 0 | 0 | 0 | 10 | 18 |
| Ethnicity, % | | | | | | | |
| Hispanic or Latino | 0 | 0 | 0 | 0 | 0 | 0 | 9 |
| Not Hispanic or Latino | 100 | 100 | 100 | 100 | 100 | 100 | 91 |

Panel E was not conducted.

^aOne participant turned 51 after screening.

Table 2 Statistical summary for plasma pharmacokinetic parameters of oral ubrogepant (SD-OCT formulation)

| Pharmacokinetic parameters | Trial A, part 1 (single dose of ubrogepant) | | | | Trial A, part 2 (once-daily ubrogepant for 10 days) | | | | Trial B (once-daily ubrogepant for 28 days) | |
|---|---|----------------------|----------------------|----------------|---|----------------------|----------------------|----------------------|---|-----------------|
| | 100 mg (n = 6) | 200 mg (n = 6) | 400 mg (n = 6) | 400 mg (n = 6) | 40 mg (n = 6) | 100 mg (n = 6) | 200 mg (n = 6) | 400 mg (n = 6) | 150 mg (n = 22) | 150 mg (n = 22) |
| Day 1 (first dose) | | | | | | | | | | |
| AUC _{0-∞} (95% CI), nM·hour ^a | 1,960 (1,450, 2,670) | 4,420 (3,260, 6,000) | 6,850 (5,050, 9,290) | - | - | - | - | - | - | - |
| AUC _{0-24 h} (95% CI), nM·hour ^a | 1,950 (1,430, 2,650) | 4,350 (3,200, 5,910) | 6,680 (4,910, 9,080) | 598 (461, 776) | 1,690 (1,300, 2,190) | 3,250 (2,500, 4,220) | 7,050 (5,430, 9,150) | 2,210 (1,870, 2,610) | - | - |
| C _{2hr} ^r (95% CI), nM ^a | 344 (241, 491) | 846 (590, 1,210) | 1,160 (810, 1,670) | - | - | - | - | - | 247 (186, 329) | - |
| C _{max} ^r (95% CI) ^a nM | 344 (241, 491) | 846 (590, 1,210) | 1,160 (810, 1,670) | 134 (106, 169) | 316 (250, 400) | 591 (467, 746) | 1,140 (900, 1,440) | 411 (341, 496) | - | - |
| t _{max} ^r hour ^b | 3 (1, 4) | 3 (2, 4) | 2 (2, 4) | 1.75 (1, 3) | 2.5 (2, 4) | 3 (1, 3) | 3.5 (2, 4) | 2.26 (1, 6) | - | - |
| t _{1/2} ^r hour ^c | 3.4 (7.9) | 4.2 (18.4) | 4.3 (20.3) | - | - | - | - | - | - | - |
| Day 10 (last dose) | | | | | | | | | | |
| C _{max} ^r nM (95% CI) ^a | - | - | - | 95 (75.2, 120) | 302 (239, 382) | 543 (430, 686) | 1,340 (1,060, 1,700) | - | - | - |
| t _{max} ^r hour ^b | - | - | - | 3 (2, 3) | 3.5 (1, 4) | 2 (1, 3) | 2 (1, 4) | - | - | - |
| t _{1/2} ^r hour ^c | - | - | - | 7.3 (34.7) | 6.7 (62.7) | 11.2 (80.2) | 7.8 (29.1) | - | - | - |
| Day 28 (last dose) | | | | | | | | | | |
| C _{max} ^r nM (95% CI) ^a | - | - | - | - | - | - | - | - | 465 (385, 561) | - |
| t _{max} ^r hour ^b | - | - | - | - | - | - | - | - | 3 (0.70, 4.07) | - |
| t _{1/2} ^r hour ^c | - | - | - | - | - | - | - | - | 9.9 (51.6) | - |

AUC_{0-∞}^r, area under the concentration-time curve from zero to infinity; AUC_{0-24h}^r, 0-24-hour area under the concentration-time curve; C_{2hr}^r, mean plasma concentration at 2 hours postdose; CI, confidence interval; C_{max}^r, maximum plasma concentration; SD-OCT, spray-dried oral compressed tablet; t_{1/2}^r, half-life; t_{max}^r, time to C_{max}^r.
^aBack-transformed least squares mean and 95% CI from linear mixed effects model performed on natural log-transformed values. ^bMedian (min, max) reported for t_{max}^r. ^cGeometric mean and percentage geometric coefficient of variation reported for apparent terminal t_{1/2}^r.

