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RESEARCH SUBMISSION

Comparative bioavailability of single-dose zavegepant during and between migraine attacks: A phase 1, randomized, open-label, fixed-sequence, two-period study

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Abstract

Objective: To compare the rate and extent of absorption of zavegepant 10 mg (therapeutic dose) or 20 mg (supratherapeutic dose) nasal spray during a migraine attack versus non-migraine period, assess safety, and explore efficacy and the relationship between zavegepant concentration and therapeutic response.

Background: Physiologic changes occurring during a migraine attack could affect the pharmacokinetics of treatments for migraine.

Methods: This was a Phase 1, multicenter, open-label, randomized, single-dose, two-period, fixed-sequence, comparative bioavailability study. Participants with a history of 2–8 migraine attacks per month of moderate or severe pain intensity were randomized to a single dose of zavegepant 10 or 20 mg, administered intranasally during a migraine attack (Period 1) and in a non-migraine period (Period 2). Blood samples were collected pre-dose and at pre-specified intervals up to 24 h post-dose for plasma zavegepant concentration measurement. Safety was monitored throughout, and efficacy (migraine pain intensity score, nausea, photophobia, phonophobia, aura, and functional disability) assessed during Period 1. Plasma zavegepant pharmacokinetic parameters were calculated by standard noncompartmental methods, including maximum plasma concentration (C_{max}), area under plasma concentration–time curve from time zero to infinity (AUC_{0-inf}), and time of C_{max} (T_{max}).

Results: A total of 37 participants were evaluable for pharmacokinetics. Following administration of zavegepant 10 mg, geometric mean ratios for Period 1/Period 2 were 82.8% (90% confidence interval [CI] 60.5–113.2) for C_{max} and 90.1% (90% CI 70.2–115.5) for AUC_{0-inf}. Following administration of zavegepant 20 mg, geometric mean ratios for Period 1/Period 2 were 72.5% (90% CI 57.9–90.8) for C_{max} and 73.4% (90% CI 58.8–91.7) for AUC_{0-inf}. Averaging over the study period, geometric mean ratios for zavegepant 20 mg/10 mg were 142.5% (90% CI 118.6–171.4) for C_{max} and 157.0%

Abbreviations: ANOVA, analysis of variance; AUC, area under concentration–time curve; AUC_{0-inf}, AUC from time zero to infinity; AUC_{0-t}, AUC from time zero to the last non-zero concentration; $C_{0.5h}$, observed plasma concentration at 0.5 h; C_{2h}, observed plasma concentration at 2 h; CI, confidence interval; C_{max}, observed maximum plasma concentration; CV, coefficient of variation; PK, pharmacokinetics; TEAE, treatment-emergent adverse event; T_{max}, time of C_{max}.

(90% CI 133.6–184.5) for AUC_{0-inf}. Median T_{max} was 0.5 h for both doses regardless of Period. Zavegepant was well tolerated in both study periods and effective during Period 1 at both dose levels. There was no apparent correlation between concentration at 0.5 h or 2 h post-dose and efficacy outcomes.

Conclusion: Zavegepant exposure was comparable during a migraine attack and a non-migraine period, particularly at the therapeutic dose of 10 mg. When averaging over migraine and non-migraine periods, there was a less-than-dose proportional increase in zavegepant exposure when the dose was doubled from 10 to 20 mg. The median T_{max} was 0.5 h regardless of migraine attack or dose. Zavegepant 10 and 20 mg exhibited favorable safety profiles during migraine attacks and non-migraine periods, and were effective to relieve pain, associated symptoms, and functional disability during migraine attacks, with no apparent correlation between zavegepant concentration and efficacy outcomes.

Plain Language Summary

Nasal symptoms during a migraine attack might affect treatments given as a nasal spray, so it is important to understand how zavegepant nasal spray is absorbed. This clinical trial compared the absorption of zavegepant nasal spray during and between migraine attacks. The results showed that absorption of zavegepant was similar during and between migraine attacks, so nasal administration during a migraine attack does not appear to affect how it is absorbed.

KEYWORDS
calcitonin gene-related peptide receptor antagonist, intranasal, migraine, pharmacokinetics, zavegepant

INTRODUCTION

Physiologic changes occurring during a migraine attack can affect the pharmacokinetics (PK) of treatments for migraine. The gastrointestinal stasis and delayed gastric emptying associated with migraine can delay the absorption of and exposure to orally administered treatments.[1–3] Symptoms during migraine attacks can further impact the delivery of treatment. Nausea and/or vomiting are common during migraine attacks,[4–7] so non-oral treatments such as intranasal agents[8] can be more suitable for some patients.

Zavegepant, a small molecule calcitonin gene-related peptide receptor antagonist administered as a nasal spray, is indicated in the United States for the acute treatment of migraine with or without aura in adults.[9] Zavegepant was demonstrated to be effective for the acute treatment of migraine in double-blind, placebo-controlled clinical trials.[10,11]

Migraine is associated with rhinitis,[12] and nasal symptoms (nasal obstruction, congestion) and olfactory changes (odor-related disturbances and triggers, osmophobia, microsmia) can accompany migraine attacks,[13–15] so it is important to determine the PK of zavegepant during and between attacks. The present study tested the hypothesis that there would be no effect of the presence of a migraine attack versus no attack on the absorption of zavegepant. The primary objective of this study was to compare the rate and extent of absorption of zavegepant intranasal solution, when administered as a single dose of 10 or 20 mg, to participants with migraine during a migraine attack versus a non-migraine period. Secondary objectives included assessment of safety and tolerability and PK of zavegepant 10 and 20 mg during a migraine attack and a non-migraine period. The effectiveness of zavegepant for the acute treatment of migraine and the relationship between zavegepant concentration and therapeutic response were explored.