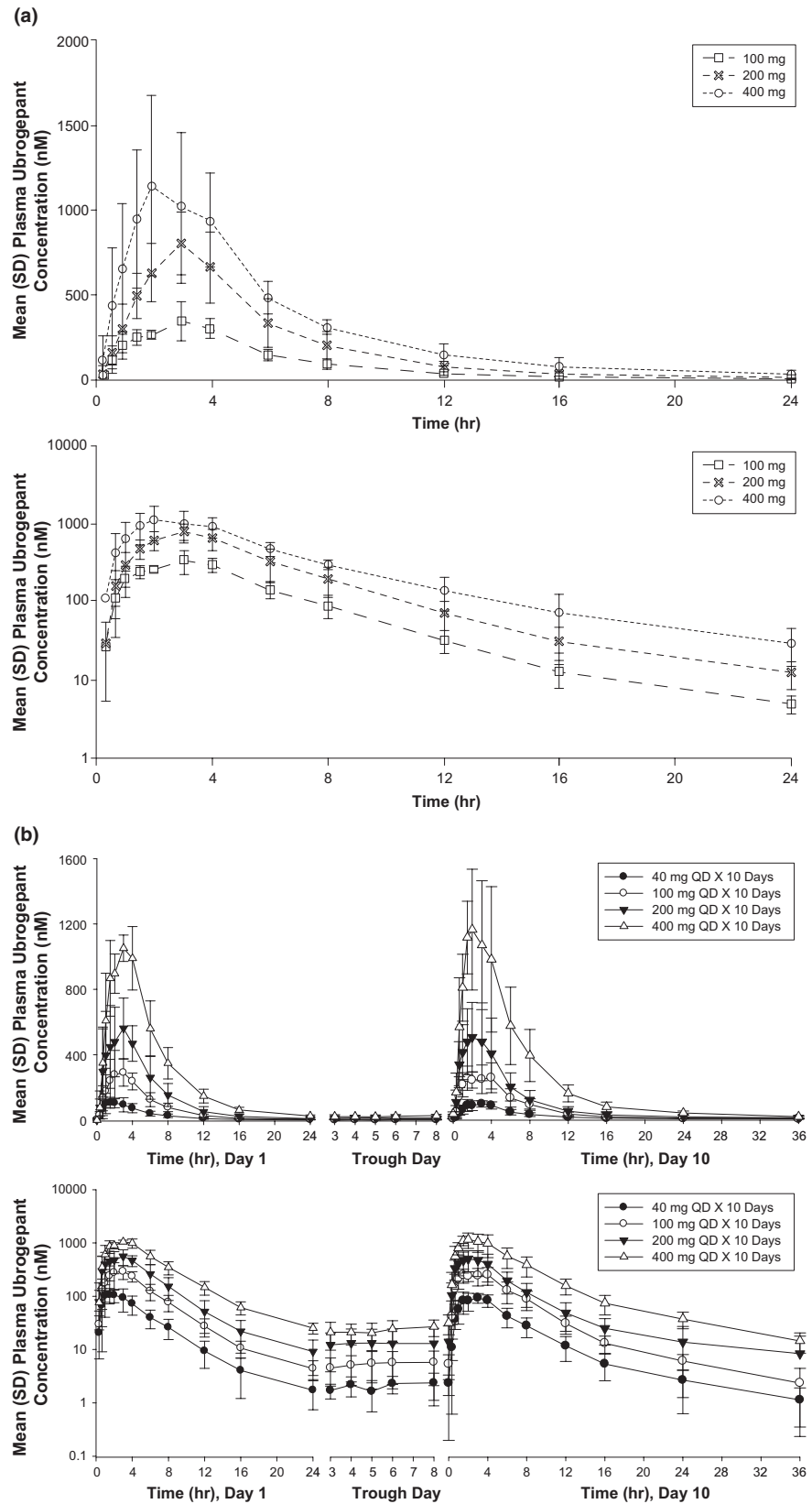


Figure 1 Trial A: Mean (\pm SD) ubrogепant plasma concentrations in healthy participants. (a) Part 1 following administration of 100–400 mg doses in 24 hours, and (b) part 2 following administration of 40–400 mg doses once daily for 10 days. Top panel: Linear scale, bottom panel: semi-log scale.