METHODS

Study design

These primary, pre-specified analyses were from a Phase 1, multicenter, open-label, randomized, single-dose, two-period, fixed-sequence study, comparing the bioavailability and absorption of zavegepant during a migraine attack (Period 1) with a non-migraine period (Period 2). The study was conducted from September 29, 2020, through August 25, 2021, across four clinical research sites (see Supplementary Materials) in accordance with Good Clinical

Practice, as defined by the International Council for Harmonisation and the United States Code of Federal Regulations, Title 21, Part 50. Before the study initiation, Institutional Review Board/Independent Ethics Committee approval was required for the protocol, consent form, recruitment materials/process, and other written information to be provided to participants. All participants provided written informed consent prior to any study activities.

Healthy males and females were eligible if they were aged 18–80 years with body mass index >18.5 and <35.0 kg/m^2, body weight ≥50.0 kg for males and ≥45.0 kg for females, and they were a nonsmoker or light smoker (≤five cigarettes or equivalent daily). For inclusion, participants were required to have a ≥1-year history of migraine (with or without aura) consistent with a diagnosis according to the International Classification of Headache Disorders (third edition),[16] with onset of migraine attacks prior to the age of 50 years, 2–8 migraine attacks/month of moderate or severe pain intensity in the 3 months prior to screening, and migraine attacks lasting, on average, 4–72 h if untreated. Excluded were participants with clinically significant history of nasal conditions (e.g., severe septum deviation or nasal deformity, inflammation, perforation, mucosal erosion, localized infection or ulceration, congestion, polyposis, rhinorrhea, nasal surgery within the previous 6 months, or nasal trauma). Other key exclusion criteria were chronic tension-type headache for ≥15 days/month, inability to distinguish between tension and migraine headaches, and basilar or hemiplegic migraine.

Participants were admitted to the clinical site for Period 1 as soon as possible after the onset of a migraine of moderate or severe pain intensity. They were randomized and dosed in Period 1 if they met the following criteria at admission: migraine onset was within the 4 h prior to admission; the migraine was of moderate or severe pain intensity and was maintained at this intensity at the time of dosing (based on a 4-point numeric rating scale: 0 = none, 1 = mild, 2 = moderate, 3 = severe); no prescription or non-prescription medication had been taken since onset of the migraine; and the migraine was associated with at least one of nausea, photophobia, phonophobia, or aura. Participants returned and were admitted to the clinical site during a non-migraine period for Period 2 dosing, at least 4 days but no more than 60 days (washout period) after Period 1 dosing. In both periods, they were discharged on Day 2.

Intervention

Zavegepant 10 mg (0.1 mL of 100 mg/mL) single intranasal dose solution in Aptar Unidose spray device was provided by Renaissance Lakewood, LCC. Participants were randomized 1:1 to parallel groups receiving zavegepant 10 mg (therapeutic dose) or zavegepant 20 mg (supratherapeutic dose). Participants were randomized according to the randomization scheme, with participant numbers from the randomization list allocated to each site, and the randomization code was concealed from the bioanalytical laboratory until the study was complete. In each period, study personnel administered one dose of the intervention to each participant.

Participants randomized to zavegepant 10 mg received one spray (0.1 mL) in one nostril, for a total dose of 10 mg, and the same nostril was used in both periods. Participants randomized to zavegepant 20 mg received one spray (0.1 mL) in each nostril, for a total dose of 20 mg, in both periods. After the dose was administered, participants were instructed to remain seated upright for ~10 min, not to blow their nose for 2 h after dosing, and to gently sniff up any nasal drip.

Assessments

The primary objective was to compare the rate and extent of absorption of zavegepant during Period 1 versus Period 2. In each period, a total of 17 blood samples (each of 2 mL) were drawn from each participant for analysis of zavegepant plasma concentration: prior to drug administration and at 5, 10, 20, 30, 40, 50, 60, 80, and 100 min, and 2, 3, 4, 8, 12, 16, and 24 h post-dose.

Secondary objectives included assessment of safety and tolerability of zavegepant during Period 1 and Period 2. Treatment-emergent adverse events (TEAEs), defined as any event not present prior to the initiation of the drug treatment or any event already present that worsened in either intensity or frequency following exposure to the drug treatment, were assessed throughout both study periods.

Efficacy was assessed as an exploratory objective in Period 1, prior to drug administration and at 0.5, 1, 2, 4, and 24 h post-dose. Four-point numeric rating scales, administered by study personnel, were used to assess migraine pain intensity (0 = none, 1 = mild, 2 = moderate, 3 = severe), the status of each migraine-associated symptom of nausea, photophobia, phonophobia, and aura (0 = none, 1 = mild, 2 = moderate, 3 = severe), and functional disability (0 = normal, 1 = mildly impaired, 2 = severely impaired, 3 = requires bedrest).

Analytical methods

Quantification of zavegepant in ethylenediaminetetraacetic acid K_2 plasma used a validated liquid chromatography, tandem mass spectrometry method. Analyte and internal standard stock, intermediate, working, and reference solutions were prepared and handled under a sodium lamp (protected from light) using glass-free material and stored in amber polypropylene tubes; sample collection and processing were conducted under ambient light conditions but away from direct sunlight; and samples were stored in amber polypropylene tubes. An internal standard (BHV3500-d_8) and automated solid phase extraction were used. Samples (0.075 mL) were analyzed on an ACE EXCEL 2 C18-PFP column (50 × 3.0 mm, 2 μm) maintained at 40°C, with a flow rate of 0.5 mL/min using isocratic analysis followed by column flush. Mobile Phase A was Milli-Q type water/acetonitrile (75/25) with ammonium acetate 5 mM and formic acid 0.1%. Mobile Phase B was Milli-Q type water/acetonitrile (5/95) with ammonium formate 2 mM and formic acid 0.2%. Detection was

performed by API 5000 equipped with an electrospray (AB Sciex, Toronto, Canada). The lower limit of quantitation was 40 pg/mL and the calibration range was 40 to 50,000 pg/mL. The precision of the assay (percentage coefficient of variation [%CV]) was 0.92% to 4.04% within runs and 1.61% to 6.44% between runs. The accuracy of the assay (% bias) was −2.96% to 5.00% within runs and 0.85% to 3.47% between runs.