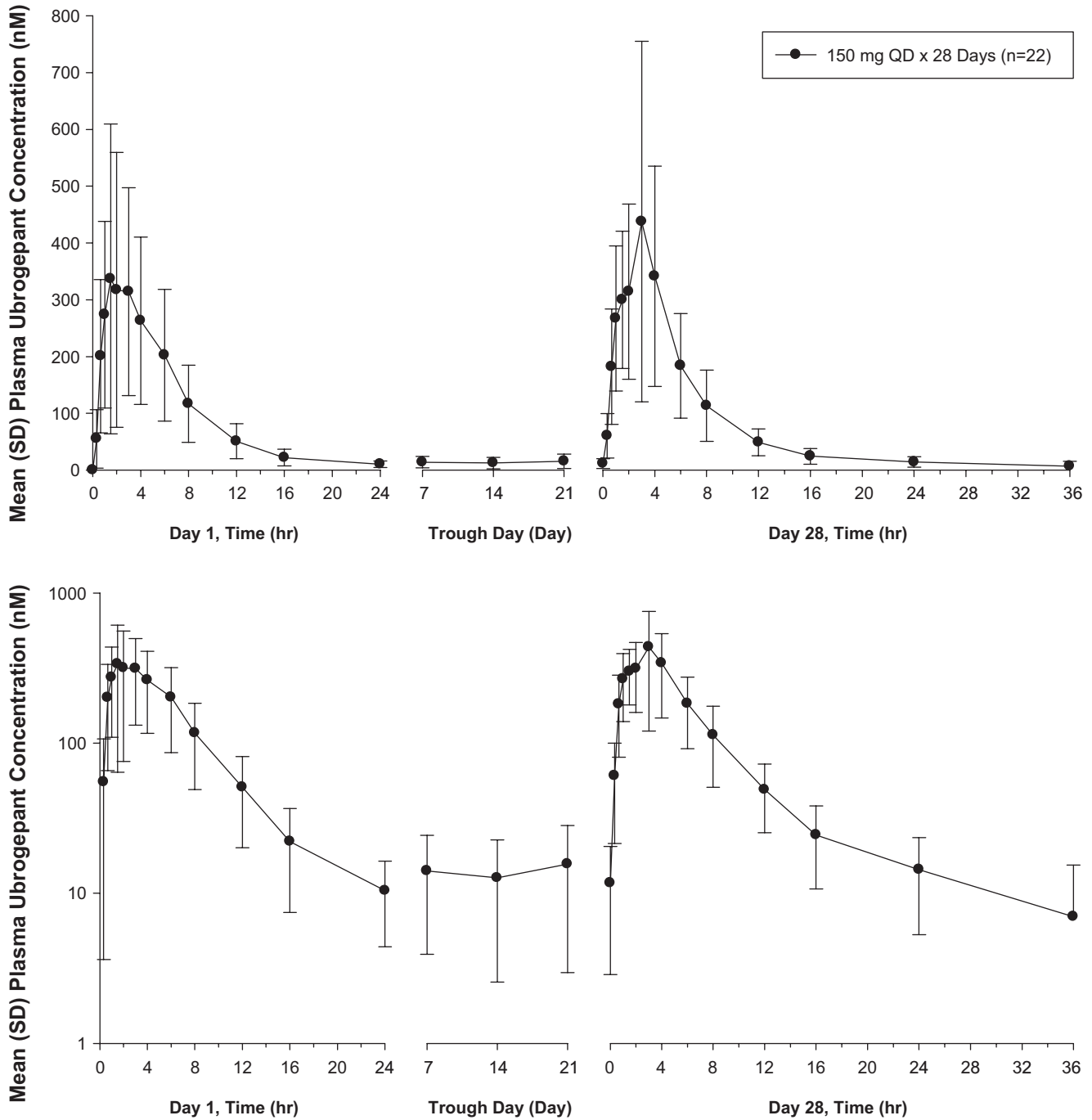


Figure 2 Trial B: Mean (\pm SD) ubrogепant plasma concentration following administration of once-daily 150 mg doses for 28 days in fasted healthy participants. Top panel: Linear scale, bottom panel: semi-log scale.

hematology, urinalysis, ECG, or vital signs. All reported clinical AEs were mild or moderate in intensity. In trial A, part 1, no AE was experienced in ≥ 1 participant, except for nasopharyngitis (one participant each from the placebo and ubrogепant groups). In trial A, part 2, AEs reported by more than two participants included nausea (ubrogепant $n = 2$, placebo $n = 2$), headache (ubrogепant $n = 1$, placebo $n = 2$), diarrhea (ubrogепant $n = 1$, placebo $n = 2$), and nasopharyngitis (ubrogепant $n = 3$, placebo $n = 0$).

In trial B, once-daily ubrogепant 150 mg for 28 days was well-tolerated, with no SAEs and no discontinuations due to an AE. There were no clinically significant abnormalities with respect to laboratory assessments, ECGs, or vital signs. All reported AEs were mild or moderate in intensity, with the exception of one participant who reported severe flank pain and nephrolithiasis; this participant continued in the trial after diagnosis of a kidney stone unrelated to trial drug administration. AEs reported by more than two participants included contusion (ubrogепant $n = 5$, placebo $n = 1$), excoriation

(ubrogapant $n = 2$, placebo $n = 1$), scratch (ubrogapant $n = 1$, placebo $n = 2$), and dizziness (ubrogapant $n = 4$, placebo $n = 0$).