PK methods and statistical analyses

There was no formal sample size evaluation. The data from the enrolled participants were considered sufficient to meet the study objectives. The PK population included all participants who completed the study and for whom the PK profile could be adequately characterized. Safety was assessed in all participants who received one or more doses of zavegepant. The efficacy population comprised all participants who received one or more doses of zavegepant who had a migraine of moderate or severe pain intensity at the time of dosing in Period 1 and who had post-dose efficacy data.

The PK parameters were calculated by standard noncompartmental methods for plasma zavegepant, including area under the concentration-time curve (AUC) from time zero to infinity (AUC_{0-inf}) and from time zero to the last non-zero concentration (AUC_{0-t}), observed maximum plasma concentration (C_{max}), observed plasma concentration at 0.5 ($C_{0.5h}$), and 2 h (C_{2h}) post-dose, residual area, time of observed maximum concentration (T_{max}), terminal elimination half-life, effective half-life (calculated as ln (2) × mean residence time extrapolated to infinity), elimination rate constant, apparent total body clearance, and apparent volume of distribution. Where plasma concentration was missing or not reportable for three or more of the last samples (i.e., time points past T_{max}), if the data were deemed reliable for C_{max} and T_{max}, these were calculated, and other PK parameters were not reported for that participant. The PK data were summarized descriptively using geometric mean with %CV and arithmetic mean with standard deviation. Actual sampling times were used for PK and statistical analyses. PK analysis was performed using a validated Phoenix WinNonlin, version 8.0 (Certara USA Inc., Radnor, PA, USA). Residuals from the model were examined for normality and the presence of outliers via visual inspection of plots of residuals versus predicted values and normal probability plots of residuals. Comparison of PK between study periods (Period 1 vs. Period 2; performed separately for the 10 and 20 mg doses) was evaluated using generalized linear model procedures, with factor period as fixed effects and participant as random effect on ln-transformed AUC_{0-t}, AUC_{0-inf}, and C_{max} using $p < 0.05$ as statistical significance. The ratio (Period 1/Period 2) of geometric means and 90% confidence intervals (CIs) for the ratio of geometric means, based on least squares mean from the analysis of variance (ANOVA) of the ln-transformed data, were calculated for AUC_{0-t}, AUC_{0-inf}, and C_{max}. Intra- and inter-participant %CV were estimated.

Comparison of PK between zavegepant doses (10 vs. 20 mg) was evaluated using generalized linear model procedures, with treatment, period, and treatment-by-period factors as fixed effects and participant(treatment) as random effect on untransformed T_{max}, effective half-life, elimination rate constant, and terminal elimination half-life and on ln-transformed AUC_{0-t}, AUC_{0-inf}, and C_{max} using $p < 0.05$ as statistical significance. The treatment effect was tested against the residual mean square error. The ratio (20 mg/10 mg) of geometric means and 90% CIs for the ratio of geometric means, based on least squares mean from the ANOVA of the ln-transformed data, were calculated for AUC_{0-t}, AUC_{0-inf}, and C_{max}. Inter-participant %CV was estimated. In the case of no statistically significant treatment-by-period interaction, the analysis was rerun, excluding this term from the ANOVA model; otherwise, the ratio (20 mg/10 mg) was derived separately for each period.

Apparent correlation between $C_{0.5h}$ and C_{2h} versus the efficacy outcomes (migraine pain intensity, phonophobia status, photophobia status, nausea status, aura status, functional disability) was analyzed by Spearman correlation coefficient.

Statistical analyses were performed using SAS, version 9.4 (SAS Institute, Cary, NC, USA).

RESULTS

Disposition and demographics

Of the 342 individuals screened, 230 did not meet the project criteria and 73 were eligible but not enrolled (they decided not to participate, or there were already enough participants). A total of 39 participants were enrolled and randomized; all 39 received zavegepant in Period 1 (10 mg, $n = 20$; 20 mg, $n = 19$), and 37 also received zavegepant in Period 2. The two participants that did not receive treatment in Period 2 discontinued zavegepant 10 mg due to an adverse event (one) and withdrawn consent (one). All 39 participants were included in the efficacy and safety analyses, and 37 participants were included in the PK analyses.

The 39 participants in the efficacy and safety populations ($N = 39$) were White (100%), mostly Hispanic or Latino (97%) and female (72%), with a median (range) age of 48 (23–71) years and median (range) body mass index of 27.2 (18.6–32.9) kg/m^2. The demographics and characteristics of the PK population ($N = 37$) were similar (Table 1).

PK

Mean plasma zavegepant concentrations were comparable regardless of the presence or absence of migraine attack at 10 mg, but at 20 mg, mean plasma zavegepant concentrations appeared to be lower during a migraine attack (Period 1) than in a non-migraine period (Period 2) (Figure 1). A summary of PK parameters, including C_{max} and AUC_{0-inf}, is shown in Table 2. A moderate to high variability (~44–86%) in C_{max} and AUC was observed across study periods (Table 2).

TABLE 1 Participant demographics and characteristics.

Variable	Zavegepant 10 mg ($n = 18$)	Zavegepant 20 mg ($n = 19$)	Overall PK population ($N = 37$)
Age, years, mean (SD)	46.6 (13.0)	48.5 (13.0)	47.6 (13.0)
Sex, *n* (%)			
Female	16 (89)	11 (58)	27 (73)
Male	2 (11)	8 (42)	10 (27)
Ethnicity, *n* (%)			
Hispanic or Latino	17 (94)	19 (100)	36 (97)
Not Hispanic or Latino	1 (6)	0	1 (3)
Race, *n* (%)			
White	18 (100)	19 (100)	37 (100)
Body mass index, kg/m^2			
Mean (SD)	25.58 (3.5)	27.78 (3.9)	26.71 (3.8)
Median (minimum, maximum)	25.7 (18.6, 31.7)	29.1 (21.7, 32.9)	27.6 (18.6, 32.9)

Abbreviations: PK, pharmacokinetic; SD, standard deviation.

Statistical comparisons of plasma zavegepant PK parameters are shown in Table 3. Following administration of zavegepant 10 mg, geometric mean ratios for Period 1/Period 2 were 82.8% (90% CI 60.5–113.2; $p = 0.309$) for C_{max} and 90.1% (90% CI 70.2–115.5; $p = 0.473$) for AUC_{0-inf}. Following administration of zavegepant 20 mg, geometric mean ratios for Period 1/Period 2 were 72.5% (90% CI 57.9–90.8; $p = 0.023$) for C_{max} and 73.4% (90% CI 58.8–91.7; $p = 0.027$) for AUC_{0-inf}.

Averaging over study periods, there was a less-than-dose-proportional increase in zavegepant exposure when the dose was doubled from 10 to 20 mg. The geometric mean ratios for 20 mg/10 mg were 142.5% (90% CI 118.6–171.4) for C_{max} and 157.0% (90% CI 133.6–184.5) for AUC_{0-inf} (Table 4). The treatment-by-period interaction was not statistically significant, so this term was not included in the final ANOVA model.

The median T_{max} was 0.5 h for both doses of zavegepant, regardless of the presence or absence of migraine attack (Table 2).

Safety

Overall, 87% (34/39) of participants experienced 100 TEAEs during the study. Following zavegepant 10 mg, 65% (13/20) of participants reported 24 TEAEs in Period 1, and 72% (13/18) reported 19 TEAEs in Period 2. Following zavegepant 20 mg, 89% (17/19) of participants reported 30 TEAEs in Period 1 and 84% (16/19) reported 27 TEAEs in Period 2.

The most frequently reported TEAEs overall were dysgeusia (67% [26/39] participants), throat irritation (31% [12/39] participants), cough (21% [eight of 39] participants), and nasal discomfort (10% [four of 39] participants). Headache, somnolence, nasal pruritus, nasal mucosal erosion, and rhinorrhea were each reported in 5% (two of 39) participants, with other TEAEs each reported in fewer than two participants.

All TEAEs were mild. Most (97 TEAEs) were considered to be related to zavegepant. There were no deaths and no serious TEAEs. There was one TEAE that led to discontinuation of study drug (electrocardiogram PR interval prolongation) occurring in a participant in the 10 mg dose group.

Efficacy

After both doses of zavegepant, fewer participants reported pain (Figure 2A), migraine-associated symptoms (Figure 2B-E), and functional disability (Figure 2F). Before administration of zavegepant 10 mg, 60% (12/20) and 40% (eight of 20) participants had moderate and severe pain, respectively; at 2 h after the 10 mg dose, 20% (four of 20) of participants reported no pain, 70% (14/20) had mild pain, 10% (two of 20) had moderate pain, and none had severe pain. Similarly, before administration of zavegepant 20 mg, 53% (10/19) and 47% (nine of 19) participants had moderate and severe pain, respectively; at 2 h after the 20 mg dose, 16% (three of 19) of participants reported no pain, 53% (10/19) had mild pain, 32% (six of 19) had moderate pain, and none had severe pain.

Correlation between PK and efficacy

Spearman correlation analyses showed no apparent correlation between zavegepant concentration ($C_{0.5h}$ or C_{2h}) and efficacy outcomes (Table 5).

DISCUSSION

The PK of orally administered rizatriptan were investigated during and between migraine attacks,[17] but there have been few comparisons of