Hepatic safety. In trial A, part 1, the mean percentage changes from baseline in ALT at 24 hours with single-dose ubrogapant under fasted conditions ranged from -0.21% to 1.91% , compared with a placebo change of -1.63% (Table 3). Under fed conditions, the percentage ALT change from baseline was 10.04% and -6.25% for ubrogapant and placebo, respectively. In trial A, part 2, the mean percentage changes from baseline in ALT at day 10 following once-daily SD-OCT ubrogapant (40–400 mg) ranged from -33.57% to 3.69% , compared with a -2.86% change with placebo (Table 3). There was no evidence of a dose relationship with respect to percentage change from baseline in ALT. No participant demonstrated an ALT elevation $\geq 3 \times$ ULN.

In trial B, mean serum ALT levels in the ubrogapant 150 mg group were similar to placebo throughout the 28-day trial duration (Figure 3). The mean percentage change from baseline in ALT 24 hours after the day 28 dose was -4.15% vs. 7.09% in ubrogapant and placebo, respectively (Table 4). During the 28-day treatment period, the mean percentage change from baseline in ALT ranged from -15.69% to 0.83% for ubrogapant and -2.22% to 9.22% for placebo. No individual participant demonstrated an ALT elevation $\geq 3 \times$ ULN.

Mean treatment differences in ALT (ubrogapant/placebo percentage change) and posterior probabilities are summarized in Table S1. Based on the observed patterns of ALT values, the percentage changes in treatment differences were negative at all time points. Given these values, the corresponding probability that the “true” percentage change exceeded 50% was $< 0.1\%$ throughout the trial.