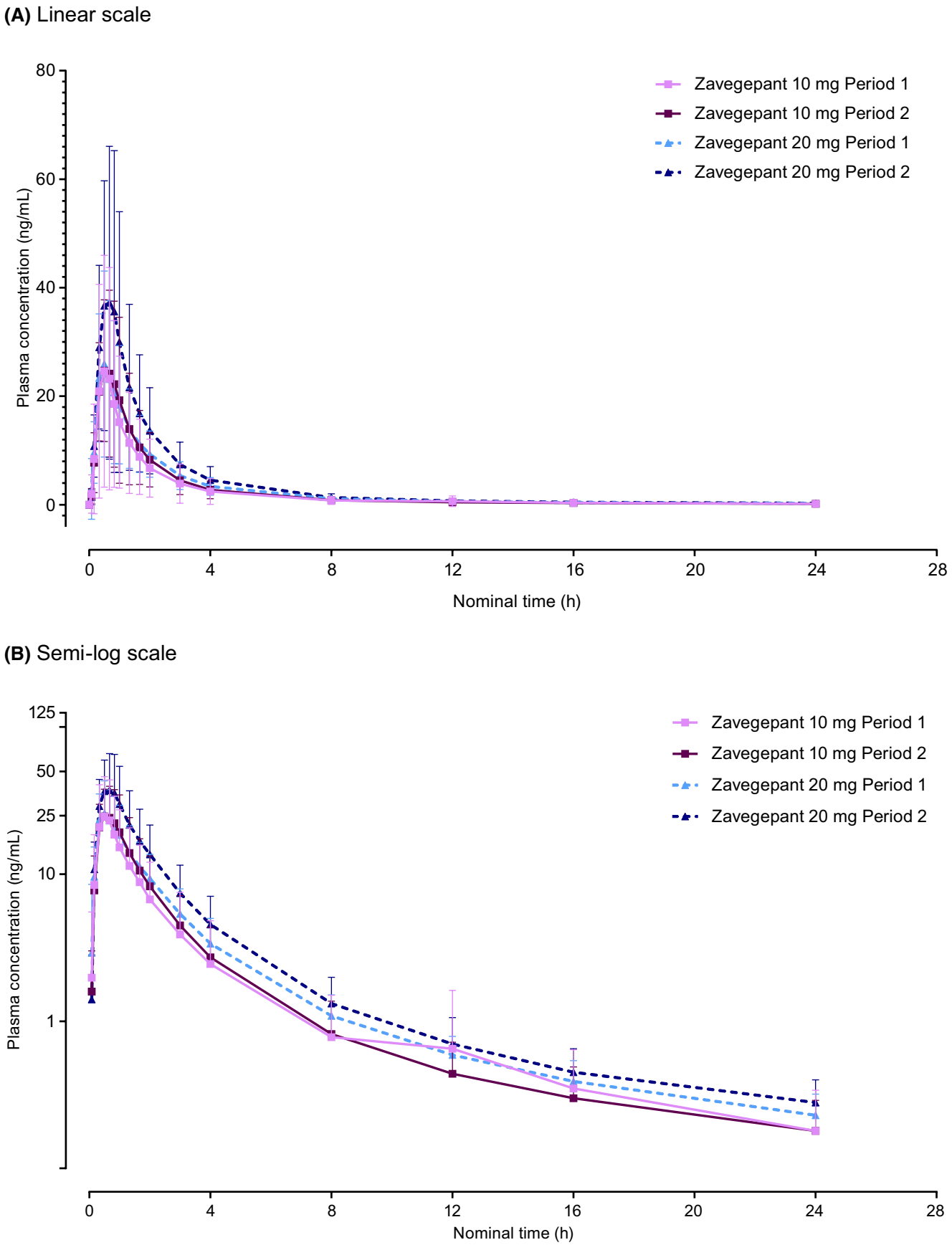

FIGURE 1 Zavegepant plasma concentration–time profiles, on linear (A) and semi-log (B) scales. For the pharmacokinetic population: Period 1 is during migraine attack; Period 2 is a non-migraine period. Only data from participants who completed both periods are presented. Data are mean and standard deviation. [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 2 Summary of zavegepant pharmacokinetic parameters.

	Zavegepant 10 mg		Zavegepant 20 mg	
Variable	**Period 1 ($n=18$)**	**Period 2 ($n=18$)**	**Period 1 ($n=19$)**	**Period 2 ($n=19$)**
AUC_{0-t}, h·ng/mL				
Geometric mean (%CV)	37.3 (78.0)	45.0 (54.1)	55.3 (43.8)	73.4 (56.9)
Mean (SD)	49.4 (38.5)	53.7 (29.0)	59.9 (26.2)	84.5 (48.1)
AUC_{0-inf}, h·ng/mL				
Geometric mean (%CV)	41.1 (75.4)[a]	47.0 (53.9)	57.7 (43.5)	79.3 (54.4)[b]
Mean (SD)	53.4 (40.3)[a]	56.0 (30.2)	62.4 (27.2)	90.5 (49.3)[b]
C_{max}, ng/mL				
Geometric mean (%CV)	18.5 (85.7)	22.3 (54.9)	24.6 (60.4)	34.0 (68.2)
Mean (SD)	26.6 (22.8)	27.1 (14.9)	27.6 (16.6)	41.0 (27.9)
$C_{0.5h}$, ng/mL				
Geometric mean (%CV)	17.2 (87.0)	20.3 (52.8)	22.7 (65.8)	30.6 (63.1)
Mean (SD)	24.6 (21.4)	24.6 (13.0)	26.0 (17.1)	36.5 (23.0)
C_{2h}, ng/mL				
Geometric mean (%CV)	5.0 (79.0)	6.7 (61.2)	8.5 (45.9)	11.6 (58.4)
Mean (SD)	6.8 (5.3)	8.3 (5.1)	9.4 (4.3)	13.6 (8.0)
T_{max}, h				
Median (minimum, maximum)	0.5 (0.3, 0.7)	0.5 (0.3, 0.8)	0.5 (0.2, 1.4)	0.5 (0.3, 1.0)
$T_{1/2\ el}$, h				
Geometric mean (%CV)	7.7 (31.8)	8.2 (29.1)	6.9 (34.5)	8.0 (38.1)[b]
Mean (SD)	8.1 (2.6)	8.6 (2.5)	7.4 (2.6)	8.7 (3.3)[b]
$T_{1/2\ eff}$, h				
Geometric mean (% CV)	3.5 (60.0)	3.1 (25.5)	3.3 (19.9)	3.3 (38.0)
Mean (SD)	3.8 (2.3)	3.2 (0.8)	3.4 (0.7)	3.4 (1.3)
CL/F, L/h				
Geometric mean (% CV)	243.5 (74.6)[a]	213.0 (105.9)	346.9 (39.6)	252.2 (47.3)[b]
Mean (SD)	315.5 (235.3)[a]	280.5 (297.1)	373.8 (147.9)	284.4 (134.5)[b]
V_d/F, L				
Geometric mean (%CV)	2635.4 (107.2)[a]	2518.0 (69.8)	3473.6 (60.0)	2922.7 (70.0)[b]
Mean (SD)	3875.6 (4153.2)[a]	3068.6 (2140.9)	3924.9 (2355.4)	3622.2 (2536.1)[b]

Note: For the pharmacokinetic population: Period 1 is during migraine attack; Period 2 is a non-migraine period. Only data from participants who completed both periods are presented.

Abbreviations: AUC, area under the plasma concentration–time curve; AUC_{0-t}, AUC from time zero to the last non-zero concentration; AUC_{0-inf}, AUC from time zero to infinity; $C_{0.5h}$, observed plasma concentration at 0.5 h post dose; C_{2h}, observed plasma concentration at 2 h post dose; CL/F, apparent total body clearance; C_{max}, observed maximum plasma concentration; CV, coefficient of variation; *n*, number of participants dosed; SD, standard deviation; $T_{1/2\ eff}$, effective half-life; $T_{1/2\ el}$, elimination half-life; T_{max}, time of observed C_{max}; V_d/F, apparent volume of distribution.

[a]$n=17$.

[b]$n=18$.

PK data during and between migraine attacks for the class of calcitonin gene-related peptide antagonists, or for intranasal agents.

This study found zavegepant exposure (C_{max} and AUC_{0-inf}) was comparable during a migraine attack compared with a non-migraine period at the therapeutic dose of 10 mg nasal spray. The objective of this study was not bioequivalence, so the standard United States Food and Drug Administration bound for bioequivalence (80% to 125%) was not used; as the magnitude of the differences in exposure are well within the efficacy and safety margin, they are considered comparable. Zavegepant exposure was within 17% for C_{max} and 10% for AUC_{0-inf} during a migraine attack compared with a non-migraine period, with no statistically significant difference between study periods. At the suprathera-peutic dose of 20 mg nasal spray, zavegepant exposure was statistically significantly lower (28% lower for C_{max} and 27% lower for AUC_{0-inf}) during a migraine attack compared with a non-migraine period. However, such difference is not considered to be clinically relevant given the moderate to high PK variability of zavegepant nasal spray. In addition, migraine status was not a significant covariate in a population PK analysis using pooled zavegepant

TABLE 3 Comparison of plasma zavegepant pharmacokinetic exposure parameters between periods.

Variable	Geometric LSM Period 1	Geometric LSM Period 2	Ratio of Period 1/ Period 2, %	Geometric 90% CI, %	Intra-participant %CV	Inter-participant %CV	*p* (for period)
Zavegepant 10 mg							
AUC_{0-t}, h·ng/mL	37.3	45.0	82.8	63.0, 109.0	50.1	60.7	0.249
AUC_{0-inf}, h·ng/mL	41.1	45.6	90.1	70.2, 115.5	43.4	65.0	0.473
C_{max}, ng/mL	18.5	22.3	82.8	60.5, 113.2	58.3	73.0	0.309
Zavegepant 20 mg							
AUC_{0-t}, h·ng/mL	55.3	73.4	75.4	60.5, 93.9	40.6	27.7	0.039
AUC_{0-inf}, h·ng/mL	58.2	79.3	73.4	58.8, 91.7	39.7	28.1	0.027
C_{max}, ng/mL	24.6	34.0	72.5	57.9, 90.8	41.7	37.2	0.023

Note: For the pharmacokinetic population: Period 1 is during migraine attack; Period 2 is a non-migraine period. The *p* values are derived from Type III sums of squares.

Abbreviations: AUC, area under the concentration–time curve; AUC_{0-t}, AUC from time zero to the last non-zero concentration; AUC_{0-inf}, AUC from time zero to infinity; CI, confidence interval; C_{max}, observed maximum plasma concentration; CV, coefficient of variation; LSM, least squares mean.

TABLE 4 Comparison of plasma zavegepant pharmacokinetic exposure parameters between doses.

Variable	Geometric LSM Zavegepant 10 mg	Geometric LSM Zavegepant 20 mg	Ratio of 20 mg/10 mg, %	Geometric 90% CI, %	Intra-participant %CV	Inter-participant %CV	*p* (for dose)	*p* (for period)
AUC_{0-t}, h·ng/mL	41.0	63.7	155.5	131.4, 183.9	44.8	46.0	<0.001	0.023
AUC_{0-inf}, h·ng/mL	43.3	67.9	157.0	133.6, 184.5	41.6	48.3	<0.001	0.035
C_{max}, ng/mL	20.3	28.9	142.5	118.6, 171.4	49.7	56.4	0.003	0.024

Note: For the pharmacokinetic population: *p* values are derived from Type III sums of squares. Treatment and Period were pooled together as the treatment by period interaction was not statistically significant.

Abbreviations: AUC, area under the concentration–time curve; AUC_{0-t}, AUC from time zero to the last non-zero concentration; AUC_{0-inf}, AUC from time zero to infinity; CI, confidence interval; C_{max}, observed maximum plasma concentration; CV, coefficient of variation; LSM, least squares mean.

concentration data from this study and all other healthy volunteer studies.[18]

The increase in zavegepant exposure was less than dose proportional when the dose was doubled from 10 to 20 mg. This is consistent with previous findings of a slightly less than dose-proportional increase in exposure following single intranasal dose administration up to 40 mg.[9,19]

The T_{max} was not affected by dose or the presence of a migraine attack with a median value of 0.5 h following the administration of zavegepant 10 and 20 mg nasal spray. The T_{max} of zavegepant in the present study is also consistent with previous data.[9,19]

Zavegepant was well tolerated in this single-dose study, with a safety profile consistent with that reported previously.[10,11] Both doses exhibited favorable safety profiles during migraine attacks and non-migraine periods. After both doses of zavegepant, fewer participants reported pain, migraine-associated symptoms, and functional disability; however, there was no correlation between exposure and these efficacy responses in the present study. This is probably due to the moderate to high zavegepant PK variability and the potential maximum effect reached by zavegepant 10 and 20 mg nasal spray.