DISCUSSION

Taken together, the results of these two trials provide support for the safety and tolerability of ubrogapant, and, importantly, its hepatic safety profile. Ubrogapant, administered at single doses up to 400 mg and multiple doses up to 400 mg q.d. for 10 days (trial A) and at 150 mg q.d. for 28 days (trial B) to healthy male participants, was not associated with any SAEs or clinically significant abnormalities in ECGs, vital signs, or laboratory safety assessments. In trial A, changes in serum ALT were minimal and similar between ubrogapant and placebo; there was no evidence of a dose effect. In trial B, once-daily administration of ubrogapant 150 mg (a dose 1.5-fold greater than the anticipated clinical dose) did not have a clinically meaningful effect on serum ALT levels over 28 days of administration. Percentage changes from baseline in serum ALT following ubrogapant treatment were low ($< 5\%$) and lower than the time-matched changes from baseline for

Table 3 Percentage change from baseline in ALT associated with oral ubrogapant in fasted healthy men for 10 days

| Treatment | Trial A, part 1 (single doses of ubrogapant) ^a | | | Trial A, part 2, once-daily ubrogapant for 10 days ^b | | |
|-----------|---|--|------|---|--|------|
| | N | Percentage change from baseline ^c | SE | N | Percentage change from baseline ^c | SE |
| Placebo | 8 | -1.63 | 7.66 | 8 | -2.86 | 4.93 |
| 40 mg | - | - | - | 6 | -11.28 | 7.65 |
| 100 mg | 6 | 1.91 | 7.30 | 6 | 3.69 | 7.75 |
| 200 mg | 6 | 0.51 | 9.15 | 6 | -19.39 | 7.23 |
| 400 mg | 6 | -0.21 | 3.69 | 6 | -33.57 | 3.66 |

ALT, alanine aminotransferase.

^aData from 24 hours following single doses of 100–400 mg of oral ubrogapant. ^bData from day 10, 24 hours following multiple-dose administration of 40–400 mg oral ubrogapant. ^cDay 1, predose measurement serves as baseline.

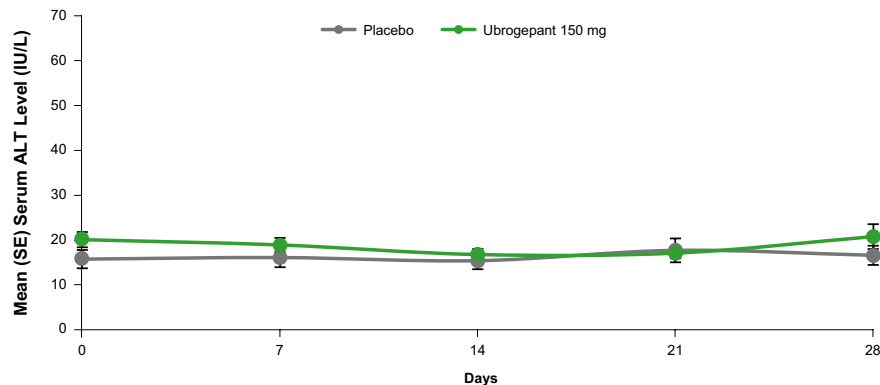


Figure 3 Trial B: Mean (\pm SE) serum ALT following the administration of ubrogapant 150 mg or placebo for 28 days. ALT, serum alanine aminotransferase.

Table 4 Statistical summary for serum ALT following multiple-dose administration of ubrogепant 150 mg or placebo

| Time | Percentage change (95% CI) from baseline ^a | |
|------------------|---|----------------------------------|
| | Placebo (n = 10), mean | Ubrogепant 150 mg (n = 22), mean |
| Day 1, 24 hours | -2.22 (-15.52, 13.18) | -3.59 (-12.64, 6.40) |
| Day 7, predose | 3.05 (-10.97, 19.27) | -5.08 (-13.99, 4.76) |
| Day 14, predose | -1.76 (-15.12, 13.71) | -15.69 (-23.60, -6.95) |
| Day 21, predose | 9.22 (-5.64, 26.42) | -12.65 (-20.85, -3.60) |
| Day 28, predose | 5.63 (-8.74, 22.26) | -0.83 (-10.14, 9.44) |
| Day 28, 24 hours | 7.09 (-7.48, 23.95) | -4.15 (-13.14, 5.78) |

ALT, alanine aminotransferase; CI, confidence interval.

^aBaseline is the geometric mean of the day - 1 and day 1 predose values.

placebo. In addition, participants were evaluated for 2 months after the final ubrogепant dose to rule out the possibility of delayed ALT elevations as were observed in previous trials of first-generation CGRP antagonists; no elevations were detected.

The PK profile of ubrogепant SD-OCT as observed in trials A and B, achieving maximal plasma levels in 1.75 to 3.5 hours and demonstrating a half-life of ~ 7 to 11 hours, is consistent with its suitability for use as an acute treatment for migraine attacks. The SD-OCT formulation differs slightly from the final formulation of ubrogепant used in phase III clinical trials.^{36,37} The final ubrogепant formulation is a hot-melt extrusion tablet, which exhibited faster absorption (k_a increased by approximately eightfold) and higher bioavailability (F1 increased by 14%) and, thus, modestly higher C_{2hr} than the SD-OCT formulation.³⁸ In trial A, C_{2hr} following 10 days of dosing with the SD-OCT formulation ranged from 77.51 to 110 nM, well above the human effective concentration 90% target of 23 nM estimated using the CIDV model of CGRP target engagement shown to predict clinical efficacy with previously studied CGRP antagonists (E. Moore, M.E. Fraley, I.M. Bell, C.S. Burgey, R.B. White, C.-C. Li et al., unpublished data).^{39,40} The 2-hour time point is an important point of reference, given that pain freedom at 2 hours is a recommended efficacy measure in clinical trials for treatment of migraine attacks.

The upper range of the doses evaluated in trial A resulted in peak concentrations after 10 days of daily dosing that were more than fourfold greater ($C_{max} = 1,340$ nM with ubrogепant 400 mg) than observed with the highest phase III clinical dose (100 mg; $C_{max} = 302$ nM). The 150 mg dose evaluated in trial B resulted in maximum plasma drug concentrations that were 54% higher on the 28th day of daily dosing ($C_{max} = 465$ nM) than those observed with the 100 mg dose after 10 days of daily dosing in trial A. Thus, both trials evaluated the safety profile of doses of ubrogепant that resulted in plasma concentrations that were substantially greater than therapeutically relevant levels (i.e., suprathеrapeutic). Assessing safety outcomes with suprathеrapeutic doses is recommended for the evaluation of the cardiovascular safety of new drugs⁴¹ and is an important strategy for characterizing hepatic safety in early drug development.

Ubrogепant demonstrated significant efficacy in the acute treatment of migraine attacks in two phase III clinical

trials, ACHIEVE I and ACHIEVE II. In both trials, participants were administered one dose of trial medication (placebo or ubrogепant 25, 50, or 100 mg) to treat a single migraine attack of moderate/severe pain intensity, with an optional second dose of study medication after 2 hours.^{36,37} Thus, the dosage and administration frequency of ubrogепant in the current trials were higher than in the phase III trials or what would be expected in real-world use. All cases of ALT or AST elevation $\geq 3 \times$ ULN in the ACHIEVE trials were evaluated by a panel of liver experts blinded to treatment allocation. Among the total safety population of the two ACHIEVE trials ($N = 2,901$), there were six cases of ALT or AST elevation $\geq 3 \times$ ULN in ACHIEVE I and four cases in ACHIEVE II. In ACHIEVE I, four of the six cases (all ubrogепant) were adjudicated as unlikely to be related, two of the six (one ubrogепant and one placebo) were adjudicated as possibly related, and no cases were adjudicated as probably related to study medication.³⁶ In ACHIEVE II, three of the four cases (all ubrogепant) were adjudicated as unlikely to be related, one of four cases (placebo) was adjudicated as possibly related, and no cases were adjudicated as probably related to study medication.³⁷

The long-term safety of the 50 and 100 mg doses of ubrogепant was also studied in a 52-week trial.⁴² In this trial, ALT or AST $\geq 3 \times$ ULN were found in 1.3% (5/399) and 2.7% (11/406) of participants receiving ubrogепant 50 and 100 mg, respectively. In this trial, three cases were considered possibly or probably related to ubrogепant; however, these three ubrogепant participants with ALT or AST elevations $\geq 3 \times$ ULN had possible confounding factors, including alcohol use, urinary tract infection, and psoriasis flare, that may have caused the abnormalities. All three cases were asymptomatic, with no concurrent bilirubin elevation, and resolved in participants who continued treatment. The findings from this trial suggested little to no sign of ubrogепant-related hepatotoxicity with long-term ubrogепant use.