This study has some limitations. The study did not include a pretreatment assessment of migraine-related nasal symptoms or migraine-related olfactory changes. The impact of nasal symptoms on the bioavailability of zavegepant could therefore not be assessed in the present study. The study population was largely Hispanic, but race/ethnicity are known to have no clinically relevant effect on the PK of zavegepant.[18] The open label study design is subject to bias. Although treatment allocation was not blinded, both groups received an effective dose of zavegepant. This efficacy and safety of zavegepant 10 and 20 mg nasal spray were further confirmed in randomized and double-blind studies.[10,11]

CONCLUSIONS

Zavegepant exposure was comparable during a migraine attack and a non-migraine period particularly at the therapeutic dose of 10 mg nasal spray. When averaging over migraine and non-migraine periods, there was a less-than-dose proportional increase in zavegepant exposure when the dose was doubled from 10 to 20 mg. The median T_{max} was 0.5 h regardless of migraine attack or dose. Zavegepant 10 and 20 mg

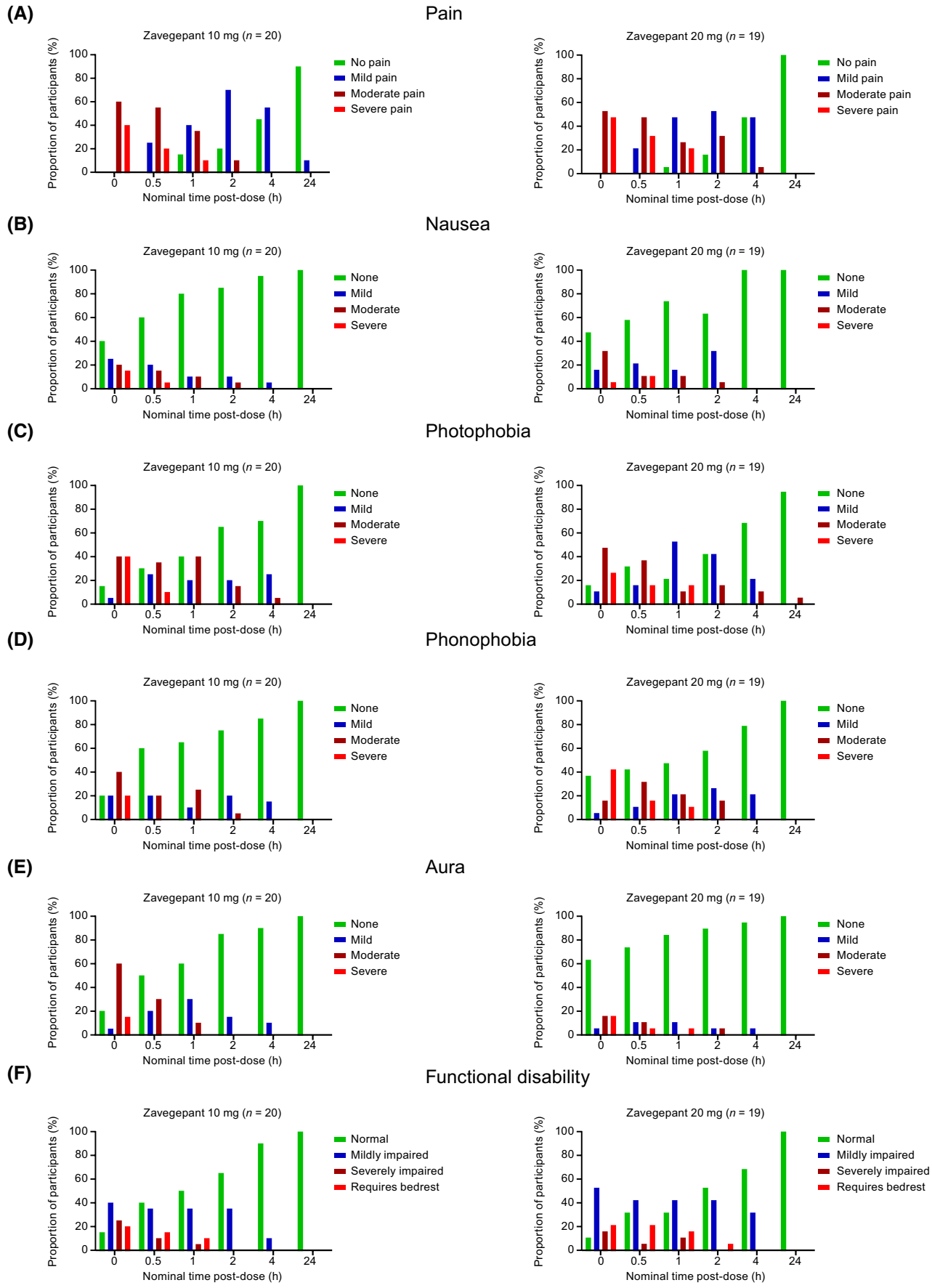

FIGURE 2 Migraine pain intensity (A), symptoms (B-E), and functional disability (F). Efficacy population. [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 5 Correlation between zavegepant exposure and efficacy during migraine attack (Period 1).

	Zavegepant 10 mg		Zavegepant 20 mg	
	$C_{0.5h}$	C_{2h}	$C_{0.5h}$	C_{2h}
Migraine pain intensity score	0.11 (0.631)	−0.24 (0.307)	−0.33 (0.168)	0.19 (0.434)
Nausea	0.07 (0.783)	0.33 (0.155)	0.33 (0.169)	0.27 (0.256)
Photophobia	0.01 (0.966)	0.34 (0.146)	−0.15 (0.538)	0.28 (0.239)
Phonophobia	−0.19 (0.435)	0.17 (0.473)	−0.18 (0.456)	−0.15 (0.539)
Aura	−0.27 (0.258)	0.04 (0.879)	−0.00 (0.989)	0.20 (0.410)
Functional disability	−0.16 (0.507)	−0.16 (0.515)	−0.12 (0.632)	0.19 (0.442)

Note: For the pharmacokinetic population: data are Spearman's rank correlation coefficient ρ (p value) between the efficacy parameter and the pharmacokinetic parameter.

Abbreviations: $C_{0.5h}$, observed plasma concentration at 0.5 h post dose; C_{2h}, observed plasma concentration at 2 h post dose.

exhibited favorable safety profiles during migraine attacks and non-migraine periods. Zavegepant was effective to relieve pain, associated symptoms, and functional disability during migraine attacks at both 10 and 20 mg; however, there was no apparent correlation between zavegepant concentration, and the efficacy outcomes assessed in this study.

AUTHOR CONTRIBUTIONS

Richard J. Bertz: Conceptualization; data curation; formal analysis; visualization; writing – original draft; writing – review and editing. **Julie L. Collins:** Conceptualization; data curation; formal analysis; visualization; writing – original draft; writing – review and editing. **Jennifer Madonia:** Conceptualization; data curation; formal analysis; visualization; writing – original draft; writing – review and editing. **Rajinder Bhardwaj:** Conceptualization; data curation; formal analysis; visualization; writing – original draft; writing – review and editing. **Lisa Kamen:** Conceptualization; data curation; formal analysis; visualization; writing – original draft; writing – review and editing. **Kyle T. Matschke:** Formal analysis; visualization; writing – original draft; writing – review and editing. **Jing Liu:** Formal analysis; visualization; writing – original draft; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

Richard J. Bertz is an employee of Biohaven and owns stock/options in Biohaven. **Julie L. Collins** was an employee of Biohaven at the time the study was conducted, is an employee of Pfizer, and owns stock/options in Biohaven and Pfizer. **Jennifer Madonia** was an employee of Biohaven at the time the study was conducted and owns stock/options in Biohaven. **Rajinder Bhardwaj** is an employee of Certara Strategic Consulting and serves in a consultant/advisory role for Biohaven. **Lisa Kamen** is an employee of Biohaven and owns stock/options in Biohaven. **Kyle T. Matschke** is an employee of Pfizer and owns stock/options in Pfizer. **Jing Liu** is an employee of Pfizer and owns stock/options in Pfizer.

DATA AVAILABILITY STATEMENT

Upon request, and subject to review, Pfizer will provide the data that support the findings of this study. Subject to certain criteria, conditions and exceptions, Pfizer may also provide access to the related individual de-identified participant data. See https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information.

REFERENCES

1. Aurora S, Kori S, Barrodale P, Nelsen A, McDonald S. Gastric stasis occurs in spontaneous, visually induced, and interictal migraine. *Headache*. 2007;47:1443-1446.
2. Parkman HP. Migraine and gastroparesis from a gastroenterologist's perspective. *Headache*. 2013;53(suppl. 1):4-10.
3. Aurora SK, Shrewsbury SB, Ray S, Hindiyeh N, Nguyen L. A link between gastrointestinal disorders and migraine: insights into the gut-brain connection. *Headache*. 2021;61:576-589.
4. Lipton RB, Buse DC, Saiers J, Fanning KM, Serrano D, Reed ML. Frequency and burden of headache-related nausea: results from the American Migraine Prevalence and Prevention (AMPP) study. *Headache*. 2013;53:93-103.
5. Silberstein SD. Migraine symptoms: results of a survey of self-reported migraineurs. *Headache*. 1995;35:387-396.
6. Ailani J, Burch RC, Robbins MS, Board of Directors of the American Headache Society. The American Headache Society consensus statement: update on integrating new migraine treatments into clinical practice. *Headache*. 2021;61:1021-1039.
7. Eigenbrodt AK, Ashina H, Khan S, et al. Diagnosis and management of migraine in ten steps. *Nat Rev Neurol*. 2021;17:501-514.
8. Li G, Duan S, Zhu T, et al. Efficacy and safety of intranasal agents for the acute treatment of migraine: a systematic review and network meta-analysis. *J Headache Pain*. 2023;24:129.
9. Pfizer Labs. *Zavzpret (Zavegepant) Nasal Spray Prescribing Information*; 2023. Accessed September 20, 2023. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/216386s000lbl.pdf
10. Croop R, Madonia J, Stock DA, et al. Zavegepant nasal spray for the acute treatment of migraine: a phase 2/3 double-blind,

randomized, placebo-controlled, dose-ranging trial. *Headache*. 2022;62:1153-1163.
11. Lipton RB, Croop R, Stock DA, et al. Safety, tolerability, and efficacy of zavegepant 10 mg nasal spray for the acute treatment of migraine in the USA: a phase 3, double-blind, randomised, placebo-controlled multicentre trial. *Lancet Neurol*. 2023;22:209-217.
12. Martin VT, Fanning KM, Serrano D, et al. Chronic rhinitis and its association with headache frequency and disability in persons with migraine: results of the American Migraine Prevalence and Prevention (AMPP) study. *Cephalalgia*. 2014;34:336-348.
13. Fornazieri MA, Neto AR, de Rezende PF, et al. Olfactory symptoms reported by migraineurs with and without auras. *Headache*. 2016;56:1608-1616.
14. Marmura MJ, Monteith TS, Anjum W, Doty RL, Hegarty SE, Keith SW. Olfactory function in migraine both during and between attacks. *Cephalalgia*. 2014;34:977-985.
15. Arslan HH, Tokgöz E, Yildizoğlu Ü, Durmaz A, Bek S, Gerek M. Evaluation of the changes in the nasal cavity during the migraine attack. *J Craniofac Surg*. 2014;25:e446-e449.
16. Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition. *Cephalalgia*. 2018;38:1-211.
17. Cutler NR, Jhee SS, Majumdar AK, et al. Pharmacokinetics of rizatriptan tablets during and between migraine attacks. *Headache*. 1999;39:264-269.
18. Food and Drug Administration. *Zavzpret Office of Clinical Pharmacology Integrated Review*; 2022. Accessed March 7, 2024. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2023/216386Orig1s000ClinPharmR.pdf
19. Bertz R, Donohue M, Madonia J, et al. Safety, tolerability, and pharmacokinetics of single and multiple ascending doses of intranasal zavegepant in healthy adults (S31.004). *Neurology*. 2022;98(suppl. 18):1003.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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