In a dedicated hepatic safety trial of ubrogепant, 518 healthy adults were randomized to placebo or ubrogепant 100 mg administered via high-frequency intermediate dosing (2 days of ubrogепant followed by 2 days of placebo).⁴³ A total of seven cases of ALT/AST $\geq 3 \times$ ULN were reported during the 8 weeks of treatment, with five cases occurring in placebo participants and two cases reported in the ubrogепant group. Within the ubrogепant group, one case was judged possibly related to trial medication and the other case was judged probably related to trial medication. Both cases were asymptomatic and resolved with continued dosing.

Limitations of the current trials include a relatively small sample size and the inclusion of healthy men only. However, results from recently completed clinical trials in men and women with migraine have demonstrated a hepatic safety profile consistent with the results reported in the current study, suggesting these results are generalizable to the larger migraine population. Trial strengths include the use of varying doses (40–400 mg in trial A; 150 mg in trial B) and duration of treatment (single dose, 10 or 28 days of once-daily treatment). These regimens involve dosing and an administration frequency well above those expected in

either clinical trials or real-world clinical practice. The absence of hepatotoxicity in these trials, along with the lack of serious hepatic enzyme elevations in larger randomized clinical trials, strongly supports the absence of ubrogepant-associated hepatotoxicity.

In conclusion, the PK and safety results from these two studies, particularly the hepatic safety profile, support the continued development of ubrogepant for treatment of migraine. In addition to its PK profile, which is suitable for the acute treatment of migraine attacks, single and multiple daily ubrogepant doses up to 400 mg were safe and well-tolerated. There was no evidence of clinically meaningful drug-related ALT elevations in healthy men who received daily dosing of ubrogepant up to 400 mg over 10 days or 150 mg over 28 days, supporting its lack of hepatotoxicity. More generally, although these studies were relatively small and short, results from subsequent larger and longer safety studies support the use of short-duration, suprathreshold dosing as an appropriate derisking assessment for hepatic safety in early drug development.

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

Figure S1. Comparison of mean AUC_{0-24hr} and C_{max} of ubrogepant vs. dose following administration of multiple oral doses in healthy male participants. AUC_{0-24hr} , area under the curve from 0 through 24 hours; C_{max} , maximum plasma concentration.

Table S1. Summary of percentage change in treatment difference and posterior probabilities.

Table S2. Adverse events reported by ≥ 1 participant in trial A (SD-OCT formulation).

Table S3. Adverse events reported by ≥ 1 participant in trial B.

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Conflict of Interest. W.A., P.B., J.P., W.L., M.F.D., C.M., and D.P. are employees of Merck Sharp & Dohme, a subsidiary of Merck Kenilworth, NJ, USA, and owns/holds stock/stock options of Merck, Kenilworth, NJ, USA. E.E.M., C.-C.L., and J.A.W. worked for Merck at the time of the study and owned Merck stock. T.R. is an employee of MSD Belgium, with stock in the company. A.J. is an employee and shareholder of Allergan plc. As Editor-in-Chief for *Clinical and Translational Science*, J.A.W. was not involved in the review or decision process for this paper. S.M. has no conflicts to report. W.K.K. has no conflicts to report.

Data Availability Statement. Data reported in this paper are available within the article and its **Supplementary Materials**. Allergan may share de-identified patient-level data and/or study-level data, including protocols and clinical study reports, for phase I trials completed after 2008 that are registered on ClinicalTrials.gov or EudraCT. The indication studied in the trial must have regulatory approval in the United States and/or the European Union and the primary manuscript from the trial must be published prior to data sharing. To request access to the

data, the researcher must sign a data use agreement. All shared data are to be used for noncommercial purposes only. More information can be found on <http://www.allerganclinicaltrials.com/>.

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